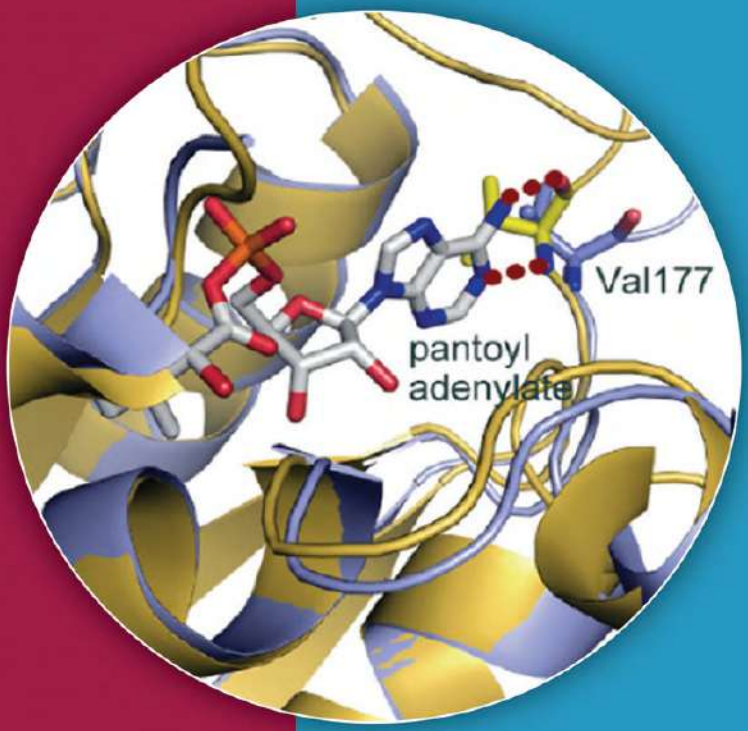
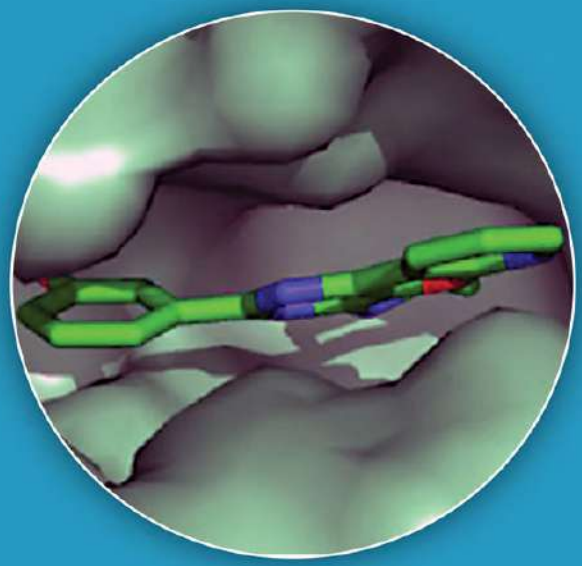
MICHAEL B. SMITH





THIRD EDITION

ORGANIC CHEMISTRY

AN ACID–BASE APPROACH

CRC Press
Taylor & Francis Group

Organic Chemistry

Organic Chemistry

An Acid–Base Approach

Third Edition

Michael B. Smith

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This book is dedicated to Professor Madeleine M. Joullié

Contents

Preface to the Third Edition

In my first edition of *Organic Chemistry. An Acid-Base Approach*, I introduced the idea of using an acid–base approach to teach organic chemistry. This concept continued in the second edition, and I used these books to teach several classes of the typical sophomore organic chemistry class. My class sizes each semester ranged from 250 to 400 students. These students were primarily STEM majors, including pre-pharmacy, pre-med, several of the biological sciences, and some chemistry majors.

The rationale for an acid–base approach rests on the fact that most reactions in organic chemistry involve an acid or a base. Laying a good foundation in acid–base chemistry greatly improves a student's understanding of nucleophiles and nucleophilic reactions. Amines, for example, are important bases and generate weakly acidic ammonium salts by reaction with an acid. Both ethers and alcohols react with a suitable acid to generate an oxonium ion as a reactive intermediate. Aldehydes and ketones react with an acid to give a resonance-stabilized oxocarbenium ion, which enhances the reactivity of acyl addition reactions with water, alcohols, or amines. Acid derivatives react with an acid catalyst to generate an oxocarbenium ion intermediate that facilitates formation of a tetrahedral intermediate for acyl substitution reactions. Alkenes react as Brønsted-Lowry bases with Brønsted-Lowry acids to give a carbocation intermediate for addition reactions. Similarly, alkynes react as bases to give a vinyl carbocation for addition reactions. When an alkene or an alkyne reacts with mercury derivatives, the product is a mercury-stabilized carbocation, facilitating oxymercuration-demercuration reactions. When an alkyne or an alkyne reacts with borane in hydroboration reactions, the product is an alkylborane via a four-center transition state. Both reactions are Lewis-base-like. Neither reaction forms an "ate"-complex, but the alkene or alkyne donates two electrons to mercury or boron to form a C—Hg or C—B bond. When a benzene ring reacts with an electrophilic species such as Br^+, Cl^+, or NO_2^+, the benzene ring donates two electrons in a Lewis-base-like reaction to give an arenium ion, which leads to S_EAr reactions. Alcohols react with a base to generate an alkoxide, which is both a base and a nucleophile. Alkyl halides or a pertinent substrate have a weakly acidic β-hydrogen that reacts with a suitable base to give an alkene in E2 and E1 reactions. The proton of a terminal alkyne reacts with a suitable base to generate the nucleophilic alkyne anion. Enolate anions are generated by reaction of the α-hydrogen of an aldehyde, ketone, or an acid derivative with a strong base. Enolate anion chemistry, which includes the aldol condensation and the Claisen condensation, is rooted in acid–base chemistry. Most of the steps in the chemistry of carboxylic acid derivatives involve acid–base chemistry. The hydrolytic workup for many reactions is an acid–base reaction.

Nucleophiles and their reactions are the basis of most organic chemistry books. Nucleophiles are electron donors to carbon, which is nothing more than a variation of the Lewis-base definition. A nucleophile donates electrons to an electrophilic carbon in a S_N2 or S_N1 reaction or to an acyl carbon of an aldehyde, ketone, or acid derivative. Understanding the two-electron donor properties of Lewis bases is an obvious and important lead-in to understanding how and why nucleophiles react in substitution reactions, in acyl addition, or in acyl substitution reactions.

Over the years, students who shared their views commented that this approach made the concepts of organic reactions easier to understand. This approach provides a "safety-net" of fundamental principles that allowed them to understand principles rather than simply memorizing information. This third edition was rewritten largely with the comments of those students in mind. It is also based on my classroom experiences of using the first and second editions and my observations of how organic chemistry has changed over the years. Therefore, several important changes are incorporated in the third edition.

Many classical chemical reactions are presented in this revision, but there are also reactions used in modern organic chemistry. These new reactions are presented to show how organic chemistry has matured and changed as a science over the last 50 years or so. Apart from Grignard reagents, organolithium reagent, and organocuprates, many organometallic reactions using Pd, Rh, Fe, and Cr

catalysts are included in this edition. These reactions include metathesis reactions, ylid reactions other than the Wittig reaction, the Mizoroki-Heck reaction, the Suzuki-Miyaura reaction and other aryl coupling reactions, C—H coupling reactions, the Nazarov cyclization, the Grob fragmentation, Negishi coupling, Fukuyama coupling, the Nozaki-Hiyama-Kishi reaction, the Tsuji-Trost reaction, the Mukaiyama aldol reaction, the Mitsunobu reaction, and Sonogashira coupling. Models for predicting stereoselectivity are discussed, including the Cram model and the Zimmerman-Traxler model. The Sharpless asymmetric epoxidation, the Jacobson-Katsuki reaction, the Shi epoxidation, and Noyori annulation are discussed. Many reactions that are important in biochemistry but have their roots in organic chemistry are presented at the end of many chapters and in Chapters 24 and 25. Research done by 35 current organic chemists is also included in this revision. Their cutting edge work illustrates the breadth and variety of modern organic chemistry.

Before retirement I put together online courses for both semesters of organic chemistry. I recorded more than 200 short videos for use as the lecture part of those courses. I made these videos available to my regular lectures and found they were extremely valuable as a course auxiliary. For this new edition I recorded 329 new video clips in a .mov format. These clips are distributed throughout the book and each is available in the e-book as a hyperlink. These videos are a "built-in" teaching ancillary, and they are accessible via any browser by clicking on the URL hyperlink from the e-book. I do not appear on these videos but give a voice presentation of pertinent concepts. There are a total of just over 36 hours of video, and the average video is 6.4 minutes in length. The longest video is 17.2 minutes and the shortest is 0.32 minutes. For those who have purchased this book but do not have the e-book, the URL for the video clips of each chapter can be found at the top of the respective chapter opener. The URL can be entered into any browser to access the video clips.

The first and second editions of this book, as well as most other organic chemistry textbooks, lack the diversity that is so important to organic chemistry. I attempt to correct this oversight in the third edition by introducing the work of 69 scientists who have not appeared in organic textbooks. Of these scientists, the contributions of 35 chemists who worked in the latter part of the 19th century or during the 20th century but have not been recognized in textbooks are distributed throughout the book. The work of 34 current organic chemists is also included throughout the chapters to show the research done in modern organic chemistry. The photos of all 69 of these scientists are also shown to highlight the diversity in organic chemistry.

Every chapter in this third edition has been extensively revised. Chapter 1 presents a brief history of organic chemistry. Chapter 1 also introduces 19 scientists who made significant contributions to organic chemistry but whose work has not been reported in a textbook prior to this work. Chapters 2 and 6 introduce acid–base reactions based on general chemistry principles and the organic chemistry of organic chemicals. Chapter 6 elaborates the acid–base properties of organic functional groups. The structure of alkanes and the fundamentals of nomenclature are presented in Chapter 4. Chapter 5 introduces important functional groups, along with their nomenclature. The energy considerations that are important to reactions in organic chemistry are discussed in Chapter 7. Bond rotation and conformations are discussed in Chapter 8, as well as a discussion of large ring compounds. The concepts and applications of chirality and stereochemistry are discussed in Chapter 9.

The reactions in Chapter 10 introduce reactions of carbocations, including the acid–base reactions of π-bonds reacting as bases with Brønsted-Lowry acids or with Lewis acids. Such reactions are traditionally labeled as addition reactions. Metathesis reactions are discussed as well as radical reactions and polymerization. Chapter 11 discusses S_N2, S_N1, and S_Ni reactions of alkyl halides. Substitution reactions of alcohols and ethers are also discussed. Chapter 12 discusses E2, E1, and Ei reactions. The Grob fragmentation is also introduced. Chapter 12 also summarizes the competition between substitution and elimination reactions of alkyl halides, showing how simple assumptions allow one to predict the product of these reactions. Chapter 13 discusses various spectroscopic methods and more or less stands apart from the remainder of the book. This chapter discusses mass spectrometry, infrared spectroscopy, ^{1}H NMR, and ^{13}C NMR and 2D NMR. Beginning with Chapter 8, clearly marked spectroscopic homework problems are presented at the end of each chapter. Therefore, spectroscopy can be introduced any time the instructor chooses to discuss it.

The preparation and reactions of Grignard reagents, organolithium reagents, and organocuprates are discussed in Chapter 14. Other organometallic compounds are also introduced. Chapter 15 discusses the oxidation reaction of alcohols and alkenes and also oxidative cleavage reactions. Chapter 16 introduces acyl addition reactions of aldehydes and ketones with strong and weak nucleophiles. The reaction of aldehydes and ketones to give an oxocarbenium intermediate to facilitate reactions with weak nucleophiles is also discussed. Chapter 17 introduces reduction reactions of carbonyl compounds, alkenes, and alkynes. Hydride reductions, catalytic hydrogenation, and dissolving metal reductions are discussed.

Chapter 18 discusses the acid–base reactions and the acyl substitution reactions of carboxylic acid and sulfonic acid derivatives. Dicarboxylic acid derivatives are discussed as well as derivatives of nitric acid, sulfuric acid, and phosphoric acid. Fatty acids and lipids are introduced. Chapter 19 discusses aromatic derivatives, their nomenclature, and aromatic substitution reactions. Both S_EAr and S_NAr reactions are discussed, as well as benzyne reactions and reactions of diazonium salts. A

variety of aromatic compounds are introduced including polynuclear aromatic systems. Chapter 20 discusses enolate anion reactions including the aldol condensation and the Claisen condensation. The Cram model and the Zimmerman-Traxler model are introduced to predict the diastereoselectivity of these reactions. Decarboxylation is introduced and ylid reactions are discussed. Chapter 21 introduces the properties and reactions of conjugated systems including the Michael reaction, Robinson annulation, and the Nazarov cyclization. The fundamentals of photochemistry are presented, and there is a brief introduction to ultraviolet spectroscopy. Chapter 22 discusses pericyclic reactions, including the Diels-Alder reaction [4+2]-cycloaddition, [2+2]-cycloaddition, and [3+2]-cycloaddition reactions. Sigmatropic rearrangements are discussed, including the Cope rearrangement and the Claisen rearrangement. Chapter 23 discusses heteroaromatic compounds and also reduced forms of heteroaromatic compounds. This chapter focuses on heterocycles that contain nitrogen, oxygen, and sulfur. Monocyclic, bicyclic, and polycyclic heterocyclic compounds are presented. Simple chemical transformations of monocyclic and bicyclic heterocycles are included. Chapters 24 and 25 offer brief discussions of biochemistry, with a focus on amino acids and proteins, carbohydrates, and nucleic acids. Chapter 24 focuses on amino acids, peptides, proteins enzymes, and hormones. There is a section of combinatorial chemistry. Chapter 25 focuses on carbohydrates, primarily monosaccharides, although disaccharides and polysaccharides are discussed. Reactions of carbohydrates are included. There is a discussion of glycosides, nucleosides, nucleotides, and polynucleotides such as DNA and RNA.

The homework in the third edition is largely the same as that in the second edition, but there are changes. This decision was taken with the recognition that substantive changes have been made in the discussions of every chapter, as well as the examples that are used. The solutions manual is a free download, as a pdf file, that is available from the CRC website to those who purchase the book.

I thank the many students I taught in my undergraduate organic chemistry classes over many years. Their interest, enthusiasm, and input not only inspired this book but have made it significantly better and hopefully more useable. If not for them, this book and this organization would not exist. I thank Courtney Stanford (Rochester), Dee Casteel (Bucknell), Fred Luzzio (Louisville), Amber Onorato (Northern Kentucky), John D'Angelo (Alfred University), and Spencer Knapp (Rutgers). They reviewed portions of the manuscript, provided many suggestions and comments that improved the textbook, and I thank them very much. I thank the many other friends and acquaintances who made suggestions that influenced this book.

I give my sincere thanks to the organic chemists who agreed to participate in this book, for their help and for their many contributions to organic chemistry. They not only provided photos and descriptions of their research but provided inspiration for the chemistry and examples used. This endeavor has cemented my belief that diversity of the people and of ideas in organic chemistry lies at the heart of our science and keeps it growing. Incorporation in an undergraduate textbook is long overdue.

I thank Hilary Rowe, the editor for the third edition, and Dr. Fiona MacDonald, the publisher. Their help, dedication to the project, and their willingness and ability to solve problems were essential to completion of this revision. I thank Ms. Danielle Zarfati and Cynthia Klivecka for their expertise in bringing the manuscript to fruition as a typeset book. I thank Ms. Christine Elder for her graphic arts expertise to render several images in a form that is clearer and more attractive. Ms. Elder's graphics appear in several places throughout the book: Figures 3.9, 3.11, 3.12, 5.1, 5.2, 5.3, 5.4, 5.12, 5.15, 8.2, 8.11, 9.1, and 9.4I. I thank Dr. Warren Hehre and Dr. Sean Ohlinger of Wavefunction Inc. for their gift of Spartan 18 v. 1.4.8 (200921), which was used to generate the molecular models used throughout the book. I thank PerkinElmer Inc. for their gift of ChemDraw Professional v. 18.0.0.231 (4318), which was used to draw all reaction figures and schemes in this book and also used to render ^{1}H and ^{13}C NMR spectra throughout the book.

Finally, I thank my wife Sarah for her love and continued support throughout the months required to revise this book.

Michael B. Smith
Professor Emeritus
November, 2021
Willington, Connecticut

Common Abbreviations

Other, less common, abbreviations are given in the text when the term is used.

Ac	Acetyl	
AIBN	Azobisisobutyronitrile	
aq	Aqueous	
AIBN	Azobisisobutyronitrile	
Ax	Axial	
	9-Borabicyclo[3.3.1] nonylboryl	
9-BBN	9-Borabicyclo[3.3.1] nonane	
Bn	Benzyl	$-CH_2Ph$
Boc	***tert*-Butoxycarbonyl**	
Bu	***n*-Butyl**	$-CH_2CH_2CH_2CH_3$
BUN	Blood urea nitrogen	
Bz	Benzoyl	
°C	Temperature in Degrees Celcius	
^{13}C NMR	Carbon Nuclear Magnetic Resonance	
cat	Catalytic	
Cbz	Carbobenzyloxy	
CIP	Cahn-Ingold-Prelog	
CoA	Coenzyme A	
mCPBA	3-Chloroperoxybenzoic acid	
DCC	1,3-Dicyclohexylcarbodi-imide	***c*-C_6H_{11}-N=C=N-*c*-C_6H_{11}**
DDT	Dichlorodiphenyltrichlo-roethane	
DEA	Diethylamine	$HN(CH_2CH_3)_2$
DMAP	4-Dimethylaminopyridine	
DME	Dimethoxyethane	$MeOCH_2CH_2OMe$
DMF	***N,N'*-Dimethylformamide**	
DMSO	Dimethyl sulfoxide	
DNA	Deoxyribonuleic acid	
EA	Electron affinity	
EDTA	Ethylenediaminetetraace-tic acid	
ee or % ee	% Enantiomeric excess	
Equiv	Equivalent(s)	
Er	Enantiomeric ratio	
Et	Ethyl	$-CH_2CH_3$
Ether	Diethyl ether	$CH_3CH_2OCH_2C_3$
Eq	Equatorial	
FC	Formal charge	
FDNB	Sanger's reagent, 1-fluoro-2,4-dinitroben-zene	
FMO	Frontier molecular orbitals	
FVP	Flash Vacuum Pyrolysis	
GC	Gas chromatography	
h	Hour (hours)	
^1H NMR	Proton Nuclear Magnetic Resonance	
HDL	High-density lipoprotein	
HDPE	High-density poly(ethylene)	
HIV	Human immunodefi-ciency virus	
HMPA	Hexameth-ylphosphoramide	
HOMO	Highest occupied molecular orbital	
HPLC	High performance liquid chromatography	
hv	Irradiation with light	
IP	Ionization potential	
*i*Pr	Isopropyl	$-CH(Me)_2$
IR	Infrared	
IUPAC	International Union of Pure and Applied Chemistry	
K	Temperature in Kelvin	
LCAO	Linear combination of atomic orbitals	
LDA	Lithium diisopropylamide	$LiN(i\text{-}Pr)_2$
LDL	Low-density lipoprotein	
LTA	Lead tetraacetate	
LUMO	Lowest unoccupied molecular orbital	
mcpba	***meta*-Chloroperoxyben-zoic acid**	

MDPE	Medium-density poly(ethylene)	
Me	Methyl	$-CH_3$ or Me
min	Minutes	
MO	Molecular orbital	
MRI	Magnetic resonance imaging	
mRNA	Messenger ribonucleic acid	
MS	Mass spectrometry	
NMR	Nuclear magnetic resonance	
N.R.	No reaction	
NAD^+	Nicotinamide adenine dinucleotide	
NADH	Reduced nicotinamide adenine dinucleotide	
$NADP^+$	Nicotinamide adenine dinucleotide phosphate	
NADPH	Reduced nicotinamide adenine dinucleotide phosphate	
NBS	***N*-Bromosuccinimide**	
NCS	***N*-Chlorosuccinimide**	
Ni(R)	Raney nickel	
NMO	***N*-Methylmorpholine *N*-oxide**	
Nu (Nuc)	Nucleophile	
Oxone®	$2\ KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$	
PCB	Polychlorobiphenyl	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Poly(ethylene glycol)	
PES	Photoelectron spectroscopy	
Ph	Phenyl	
PhMe	Toluene	
PPA	Polyphosphoric acid	
Ppm	Parts per million	
Pr	***n*-Propyl**	$-CH_2CH_2CH_3$
PTFE	Poly(tetrafluoroethylene)	
PVC	Poly(vinyl chloride)	
Py	Pyridine	
rf	Radio frequency	
RNA	Ribonucleic acid	
ROS	Reactive oxygen species	
rt	Room temperature	
s	Seconds	
SCF	self-consistent field	
$(Sia)_2BH$	Disiamylborane (Siamyl is ***sec*-Isoamyl)**	
sBuLi	***sec*-Butyllithium**	$CH_3CH_2CH(Li)CH_3$
S_EAr	Electrophilic aromatic substitution	
SET	Single electron transfer	
S_NAr	Nucleophilic aromatic substitution	
SOMO	singly occupied molecular orbital	
T	Temperature	
***t*-Bu**	***tert*-Butyl**	$-CMe_3$
TBHP (***t*-BuOOH)**	***tert*-Butylhydroperoxide**	Me_3COOH
TFA	Trifluoroacetic acid	CF_3COOH
$ThexBH_2$	Thexylborane (***tert*-hexylborane)**	
THF	Tetrahydrofuran	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	$Me_2NCH_2CH_2NMe_2$
Tol	Tolyl	$4\text{-}(Me)C_6H_4$
TS	Transition state	
Ts(Tos)	Tosyl = ***p*-Toluenesulfonyl**	$4\text{-}(Me)C_6H_4SO_2$
TTP	Thiamine pyrophosphate	
TTP	Thiamine pyrophosphate	
UTP	Uridine 5′-triphosphate	
UV	Ultraviolet spectroscopy	
VIS	Visible	
VDW	van der Walls	

Videos to Accompany the Third Edition

AB3 Videos	Title	Time (min)
Chapter 2: Why Is an Acid–Base Theme Important?		
001-c02.mov	Traditional Acid and Base Theory	8.55
002-c02.mov	Acid and Base Strength	11.23
003-c02.mov	Bases are Electron Donors	9.19
004-c02.mov	How are the Two Acid–Base Definitions Related?	5.33
005-c02.mov	Electronegativity and Atom Size	12.51
006-c02.mov	Acid–Base Strength	6.54
007-c02.mov	Resonance and Acid Strength	5.38
008-c02.mov	Lewis Acids and Lewis Bases	6.07
009-c02.mov	Nucleophiles	6.17
Chapter 3: Bonding		
010-c03.mov	Atomic Orbitals	16.27
011-c03.mov	Chemical Bonding	8.12
012-c03.mov	σ-Covalent Bonds	10.04
013-c03.mov	Bond Length	2.14
014-c03.mov	LCAO Model and Hybrid orbitals	8.40
015-c03.mov	Methane and Hybridization	11.18
016-c03.mov	VSEPR Model	4.33
017-c03.mov	Bond Dissociation Energy	8.12
018-c03-mov	Dipole Moments	10.50
Chapter 4: Alkanes, Isomers, and an Introduction to Nomenclature		
019-c04.mov	Alkanes	7.06
020-c04.mov	Isomers	13.58
021-c04.mov	IUPAC Nomenclature Rules	10.00
022-c04.mov	Multiple Substituents	6.08
023-c04.mov	Complex Substituents	.32
024-c04.mov	Common Names	2.42
025-c04.mov	Cyclic Alkanes	6.18
026-c04.mov	Combustion Analysis	6.32
Chapter 5: Heteroatoms and Functional Groups		
027-c05.mov	π-Bonds and Alkenes	8.24
028-c05.mov	Alkene Nomenclature	5.24
029-c05.mov	Alkynes	5.32
030-c05.mov	Alkyne Nomenclature	4.52
031-c05.mov	Dienes, Diynes and Allenes	6.23
034-c05.mov	Alkyl Halides	2.48
035-c05.mov	Amines	7.13
036-c05.mov	Alcohols and Ethers	9.23
037-c05.mov	Acid-Base Properties of Functional Groups	4.10
038-c05.mov	Aldehydes and Ketones	9.26
039-c05.mov	Carboxylic Acids	9.29
040-c05.mov	Imines (C=N) and Nitriles (C≡N)	3.55
041-c05.mov	Physical Properties	16.43
042-c05.mov	Benzene	5.30
285-c05.mov	Terpenes	6.50
Chapter 6: Acids, Bases, and Nucleophiles		
043-c06.mov	Acid-Base Equilibria	8.02
044-c06.mov	Alcohols are Acids	4.23
045-c06.mov	Carboxylic Acids and Sulfonic Acids	8.40
046-c06.mov	Structural Variations in Carboxylic Acids	7.05
047-c06.mov	C—H Acids	5.2
048-c06.mov	Lewis Acids and Lewis Bases	3.10
049-c06.mov	Organic Bases	14.18
050-c06.mov	Amines and pK_{BH}	3.56
051-c06.mov	Nucleophiles and Organic Molecules	3.55
Chapter 7. Chemical Reactions, Bond Energy, and Kinetics		
032-c05.mov	Reactive Intermediates-A	6.36
033-c05.mov	Formal Charge	3.57
052-c07.mov	The Free Energy Equation	6.34
053-c07.mov	Bond Dissociation Energy and Bond Strength	6.37
054-c07.mov	Reactive Intermediates-B	4.18
055-c07.mov	Transition States	3.21
056-c07.mov	Reversible Reactions	12.47
057-c07.mov	Mechanisms	11.13
058-c07.mov	Kinetics and Half-Life	13.43

(*Continued*)

AB3 Videos	Title	Time (min)
Chapter 8: Rotamers and Conformation		
059-c08.mov	Rotamers	10.11
060-c08.mov	Ethane	5.36
061-c08.mov	Propane and Butane	10.21
062-c08.mov	π-Bonds and Rotamers	2.15
063-c08.mov	Pseudorotation, C3-C5 Cyclic Alkanes	10.23
064-c08.mov	Conformations of Cyclohexane	13.33
065-c08.mov	$A^{1,3}$ Strain	7.25
066-c08.mov	Larger Ring Cyclic Compounds	4.05
067-c08.mov	Cyclohexene	1.34
286-c08.mov	Macrocycles	7.45
Chapter 9: Stereoisomers: Chirality, Enantiomers, and Diastereomers		
068-c09.mov	Defining a Stereogenic Center	3.41
069-c09.mov	Enantiomers and Non-Superimposability	6.38
070-c09.mov	Fischer Projections	3.53
071-c09.mov	Cahn-Ingold-Prelog Selection Rules	10.45
072-c09.mov	Chiral Molecules with Substitution	6.52
073-c09.mov	Specific Rotation	15.18
074-c09.mov	Diastereomers and the 2^n Rule	9.40
075-c09.mov	Meso Compounds	4.00
076-c09.mov	Stereoisomers in Cyclic Molecules	6.33
077-c09.mov	*cis-trans* and *E-Z* Nomenclature	10.12
078-c09.mov	Bicyclic Compounds	4.26
079-c09.mov	Optical Resolution	3.11
295-c09.mov	Circular Dichroism	3.54
Chapter 10: Acid–Base Reactions of π-Bonds: Addition Reactions		
080-c10.mov	Carbocation Stability	4.03
081-c10.mov	Alkenes are Brønsted-Lowry Bases	6.39
082-c10.mov	Regioselectivity	6.24
083-c10.mov	Other Acids React with Alkenes	3.27
084-c10.mov	Carbocation Rearrangements	12.07
085-c10.mov	Hydration Reactions	6.01
086-c10.mov	Dihalogenation	7.34
087-c10.mov	Diastereoselective Dihalogenation	8.55
088-c10.mov	Alkenes with Hypohalous Acids	3.32
089-c10.mov	Hydroboration	9.29
090-c10.mov	Oxidation of Boranes to Alcohols	6.05

(*Continued*)

AB3 Videos	Title	Time (min)
091-c10.mov	Oxymercuration-Demercuration	9.30
092-c10.mov	Alkynes With HX	5.26
093-c10.mov	Hydration and Hydroboration of Alkynes	8.15
094-c10.mov	Dihalogenation of Alkynes	1.42
095-c10.mov	Alkenes React with HBr and Radicals	7.45
096-c10.mov	Alkene Polymerization	5.43
287-c10.mov	Alkene Metathesis	8.00
288-c10.mov	Pinacol Rearrangement	3.12
289-c10.mov	Polymerization	9.01
Chapter 11: Nucleophiles: Lewis Base-Like Reactions At sp^3 Carbon		
097-c11.mov	Nucleophiles	5.25
098-c11.mov	Defining S_N2 Reactions	7.30
099-c11.mov	Pentacoordinate Transition State	9.54
100-c11.mov	Substitution and Structure	6.10
101-c11.mov	Solvent Effects in S_N2 Reactions	14.14
102-c11.mov	Alkyl Halides & Sulfonate Esters	4.12
103-c11.mov	Functional Group Transformations. Halide and O Nucleophiles	4.19
104-c11.mov	Functional Group Transformations. N and C Nucleophiles	6.59
105-c11.mov	Ionization of Tertiary Halides	4.51
106-c11.mov	The S_N1 Reaction	5.07
107-c11.mov	Stereochemistry and S_N1 Reactions	2.25
108-c11.mov	Rearrangement and S_N1 Reactions	5.28
109-c11.mov	Alcohols React H—X Acids	5.11
110-c11.mov	S_Ni Reactions	9.18
111-c11.mov	Ethers React with Strong Acids	4.07
112-c11.mov	Epoxides React By S_N2 and S_N1 Reactions	5.57
113-c11.mov	Radical Halogenation	5.37
114-c11.mov	Rate of Substitution of Different H Atoms	8.34
115-c11.mov	Radical Bromination of Alkanes	6.04
116-c11.mov	Allylic Halogenation	6.53
290-c11.mov	Mitsunobu Reaction	7.25
291-c11.mov	Alkyne Coupling	2.54
Chapter 12: Base-Induced Elimination Reactions		
117-c12.mov	Alkenes From Alkyl Halides	7.53
118-c12.mov	The E2 Reaction	10.46
119-c12.mov	E/Z-Selectivity of the E2 Reaction	7.12

(*Continued*)

AB3 Videos	Title	Time (min)
120-c12.mov	The E2 Reaction with Cyclic Molecules	12.03
121-c12.mov	The E1 Reaction	7.59
122-c12.mov	Hoffman Elimination	7.00
123-c12.mov	Formation of Alkynes	1.55
124-c12.mov	Substitution Competes with Elimination	3.01
125-c12.mov	Four Assumptions	4.30
126-c12.mov	Examples of the Four Working Assumptions	10.55
292-c12.mov	Other Intramolecular Elimination Reactions	3.58
293-c12.mov	Grob Fragmentation	4.14
13: Spectroscopic Methods of Identification		
127-c13.mov	Light and Energy	5.49
128-c13.mov	Mass Spectrometry	6.00
129-c13.mov	Radical Cations	3.59
130-c13.mov	The Mass Spectrum	7.26
131-c13.mov	Isotopic Peaks	7.02
132-c13.mov	Determining a Molecular Formula	14.38
133-c13.mov	Absorption of Infrared Light	5.29
134-c13.mov	Stretching and Bending Vibrations	5.52
135-c13.mov	An Infrared Spectrophotometer	3.09
136-c13.mov	Characteristics of an Infrared Spectrum	7.45
137-c13.mov	IR of Common Functional Groups	10.58
138-c13.mov	Rings or π-Bonds	8.12
139-c13.mov	H is a Magnet	5.47
140-c13.mov	Spin Quantum Number	4.35
141-c13.mov	NMR Spectrometer and the NMR Spectrum	10.02
142-c13.mov	Chemical Shift	9.00
143-c13.mov	Influence of Functional Groups on Chemical Shift	13.19
144-c13.mov	Magnetic Anisotropy	7.00
145-c13.mov	n+1 Rule	10.00
146-c13.mov	Non-First Order Coupling	8.22
147-c13.mov	Integration	4.00
148-c13.mov	Determine a Structure. Examples 1-3	13.03
149-c13.mov	Determine a Structure. Examples 4-7	15.30
150-c13.mov	Carbon-13 NMR	8.02
294-c13.mov	Two-Dimensional (2D)-NMR	4.17
296-c13.mov	Proteomics	4.00
Chapter 14: Organometallics		
151-c14.mov	Grignard Reagents	5.31
152-c14.mov	Structure of Grignard Reagents	5.34
153-c14.mov	Grignard Reagents are Strong Bases	6.06
154-c14.mov	Organolithium Reagents	6.36
155-c14.mov	Organocuprate Reagents	5.06
297-c14.mov	Other Organometallic Compounds	5.17
Chapter 15: Oxidation		
156-c15.mov	Defining an Oxidation	4.11
157-c15.mov	Chromium(VI) Oxidation of Alcohols	12.11
158-c15.mov	PCC, PDC and Swern Oxidation	10.28
159-c15.mov	Dihydroxylation with $KMnO_4$	8.20
160-c15.mov	Dihydroxylation with OsO_4	9.00
161-c15.mov	Epoxidation	10.34
162-c15.mov	Ozonolysis	10.40
163-c15.mov	Oxidative Cleavage of Diols	4.16
298-c15.mov	Asymmetric Epoxidation	12.25
Chapter 16: Reactions of Aldehydes and Ketones		
164-c16.mov	Aldehydes and Ketones and Nomenclature	11.06
165-c16.mov	Carbonyls React as Bases	3.04
166-c16.mov	Nucleophilic Acyl Addition	7.41
167-c16.mov	Cyanide	6.58
168-c16.mov	Grignard Reagents and Organolithium Reagents	8.37
169-c16.mov	Alkyne Anions	4.22
170-c16.mov	Acyl Addition. "C" Nucleophiles	2.53
171-c16.mov	Water and Hydrates	8.22
172-c16.mov	Alcohols and Acetals	14.40
173-c16.mov	The Acetal-Alcohol Equilibrium	6.27
174-c16.mov	Reactions with Alcohols	4.37
175-c16.mov	Dithioacetals	5.30
176-c16.mov	Reactions of Thiols	3.56
177-c16.mov	Primary Amines	5.47
178-c16.mov	Secondary Amines	8.07
179-c16.mov	Functionalized Primary Amines	5.34
299-c16.mov	Cram's Rule	5.12
Chapter 17: Reduction		
180-c17.mov	Defining a Reduction	2.23
181-c17.mov	Hydride Reducing Agents	10.14
182-c17.mov	Reduction of Heteroatom Functional Groups	5.54
183-c17.mov	Catalytic Hydrogenation of Alkenes	11.22
184-c17.mov	Hydrogenation of Alkynes	9.44
185-c17.mov	Hydrogenation of Other Functional Groups	8.19
186-c17.mov	Dissolving Metal Reductions	9.30

(*Continued*)

AB3 Videos	Title	Time (min)
187-c17.mov	Zn, Sn, Wolff Kishner and Clemmensen Reductions	7.47
188-c17.mov	Dissolving Metal Reactions	1.35
300-c17.mov	Homogenous Hydrogenation	7.06
301-c17.mov	Pinacol Coupling	2.49
302-c17.mov	Acyloin Condensation	2.25
Chapter 18: Carboxylic Acid Derivatives and Acyl Substitution		
189-c18.mov	Carboxylic Acids	5.16
190-c18.mov	Dicarboxylic Acids	9.18
191-c18.mov	Acid chlorides, Anhydrides, Esters, Amides	6.38
192-c18.mov	Sulfonic Acids	2.43
193-c18.mov	Acyl Substitution	7.04
194-c18.mov	Hydrolysis of Acid Chlorides and Anhydrides	7.05
195-c18.mov	Hydrolysis of Esters	7.25
196-c18.mov	Hydrolysis of Amides	4.29
197-c18.mov	Preparation of Acid Chlorides and Anhydrides	7.20
198-c18.mov	Preparation of Esters	12.22
199-c18.mov	Lactones	3.13
200-c18.mov	Preparation of Amides	6.33
201-c18.mov	Lactams and Imides	4.18
202-c18.mov	Reactions of Carboxylic Acid Derivatives	10.25
203-c18.mov	Nitriles and Organocuprates	5.02
204-c18.mov	Dicarboxylic Acid Derivatives	6.23
205-c18.mov	Baeyer-Villiger Oxidation	6.38
206-c18.mov	Sulfonic Acid Derivatives	6.47
207-c18.mov	Nitriles	2.45
208-c18.mov	Reactions of Acid Derivatives	5.26
209-c18.mov	Spectroscopy of Acid Derivatives	5.56
303-c18.mov	Fatty Acids and Lipids	17.17
Chapter 19: Aromatic Compounds and Benzene Derivatives		
210-c19.mov	Structure of Benzene	4.06
211-c19.mov	Hückel's rule	1.33
212-c19.mov	Nomenclature of Arenes	6.32
213-c19.mov	Nomenclature of Functionalized Benzene Derivatives	9.35
214-c19.mov	Electrophilic Aromatic Substitution	4.58
215-c19.mov	Halogenation, Nitration and Sulfonation	7.03
216-c19.mov	Friedel–Crafts Alkylation	8.12
217-c19.mov	Friedel–Crafts Acylation	3.59
218-c19.mov	Regioselectivity	3.50
219-c19.mov	Predicting Regioselectivity	8.03
220-c19.mov	Activating and Deactivating Groups	8.01
221-c19.mov	S_EAr Reactions of Halobenzenes	3.55
222-c19.mov	S_EAr Reactions of Aniline	2.59
223-c19.mov	S_EAr Reactions	2.46
224-c19.mov	S_EAr Reactions of Disubstituted Benzenes	3.44
225-c19.mov	Reduction of Benzene Derivatives	9.38
226-c19.mov	Aromatic Compounds	9.21
227-c19.mov	Polycyclic Aromatic Compounds	10.01
228-c19.mov	Nucleophilic Aromatic Substitution	7.25
229-c19.mov	Benzyne Intermediates	4.21
230-c19.mov	Diazonium Salts	4.18
231-c19.mov	Reactions of Diazonium Salts	7.13
232-c19.mov	Spectroscopy of Benzene Derivatives	4.50
233-c19.mov	Synthesis of Benzene Derivatives	4.22
304-c19.mov	Aromatic Coupling Reactions	7.44
305-c19.mov	Polycyclic Aromatic Hydrocarbons (PAH)	4.48
Chapter 20: Enolate Anions: Acyl Addition and Acyl Substitution		
234-c20.mov	Aldehydes, Ketones and Enols	6.10
235-c20.mov	Enolate Anions	4.38
236-c20.mov	The α-Hydrogen and Electronic Effects	7.08
237-c20.mov	The Aldol Condensation	8.35
238-c20.mov	Mixed Aldol Condensations	6.30
239-c20.mov	Kinetic and Thermodynamic Conditions	7.01
240-c20.mov	Reaction Conditions and Equilibria	6.12
241-c20.mov	Return to Mixed Aldol Condensations	4.18
242-c20.mov	Intramolecular Aldol Condensation	4.58
243-c20.mov	Aldol Reactions	4.34
244-c20.mov	Acyl Substitution of Ester Enolates	7.52
245-c20.mov	Ester Enolates with Aldehydes and Ketones	2.40
246-c20.mov	Ester Enolate Anion Reactions	2.00
247-c20.mov	Malonic Esters and the Knoevenagel Reaction	4.47
248-c20.mov	Decarboxylation	2.59
249-c20.mov	Enolate Alkylation	5.45
250-c20.mov	Wittig Reaction	8.05
306-c20.mov	Stork Enamine Reaction	2.51
307-c20.mov	The Zimmerman-Traxler Model	7.10

(*Continued*)

AB3 Videos	Title	Time (min)
308-c20.mov	The Acid-Catalyzed Aldol Condensation	5.43
309-c20.mov	The Reformatsky Reaction	2.25
310-c20.mov	Tsuji-Trost Reaction	2.36
311-c20.mov	Tebbe and Petasis Reactions	3.23
Chapter 21: Difunctional Molecules: Dienes and Conjugated Carbonyl Compounds		
251-c21.mov	Conjugated Dienes and Conjugated Carbonyl Compounds	9.37
252-c21.mov	Ultraviolet Spectroscopy	11.19
253-c21.mov	Reactions of Dienes	8.08
254-c21.mov	Michael Addition	9.54
312-c21.mov	General Principles of Photochemistry	11.31
313-c21.mov	Nazarov Cyclization	2.10
314-c21.mov	Morita-Baylis-Hillman Reaction	2.02
255-c21.mov	Conjugate Reduction	2.19
Chapter 22: Difunctional Molecules: Pericyclic Reactions		
256-A-c22.mov	The Diels-Alder Reaction	13.04
256-B-c22.mov	Reactivity	3.44
257-c22.mov	Alder Endo Rule	3.37
258-c22.mov	Regioselectivity and Diastereoselectivity	11.47
259-c22.mov	Sigmatropic Rearrangements	5.53
260-c22.mov	Cope rearrangement and Claisen rearrangement	6.18
315-c22.mov	[2+2] and [3+2] Cycloaddition Reactions	15.35
316-c22.mov	oxy-Cope Rearrangement	2.20
317-c22.mov	Ireland–Claisen Rearrangement	2.45
Chapter 23: Heteroaromatic Compounds		
261-c23.mov	N-Containing 5 and 6-Membered rings	6.54
262-c23.mov	Nitrogen Heterocycles in Everyday Life	3.29
263-c23.mov	O and S-containing 5 and 6-Membered Rings	4.59
264-c23.mov	Reactions of 5-membered Ring Heterocycles	5.19
265-c23.mov	Reactions of 6-Membered Rings	5.20
266-c23.mov	Polycyclic Aromatic Heterocycles	5.34
318-c23.mov	Triazines	4.09
319-c23.mov	Tetazines	6.53
320-c23.mov	Other N, O, S Heterocycles	3.41
321-c23.mov	Bicyclic Heterocycles and Alkaloids	9.37
Chapter 24: Multifunctional Compounds: Amines, Amino Acids and Peptides		
267-c24.mov	Amines with Alkyl Halides	4.23
268-c24.mov	Amine Surrogates	8.40
269-c24.mov	More Amine Surrogates	6.23
270-c24.mov	Amino Acids	6.13
271-c24.mov	Twenty α–Amino Acids	7.13
272-c24.mov	Reactions of Amino Acids	5.04
273-c24.mov	Peptides and Proteins	5.46
274-c24.mov	Secondary, Tertiary and Quaternary Structures	9.16
275-c24.mov	Determining the Primary Structure	11.01
322-c24.mov	Cyclic Peptides	1.44
323-c24.mov	Proteins	6.06
324-c24.mov	Enzymes	6.14
325-c24.mov	Combinatorial Chemistry	8.05
326-c24.mov	Proteomics, Peptides and Proteins	4.12
327-c24.mov	Hormones	6.30
Chapter 25: Multifunctional Compounds: Carbohydrates		
276-c25.mov	Monosaccharides	5.32
277-c25.mov	Furanoses and Pyranoses	3.57
278-c25.mov	Anomeric Centers	4.15
279-c25.mov	Mutarotation	8.36
280-c25.mov	Ketone Monosaccharides	2.43
281-c25.mov	Disaccharides and Trisaccharides	5.06
282-c25.mov	Reactions of Carbohydrates	7.14
283-c25.mov	Nucleotides and Nucleosides	3.56
284-c25.mov	RNA and DNA	10.20
328-c25.mov	Amino Sugars	3.24
329-c25.mov	Glycans and Glycosides	10.20
Total Time	2168.44 min = 36.14 h	
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Shortest Video	MIN 0.32 min	

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Infrared Spectra Reprinted from SBDS

Obtained from Appendix A, from Integrated Spectral Data Base System for Organic Compounds (SDBS) by the National Metrology Institute of Japan (NMIJ), National Institute of Advanced Industrial Science and Technology. Umezono 1-1-1, Tsukuba, Ibaraki, 305-8563, Japan

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490	isobutyronitrile	IR-NIDA-04675
507	2-butanol	IR-NIDA-06521
542	3-methoxy-1-butanol	IR-NIDA-05740
568	1-hexyne	IR-NIDA-05748
580	4-methyl-2-pentanone	IR-NIDA-05410
654	2,3-dimethylbutane	IR-NIDA-02888
798	1,1,3,3-tetramethybutylamine	IR-NIDA-00510
898	benzene	IR-NIDA-63541
899	p-xylene	IR-NIDA-63598
1275	diethyl allylmalonate	IR-NIDA-17726
1305	2,5-dimethyl-2,4-hexadiene	IR-NIDA-07292
1672	dibutylamine	IR-NIDA-04481
1891	isobutyl formate	IR-NIDA-06512
2208	diisopropylamine	IR-NIDA-55790
2396	heptane	IR-NIDA-05790
2673	2-pentanone	IR-NIDA-06910
3047	dipropyl ether	IR-NIDA-07299
3978	2,4-dimethyl-3-pentanone	IR-NIDA-01636
4000	N,N-dimethylethylamine	IR-NIDA-01670
4613	2-methylbutyronitrile	IR-NIDA-02476
4717	2-hexene	IR-NIDA-05742
5399	4-pentenoic acid	IR-NIDA-14245
5487	4-pyridinemethanol	IR-NIDA-09156
5745	1-ethyl-1-cyclopentene	IR-NIDA-13591
5894	priopionaldehyde diethyl acetal	IR-NIDA-18293
6064	2,2-diethoxypropane	IR-NIDA-58274
10224	2-methylpentanal	IR-NIDA-02541
10223	3-methylvaleric acid	IR-NIDA-67865
10231	2-hexyne	IR-NIDA-02550
10415	DL-alanyl-DL-serine	IR-NIDA-13812
17066	p-isopropylphentole	IR-NIDA-61290
19312	p-isobutylbenzaldehyde	IR-NIDA-62348
21918	allyl ethyl ether	IR-NIDA-29522
22747	trans-2-pentenal	IR-NIDA-26937
24541	N-benzylacetoacetamide	IR-NIDA-31737
26023	2,6-dimethylbenzonitrile	IR-NIDA-35184
26368	N,2,2-trimethylpropionamide	IR-NIDA-35950
27416	hexaethylbenzene	IR-NIDA-38383
34191	N-formyl-2-phenyl alanine methyl ester	IR-NIDA-52915
51928	1-phenyl-1-butanol	IR2007-86343TK
52449	3-bromo-2-(bromomethyl) propionate	IR2009-87596TK
52793	2-methylbutyl isobutyrate	IR2010-88216TK
53258	ethyldipropylamine	IR2013-89281TK

The scientist photographs are also available at:
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1

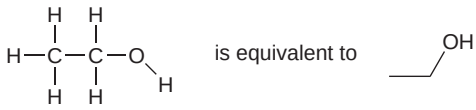
Introduction

Since you are taking organic chemistry, it is likely that you are a STEM major, in a class of students with a wide range of interests and career choices. Why is organic chemistry important? The answer lies in the fact that virtually every aspect of life, mammalian and non-mammalian as well as plant and microscopic life, involves organic chemistry. In addition, many of the products used every day (pharmaceuticals, plastics, clothing, etc.) involve organic molecules. Organic chemistry holds a central place in chemical studies because its applications touch virtually all other disciplines.

Most organic chemistry textbooks have a brief section to introduce organic chemistry. I was a graduate student when I first read an organic chemistry textbook that presented some historical facts as part of the normal presentation. The book was *Advanced Organic Chemistry*[1] by Louis F. Fieser (USA; 1899–1977). This book gave a perspective to my studies that helped me to better understand many of the concepts. I believe that putting a subject into its proper context makes it easier to understand. I am therefore introducing an abbreviated history of organic chemistry as an introduction to this book. I will include material from Fieser's book, and also from a book on the history of chemistry by Henry M. Leicester.[2] The early work described in these books laid the foundations of modern organic chemistry and many classical chemical reactions that are important in modern organic chemistry. This book will also introduce the work of many chemists whose contributions have not been heretofore recognized in a textbook. The contributions of women scientists and scientists of diverse ethnicity will be discussed. Further, the research of current chemists will be introduced to show the scope of modern organic chemistry and the diversity of the scientists.

1.1 A BRIEF HISTORY OF ORGANIC CHEMISTRY

In the 19th century, organic chemistry was defined as the chemistry of *carbon* compounds. For most of human history, however, both simple chemicals and complex mixtures of chemicals have been used without an understanding of the science behind them. Indeed, plants have been "milked," cut, boiled, and eaten for thousands of years as folk medicine remedies. Modern science has determined that many of these plants contain organic chemicals with effective medical uses, and many modern medicines are derived from them.



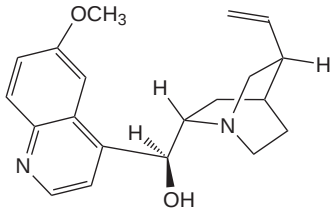
Ethyl alcohol (ethanol)

A simple but common organic chemical is ethyl alcohol (ethanol), produced by fermentation of grains and fruits. Ethanol has been known and consumed for thousands of years in various forms, including in a beer consumed by ancient Egyptians beginning around 5000 BCE. The structure shown requires some explanation. Each hydrogen atom bonded to a

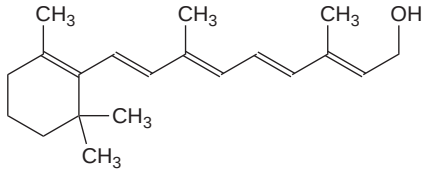
[1] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry*, Reinhold, NY, 1961, pp. 1–31.
[2] Leicester, H.M. *The Historical Background of Chemistry*, Wiley, NY, 1956, pp. 172–188.

DOI: 10.1201/9781003174929-1

carbon atom is represented as H—C, where the "line" (—) represents a chemical bond and C—C is a carbon–carbon bond. Likewise there is a C—O bond and an O—H bond. In the second structure, the carbon atoms (C) are omitted, but a line — is used as a shorthand notation to represent a bond between two atoms. In this simplified drawing, the "intersection of two bonds" is shown by a "bend" or an "angle" (=), and each point of the bend or angle represents a carbon atom in what is called *line notation*. Although the hydrogen atoms connected to each point (each carbon) are not shown in line notation, they are understood to be there. The C—O bond (carbon–oxygen) is shown by —O. The O—H unit is shown as just OH. Line notation uses one line for each bond, so C=C can be shown as = to indicate two bonds between the carbon atoms (a carbon-carbon double bond). A C=O bond (=O) has two bonds between carbon and oxygen (a carbon-oxygen double bond). Similarly, C≡C is shown as ≡ to represent three bonds between the two carbon atoms, a carbon–carbon triple bond.



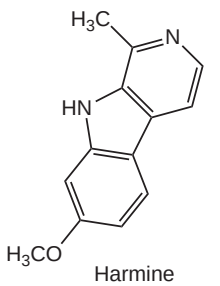
Quinine



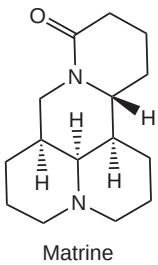
Vitamin A

Many naturally occurring materials contain important organic compounds that are well known in human history. The bark of the *Cinchona* tree, for example, has been used by the indigenous peoples of modern-day Peru, Bolivia, and Ecuador to treat symptoms of malaria. In the 19th century, it was discovered that this bark contains *quinine*, which is an antipyretic (fever reducing), an analgesic (pain reducing), an anti-inflammatory, and an anti-malarial. Ancient Egyptians ate roasted ox liver in the belief that it improved night vision. Ox liver is rich in *Vitamin A*. The structure of Vitamin A was determined in the 20th century, and it is a chemical important for maintaining healthy eyesight.

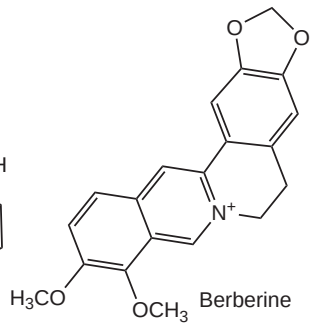
Quinine is an example of an *alkaloid*. Alkaloids (Section 23.6) are structurally diverse nitrogenous compounds, usually of plant origin, that are physiologically active and exhibit reactivity as a chemical base. There are thousands of known alkaloids but three illustrative examples of alkaloids with physiological properties are *harmine*, *matrine*, and *berberine*. Harmine, a beta-carboline alkaloid, is isolated from natural sources so it is a *natural product*. It has therapeutic potential as an antitumor compound, and it shows anti-HIV activity. Matrine is the most abundant alkaloid found in many *Sophora* plants, small trees, and shrubs in the pea family *Fabaceae*. It exhibits antibacterial, antiviral, anti-inflammatory, anti-asthmatic, anti-arrhythmic, anti-obesity, anti-cancer, diuretic, choleretic, hepatoprotective, nephroprotective, and cardioprotective effects. *Berberine* is isolated from Chinese herbs such as *Coptidis Rhizome*. It has been used for the treatment of diarrhea as an antibacterial drug, and it has beneficial effects on the metabolism disorders associated with diabetes.



Harmine



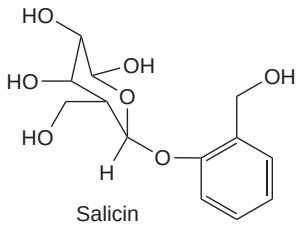
Matrine



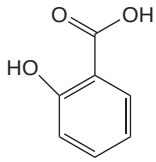
Berberine

People in ancient Assyria, Sumer, and Egypt chewed willow bark as an antipyretic treatment. In the 19th century it was discovered that willow bark contained *salicin*, a derivative

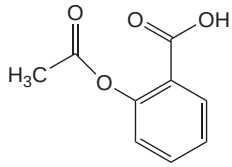
of *salicylic acid*. Nowadays it is recognized that salicin is a glycoside, which is a compound formed from a simple sugar and another compound (Section 25.4). *Synthesis* is the conversion of one compound into another, often in several chemical steps, and an important application is the preparation of organic molecules with a more complex structure from compounds that are structurally simple.



Salicin



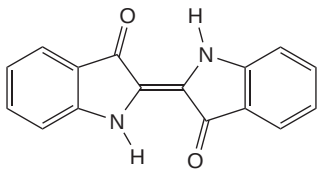
Salicylic acid



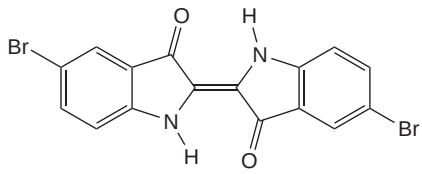
Acetylsalicylic acid (Aspirin)

In the mid-19th century a new compound was synthesized (chemically prepared from other chemicals) called *acetylsalicylic acid*, better known as aspirin. Aspirin is an effective analgesic, and it is an example of a so-called non-steroidal anti-inflammatory drug (an NSAID).

In ancient India, Java, and Guatemala certain plants provided a deep blue substance used to color clothing. In recent times, the main constituent was identified as *indigo*. The ancient Phoenicians discovered an extract from a sea snail (*Bolinus brandaris*, originally called *Murex brandaris*) found in the Mediterranean, traditionally off the coast of Tyre (now called Lebanon). This snail was the source of a beautiful and very expensive dye called *Tyrian purple*. This dye was so prized that Roman emperors used it to color their clothing, and for many years no one else was permitted to wear this color, which gave rise to the term "born to the purple." When the actual structure of the organic chemical Tyrian purple is compared with indigo, the only difference is the presence of two bromine atoms in the latter.



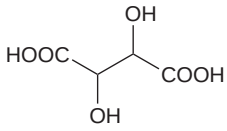
Indigo



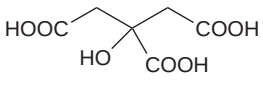
Tyrian purple

For most of history the actual chemical structure of the material isolated and used from natural sources was unknown. However, the importance of these materials led people to isolate pure compounds and then attempt to identify them. Isolation and purification was followed by characterization of the physical properties (melting point, boiling point, solubility in water, etc.) of these compounds. It was not until the mid- to late-19th century and even into the early-20th century that the structures of most of these compounds were known absolutely. Many of the pertinent identification procedures for the analysis of organic compounds were instituted and perfected by Justus von Liebig (Germany; 1803–1873), who built on the early work of Antoine Lavoisier (France; 1743–1794).

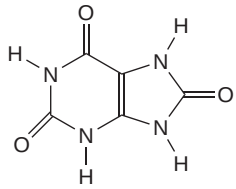
In the 18th century, Lavoisier made an important contribution to understanding the structure of organic molecules by burning natural materials in air. Lavoisier knew that air was composed mainly of oxygen (O_2) and nitrogen (N_2). He discovered that carbon in the burned material was converted to carbon dioxide (CO_2) and that hydrogen in the material was converted to water (H_2O). By trapping and weighing the carbon dioxide and the water, he was able to calculate the percentage of carbon and hydrogen in molecules. This knowledge allowed a determination of the *empirical formula* (Section 4.6). Organic molecules are composed of substantial amounts of carbon and hydrogen, and this *elemental analysis* procedure known as *combustion analysis* was, and is, an invaluable tool for determining structure (Section 4.6).



Tartaric acid



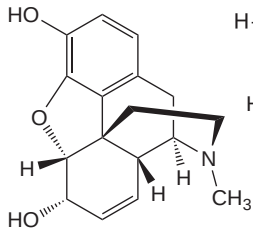
Citric acid



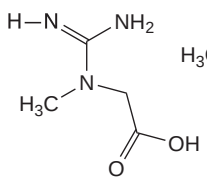
Uric acid

One of the first people to identify specific chemicals from natural sources was Carl Wilhelm Scheele (Sweden; 1742–1786). He isolated acidic components from grapes and lemons by forming precipitates with calcium or lead salts, and then added mineral acids to obtain the actual compounds. The acidic compound isolated from grapes is now known to be *tartaric acid*, and the one from lemon is now known to be *citric acid*. Scheele also isolated *uric acid* (Section 23.3) from urine. Friedrich W. Serturner (Germany; 1783–1841) isolated a compound from opium extracts in 1805 that is now known to be the alkaloid *morphine*. In 1815, Michel E. Chevreul (France; 1786–1889) isolated a material from skeletal muscle now known to be *creatine*, which has been used as a dietary supplement despite the observation that it can cause kidney damage and muscle cramping. He isolated *butyric acid* from rancid butter. He also elucidated the structure of simple soaps, which are salts of *fatty acids*. A fatty acid has the structure RCOOH, where "R" is a long chain of carbon atoms with hydrogen atoms on each carbon (Section 18.12). Between 1818 and 1820, Pierre J. Pelletier (France; 1788–1842) and Joseph Caventou (France; 1795–1877) isolated a poisonous alkaloid from Saint-Ignatius'-beans (*S. ignatii)* now known to be *strychnine* [found in the seeds of the nux vomica tree (*S. nux-vomica*) and also from related plants of the genus *Strychnos*]. The practice of isolating specific compounds (now known to be organic compounds) from natural sources continues today.

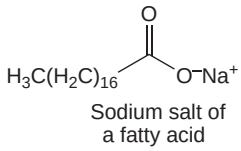
In the structures of matrine, morphine, and strychnine, some of the lines used for chemical bonds have been replaced with *solid wedges* or *dashed lines*. These are used to indicate the three-dimensional spatial relationship of atoms and groups within a molecule. The solid wedge indicates that the group is projected *in front of the plane* of the page, and the dashed line indicates that the group is projected *behind the plane* of the page. This three-dimensional representation correlates with the spatial relationship of the atoms or groups and will be used throughout this book. This structural feature is known as the *stereochemistry* of an atom or group (Chapter 9).



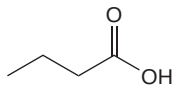
Morphine



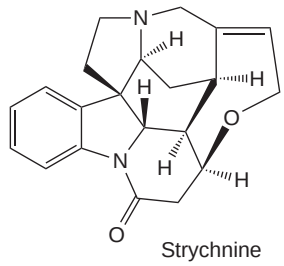
Creatine



Sodium salt of a fatty acid

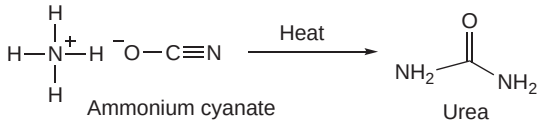


Butyric acid



Strychnine

In 1807, a Swedish chemist named Jöns J. von Berzelius (Sweden; 1779–1848) described the substances obtained from living organisms as *organic compounds*. He proposed that they were composed of only a few selected elements, including carbon and hydrogen. All organic compounds known at that time had been isolated from living organisms, and Berzelius and Charles F. Gerhardt (France; 1816–1856) described what was known as the *vital force theory*. This theory subscribed to the notion that "all organic compounds arise with the operation of a vital force inherent to living cells." The vital force theory was widely believed at the time. In 1828 Friedrich Wöhler (Germany; 1800–1882) synthesized the organic molecule urea from chemicals that had not been obtained from living organisms. Wöhler heated ammonium cyanate, and urea was isolated as the product. Urea is an organic compound that is a component of urine and also a component of bird droppings (commonly used for centuries as fertilizer). This work, along with that of others, demonstrated the fallacy of the vital force theory because it showed that an organic compound could be obtained from a source that was not associated with a living organism. However, it was not until Pierre Eugene-Marcellin Berthelot (France; 1827–1907) showed that all classes of organic compounds could be synthesized that the vital force theory finally disappeared.



By the middle of the 19th century, chemists were beginning to understand that organic molecules were discreet entities that could be prepared in the laboratory. The structures of these compounds (how the atoms are connected together) had to be determined before they could prepared, however, and structure determination posed many problems. Aleksandr M. Butlerov (Russia; 1828–1886) introduced the term *chemical structure* in 1861. In 1859, August Kekulé (Germany; 1829–1896) suggested the idea of discrete *valence bonds*. Until that time, there was no accepted method to determine how atoms in a molecule were arranged in a molecular structure. The idea of *valence*, which is how many bonds a given atom can form to remain neutral, was introduced by C.W. Wichelhaus (1842–1927) in 1868. It was actually Jacobus H. van't Hoff (Netherlands; 1852–1911) and Joseph A. Le Bel (France; 1847–1930) who deduced that when carbon appeared in organic compounds, it was connected to four other atoms, and the atoms around carbon assumed a *tetrahedral shape.* In other words, carbon is joined to other elements by *four chemical bonds*.

In the 19th century, the concept of a bond was vague and largely undefined. It was not until 1916 that Gilbert N. Lewis (USA; 1875–1946) introduced the modern concept of a bond, *formed by sharing two electrons.* He called a bond connecting two atoms by two shared electrons a *covalent bond* (Section 3.3). Understanding covalent bonds is essential for an understanding of the structure of an organic molecule. An example is *methane*, with four covalent bonds to carbon represented as a line (C—H).

Each line in the structure connecting the atoms represents a chemical bond as mentioned above for ethanol. If the structure is drawn again using ":" to represent the two shared electrons, this structure is commonly known as a *Lewis electron dot structure*, after G.N. Lewis. In 1923, Lewis suggested that a molecule that accepts an electron pair should be called an acid and a molecule that donates an electron pair should be called a base. Such compounds are called *Lewis acids* and *Lewis bases* to this day (Sections 2.7 and 6.8). Understanding the position of electrons in an organic molecule and how they are transferred is important for an understanding of both the structure and chemical reactions of molecules.

Maria Goeppert-Mayer

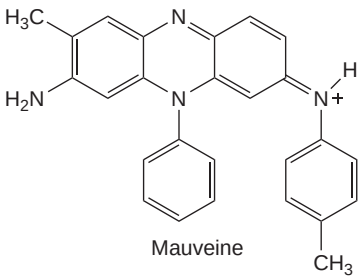
Nobel laureate Maria Goeppert-Mayer (Germany; 1906–1972) formulated the nuclear shell model that protons and neutrons within the nucleus are distributed in shells, according to their energy level (Section 3.1.2). Quantum mechanics was developed by several physicists, including Niels Bohr, Louis de Broglie, Max Born, Werner Heisenberg, Pascual Jordan, Wolfgang Pauli, Erwin Schrödinger, and Paul Adrien Maurice Dirac. Erwin Rudolf Josef Alexander Schrödinger (Austria-Ireland; 1887–1961) was a Nobel Prize-winning physicist who developed the Schrödinger equation, which describes the wave function of a system (Section 3.1.1). *Quantum chemistry* is considered to be the application of quantum mechanics to chemical systems. An early application of quantum mechanics examined the structure of diatomic hydrogen molecules and contributed to a understanding of the chemical bond. In 1925 two physicists, W. Karl Heisenberg (Germany; 1901–1976) and Erwin Schrödinger, described the orbital concept of molecular structure. In other words, they introduced the idea of *orbitals in chemistry and bonding* (Section 3.1). Erich Hückel (Germany; 1896–1980) developed theories of bonding and orbitals. Today, these ideas are combined by saying that electrons reside in orbitals, and orbital interactions control chemical reactions and explain chemical bonding. Joyce Jacobson Kaufman (USA; 1929–2016) advanced quantum chemistry and introduced the concept of conformational topology (see Chapter 8) and applied it to biomedical molecules. She also described a new theoretical method for coding and retrieving certain carcinogenic hydrocarbons.

Joyce Jacobson Kaufman

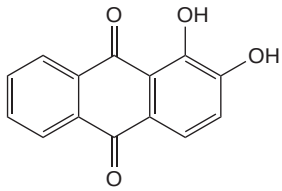
As part of his work on bonding, Hückel speculated on the nature of the C=C unit, although it was Alexander Crum Brown (England; 1838–1922) who first used C=C to represent a "double bond" for ethylene ($H_2C{=}CH_2$) in 1864. The research of Julia Lermontova (Russia; 1846–1919) focused on oil research, and she contributed to the development of a new method for the preparation of hydrocarbons that we now know as alkenes (Section 5.1). In 1862, Emil Erlenmeyer (Germany; 1825–1909) first represented the structure of acetylene with a triple bond, HC≡CH.

Julia Lermontova

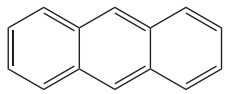
The synthesis of organic molecules began in the mid-19th century, beginning with molecules that have a relatively simple structure. Hermann Kolbe (Germany; 1818–1884) prepared ethane (CH_3CH_3) by electrolysis of potassium acetate ($CH_3CO_2^-K^+$), and Sir Edward Frankland (England; 1825–1899) prepared butane ($CH_3CH_2CH_2CH_3$) from iodoethane (CH_3CH_2I) and zinc (Zn). Charles A. Wurtz (France; 1817–1884) discovered *amines* in 1849, and August W. von Hofmann (Germany-England; 1818–1892) prepared many amines and also their ammonium salts by an acid-base reaction (Chapters 2 and 6) of the amine with a mineral acid. Amines are organic compounds that contain nitrogen and will be described in Section 5.5.3. Alexander W. Williamson (England; 1824–1904) showed that *ethers* contain the C—O—C linkage (Section 5.5.2). He showed that ethers can be prepared from the potassium salt of an alcohol. An *alcohol* contains a C—O—H unit, and the potassium salt is ROK (Section 5.7.1). An *alkyl halide* is represented as RX, where "R" is an *alkyl* or carbon group and X is a halogen, Cl, Br, I (Section 4.3.3). The nomenclature for all of these compounds will be described in Chapters 4 and 5.



Mauveine



Alizarin



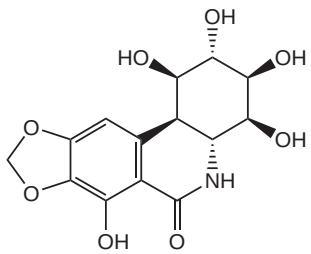
Anthracene

As the structure of more complex molecules and their chemistry is better understood, the synthesis of such molecules has become an important part of organic chemistry. In addition to molecules derived from nature, molecules that were unknown in nature could be envisioned and prepared. In 1863, William H. Perkin (England; 1838–1907) prepared the first commercially useful dye, *mauveine*, which was made from simpler molecules and possessed a purple color that had *not* been previously known. In 1869, the synthesis of a dye was reported by Carle Graebe (Germany; 1841–1927) and Carl Liebermann (Germany; 1882–1914). They prepared the natural dye *alizarin* from *anthracene* (Section 19.9.1), which was

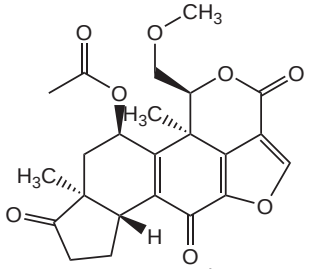
obtained from petroleum distillates. Adolf von Baeyer (Germany; 1835–1917) was the first to synthesize the previously mentioned dye *indigo*. *Aspirin*, also mentioned previously, was first prepared by Felix Hoffmann (Germany; 1868–1946) and later commercialized. The synthesis of the various dyes and of aspirin were important to the economies of both England and Germany in the late-19th and early-20th centuries.

In several structures cited in this chapter, including matrine, quinine, morphine, and strychnine, some of the lines used for chemical bonds were replaced with solid wedges or dashed lines. As previously noted, this three-dimensional drawing represents the *stereochemistry* of atoms or groups (Chapter 9). It was not until the mid- and late-20th century that the stereochemistry of organic compounds could be accurately determined, although its discovery dates to the mid-19th century. In 1848, Louis Pasteur (France; 1822–1895) found that there were two different crystalline forms of the sodium ammonium salt of tartaric acid. These crystals had a different *morphology*, defined here as their external structure. He was able to differentiate these two crystalline forms through a microscope and used a pair of tweezers to physically separate them (Section 9.10). They are examples of *stereoisomers* (Sections 9.1–9.3). This experiment showed that tartaric acid exists as two different compounds, now called *enantiomers* (Section 9.1). Enantiomers are stereoisomers that differ only in their ability to rotate plane-polarized light in different directions. Note that most enantiomers cannot be separated in this manner (Section 9.10). Van't Hoff, mentioned above, found that alkenes existed as a different type of stereoisomer now identified as an *(E)*- or a *(Z)-isomer*, a concept that is discussed in Section 9.8. Many scientists have helped develop the concept of stereochemistry, including John Cornforth (Australia-England 1917–2013), Vladimir Prelog (Yugoslavia-Switzerland; 1906–1998), and Donald J. Cram (USA; 1919–2001).

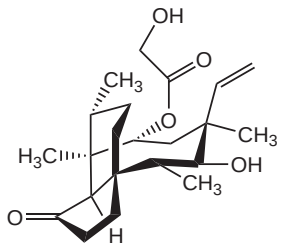
The isolation of organic compounds from natural resources continues to be important. New organic molecules are isolated from terrestrial and marine plants, fungi, bacteria, as well as some animals. G. Robert Pettit (USA, 1929–2021) and S. Morris Kupchan (USA, 1922–1976) are two of many organic chemists who discovered new and interesting organic compounds with potent biological activity against cancer and other human diseases. Inspired in large part by the isolation of new compounds with interesting structures, the synthesis of organic compounds has continued unabated since the 19th century. Over the years, increasingly more complex molecules have been synthesized, as illustrated by *pancratistatin*, *wortmannin*, and *pleuromutilin*. A discussion of the theory and practice of modern organic synthesis and many examples can be found in the book[3] by Nobel laureate Elias J. Corey (USA; 1928–). Many syntheses reported in the last 50 years have contributed enormously to organic chemistry, and ever more complex organic molecules continue to be synthesized. In addition, new chemical reactions as well as new chemical reagents (molecules that induce a chemical transformation in another molecule) have been developed.



Pancratistatin



Wortmannin



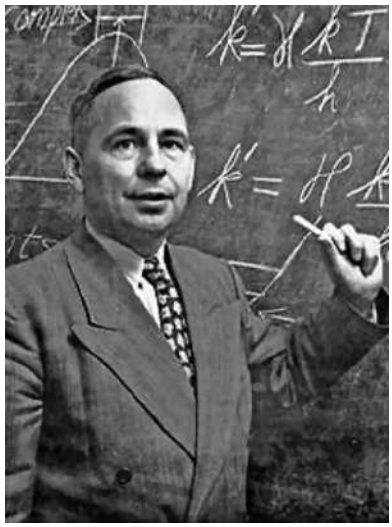
Plueromutilin

Prior to the late 1940s and 1950s, chemists did not really understand *how* chemical reactions occurred. In other words, what happened during the bond-making and bond-breaking processes remained a mystery. Understanding these processes, now called *reaction mechanisms*, required an enormous amount of work in the period of the late 1940s throughout the 1960s, and it continues today. Pioneers in this area include Franz Sondheimer (Germany-England; 1926–1981), Saul Winstein (Canada-USA; 1912–1969), Sir Christopher. K. Ingold

[3] Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, John Wiley & Sons, NY, 1989.

(England; 1893–1970), John D. Roberts (USA; 1918–2016), and three Nobel laureates Donald J. Cram (USA; 1919–2001), Herbert C. Brown (England-USA; 1912–2004), and George A. Olah (Hungary-USA; 1927–2017), as well as many others. Nobel laureates Roald Hoffman (Poland-USA; 1937–) and Robert Woodward (USA; 1919–1979), and Kenichi Fukui (Japan; 1918–1998) pioneered the use of orbital symmetry considerations and then frontier molecular orbital theory (Section 22.1) to explain many concerted or synchronous reactions. The concept of *reaction mechanism* allows a fundamental understanding of how organic reactions work. It is perhaps the most important aspect, however, because understanding the mechanism of chemical reactions allows chemists to predict products and reaction conditions without having to memorize everything.

An important part of a mechanism is the identification of transient products in many reactions called *intermediates*. Indeed, an intermediate is a transient and high-energy product that is formed initially but not isolated. An intermediate reacts further to give either other intermediates or a more stable and isolable product (Section 7.2). Reactions have been studied that have reactive ionic intermediates such as a *carbocation*, which is a carbon having three covalent bonds and a positive charge on carbon. Another ionic intermediate is a *carbanion*, which is a carbon having three covalent bonds and a negatively charged carbon atom. A non-ionic intermediate is a carbon *radical*, which is a carbon having three covalent bonds and one extra electron. Methods were developed to ascertain the presence of these intermediates.



Henry Eyring

The concept of reaction *kinetics* was developed for organic chemistry. Reaction kinetics examines how fast products are formed (the *reaction rate*) and how fast reactants disappear. Henry Eyring (Mexico/USA; 1901–1981) was a theoretical chemist who studied chemical reaction rates and intermediates. He developed the absolute rate theory or transition state theory for chemical reactions. This information gives clues as to how the reaction proceeds and what, if any, intermediates may be involved.

How are organic compounds isolated and identified? In early work, inorganic materials (e.g., metal salts and acids or bases) were added to force precipitation of organic compounds. In other cases, liquids were distilled from a mixture or solids were crystallized. In the 1950s, Nobel laureates Archer J.P. Martin (USA; 1910–2002) and Richard Synge (England; 1914–1994) developed the concept of *chromatography*. This technique allowed chemists to conveniently separate mixtures of organic compounds into individual components.

The origins for determining the mass of compounds dates to the 1890s. Instruments were developed that could exploit this concept. Bombarding an organic molecule with a high energy electron beam induces fragmentation of that molecule. Identifying these fragments gives important structural formation. This technique is known as *mass spectrometry* (MS),

built on the accomplishments of Arthur J. Dempster (Canada-USA, 1886–1990). This methodology has been greatly expanded and modified in recent years to become a very powerful tool for structural identification of organic molecules, including the field of *proteomics*, which is used for structural evaluation of proteins.

Mary Elliott Hill

Light has always been an important tool in chemistry, as will be described in Chapter 13. Both *ultraviolet spectroscopy* and *infrared spectroscopy* are major tools for the identification of organic compounds. In the early mid-20th century, ultraviolet (UV) light was shown to interact with organic molecules at certain wavelengths. Mary Elliott Hill (USA; 1907–1969) worked on the properties of ultraviolet light and developed analytic methodology to track the progress of chemical reactions that utilized ultraviolet spectrophotometry. In the 1940s and 1950s, molecules were exposed to infrared (IR) light, and individual molecules were found to absorb only certain wavelengths. Alma Levant Hayden (USA; 1927–1967) was an American chemist who used infrared and other techniques for analyzing chemicals. Identification of the wavelengths of light absorbed can be correlated with structure, a major step in the structure elucidation of organic molecules.

Alma Levant Hayden

It was discovered in the late 1940s that some atoms in organic molecules interact with electromagnetic radiation at wavelengths in the radio signal range if the molecules are suspended in a strong magnetic field. Initially, it was shown that hydrogen atoms in an organic molecule interacted with the radio signal and the magnetic field. The connectivity of different hydrogen atoms in an organic molecule can be identified, allowing the chemical structure to be puzzled together. This technique is now known as *nuclear magnetic resonance* (*NMR*) *spectroscopy* and it is one of the most essential tools for an organic chemist. With the power of modern computers, NMR analysis is used to determine the number and type of carbon, nitrogen, fluorine, and lithium atoms, as well as any other atoms in an organic molecule. Stable but not always the most abundant natural isotopes of atoms are used in NMR: ^{13}C, ^{15}N, ^{19}F, and ^{6}Li for example. Structural information on large enzyme/inhibitor complexes

can be obtained using NMR techniques. Mildred Cohn (USA; 1913–2009) studied chemical reactions within animal cells, pioneering the use of nuclear magnetic resonance spectroscopy (NMR) to study enzyme reactions and enzymatic catalysis. It is noteworthy that the important medical tool MRI (magnetic resonance imaging) is in reality an NMR technique that was developed in the 1970s. Note that MRI was developed at the height of the Cold War. It was decided that the word "nuclear" would be kept out of the technique name. The focus was kept on magnets to keep from alarming the public.

Mildred Cohn

Other tools include *X-ray crystallography*, known for many years and used to determine the crystal structure of molecules. When X-rays interact with a molecule with a distinct crystal structure, the resulting X-ray scattering patterns provide clues to its chemical structure. With modern computer technology, a picture of the structural features of a molecule can be produced, and the methodology has been expanded to include structures of proteins, biologically active small molecules docked to a protein and other biological molecules (see Section 25.6). Dorothy June Sutor (New Zealand; 1929–1990) studied attractive hydrogen bonding interactions involving hydrogen atoms attached to carbon atoms. She used crystallography to study the crystal structure of 1,3,7,9-tetramethyluric acid (theacrine); and she measured the distance between the methyl hydrogen and the oxygen. With modern electron tunneling microscopes, pictures of atoms have been made. Scanning Transmission Electron Microscopes can image objects a million times smaller than a human hair; and they have been used to visualize atoms in molecules.

Dorothy June Sutor

1.2 THE VARIETY AND BEAUTY OF ORGANIC MOLECULES

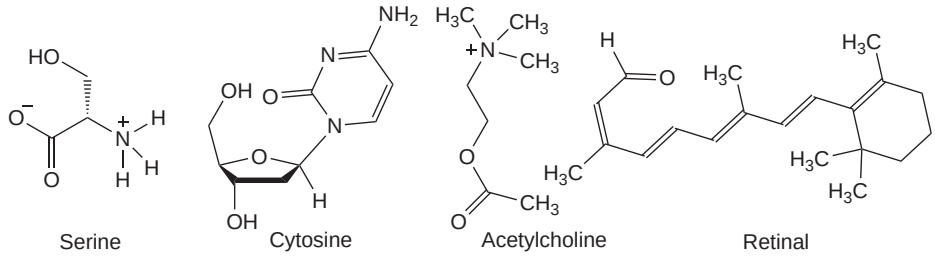
Weisun Tao

Marie Maynard Daly

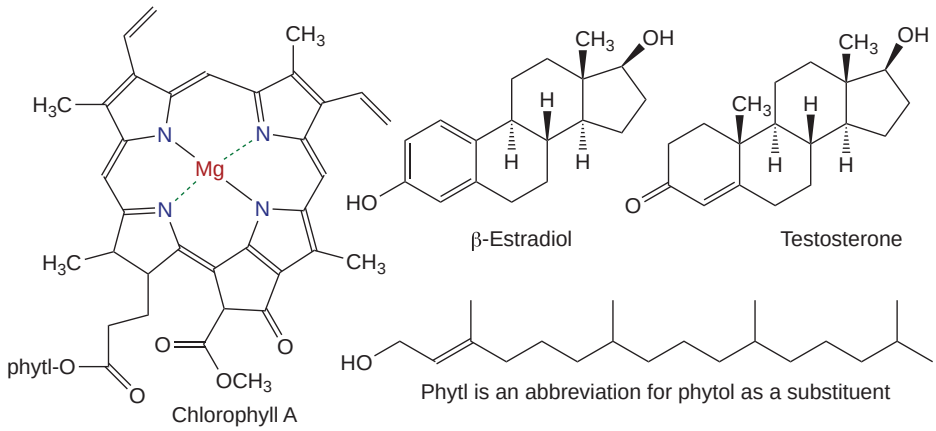
Section 1.1 described the development of organic chemistry as a unique science. Chemical reactions involving organic molecules are a part of the life process. In one sense, much of molecular biology and biochemistry can be categorized as organic chemistry at the cellular level. Proteins (Section 24.5) are large structures composed of many small organic chemical units known as amino acids (e.g., *serine*; Section 24.3). Weisun Tao (China; 1895–1982) was one of the founders of protein chemistry research in China. Enzymes (Section 24.6) are proteins that function as biological catalysts so almost all cellular metabolic processes occur at rates fast enough to sustain life. Marie Maynard Daly (USA; 1921–2003) made important contributions in four areas of research: the chemistry of histones, protein synthesis, the relationship between cholesterol and hypertension, and the update of creatine by muscle cells. The genetic instructions for the development, functioning, growth, and reproduction of all known organisms and many viruses are carried by DNA (deoxyribonucleic acid; Sections 25.5,6) and the RNA (ribonucleic acid; Sections 25.5,6), which is essential for many biological roles in coding, decoding, regulation, and expression of genes. DNA is made up of many nucleobase units such as *cytosine*.

If you are blinking an eye while reading, or moving your arm to turn the page, that nerve impulse from your brain was induced, in part, by one of several important organic molecules

called neurotransmitters. An important neurotransmitter is *acetylcholine*. If you see this page, the light is interacting with a photopigment in your eye called rhodopsin, which releases *retinal* upon exposure to the light. Retinal reacts with a lysine fragment (another amino acid; Section 24.3) of a protein as part of the process known as vision.



Note the similarity of retinal to Vitamin A (Section 1.1), which is simply the reduced form of retinal. Oxidation and reduction are discussed in Chapters 15 and 17. What you see, at least the color associated with what you see, is due to one or more organic molecules in each object. If the leaves on trees and the grass in your yard appear green, one of the chemicals responsible is called *chlorophyll A*. The ------ in the structure of chlorophyll A means there is an interaction between N and Mg (a coordinate bond) rather than a formal covalent N—Mg bond (see Chapter 14).

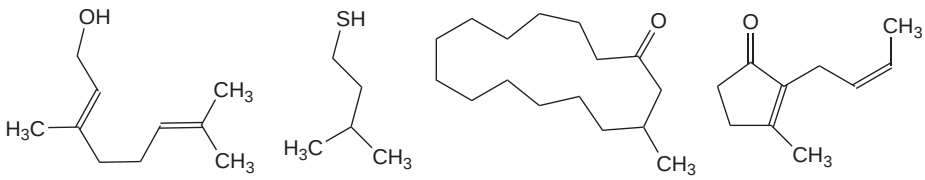


Percy Lavon Julian

There are many other things about human physiology that involve organic chemistry, including the physiological influences of organic chemicals. One of the principal female sex hormones is the steroid β-*estradiol*, and the principle male sex hormone is the steroid *testosterone*. Note that each gender has both hormones (and others), but in quite different proportions. Note also how the chemical structures of estradiol and testosterone have some structural similarities. A steroid (Section 5.4) is a biologically active organic compound composed of four fused rings in a 6:6:6:5 membered ring arrangement. Steroids are important components of cell membranes and are found in plants, animals, and fungi (Section 5.4). Some steroids are hormones, produced by your body to help your organs, tissues, and cells do their jobs. Steroids produced in animals and synthetic steroid drugs include sex hormones, corticosteroids, and anabolic steroids. Many steroids have been produced chemically by synthesis. Percy Lavon Julian (USA; 1899–1975) played a major role in the chemical synthesis of medicinal drugs from plants. He was the first to synthesize physostigmine, and he was a leader in developing industrial syntheses of the steroids progesterone, testosterone, cortisone, and other corticosteroids as well as birth control pills. Luis Ernesto Miramontes Cárdenas (Mexico; 1925–2004) was an organic chemist known as the co-inventor of the progestin norethisterone used in one of the first three oral female contraceptives. He was the first to synthesize norethisterone.

Luis Ernesto Miramontes Cárdenas

Smells are a very important part of life. What are smells anyway? They are the interaction of organic chemicals with olfactory receptors in your nose. If you walk into a garden and smell a rose, one of the chemicals in that aroma is *geraniol*, which interacts with those olfactory receptors. If a skunk has ever sprayed your dog or cat, many organic chemicals are part of the spray, including the mercaptan (also called a thiol; Section 5.5.1) *3-methylbutane-1-thiol*. Clearly, this odor is an unpleasant smelling organic chemical.

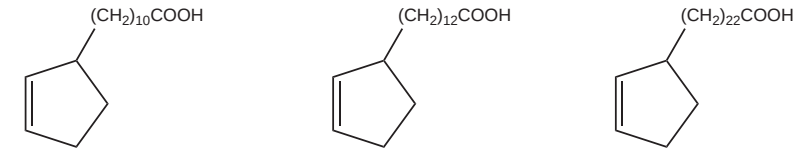


Geraniol 3-Methylbutane-1-thiol Muscone Jasmone

If you are wearing musk cologne, it probably contains *muscone* if it is natural musk (scraped from the hind-quarters of a male musk deer). If you are wearing a jasmine perfume it probably contains *jasmone*, which is part of the essential oil of jasmine flowers. If your feet have not been washed recently, you probably detect a pungent odor which is due to a chemical called *butyric acid*, among other things. Butyric acid ($CH_3CH_2CH_2COOH$) is a simple member of a carboxylic acid (Sections 5.6.3 and 18.1), an organic acid that contains a

carboxyl group (COOH) attached to an alkyl, alkenyl, aryl, or other group, generically represented as an R group. The general formula of a carboxylic acid is therefore R–COOH. In early work that focused on carboxylic acid derivatives, Alice Augusta Ball (USA; 1892–1916) developed the most effective treatment for leprosy known at that time.

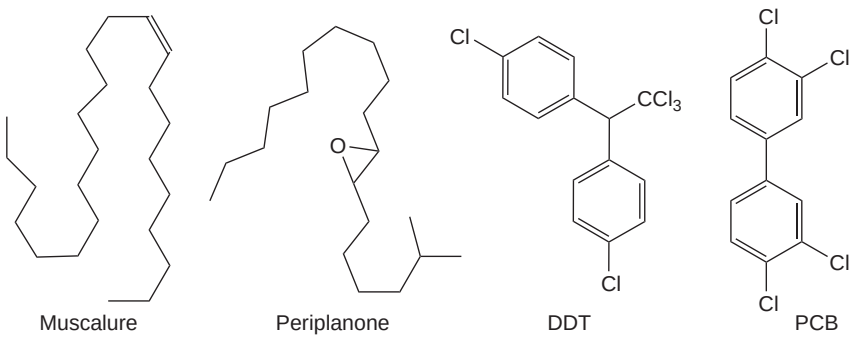
Alice Augusta Ball



Hydnocarpic acid Chaulmoogric acid Gorlic acid

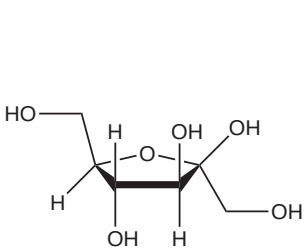
The best available treatment was chaulmoogra oil from the seeds of the *Hydnocarpus wightianus* from India. Ball isolated the ester components from the oil (esters have the formula RCOOR', where R' is derived from an alcohol; Sections 18.2,8). She chemically modified them and developed a technique to make the oil injectable and absorbable by the body. Derivatives of three carboxylic acids are found in chaulmoogra oil: hydnocarpic acid, chaulmoogric acid, and gorlic acid.

If you see a housefly, know that they use a chemical called a pheromone (in this case *muscalure*) in order to attract a mate and reproduce. The American cockroach (hopefully there are none in your dorm) similarly attracts a mate by exuding *periplanone*.

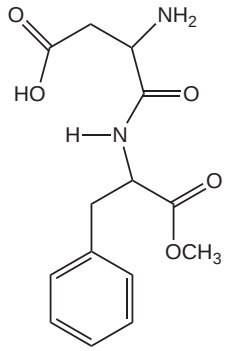


Muscalure Periplanone DDT PCB

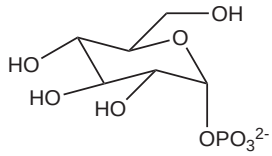
To control insect pests, we sometimes use the pheromone of that pest to attract it to a trap. A pheromone is a secreted or excreted chemical factor that triggers a social response in members of the same species. Alternatively, insecticides such as *DDT* can be used, sometimes with devastating environmental consequences. The chemical name is 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane, but DDT comes from the trade name, *p,p'*-**D**ichloro**D**iphenyl**T**richloroethane.



Fructose



Aspartame



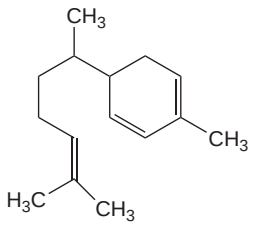
Glucose 1-phosphate
(Cori ester)

Poly**C**hlorinated **B**iphenyls (PCBs) are in the news as environmental pollutants. These *PCB*s are also used in transformers and as stabilizers in poly(vinyl chloride) coatings (PVC coatings). PCBs can leach into soil and water, with serious environmental consequences. Understanding of organic chemistry is important for the development of new and environmentally safer compounds.

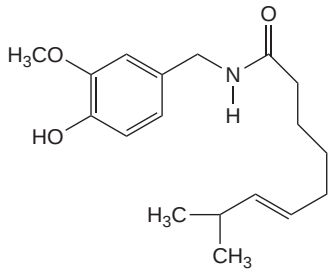

Gerty Theresa Cori

Eating is obviously an important part of life, and the taste of the food is important. What are tastes? They are the interaction of organic chemicals (and other chemicals as well) with receptors on your tongue, although smell is also associated with taste. Are you drinking a soda? Does it taste sweet? If it is not a diet soda, it probably contains a sugar called *fructose*, but if it is a diet drink it may contain one of the "sugar substitutes" (e.g., *aspartame*). Fructose is an example of a carbohydrate (Sections 25.1,2,3). Carbohydrates literally mean hydrates of carbon, and they contain carbon, hydrogen, and oxygen in a 1:2:1 ratio. A carbohydrate is an organic compound found in foods and living tissues that includes sugars, starch, and cellulose. Many carbohydrates are broken down to release energy in the animal body. Gerty Theresa Cori (Austro-Hungary/USA; 1896–1957) was

a biochemist who won the Nobel Prize in medicine for her work leading to the discovery of the course of the catalytic conversion of glycogen. She helped discover the so-called *Cori ester*, *glucose-1-phosphate*, an intermediate compound in frog muscles that enabled the breakdown of glycogen. She helped establish the compound's structure, identified the enzyme *phosphorylase* that catalyzed its chemical formation, and showed that the Cori ester is the beginning step in the conversion of the carbohydrate glycogen into glucose.

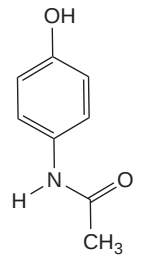


Zingiberene

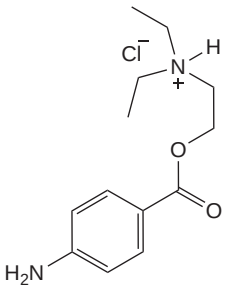


Capsaisin

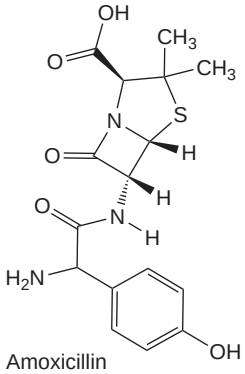
Different chemicals in different foods have their own unique tastes. Do you like the taste of ginger? The active ingredient that gives ginger (from ginger root, *Zingiber officinale* Roscoe) its "spicy" taste is an organic compound called *zingiberene*. Do you like the taste of red chili peppers? If so, the "hot" taste is due to an organic chemical called *capsaicin*. These chemicals interact with your taste buds to produce each characteristic taste. Capsaicin is also found in some topical ointments and creams used to alleviate symptoms of arthritis and muscular aches.



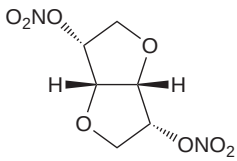
Acetaminophen



Novocain



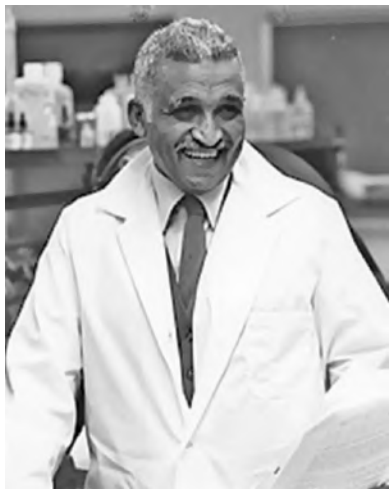
Amoxicillin



Isosorbide dinitrate

Sir Prafulla Chandra Ray

Most medicines used today are organic chemicals. Do you have a headache after reading all of this stuff? If so, you are probably looking for a bottle of aspirin. An alternative is *acetaminophen*, better known as Tylenol. Have you been to the dentist recently? If so, you might have had a shot of *Novocaine* (procaine hydrochloride) so you would not feel the pain (it is a local anesthetic). If you have recently been ill, you may have been given a prescription for an antibiotic from your physician. Commonly prescribed antibiotics include the penicillin *amoxicillin* or a tetracycline antibiotic (e.g., *aureomycin*). Nitrate compounds are used for treating or preventing heart pain (angina, chest pain) caused by heart disease, usually of the arteries in the heart. Common nitrate medicines include *isosorbide dinitrate* and isosorbide mononitrate. Sir Prafulla Chandra Ray (India; 1861–1944) contributed to understanding nitrite chemistry. His work focused on nitrites and hyponitrites of different metals, and on nitrites of ammonia and organic amines.



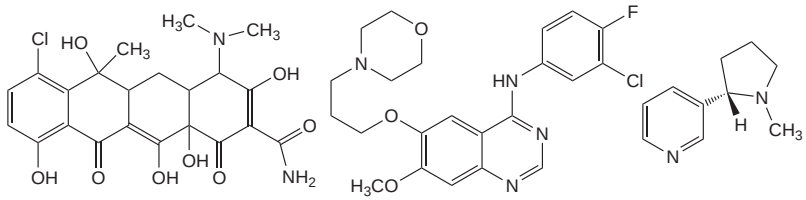
Samuel Proctor Massie, Jr.

There are many devastating diseases that afflict humans and myriad drugs have been developed to treat many of them. Has a friend or relative been treated for cancer? *Gefitinib* was approved by the FDA in 2003 for the treatment of locally advanced or metastatic non-small-cell lung cancer in patients, but who did not respond to platinum-based and/or docetaxel chemotherapy. Do you smoke? If so, you are breathing in *nicotine* as well as many other organic compounds into your lungs, which then make their way into your bloodstream. *Azidothymidine (AZT)* is used to treat HIV, the virus that causes AIDS (acquired immunodeficiency syndrome). Samuel Proctor Massie, Jr. (USA; 1919–2005) was a chemist who made major contributions to the development of therapeutic drugs, including *phenothiazine*. Phenothiazine is one member of a class of agents exhibiting antiemetic, antipsychotic, antihistaminic, and anticholinergic activities. During the recent pandemic one of the anti-viral medications used to treat some patients affected by COVID-19 is *remdesivir*, whose structure is shown.

Asima Chatterjee

Many drugs have been developed based on the structures of natural alkaloids. Asima Chatterjee (India; 1917–2006) was noted for her work in the fields of organic chemistry and phytomedicine and she worked with vinca alkaloids, developed anti-epileptic, and anti-malarial drugs. Her work focused primarily on alkaloids.

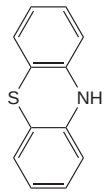
Finally, there are organic molecules that touch vast areas of your life, often in subtle ways. When I say they touch you, I mean that quite literally. Are you wearing clothes? If so, you might be wearing a synthetic blend of cloth made from a polymer, rayon (*cellulose acetate*). A polymer is a large molecule made by bonding many individual units together.



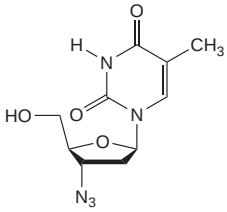
Aureomycin

Geftitinib

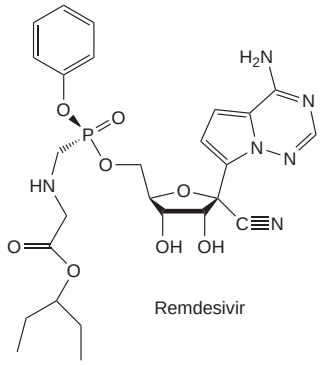
Nicotine



Phenothiazine

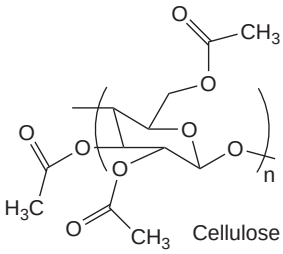


AZT

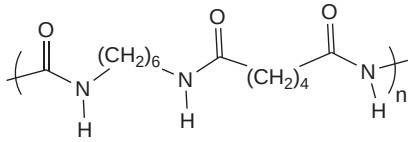


Remdesivir

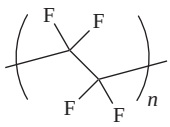
The *"n"* beside the bracket represents the number of repeating units, which is common nomenclature for all polymers. You might be wearing Nylon, specifically something made from *Nylon 6-6*. There are several types of Nylon, a family of synthetic polymers composed of polyamides. Many things are made of Nylon, including gears for fine machines and guitar strings for classical guitars.



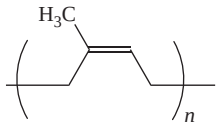
Cellulose acetate



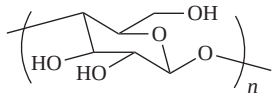
Nylon 66



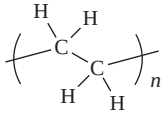
Teflon



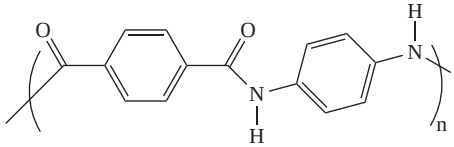
Poly(isoprene)



Cellulose

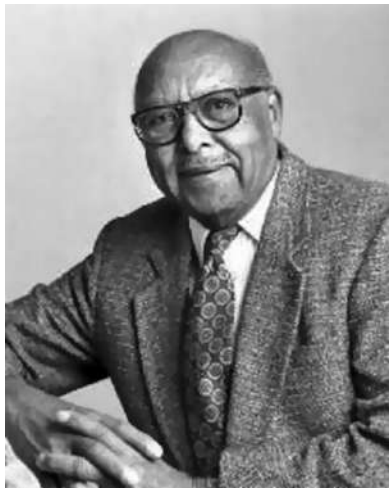


Polyethylene



Kevlar

Stephanie Louise Kwolek



Walter Lincoln Hawkins

Have you ever heard of *Teflon*? This polymer finds uses in many machines and devices that you use every day. Natural rubber is a polymer obtained from the sap of certain trees, and it is used for automobile tires and other things. Nowadays, tires have a more complex composition, but natural rubber is *poly(isoprene)*, obtained from latex by tapping certain trees. You might be using a piece of paper to describe your thoughts about organic chemistry at this moment. If so, you are probably writing on something with *cellulose* in it. Cellulose is the main constituent of wood fiber, and it is found in many plants, including trees. When you crumple up the paper and throw it into a "plastic" waste container (Section 10.11), that container might be made of *poly(ethylene).* Many pipes and "plastic" wrap are made from poly(ethylene). Stephanie Louise Kwolek (USA; 1923–2014) discovered the first of a family of synthetic fibers of exceptional strength, *Kevlar*, which is *poly(paraphenylene terephthalamide)*. Walter Lincoln Hawkins (USA; 1911–1992) made significant contributions to polymer chemistry. He worked at Bell Laboratories and was a key player in the design of a long-lasting plastic and a polymer-based cable sheath for telephone cables. Later in his career he shifted his research focus towards minimizing plastic waste.

A lot of structures have been thrown at you. Why? Organic chemistry is all around you and it is an integral part of your life. Understanding these things will help as you move into the program of your dreams. Such an understanding can also help you make informed choices in problems and issues that will confront you throughout your life. The journey begins here. Good luck!

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-2.php

2

Why Is an Acid–Base Theme Important?

A study of acid and base chemistry is fundamental to organic chemistry. The understanding of many reactions can be predicted by the application of acid-base principles. To begin, this chapter will review the principles of acid-base reactions found in general chemistry.

You should know the following points from standard general chemistry courses:

- Define and recognize the structures of simple Brønsted–Lowry acids and bases.
- Define and recognize the structures of simple Lewis acids and bases.
- Understand the definitions of a conjugate acid and a conjugate base.
- Understand the fundamentals of acid-base strength in aqueous media.
- Understand K_a and pK_a.
- Recognize classical mineral acids and mineral bases.

2.1 TRADITIONAL ACID AND BASE THEORY

Traditional Acid and Base Theory

In 1884, Svante Arrhenius (Sweden; 1859–1927) defined an acid as a material that can release a *proton*, which is a hydrogen ion (H^+) via ionization. A "free" proton does not exist. In water H^+ is actually a hydronium ion, H_3O^+. Using Arrhenius' original definition, a base (then called an alkali) is a material that can release a hydroxide ion (^-OH) in water. Sodium hydroxide in water solution ionizes to hydrated sodium ions and hydrated hydroxide ions. A related definition of acids and bases was reported by Thomas M. Lowry (England; 1874–1936) and Johannes Nicolas Brønsted (Denmark; 1879–1947), independently in 1923. According to this *Brønsted-Lowry definition*, an acid is a material that donates a hydrogen ion, and a base is a material that can accept a hydrogen ion.[1] An acid has an ionizable hydrogen atom, a *proton*. In water, an aqueous solution of hydronium ions is produced. An acid-base reaction is an equilibrium reaction that generates a conjugate acid and a conjugate base. The reaction of hydrated HCl with water, for example, leads to a proton transfer from HCl to water to generate the conjugate acid, the hydronium ion H_3O^+, as well as the conjugate base, the chloride ion. The term hydrated means that each ion is surrounded by water molecules, which is indicated by the subscript (aq).

Water at pH 7 is neutral and the hydrogen ion concentration is 1.0×10^{-7} M. An acid is ionized in water and the concentration of H_3O^+ ions is $> 1.0 \times 10^{-7}$ M. The mineral acids HCl, HBr, HI, H_2SO_4, HNO_3, H_3PO_4, and $HClO_4$ are all strong acids that give a high concentration of H_3O^+ ions. Bases are ionized in water, and there is a decrease in the concentration of

[1] Lowry, T.M. *Chemistry and Industry* 1923, 42, 43–47; Brønsted, J.N. *Recueil des Travaux Chimiques* 1923, 42, 718–728.

DOI: 10.1201/9781003174929-2

hydrogen ions, $< 1.0 \times 10^{-7}$ M. Common strong bases include NaOH (soda lye), KOH (potash lye), LiOH, CsOH, $Mg(OH)_2$, $Ca(OH)_2$, and $Ba(OH)_2$. Weak acids and weak bases will only partially ionize in water relative to the strong acids or bases.

2.1 Write out the structures of hydrochloric acid, hydrobromic acid, sulfuric acid, and nitric acid. Show the lone electron pairs.
2.2 What is the conjugate base formed when HNO_3 reacts with NaOH?

Weak acids are defined as solutes that partially ionize in a reaction with water molecules. Simple examples of weak acids include hydrofluoric acid (HF), nitrous acid (HNO_2), sulfurous acid (H_2SO_3), and phosphoric acid (H_3PO_4). Many common organic acids are weak acids. Examples include acetic acid (CH_3COOH), butanoic acid ($CH_3CH_2CH_2COOH$), and formic acid (HCOOH). The structure and properties of these carboxylic acids will be discussed in Sections 5.6.3 and 18.1,2. Weak bases are defined as solutes that partially ionize in a reaction with water molecules. An example is ammonia, which reacts with an acid to give the ammonium cation. The most common type of organic base is probably an amine, discussed in Section 5.5.3. An amine has the structural fragments CNH_2, C_2NH, or C_3N, where each "C" represents a carbon group. Amines are weak bases when compared to mineral bases. Amines such as methanamine (CH_3NH_2) and trimethylamine [*N*,*N*-dimethylmethanamine, $(CH_3)_3N$]) react with an acid, HX, to form ammonium salt conjugate acids: $[CH_3NH_3]^+X^-$ and $[(CH_3)_3NH]^+X^-$, respectively, where X is usually a halide counterion.

2.3 In the reaction of nitric acid and KOH, which atom in nitric acid (HNO_3) accepts the electron pair from the base, and which atom in KOH donates the electrons to that proton?
2.4 If carbonic acid (H_2CO_3) reacts with a suitable base, what is the conjugate base of this reaction?

How are the Two Acid-Base Definitions Related?

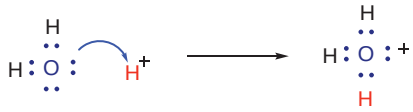
2.2 THERE ARE TWO ACID-BASE DEFINITIONS: HOW ARE THEY RELATED?

As noted in Section 2.1, a *Brønsted-Lowry acid* is defined as a proton donor, and a *Brønsted-Lowry base* is a proton acceptor. In 1923, Gilbert N. Lewis (USA; 1875–1946) proposed an alternative definition of acids and bases, with a focus on transfer of electrons from one species to another. A *Lewis acid* is defined as a species that accepts an electron pair from a *Lewis base*, which is defined as an electron-pair donor. There may be confusion about how these two different definitions are related, not just how they differ. When HCl reacts with water, for example, the Brønsted-Lowry definition states that the proton (H^+) is "donated" to water, forming the hydronium ion. In this reaction, the oxygen atom of the water "accepts" the proton. How does an oxygen accept a proton?

2.5 If HCl were to react with ammonia rather than water, which atom accepts the proton?

In the acid-base reaction of water with a proton (H^+), the oxygen atom in water "accepts" the proton to form the hydronium ion. To form the H—O bond in a hydronium ion the oxygen atom *donates* two electrons to H^+. The H—O bond is known as a σ-covalent bond, which *requires two shared electrons* (Section 3.3). In the reaction of water with H^+, the oxygen atom reacts as a *base and* "accepts" a proton by donating two electrons to H^+ to form the new bond. Therefore, a Brønsted-Lowry base accepts a proton, by donating two electrons to that proton. A Lewis base is defined by donating two electrons to an atom other than a proton. *In an acid-base reaction, both a Brønsted-Lowry and a Lewis base donate electrons from an*

electron rich species to an electron poor species. This statement is important because it places the focus on electron transfer rather than transfer of a proton.



Hydronium ion

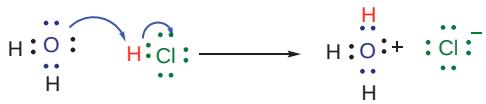
2.6 Draw the Lewis electron dot formula for ammonia and for HCl.

A base is electron rich, and the term excess electron density usually indicates the presence of unshared electrons or a formal negative charge. All bases donate two electrons in an acid-base reaction and *the electron flow is always from the base to the acid, not from the acid to the base*. In other words, an acid does *not* donate a proton, but that proton is "pulled off" by the base to form a new bond. This electron transfer is shown by the *curved arrow* in the reaction of water and H^+ to give the hydronium ion. The use of a curved arrow in this manner is called the *curved arrow formalism* where the curved arrow indicates the transfer of two electrons from one atom to the other. To repeat, the electron flow is always *from* a source of high electron density *to* a point of low electron density.

2.7 Can the phosphorus atom in a molecule function as a base? The sulfur atom? The sodium atom in Na^+? Can the N in the ammonium ion, NH_4^+ be a base? In each case explain your answer.
2.8 Why is it incorrect to draw the arrow from H^+ to oxygen in the reaction of water and H^+?

The oxygen of water is shown to donate electrons to H^+, which represents a "free" proton. However, as noted previously there is no such thing as a free proton. The proton in common acids is a hydrogen atom attached to another atom by a covalent bond (Section 3.3), as in H—Cl. The hydrogen atom in HCl is susceptible to attack due to bond polarization because chlorine is more electronegative than hydrogen (Section 2.4.1). Since it is more electronegative, the chlorine withdraws electron density toward itself. This electronegativity difference leads to distortion of the electron density in the covalent bond away from the hydrogen and toward the more electronegative chlorine atom (Section 2.4.1).

In HCl, the chlorine is electron rich and the hydrogen is electron deficient and susceptible to attack by an electron rich atom such as oxygen. The electron-rich oxygen atom donates electrons to the acidic H of HCl, as indicated by the *curved arrow*, forming a new bond to the hydrogen atom. The use of the arrow is called the *curved arrow formalism*. The oxygen atom literally pulls the proton away as the new O—H bond is formed. Removal of the proton leads to cleavage of the bond between H and Cl, as shown by the second *curved arrow*. The two electrons in this bond will migrate toward the electronegative chlorine atom forming the chloride ion, the conjugate base.



2.9 In a reaction of HCl and ammonia, identify the electron-donating atom of the base, and draw the reaction using the curved arrow formalism, yielding the products of the reaction.
2.10 For a reaction of H_2SO_4 and NaOH, write out the acid-conjugate base pair and also the base-conjugate acid pair.

The curved arrow formalism and the concept of electron donation from an electron rich atom to an electron poor atom can be applied to many reactions other than acid-base reactions. The identification of electron-rich and electron-poor components of molecules and an understanding of the electron flow can be used to predict products in a variety of reactions. It is important to make the transition to thinking about reactions in terms of electron donators/electron acceptors analogous to the Lewis definition rather than the Brønsted-Lowry definition. Knowledge of this principle leads to an understanding of reactions rather than memorization of those reactions.

Bases Are Electron Donors

2.3 ACID-BASE EQUILIBRIA AND EQUILIBRIUM CONSTANTS

Strong acids ionize in water to a greater extent when compared to a weak acid. An example in Figure 2.1 compares the reaction of the strong acid HCl and the weak organic acid formic acid (HCOOH) with water. In these acid-base reactions, water is both the base and the solvent, and there are two competing chemical reactions. The "forward" acid-base reaction with HCl and water gives the hydronium ion and the chloride ion. The "forward" acid-base reaction of formic acid and water gives the formate anion ($HCOO^-$) and the hydronium ion H_3O^+. In both cases, the "reverse" acid-base reaction of the conjugate base with the conjugate acid produces the original acid and base.

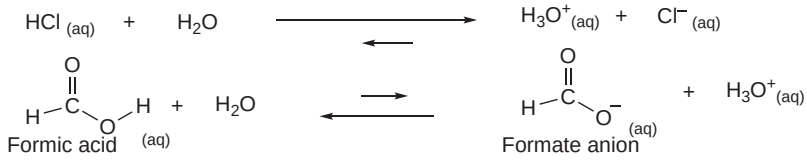


FIGURE 2.1 Hydrochloric acid, formic acid, as acids in water.

In these reverse reactions, chloride ion and the hydronium ion react to give HCl and water whereas the formate anion and the hydronium ion react to give formic acid and water. The "forward" (⟶) and the "reverse" (⟵) reactions are indicated in the equilibrium by two arrows pointed in opposite directions, (⇄). The strength of the acid depends on the position of the equilibrium, which is determined by the facility of each competing acid-base reaction: the reaction of the acid with a base and the reverse reaction of the conjugate acid with the conjugate base. Ionization of the strong acid HCl in water is greater than ionization of the weaker acid formic acid in water so the HCl/water equilibrium is pushed toward the conjugate acid and the conjugate base. The HCOOH/water equilibrium is pushed toward HCOOH and water. The formate anion is a stronger base than the chloride ion, so the equilibrium is pushed to the left by the reaction of the conjugate base and the conjugate acid. The chloride ion is a weaker base, and the equilibrium for the strong acid HCl with water is pushed further to the right. In other words, there is a higher concentration of the conjugate acid and the conjugate base with HCl. Conversely, the equilibrium for the weak acid formic acid with water shows a much lower concentration of the conjugate acid and the conjugate base. Note the (aq) term for the species in both reactions, which indicates solvation by the solvent water. The solvation terms shown in Figure 2.1 are usually *omitted* from reactions in organic chemistry.

$$K_a = \frac{[\text{conjugate acid}][\text{conjugate base}]}{[\text{acid}][\text{base}]}$$

The position of the acid-base equilibrium is defined by the acidity constant, K_a. Determining the concentrations of the acid, the base, the conjugate acid, and the conjugate base allows the position of this equilibrium to be calculated. Values for K_a can be very large or very small, so the term pK_a is used for convenience. The term pK_a is the negative log of *K*a*:* $pK_a = -\log K_a$ and $K_a = 10^{-pKa}$. This term is analogous to pH, which is

the negative log of the hydrogen ion concentration: pH = -log [H]. A strong acid has large K_a (>> 1), and the equilibrium favors a higher concentration of conjugate acid and conjugate base with a lower concentration of acid and base. Since K_a and pK_a are inversely proportional, a strong acid with a large K_a has a small pK_a. A small K_a has a large pK_a, indicating a weak acid with a higher concentration of acid and base and a lower concentration of conjugate acid and base.

Virtually all of the acids and bases mentioned in Section 2.1 are soluble in water, and the relative acidity or basicity of those compounds is measured with water as the base. Indeed, Brønsted-Lowry acid-bases are defined in terms of their ionization in water, but ionization can occur in other solvents. Since nonaqueous solvents are commonly used in organic chemistry it is useful to compare the ionization of compounds in water with the ionization in other solvents. Other solvents may be weaker bases or stronger bases than water and the relative acidity of the acid changes with the strength of the base. In Figure 2.2 the relative strength of formic acid and HCl can be measured by their reaction in methylamine (CH_3NH_2) or in diethyl ether ($CH_3CH_2OCH_2CH_3$), which is a weaker base than the amine (Sections 5.5.2,3 and 6.7.1,3). Since HCl is a stronger acid than formic acid, ionization of HCl is greater than ionization of formic acid in either methylamine or diethyl ether as indicated by the longer and shorter reaction arrows. When HCl reacts with the amine, the products are the chloride ion as the conjugate base and the methylammonium ion as the conjugate acid. When formic acid reacts with the amine, formate anion is the conjugate base and the methylammonium ion is the conjugate acid. Diethyl ether and HCl react to give the chloride ion and the protonated form of the ether known as an *oxonium ion* is the conjugate acid. Formic acid reacts with diethyl ether to give the formate anion and the oxonium ion. The amine is the stronger base, so HCl is ionized to a greater extent in methylamine when compared to the reaction in diethyl ether. Similarly, formic acid is ionized to a greater extent in the stronger base methylamine when compared to the reaction in diethyl ether. Although HCl is a stronger acid than formic acid, both acids are stronger acids in methylamine than in diethyl ether.

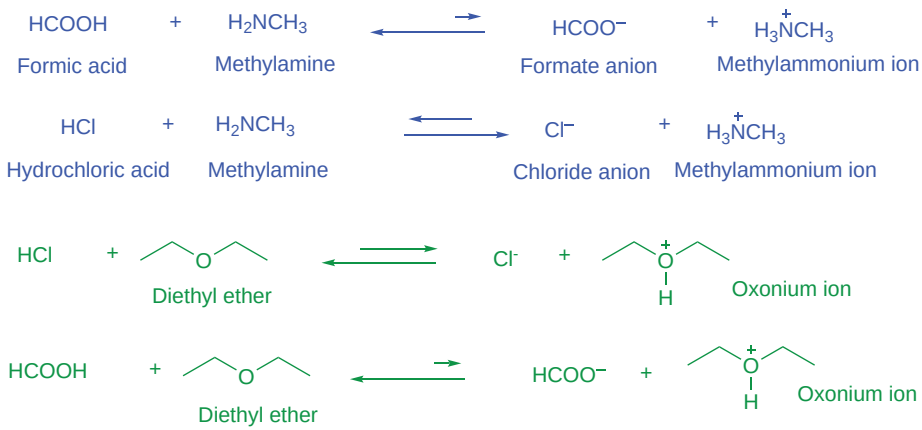


FIGURE 2.2 The acid-base reactions of formic acid and HCl in methylamine. The acid-base reaction of formic acid and HCl in ethyl ether.

The relative strength of two bases can be measured by changing the focus to their reaction with a common acid. In Figure 2.3 formic acid is shown to react with methylamine to give the formate anion and the methylammonium ion. Formic acid also reacts with diethyl ether ($CH_3CH_2OCH_2CH_3$), which reacts as a base (Sections 5.5.1 and 6.7.3) to give the formate anion and an oxonium ion. The fact that formic acid ionizes to a greater extent in methylamine than in diethyl ether shows that formic acid is a stronger acid when it reacts with methylamine than when it reacts with diethyl ether. This observation indicates that methylamine is a stronger base relative to diethyl ether.

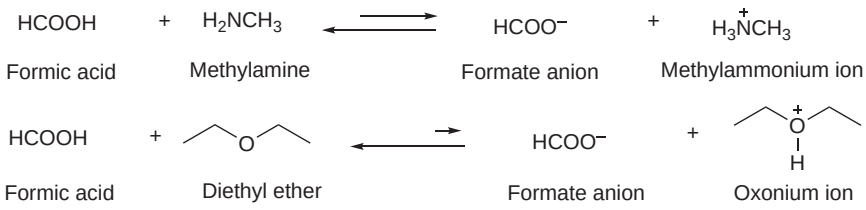


FIGURE 2.3 The reactions of formic acid with diethylamine and with ethyl ether.

2.11 In the reaction of CH_3CH_2OH (ethanol) with water, indicate which H in ethanol is most likely to be the acidic proton and which atom in water is most likely to be the base.
2.12 Which is the stronger base, water or hydroxide ion? Justify your answer.

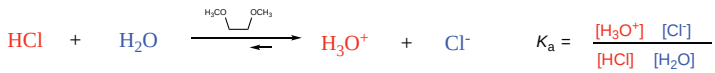
Acid-Base Strength

In general chemistry, the equilibrium constant, K_a is defined for a generic acid-base reaction but the concentration of water is omitted when the reaction is done in water:

$$K_a = \frac{[\text{conjugate acid}]\,[\text{conjugate base}]}{[\text{acid}]\,[\text{base}]} \quad \text{but for HCl in } H_2O \quad K_a = \frac{[H_3O^+]\,[Cl^-]}{[HCl]}$$

In this reaction, water is the solvent but it is also the base. Why can the molar concentration term for water as a base be *removed* from the equation? Water is present in large excess and the concentration of water remains essentially constant relative to the insignificant amount of water that reacts as a base. If the concentration term for water in the K_a equation is essentially constant, removal of the water term from the K_a equation will not cause a significant error.

If water is not the solvent and the solvent does not participate in the reaction, then the base *must* be included in the equation to properly evaluate the acid-base reaction. If the solvent in the reaction of HCl and water is dimethoxyethane (DME, $CH_3OCH_2CH_2OCH_3$), an organic solvent that is completely miscible with water, water is *not* in excess. Therefore, changes in the concentration of water during the reaction are significant and the water must be part of the K_a equation. Note that miscible means the two liquids are mutually soluble in all proportions (Section 5.8.2).



To review, when water is the solvent and it is present in large excess, the water can be *removed* from the equation. However, when water is not the solvent, but it is the base in the reaction, it cannot be removed from the K_a equation. All of the starting materials and all of the products must be included in the K_a term. Most of the reactions presented in this book do not use water as a solvent, but rather an organic solvent that does not participate in the reaction.

2.13 What is the base in the reaction of HCl that generates the hydronium ion and the chloride ion? Justify your answer.
2.14 In the reaction of ethanol with HCl, which is the Brønsted-Lowry acid?

Electronegativity and Atom Size

2.4 ELECTRONEGATIVITY AND ATOM SIZE

To properly understand differences in acid strength, the structure and reactivity of the acid and the conjugate acid as well as the structure and reactivity of the base and conjugate base

must be known. Two major parameters used to explore differences in reactivity are electronegativity and the relative size of the atoms involved.

2.4.1 ELECTRONEGATIVITY

The property of an atom to attract electrons to itself is called *electronegativity*. Different atoms have a different electronegativity and thus a different ability to attract electrons. The electronegativity of an element increases across the periodic table going to the *right* (left-to-right) toward fluorine and *up* (bottom-to-top) the table toward fluorine. Oxygen is more electronegative than carbon, and chlorine is more electronegative than bromine. Figure 2.4[2] shows the electronegativity of common elements that appear in organic molecules, arranged according to their position in the periodic table. For different atoms in a bond connecting two atoms, electronegativity has a profound effect on the shared electron density. When one atom is more electronegative than the other, the shared electrons in the bond will be distorted toward the more electronegative atom. Interestingly, carbon is more electronegative than hydrogen by a small amount. For bonding in most organic molecules, however, this difference in the electronegativities of carbon and hydrogen is assumed to be insignificant.

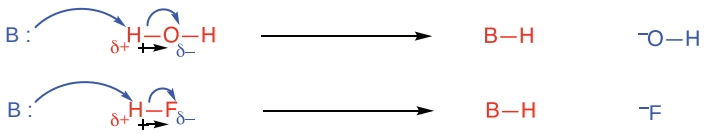
H 2.2												
Li 1.0	Be 1.5							B 2.0	C 2.6	N 3.0	O 3.4	F 4.0
Na 0.9	Mg 1.3							Al 1.6	Si 1.9	P 2.2	S 2.6	Cl 3.2
K 0.8	Ca 1.0	Sc 1.3	Ti-V 1.5-1.6	Cr-Mn 1.6-1.7	Fe-Ni 1.8-1.9	Cu 1.9	Zn 1.7	Ga 1.8	Ge 2.0	As 2.2	Se 2.6	Br 3.0
												I 2.7

FIGURE 2.4 Electronegativities of atoms in the periodic table.

Going across the periodic table, fluorine is more electronegative than carbon. Going up and down chlorine is more electronegative than iodine. Inspection across the diagonally related elements C⟶P⟶Se⟶I, however, shows that electronegativity changes from 2.6⟶2.2⟶2.6⟶2.7. Clearly, there is no trend when one compares elements that have a diagonal relationship. Therefore, no comparisons can be made without specific numbers.

2.15 Use Figure 2.4 to rank the following atoms by their electronegativity: N, S, and Ga.

A covalent bond between two atoms is composed of two electrons, and if both atoms have the same electronegativity, there should be an equal distribution of electron density between the two nuclei. If one atom is more electronegative than the other, however, there is an unequal distribution of electron density between the nuclei. The *electron density of the bond is distorted toward the more electronegative atom*. A bond between two atoms where one is more electronegative than the other is known as a *polarized covalent bond* (Section 3.8).



[2] Haynes, W.M. *CRC Handbook of Chemistry and Physics*, 94th ed., CRC Press, Boca Raton, FL, 2013–2014, pp. 9–97.

Electronegativity plays an important role in acid-base reactions. The relative acidity of HF and H_2O can be compared by examining their acid-base reactions with a common base. Since fluorine is more electronegative than hydrogen, H is electron deficient, and F is electron rich in the H—F bond. Likewise, O is more electronegative that H in the O—H bond of water so O is electron rich and H is electron deficient. The more electronegative fluorine atom or oxygen atom will have the greater electron density, so each is given the symbol δ^-. Similarly, the H in each bond will have less electron density, and each is labeled δ^+. Fluorine is more electronegative than oxygen, so the electron density is distorted toward F in the H—F bond to a greater extent than toward O in a H—O bond of water. In other words, the HF bond is more polarized, and the δ^+ H in HF is more positive than the δ^+ H in water.

The polarization of $H^{\delta+}$ in O—H and in H—F suggests that the hydrogen atom is "acid-like" since it is related to a proton, H^+. Indeed, the hydrogen atom in both HF and H_2O is acidic. Deprotonation of HF with a base is accompanied by cleavage of the H—F bond. The electrons in that bond are transferred to the electronegative fluorine atom to generate the fluoride ion. Likewise, deprotonation of water leads to cleavage of the H—O bond and transfer of electrons to the electronegative oxygen atom to form the hydroxide ion. Fluorine is more electronegative than oxygen and the hydrogen atom in H—F has a greater δ^+. Therefore, HF is more acidic and more reactive.

Since the reaction is an equilibrium, the acid strength of HF and of water also depends on the facility of the acid-base reaction of the conjugate acid and the conjugate base. In general, the stronger acid will generate the weaker conjugate base. Fluorine is more electronegative than oxygen, so it retains electrons to a greater extent and is less likely to donate them. Therefore, the fluoride ion is a weaker base and less likely than the hydroxide ion to react with the conjugate acid, consistent with HF being the stronger acid.

2.4.2 ATOM SIZE

The size of an atom plays a significant role in acid strength. For a given bond H—X, the larger the size of X the longer the H—X bond distance. In general, a longer bond is easier to break in an acid-base reaction, consistent with a larger K_a and a stronger acid. The influence of atom size can be examined by comparing the acidity of HF and HI. A bond between relatively small atoms that are close to the same size (e.g. H and F) has a shorter bond length (the distance between the two nuclei) when compared to the bond length between atoms when one is small and one is large (e.g., H and I). Figure 2.5 illustrates such a case, and the larger size of the iodine atom in **B** (HI) dictates a longer bond length when compared to the smaller size of the fluorine atom in **A** (HF). The bond length for H—F is 92 pm and that for H—I is 161 pm. The longer bond length for H—I suggests there is less electron density in the bond when compared with H—F with the smaller fluorine atom. It is therefore reasonable to assume that reaction with a base will remove the hydrogen atom of H—I easier than the hydrogen atom of H—F. Indeed, HI is the stronger acid with a larger K_a.

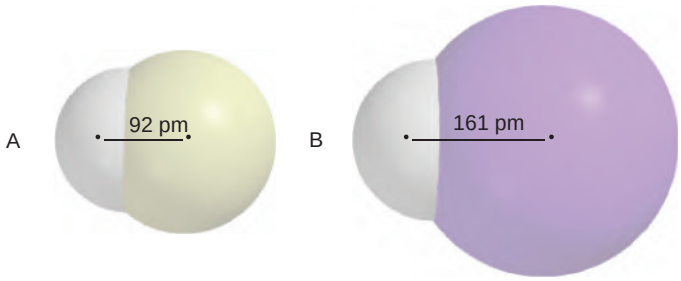


FIGURE 2.5 Comparison of atom size and bond distance for HF (**A**) and HI (**B**).

Fluorine in the fluoride anion is more electronegative than iodine in the iodide anion and therefore should retain electrons more than the iodide ion. This observation predicts that

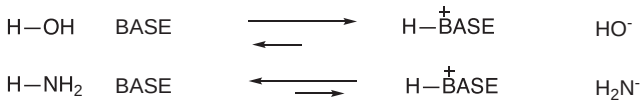
the fluoride ion is the weaker base. If electronegativity arguments were the most important factor, HF is predicted to be the stronger acid, *but HI is the stronger acid*. Clearly, another phenomenon is at work. The iodide ion is much larger than the fluoride ion. The covalent radius of the iodide ion is 135 pm (1.35 Å) and that of the fluoride ion is 71 pm (0.71 Å).[3] Since the iodide ion is larger, the charge is *dispersed over a larger area*. The more the charge is dispersed, the less likely that species is to donate electrons. Therefore, the iodide anion is a weaker base relative to the fluoride anion and the equilibrium will be shifted to the right, consistent with HI as the stronger acid (a larger K_a).

2.16 Is it possible for diatomic hydrogen to be the BASE in the reactions of HF and HI? Justify your answer.

2.5 ATOM SIZE AND ELECTRONEGATIVITY ARGUMENTS APPLIED TO ACIDS AND BASES

Acid-Base Strength

The reported pK_a of water[4] is 15.74 and that of ammonia[5] is 38. Why is water so much more acidic than ammonia? The δ^+ (electrophilic) atom is a hydrogen atom attached to O in water or N in ammonia. In an acid-base reaction, the reaction of water and ammonia with an unspecified but generic BASE yields the same conjugate acid (H—BASE$^+$). The conjugate base formed from water is the hydroxide ion and the conjugate base from ammonia is the amide anion. Oxygen and nitrogen are in the same row of the periodic table so there is only a minor change in the size of the atoms.



Therefore the bond lengths are close, 96 pm versus 101 pm, and this parameter is not expected to play a major role. Indeed, *going across the periodic table, differences in electronegativity are assumed to be more important than differences in size.* Since O is more electronegative than N, the O—H bond should be more polarized than the N—H bond. Indeed, the O—H hydrogen in water is more acidic than the N—H hydrogen in ammonia. If the O is more electronegative, oxygen in the conjugate base HO^- should retain electrons (not donate them) more than the nitrogen in H_2N^-. Therefore, hydroxide is less reactive and more stable and so a weaker base when compared to the amide anion. In other words, the hydroxide ion is less able to donate electrons. The K_a for the reaction with water is therefore larger and water is the stronger acid.

2.17 Can ammonia be considered as a Brønsted-Lowry acid? Justify your answer.
2.18 How many unshared electrons are on the nitrogen of ammonia? On the oxygen of water?

Why is ammonia a stronger base than water? This question really asks why the nitrogen atom of ammonia is a better electron donor than the oxygen atom of water. Once again, the acid-base equilibrium will be examined, but HCl will be used as the acid for both reactions so the acid and the conjugate base will be the same in both reactions. With this simplification, the base strength of water and ammonia can be compared directly. The reaction of ammonia and HCl gives the ammonium ion as the conjugate acid and the chloride ion as the conjugate

[3] Huheey, J.E. *Inorganic Chemistry, Principles of Structure and Reactivity*, Harper & Row, New York, 1972, pp. 9–67 to 9–68.
[4] Harned, H.S.; Robinson, R.A. *Transactions of the Faraday Society* 1940, 36, 973–978.
[5] Buncel, E.; Menon, B.C. *Journal of Organometallic Chemistry* 1977, 141, 1–7.

base. For the reaction with water, the conjugate acid is the hydronium ion, and the conjugate base is also the chloride ion.

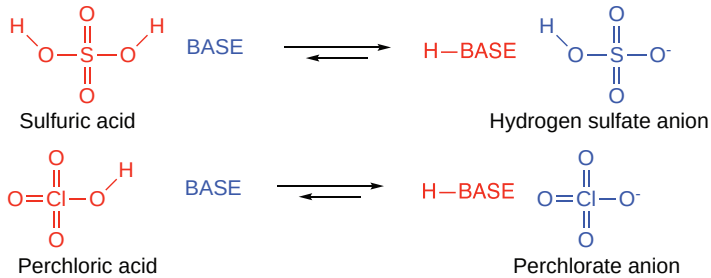
Both nitrogen and oxygen are in the second row of the periodic table, so electronegativity is assumed to be more important than the size of the atoms. Oxygen is more electronegative than nitrogen, so oxygen will retain electron density more efficiently than nitrogen and oxygen is a weaker base relative to nitrogen. The nitrogen atom of ammonia is a better electron donor and is therefore more basic. Comparing the H—O bond and the H—N bond, O is more electronegative so the O—H bond is weaker due to bond polarization. Therefore, the hydronium ion is expected to be a stronger acid than ammonia. The pK_a of the hydronium ion is estimated to be -2, and the pK_a of $^{+}NH_4$ is 9.24.[6] Since the conjugate acid for the water reaction is more reactive, the equilibrium will be pushed to the left (smaller K_a). Conversely, the equilibrium for the ammonium ion conjugate acid will be more to the right (larger K_a) since the H—N bond is stronger. The reaction of NH_3 and HCl forms the less basic ammonium chloride has a larger K_a. Ammonia is the stronger base.

Why is $^{-}NH_2$ More Basic Than NH_3? In this case, two nitrogen atoms are compared, so electronegativity and/or size arguments are not an issue. In ammonia, there are three covalent bonds, and there is one unshared pair of electrons, so the molecule is neutral (no charge). In the amide anion, there are two pairs of unshared electrons and a charge of -1 (see formal charge, Section 7.3). Therefore, there is an excess of electron density on the nitrogen of the amide anion when compared to ammonia. The amide anion is more basic simply because there is a higher concentration of electron density than can be donated to an acid.

Resonance and Acid Strength

2.6 RESONANCE, ELECTRON DISPERSION, AND BASE STRENGTH

The measured pK_a of perchloric acid is -10 and that of sulfuric acid is about -1.9,[6] so perchloric acid is the stronger acid. Why is sulfuric acid less acidic than perchloric acid? A comparison of the acid strength of these two mineral acids begins with an examination of the acid-base equilibrium for both reactions, again using a generic base so that the conjugate acid is the same in both equations. Both perchloric acid and sulfuric acid have an O—H group that contains the acidic proton. There are slight differences in the size and electronegativity of S and Cl that will have some influence on differences in the strength of the O—H bond in these two acids, but these differences are not sufficient to account for such a large difference in acid strength.



Looking at the conjugate bases for these two reactions, there is one difference in both the hydrogen sulfate (HSO_4^-) anion and the perchlorate (ClO_4^-) anion relative to the fluoride ion, iodide ion, hydroxide ion, or amide anion discussed previously. *There are π-bonds.* The structure and nature of carbon-carbon π-bonds will formally be discussed in Section 5.1, so

[6] Smith, M.B. *March's Advanced Organic Chemistry*, 8th ed., Wiley-Interscience, Hoboken, NJ, 2020, Table 8.1, pp. 341–345.

this concept is somewhat premature for a proper understanding. However, π-bonds should have been discussed in general chemistry. The hydrogen sulfate anion contains two S=O units. The S=O unit in Figure 2.6 shows two bonds between S and O. One is a so-called σ-bond (Section 3.3) and the other is a π-bond (Section 5.1). A σ-bond is stronger than the π-bond, because the σ-bond is formed by sharing electron density on a line between the two nuclei. The π-bond shares electron density between parallel adjacent p-orbitals on S and O (Figure 2.5) by sideways overlap. There is less electron density shared between the atoms and the π-bond is weaker. The perchlorate anion contains three Cl=O units, each with a σ-bond and a weaker π-bond.

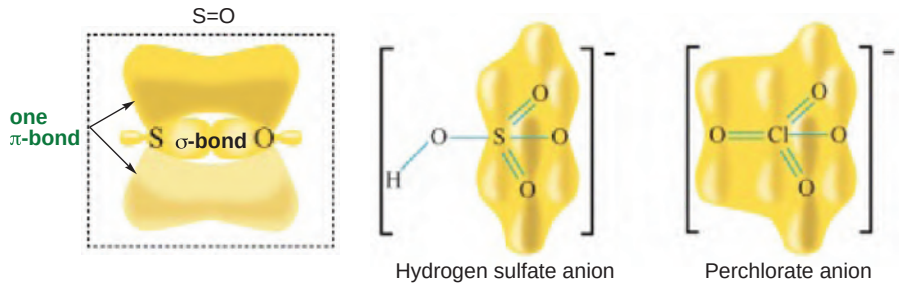


FIGURE 2.6 π-Bonds and resonance in the hydrogen sulfate anion and the perchlorate anion.

Both the hydrogen sulfate anion (HSO_4^-) and the perchlorate anion (ClO_4^-) are shown in Figure 2.6. These diagrams show that the π-orbitals can overlap such that the electron density of the negative charge is dispersed over all three oxygen atoms and S in the hydrogen sulfate anion. Dispersal is over all four oxygen atoms and Cl in the perchlorate anion. In other words, the charge is dispersed over more atoms and therefore a larger area in the perchlorate anion relative to the hydrogen sulfate anion. This type of charge dispersal (*charge delocalization*) over several atoms with participation of π-bonds is given the name *resonance*. *A resonance stabilized anion is more stable, less reactive as an electron donor and therefore a weaker base*. If the perchlorate anion is more stable and less reactive with the conjugate acid due to resonance, it is a weaker base. Therefore, the equilibrium is pushed to the right (larger K_a), consistent with perchloric acid as the stronger acid.

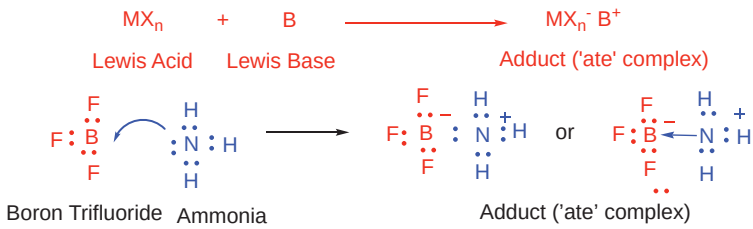
2.19 Discuss whether nitric acid is more or less acidic than perchloric acid.

2.7 LEWIS ACIDS AND BASES

Lewis Acids and Lewis Bases

As defined in Section 2.1, a Lewis base is an electron pair donor, and a Lewis acid is an electron pair acceptor. A Lewis base must be electron rich in order to donate electrons, and a Lewis acid must be electron deficient in order to accept electrons. Group 13 elements such as boron and aluminum can only form three covalent bonds and remain neutral, so they do not satisfy the octet rule and are inherently electron deficient. They are Lewis acids. A Lewis acid MX_n reacts with the electron pair from a Lewis base to form a fourth bond, which provides the two electrons needed to satisfy the octet rule. A compound with four bonds to the Lewis acid is a charged complex known as a *Lewis acid-base complex*, or an *"ate" complex. In a typical example,* ammonia reacts as a Lewis base to *donate* two electrons to the electron-deficient boron of BF_3 (the *Lewis acid*) to form the "ate" complex. Nitrogen donates two electrons to boron and becomes electron deficient in the "ate" complex, whereas the boron accepts electrons to become electron rich. Therefore, the nitrogen takes on a positive charge in the complex and the boron takes on a negative charge. An arrow can replace a bond in the second "ate" complex in what is called a *dative bond* in a Lewis acid-base "ate" complex. Either structure is an acceptable representation of an "ate" complex.

A fundamental difference between Brønsted-Lowry acid-base reactions and Lewis acid-base reactions involves the products. The reaction of a Brønsted-Lowry base with a Brønsted-Lowry acid leads to two products, a conjugate acid, and a conjugate base. The reaction of a Lewis base with a Lewis acid leads to one product, the "ate" complex.



2.20 Draw the reaction with curved arrow and the ate complex formed (using Lewis electron-dot structures) for the reaction of aluminum bromide ($AlBr_3$) and diethyl ether ($CH_3CH_2OCH_2CH_3$).

The relative order of Lewis acidity is not always straightforward. Lewis acids usually take the form MX_n, where X may be a halogen atom or X may be a molecule that contains oxygen, nitrogen, or phosphorus (other X units will be introduced later in this book). The metal is M and n in X_n is the number of units attached to M. Reaction with a Lewis base leads to formation of $MX^- B^+$, the *"ate" complex*. Transition metal salts have a metal atom that can assume multiple valences due to the presence of d-orbitals and/or f-orbitals. The salt may form compounds with 2, 3, 4, 5, or 6 bonds to other groups or atoms attached to the metal (known as *ligands*). Such compounds can function as a Lewis acid. There are several rules that can be used to estimate the relative Lewis acidity of metal salts. The reactivity of Lewis acids and bases are discussed again in Section 6.8.

1. In MX_n ($n < 4$) acidity arises from the central atom's requirement for completion of an outer electron octet by accepting one or more pairs of electrons from the base. Acidity is diminished when two electron pairs are required. Group 13 acids are more acidic than transition metal acids: $BF_3 > AlCl_3 > FeCl_3$.
2. The acidity of M will decrease within any group with increasing atomic volume (effectively, with increasing atomic number) owing to the weaker attraction between nuclear charge and incoming electron pairs. The result of these effects leads to the order: $BX_3 > AlX_3 > GaX_3 > InX_3$.
3. In general, the availability of d-orbitals for donation will be easier (especially with d-outer orbitals) and more effective, the heavier the element. This property leads to a decrease in acidity, as in the series (B⟶Al⟶Ga⟶In) above. It is therefore possible to order the more common Lewis acids by decreasing acid strength: $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > InX_3 > SnX_4 > AsX_5 > SbX_3 > ZrX_4$.

Nucleophiles

2.8 WHY IS ACID–BASE CHEMISTRY A THEME FOR ORGANIC CHEMISTRY?

If a species donates two electrons to hydrogen, it is called a Brønsted-Lowry base. If a species donates two electrons to an atom other than carbon or hydrogen (e.g., B or Al), it is called a Lewis base as described in Section 2.7. The concept of an electron rich species donating two electrons to an electron poor species can be extended to reactions that are not acid-base reactions. In organic chemistry many reactions involve a molecule or an ion that donates two

electrons to a carbon atom, forming a new bond to that carbon. Since organic chemistry is fundamentally the study of carbon compounds, reactions of carbon take on special significance. For this reason, the term *nucleophile* is given to a species that donates two electrons to an electron deficient carbon atom. An *electrophile* is a chemical species that forms bonds with nucleophiles by accepting an electron pair. In most organic chemistry textbooks, a fundamental theme is the myriad reactions of electron rich species that donates electrons to an electron poor carbon to form a new covalent bond.

In organic chemistry there are compounds that react as weak bases with strong acids. Ethene is one example of a class of compounds known as alkenes (Section 5.1). Examination of ethene shows there are two bonds between adjacent carbon atoms, a double bond (C=C). The C=C unit in ethene is analogous to the S=O bond and the Cl=O bond seen in sulfuric acid and perchloric acid in Section 2.6. When ethene is mixed with the strong acid HCl, the weaker π-bond reacts with the HCl by donating two electrons to form a new C—H bond. This acid-base reaction generates a cation with a positive charge on carbon, with a chloride counterion (Section 10.2). As shown in Figure 2.7, the reaction between HCl and the alkene ethene involves donating two electrons from the alkene to the acidic proton of HCl. The product, which is called a *carbocation*, is a reactive intermediate that will be discussed in Section 7.2.1. This positively charged species is formally the conjugate acid and the chloride ion is formally the conjugate base.

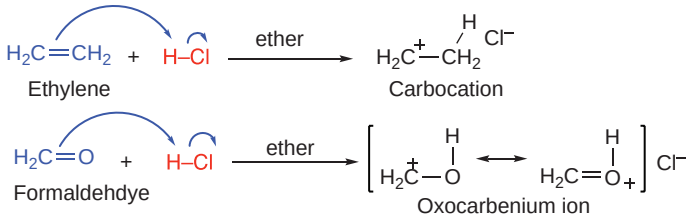


FIGURE 2.7 Acid–base reactions of ethylene and formaldehyde.

In the second reaction in Figure 2.7 an organic molecule called formaldehyde, which is an aldehyde (Section 5.6.2), has a carbon-oxygen double bond (C=O) known as a carbonyl group. The carbonyl has a strong σ bond and a weak π bond. Formaldehyde reacts as a base with HCl to yield a cation species known as an *oxocarbenium ion*, which is resonance stabilized with two resonance contributors (Section 16.2). The oxocarbenium ion is the conjugate acid and the chloride ion is the conjugate base. It is clear that ethene and formaldehyde react as weak Brønsted-Lowry bases with the strong acid HCl to yield the indicated products. The details of these two reactions will be discussed in Sections 10.2–10.7 and 16.2, respectively.

2.9 BIOLOGICAL RELEVANCE

Acid-base chemistry is quite important in biological systems, and it drives many common biological processes. A glycosidic bond is a covalent bond that joins a carbohydrate molecule to another group (Section 25.4). Enzymes called *hydrolases* mediate the cleavage of glycosidic bonds (Sections 24.6 and 25.4). In one reaction of pyranoside hydrolysis, the reaction of a basic carboxylate anion in a glutamic acid residue (Section 24.3) with water in an acid-base reaction is mediated by an enzyme from *S. lividans* Xyl10A, *glycoside hydrolase.*[7] The product is the hydroxide ion. As the proton of water is removed, the oxygen from the water reacts as a nucleophile with the carbon bearing a carboxyl unit in the glycosyl enzyme acyl intermediate shown in Figure 2.8[7] (Sections 18.4,6). Hydroxide displaces the acyl group and incorporation

[7] McCarter, J.D.; Withers, S.G. *Current Opinion in Structural Biology* 1994, 4, 885–892.

of the hydroxyl group leads to the carbohydrate derivative shown. Carbohydrate derivatives are discussed in Sections 25.1–3.

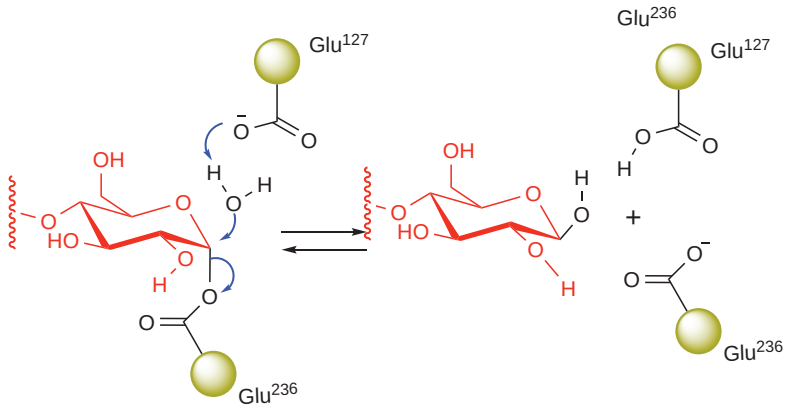
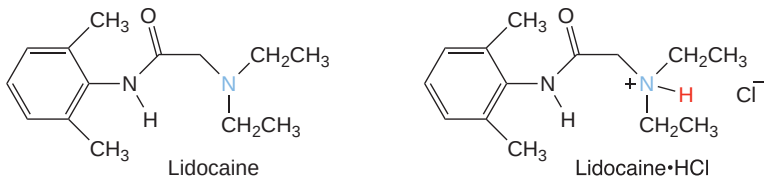


FIGURE 2.8 A step in the mechanism for hydrolysis of a pyranoside hydrolysis in *S. lividans* Xyl10A. Reprinted from McCarter, J.D.; Withers, S.G. *Current Opinion in Structural Biology*, 1994, 4, 885-892. Mechanisms of enzymatic glycoside hydrolysis. Copyright (1994), with permission from Elsevier.

Acid-base reactions are important in many areas of medicine. Local anesthetics are commonly used to block pain in medical procedures such a filling a tooth. Many local anesthetics block nerve conduction by reducing membrane permeability of sodium ions.[8] Lignocaine (also called lidocaine) is a common local anesthetic. The nitrogen atom marked in *blue* in lidocaine is an amine (Section 5.5.3) and it is a weak base.[8]



Lidocaine is usually distributed as an aqueous solution of the HCl salt (lidocaine•HCl), which is the conjugate acid of the reaction of lidocaine with HCl.[8] At physiological pH, which is usually between 7.36 and 7.44, most of the drug will exist in its ionized form (lidocaine•HCl), which is believed to combine with the excitable membrane to inhibit sodium permeability.[8] Some of the drug will exist in the unionized form since in the acid-base equilibrium both the base (lidocaine) and its conjugate acid (lidocaine•HCl) will be present. It is believed that lidocaine more easily penetrates the lipid barrier around and within the nerve tissues.[8]

2.21 Write out the acid-base reaction between lidocaine and HCl.

CORRELATION OF HOMEWORK WITH CONCEPTS

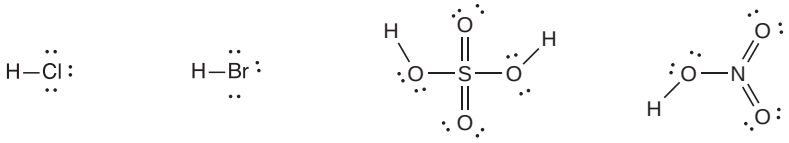
- An acid and a base react to yield a conjugate acid and a conjugate base: 2, 4, 7, 8, 9, 14, 21, 25, 34.
- A Brønsted-Lowry acid has a proton that accepts electrons, and a Lewis acid is any other atom other than H or C that accepts electrons. A Brønsted-Lowry base

[8] Grahame-Smith, D.G.; Aronson J.K. *The Oxford Textbook of Clinical Pharmacology and Drug Therapy*, Oxford University Press, Oxford, UK, 1984, pp. 551–552.

donates electrons to a proton and a Lewis base donates electrons to an atom other than H or C: 1, 3, 5, 10, 20, 36.
- There is an inverse relationship between K_a and pK_a, and a large K_a or a small pK_a is associated with a stronger acid: 22, 24, 31, 32.
- Curved arrows are used to indicate electron flow from an source of high-electron density to a point of low electron density: 12, 13, 22.
- Electronegativity for an atom increases to the right and up the periodic table: 15, 35.
- Acid strength in an acid X—H is determined by the stability and reactivity of the acid and the base but also the conjugate acid and the conjugate base: 17, 18, 23, 27, 28, 33.
- Base strength is largely determined by the stability and reactivity of the conjugate acid and base, and the electron donating ability of the basic atom: 6, 11 16, 26, 29, 30.
- A resonance stabilized conjugate base is less reactive and a weaker base: 19, 29, 30, 33, 34.

ANSWERS TO IN-CHAPTER QUESTIONS

2.1 Each line — represents two electrons (:).



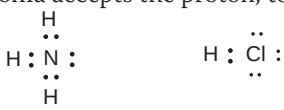
2.2 The conjugate base is the nitrate anion, NO_3^-.

2.3 The hydrogen on the OH unit of nitric acid (HO—NO_2) accepts the electron pair from the base, and the oxygen atom in KOH donates the electrons to that proton.

2.4 The conjugate base is the bicarbonate anion.

2.5 The nitrogen atom of ammonia accepts the proton, to form ammonium chloride.

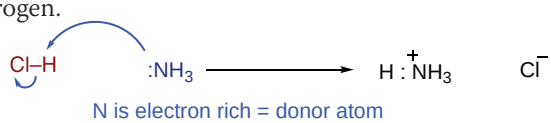
2.6



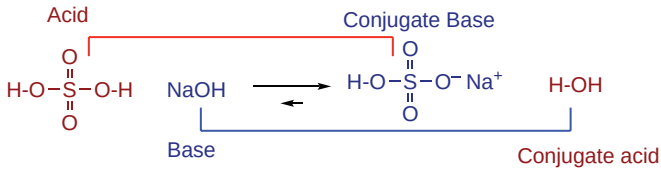
2.7 Both P and S have unshared electrons that can be donated. In compounds that contain trivalent P (three, two-electron bonds) or divalent S (two, two-electron bonds), both compounds are considered to be a base. The sodium atom in Na^+ has no electrons to donate and cannot function as a base. The nitrogen atom in the ammonium ion has no unshared electrons since there are four bonds to N rather than three and N has a positive charge. This positively charged ion has no excess electrons, so nitrogen atom cannot react as a base.

2.8 Hydrogen is the electron-deficient atom and oxygen is the electron-rich atom. There are no electrons on hydrogen to donate, so it cannot donate electrons. The arrow is *always* from the electron rich atom to the electron-poor atom, therefore, it must be oxygen to hydrogen.

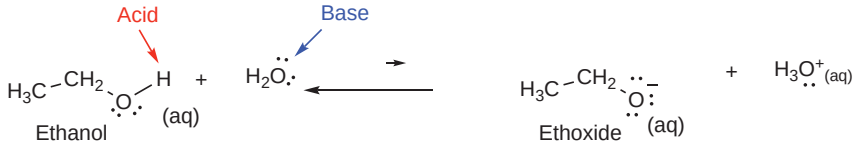
2.9



2.10



2.11 The O–H hydrogen atom in ethanol is the acidic proton and the oxygen of water is the basic atom.



2.12 The oxygen atom in hydroxide has a charge of -1 and will be electron rich relative to the oxygen atom in neutral water. In other words, there is a higher concentration of electron density on the charged oxygen atom when compared to the neutral oxygen atom. In addition, hydroxide is the conjugate base of water. Hydroxide is more basic.

2.13 Water is the base.

2.14 The Brønsted-Lowry acid is HCl.

2.15 Using Figure 2.4, N (3.0) > S (1.9) > Ga (1.8).

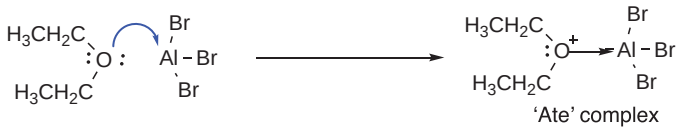
2.16 No! Diatomic hydrogen has no electrons that can be donated. The electrons are tied up in a covalent bond between the two hydrogen atoms and there are no unshared electrons. See Section 3.3 for a discussion of covalent bonds.

2.17 Yes, but it is a weak acid requiring reaction with a very strong base! Since ammonia has a hydrogen atom attached to the nitrogen, that hydrogen is slightly electron deficient and with a strong enough base, ammonia is a Brønsted-Lowry acid in the presence of a strong enough base.

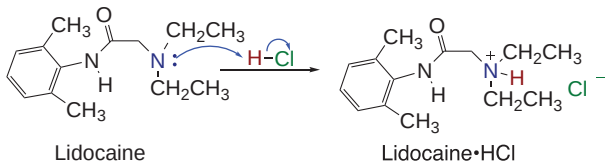
2.18 There is one unshared pair of electrons on the nitrogen of ammonia. There are two unshared pairs of electrons on the oxygen of water.

2.19 Nitric acid forms the nitrate anion, and the charge is dispersed over four atoms via two π-bonds. The charge in the perchlorate anion is dispersed over five atoms via three π-bonds. Nitrogen is also much smaller than chlorine, so the nitrate anion is expected to be smaller than the perchlorate anion. Both observations suggest that nitric acid is less acidic than perchloric acid, which is correct.

2.20 Each Br has three unshared electron pairs and the oxygen as two unshared electron pairs. These have been omitted for clarity.



2.21



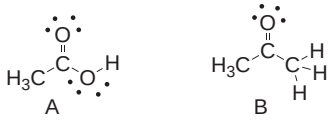
HOMEWORK

22. For each of the following, write the complete acid-base equilibrium, and then write out the equation for K_a. For each reaction, draw a curved arrow for the acid-base pair to indicate the flow of electrons during the reaction.
(a) $HNO_3 + H_2O$ (b) $H_2O + NH_3$ (c) $HBr + NH_3$ (d) $HCl + H_2O$
(e) $Cl_3CH + NaNH_2$

23. Briefly explain why HBr (pK_a -9) is more acidic than HCl (pK_a -7).
24. When HCl is dissolved in water, an acid-base reaction occurs. Write out the K_a expression excluding the concentration term for water. Now write out the expression but include the concentration term for water. Why is the water term omitted in the first K_a term?
25. Draw the structure of the conjugate base formed if each of the following reacts as an acid.
    (a) NH_4^+ (b) $CH_3CH_2CH_2OH$ (c) H_2SO_4 (d) HI (e) NH_3
    (f) H_3CH
26. Which is the stronger Lewis base, ammonia or arsine (AsH_3)? Explain your answer.
27. Briefly explain why hydrogen sulfide (HSH) with a pK_a of 6.89 is a stronger acid than phosphine (PH_3) with a pK_a 27.
28. For each series indicate which is likely to be the strongest acid. Justify your choice.

(a)	CH_4	CH_3NH_2	CH_3OH	NaF
(b)	HF	HCl	HBr	HI

29. Explain why the nitrate anion (NO_3^-) is a weaker base than hydroxide ion. Draw out the actual structure of the nitrate anion in answer this question.
30. Which of the following is the more basic? HCO_3^- or F^-? Justify your answer.
31. Determine the pK_a for each of the following.
    (a) $K_a = 1.45 \times 10^5$ (b) $K_a = 3.6 \times 10^{-12}$ (c) $K_a = 6.7 \times 10^{-31}$
    (d) $K_a = 18$ (e) $K_a = 3.8 \times 10^{14}$
32. Which of the following is likely to have the smallest pK_a ? HCl, HF, H_2O, NH_3. Justify your answer.
33. Consider the two compounds **A** and **B**. **A** has a pK_a of ~ 4.8, and **B** has a pK_a of ~ 20. Why is **A** more acidic?



34. When comparing the reaction of HCOOH and NaOH with CH_3OH with NaOH, the equilibrium concentration of the conjugate base of HCOOH is greater than the equilibrium concentration of the conjugate base of CH_3OH.
    (a) Explain why the concentration of the conjugate base from CH_3OH is lower than HCOOH.
    (b) When comparing the two reactions, how does the greater concentration of conjugate base from HCOOH influence K_a ?
35. Which is the more polarized bond, C—B or C—F? Justify your answer.
36. Which is the stronger Lewis acid, BCl_3 or $AlCl_3$? Justify your answer.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-3.php

3

Bonding

The nature of the bond between two carbon atoms or between carbon and another atom is a fundamental concept in organic chemistry. An understanding of bonding between atoms is essential to organic chemistry. For the most part, the bonds between carbon and another atom are covalent, but ionic bonds will occasionally be seen.

To begin this chapter, you should know the following points:

- The electronic configuration of elements in the first two rows of the periodic table.
- The shape of s- and p- atomic orbitals and how they relate to electronic configuration.
- The differences of s- and p- and d- orbitals.
- The difference between an ionic and a covalent bond.
- A sense of difference in the size of the elements and their respective ions.
- Covalent bonds are made of shared electrons.
- The concept of electronegativity.

3.1 ATOMIC ORBITALS AND ELECTRONS

Atomic Orbitals

Most organic compounds have C—C bonds, C—H bonds, or bonds between carbon and elements found in the second row of the periodic table (Li ⟶ F). However, many elements in the periodic table form bonds to carbon. In a chemical bond, electrons are shared between atoms, so an understanding of atoms and the electrons associated with those atoms is required. Because electrons have properties of a wave, the motion of electrons may be described by a wavefunction, and wavefunctions are used to describe atomic or molecular orbitals. Electrons in an atom and those found in chemical bonds are associated with orbitals.

3.1.1 ATOMIC ORBITALS

Atoms are discreet entities that differ from one another by the number of protons, neutrons, and electrons that make up each atom. Protons and neutrons are found in the nucleus, of course, and electrons are found outside of the nucleus in discreet energy levels (electron shells). An electron is neither a traditional wave nor a traditional particle, but rather a quantized fluctuating probability wavefunction. A wavefunction describes the position and state of the electron and its square gives the probability density of electron. A wavefunction has both a radial and an angular contribution. Radial wavefunctions depend only upon the distance from the nucleus whereas angular wavefunctions depend only upon direction. The *Schrödinger wave equation*[1] gives the quantized energies of a system and gives the form of the wavefunction: $H\psi = E\psi$, where H is a mathematical operator called the *Hamiltonian operator,* the general form of the kinetic and potential energies of the system. The *E* term is the numerical value for the *energy*, and ψ is a particular *wavefunction*. Allowed wavefunctions

[1] Puddephatt, R.J. *The Periodic Table of the Elements,* Clarendon Press, Oxford, UK, 1972, p. 6.

DOI: 10.1201/9781003174929-3

are found by using the Schrodinger equation but a solution is only possible for certain energies. Each wavefunction (ψ) describes an electron as a point $\psi(x,y,z)$ using Cartesian coordinates[2] whose magnitude varies from point to point in space.[3]

The precise position of an electron cannot be exactly determined. Indeed, the *Heisenberg uncertainty principle* states that the position and momentum of an electron cannot be simultaneously specified. The probability of finding an electron in a unit volume of three-dimensional space is given by $|\psi(x,y,z)|^2$. The ψ^2 value is always positive although the wavefunction (ψ) can have positive or negative values. The amplitude of each wavefunction (ψ) has a *maximum (represented by +) and a minimum (represented by -)*. The wavefunction indicates the allowed energies of an electron in an atom. A charge cloud that contains an electron is known as an *orbital*, and represents the probability of finding the electron in that region of space at a particular place in terms of the (x,y,z) at a particular time. Atomic orbitals result from a combination of both the radial and angular contributions of the wavefunction.

The wavefunction solutions for s, p and d orbitals are shown in Figure 3.1.[4] In addition, the shapes of 1s, 2s, and the three 2p orbitals are shown. The electron cloud for a wavefunction (ψ) that is always positive is represented as a spherically symmetrical orbital, *the s-orbital*. There are wavefunctions for electrons of different energies and they can be described in terms of the number of nodes. The point at which the wave changes its phase for + to - is a *node*. The s-orbital has zero nodes since there is no change in sign and the wavefunction remains positive. When there is one node, electron density is found in two regions relative to the node, as represented *by a p-orbital* with a "dumbbell" shape. Remember that the p-orbital represents the probability of finding an electron in ***both*** lobes and does not represent an electron travelling back and forth from lobe to lobe. A wavefunction that generates two nodes constitutes a *d-orbital*. There are five ways to generate wavefunctions that have two nodes in the (x,y,z) coordinate system, leading to d_{xy}, d_{xz}, d_{yz}, $d_{x2\text{-}y2}$ and d_{z2} orbitals. Molecules with f-orbitals will not be discussed in this book. The shapes of s, p, and two of the d-orbitals are shown in Figure 3.1.

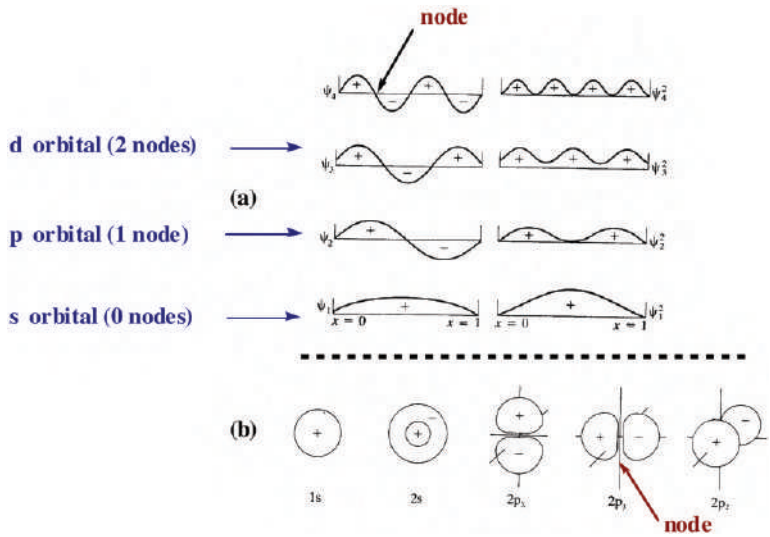
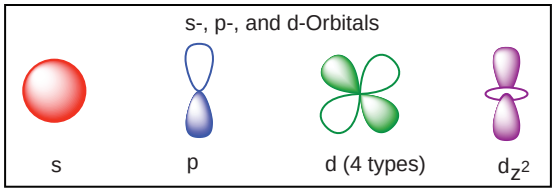


FIGURE 3.1 Wavefunction solutions and orbital pictures for those wavefunctions. [Tedder, J.M.; Nechvatal, A. *Pictorial Orbital Theory*, Pitman Publishing Inc., 1985, p. 2 (Figures 1.1 and 1.2).] Reprinted with permission of John Wiley & Sons.

[2] Coulson, C.A.; revised by McWeeny, R. *The Shape and Structure of Molecules*, 2nd ed., Clarendon Press, Oxford, UK, 1982, p. 5 (Figure 3).

[3] Coulson, C.A.; revised by McWeeny, R. *The Shape and Structure of Molecules*, 2nd ed., Clarendon Press, Oxford, UK, 1982, p. 3.

[4] Tedder, J.M.; Nechvatal, A. *Pictorial Orbital Theory,* Pitman Publishing Inc., London, 1985, p. 2 (Figures 1.1 and 1.2).



3.1 Based on Figure 3.1, describe the shape of the p-orbital shown.

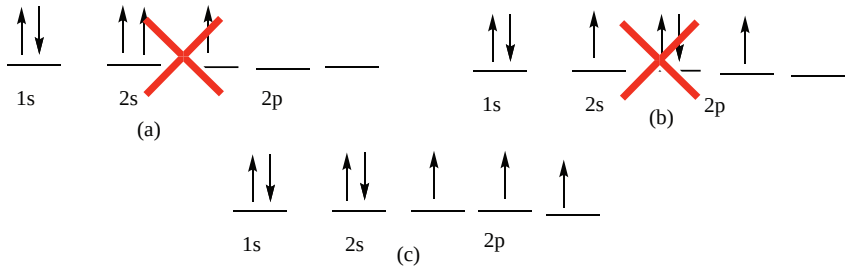
3.1.2 ELECTRONIC CONFIGURATION

The *periodic table* of the elements, which currently lists 118 elements, is organized by increasing atomic number and correlates with the number of protons in the nucleus. As the number of protons and neutrons in the nucleus increase, so do the number of electrons. The organization of elements in this manner is based on the work of Dmitri Ivanovich Mendeleev (1834–1907; Russia), in the 19th century. Electrons are found in orbitals. Those orbitals with lower principal quantum numbers are lower in energy. *In all cases, an individual orbital can hold no more than two electrons.* The first-row elements (H, He) use only the spherical 1s-orbital. In the second-row (Li, Be, B, C, N, O, F, He) the electrons are found in the spherical 1s-orbital along with the spherical 2s-orbitals and dumbbell shaped 2p-orbitals. The orbitals in this second row hold a total of eight electrons. The third-row elements introduces 3s-, and 3p-orbitals, and 4s, 4p, and 3d-orbitals appear in the fourth-row.

Elements in the second row have only one valence for each atom in a neutral molecule. *Valence* is the number of bonds an atom can form with other atoms when molecules are formed and remain neutral. A *valence electron* is found in an outer shell associated with an atom, and it can participate in the formation of a chemical bond if the outer shell is not closed. Note that valence electrons are most easily removed via chemical reactions from orbitals in rows that are further from the nucleus. These are the most available for donating or sharing with other atoms. There are other quantum levels for high atomic mass elements, so there are different higher energy orbitals associated with each type of electron energy (shell).

The *electronic configuration* of each element is essentially the order in which the various orbitals fill. The electrons are distributed among the orbital shells and subshells. Electrons have the property of spin due to self-rotation of the electron, which gives rise to an angular momentum vector associated with a magnetic dipole. The spin quantum number, introduced in general chemistry, is one of four quantum numbers. When one orbital contains two electrons, those two electrons have opposite spin quantum numbers. They are *spin paired*. An orbital with spin paired electrons is lower in energy than an orbital with two electrons that have the same spin. The 1s orbital fills with two electrons before any electron can fill the 2s orbital. When the 2s orbital is filled, the next electrons will go into the three 2p orbitals, which are of identical energy. Multiple orbitals with identical energies are said to be *degenerate*. Electrons have like charges so two electrons repel each other if they are in the same orbital. The $2p_x$, $2p_y$, and $2p_z$ orbitals therefore fill one at a time so the electrons are as far apart as possible. In other words, it is lower in energy to have one electron in each of the three 2p-orbitals before a second electron is added to another 2p-orbital. Therefore, the three degenerate 2p-orbitals are arranged in the *x*-, *y*-, and *z*- directions of a three-coordinate system to minimize the system energy. This observation is the basis for the *Pauli exclusion principle*, which states that if there are several orbitals of equal energy, each orbital will fill with one electron before any orbitals contain two. This principle is named after Wolfgang Pauli (1900–1958; Austria-Switzerland), a theoretical physicist. Orbitals fill with electrons in ascending order of orbital energy until all available electrons have been used. This concept is known as the *Aufbau procedure*. This concept is illustrated with an incorrect filling in (a) with two electrons of the same spin in one orbital. In (b), electrons are placed in the higher

energy 2p orbital before two spin paired electrons are placed in the 2s orbital. Both representations are *incorrect*. The correct filling of the orbitals is shown in (c). Note that *Aufbau* is a German word that translates to "building or construction." The electronic configuration of elements through at least the first three rows should be known for this course, because they are pertinent to the electron distribution found in organic molecules. Figure 3.2 shows the electronic configuration for the atoms in the first three rows of the periodic table.



3.2 What is the total number of electrons for an atom in a fully filled second row? What is that atom?

Orbitals generally fill s ⟶ p, but in the fourth row the 4s-orbital fills before the 3d-orbitals. There are five 3d-orbitals. Likewise, the 5s-orbital fills before the 4d-orbitals. The process of adding electrons to available atomic orbitals follows an order that is generalized by the mnemonic:

1s ⟶ 2s ⟶ 2p ⟶ 3s ⟶ 3p ⟶ 4s ⟶ 3d ⟶ 4p ⟶ 5s ⟶ 4d ⟶ p ⟶ 6s ⟶ 4f ⟶ 5d ⟶ 6p

3.3 Write the electronic configurations of N, B, P, and S.

Chemical Bonding

3.2 IONIC VERSUS COVALENT CHEMICAL BONDS

Two major types of bonds will be considered in this section. A *covalent bond* is formed by the mutual sharing of two valence electrons between two atoms. An *ionic bond* is formed when one atom in a bond has two electrons and the other has none, resulting in charged ions (+ and –) held together by electrostatic attraction. Lithium fluoride (LiF) has an ionic bond where a positively charged Li^+ is electrostatically bound to a negatively charged F^-. In the second row, a maximum of eight electrons can occupy the valence shell (the Ne configuration). The "*octet rule*" is based on the theory that main-group elements will form bonds to an atom so there are eight electrons in its valence shell, giving it the same electronic configuration as a noble gas. A Noble gas configuration has a filled outer-electronic shell and is particularly stable.

H $1s^1$								He $1s^2$
Li $1s^2 2s^1$	Be $1s^2 2s^2$		B $1s^2 2s^2 2p^1$	C $1s^2 2s^2 2p^2$	N $1s^2 2s^2 2p^3$	O $1s^2 2s^2 2p^4$	F $1s^2 2s^2 2p^5$	Ne $1s^2 2s^2 2p^6$
Na $1s^2 2s^2 2p^6 3s^1$	Mg $1s^2 2s^2 2p^6 3s^2$		Al $1s^2 2s^2 2p^6 3s^2 3p^1$	Si $1s^2 2s^2 2p^6 3s^2 3p^2$	P $1s^2 2s^2 2p^6 3s^2 3p^3$	S $1s^2 2s^2 2p^6 3s^2 3p^4$	Cl $1s^2 2s^2 2p^6 3s^2 3p^5$	Ar $1s^2 2s^2 2p^6 3s^2 3p^6$

FIGURE 3.2 Filled orbitals (electronic configuration) for elements in the first three rows.

Group 1 elements such as lithium in the second row have only one electron in the outer shell. Losing one electron to generate the He configuration is more favorable than adding seven electrons to achieve the Ne configuration. If one 2s valence electron is lost from lithium during an electron transfer reaction, for example, the result is Li^+ with a $1s^2$ configuration (the He configuration). Indeed, single electron transfer reactions are typical of Group I metals such as Li, Na, or K. Note that Li^+ with a $1s^2$ configuration is *not* He, although it has the same electronic configuration. The energy required for the loss of one electron from an atom in an electron transfer reaction is a measurable quantity called its *ionization potential*.

A similar electron-transfer argument can be made for a reaction of the Group 17 fluorine atom, which has seven electrons in the outer shell. If fluorine adds one electron the result is F^- which has the $1s^22s^22p^6$ configuration (the Ne configuration). If an electron transfer reaction removes an electron from F to give F^+, the electronic configuration is $1s^22s^22p^4$. Energetically, it is easier to form F^- rather than F^+. Indeed, reactions that transfer an electron to F, Cl, Br, and I to form the halide anion are common. The fluoride anion, F^-, is not Ne. The energy required for the gain of one electron into an atom in an electron transfer reaction is called its *electron affinity*. Based on ease of formation of Li^+ and F^- it is not surprising that LiF is an ionic compound. Similarly, NaCl, LiI, and other metal halides are ionic.

3.4 Is the bonding in NaCl ionic or a covalent? Justify your answer

3.5 Draw the electronic configuration of Na^+.

3.6 Is it easier for rubidium to lose one electron or gain one electron? Explain.

3.3 COVALENT BONDS

σ-Covalent Bonds

In molecules that contain carbon the orbitals associated with carbon are different from the orbitals associated with atomic carbon. Atomic carbon has an electronic configuration of $1s^22s^22p^2$ with four valence electrons found in the 2s- and 2p-orbitals. Carbon cannot gain four electrons or lose four electrons to attain a Noble gas configuration because the energy cost is simply too high. However, carbon can attain a Noble gas electron configuration by sharing electrons with another atom in a *covalent bond*.

When electrons are concentrated in orbitals on a single atom of a pure element, the electrons are said to be "localized" on that atom with the electrons in *atomic orbitals*. For a covalent bond in a molecule, the electrons of one atom must distort toward the other atom since the electrons are shared between the atoms. In Figure 3.3 two imaginary atoms overlap to form a bond. The atomic orbitals change their shape as they become *molecular orbitals (MO)* as the electron density in the orbital is shifted toward the other atom of the bond. Such a bond is commonly called a *covalent sigma bond (σ bond),* and the maximum electron density lies on a line between the two nuclei.

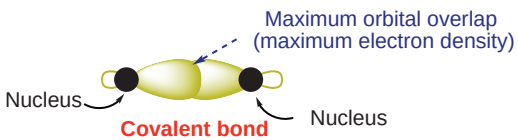


FIGURE 3.3 Overlapping molecular orbitals form a covalent bond.

Bond Length

Diatomic hydrogen (H_2 or H—H) has a covalent bond. The "line" in the H—H line drawing represents the covalent bond, and also represents two electrons shared by the two hydrogen atoms. It is possible to "visualize" this molecule and the covalent bond using molecular modeling. The *electron potential map of* H_2 is shown in Figure 3.4. The red areas in the electron potential map indicate a high concentration of electron density and *blue* areas a low

concentration of electron density. It is clear that the highest concentration of electron density is between the two hydrogen atoms in diatomic hydrogen, consistent with those atoms sharing electrons to form a bond.

An important parameter in a covalent bond is the *bond length*, which is the measured distance between the nuclei of each atom participating in the bond (the internuclear distance). Bond length has been measured in angstroms (Å, where 1 Å = 1 x 10^{-10} meters, m) but nowadays it is measured in picometers (1 pm is 1x10^{-12} m, or 0.01 Å), so 1 Å= 100 pm. A longer bond has less electron density per unit length than if the bond is short and it is a weaker bond. Conversely, a shorter bond will have more electron density per unit length, and it is assumed to be stronger. In principle, a longer bond is weaker and easier to break, but chemical reactivity depends on many factors and bond length is simply one of them.

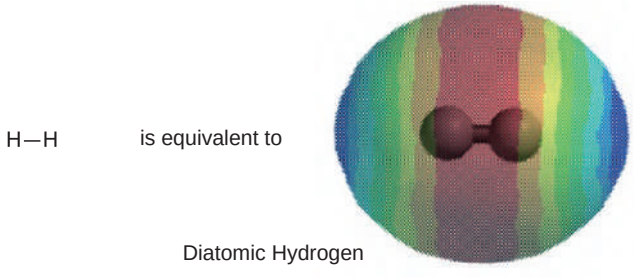


FIGURE 3.4 The electron potential map of diatomic hydrogen showing electron density concentrated between the two hydrogen atoms.

LCAO Model and Hybrid orbitals

3.4 LINEAR COMBINATION OF ATOMIC ORBITAL (LCAO) MODEL

The molecular orbitals of two atoms used to form a covalent bond are different from the atomic orbitals of the individual atoms. Models have been developed to predict the electron distribution in molecular orbitals based on the atomic orbitals of each atom. One model mathematically mixes the atomic orbitals of two hydrogen atoms and combines them to form the diatomic molecule H_2. This model is called the *Linear Combination of Atomic Orbital (LCAO) model*. It is used to predict the electron distribution in molecular orbitals and the bonding of simple molecules.

Using this model for H_2 begins with two individual hydrogen atoms, each with one electron in a 1s *atomic orbital.* The energy of those orbitals is represented as a "line" in Figure 3.5. The lower the position of the line, the lower the energy of the orbital. The higher the position of the line, the higher the energy of the orbital. If the 1s-orbitals from each hydrogen atom are mathematically "mixed" to form a new covalent H—H bond, two *molecular orbitals* are formed: a linear combination of atomic orbitals. The molecular orbitals must be of a different energy relative to the atomic orbitals, and each molecule orbital will be of a different energy. One is of higher energy, and one is of lower energy. There can be no gain or loss of orbitals or electrons, so two electrons are found in the new molecular orbitals.

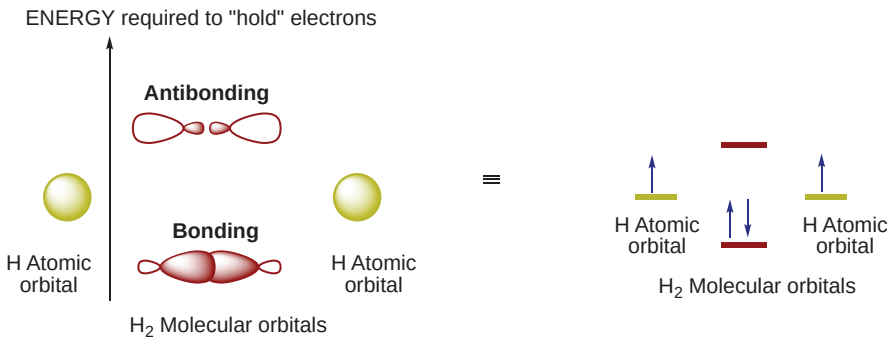


FIGURE 3.5 Molecular orbital diagram for diatomic hydrogen using the LCAO model.

Each of the two hydrogen atoms has one electron as represented by a *vertical arrow* on the orbital energy line. Since there is no gain or loss of electrons when the molecular orbitals are formed, the two electrons reside in the lowest energy molecular orbital, and they will be spin paired. As shown in Figure 3.5, this lower energy orbital is said to be *a bonding molecular orbital*. The higher energy orbital is an empty molecular orbital (no electrons), and it is usually referred to as an *anti-bonding orbital*. An anti-bonding orbital is an energy level that normally has no electrons in it. It is populated only when sufficient energy is provided to move an electron into that orbital or if an electron is added from an external source.

3.5 TETRAHEDRAL CARBONS AND SP³ HYBRIDIZATION

Mixing the atomic s-orbitals of two hydrogen atoms to form molecular orbitals predicts the bonding in diatomic hydrogen (see Figure 3.5) with reasonable accuracy. There are limitations to the LCAO method, however, and if the atoms to be mixed have both s- and p-orbitals, there are problems. When the atomic orbitals of two carbon or two oxygen atoms are mixed using the LCAO method, the LCAO model does *not* correctly describe the molecular orbitals. The LACO model requires that the 1s orbital are mixed to give two molecular orbitals and that the 2s orbitals are mixed to give two molecular orbitals. The three 2p orbitals are mixed to give six molecular orbitals. When the electrons are added, those molecular orbitals from mixing the 1s and the 2s orbitals are filled but the four electrons from the 2p orbitals give one of the 2p molecular orbitals with two spin-paired electrons but the other two have a single electron. This molecular orbital picture suggests two different kinds of bonding molecular orbitals, which is incorrect.

3.5.1 THE EXPERIMENTALLY DETERMINED STRUCTURE OF METHANE

Methane and Hybridization

The LCAO model only uses valence electrons to form molecular orbitals and therefore "mixes" the 2s- and 2p-atomic orbitals, which are at different energy levels. This model generates two "2s-type" molecular orbital and six "2p-type" molecular orbitals. When eight electrons are added to the molecular orbital diagram from the two carbon atoms, two types of bonds for carbon are predicted including unshared electrons, which is *not* correct. The simple LACAO model gives an *incorrect answer* for carbon and for any atom that has both 2 and p orbitals. The LCAO model is a mathematical model for simple diatomic molecules, and it does not apply to all molecules. A different model must be used.

3.7 Use the LCAO model to predict the molecular orbital diagram for covalent bonding for C—C.

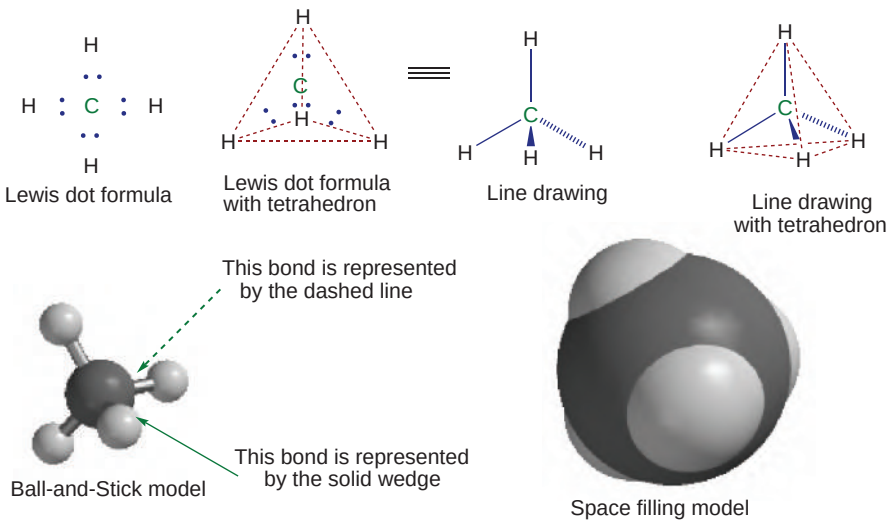


FIGURE 3.6 Structure of methane.

Before examining models that predict the bonding in carbon compounds, it is useful to examine real molecules with covalent carbon bonds that exist in nature. Methane will serve as a simple example. Methane is a gas that is found in small quantities in Earth's atmosphere and is the main constituent of natural gas. Methane is the simplest hydrocarbon, as will be described in Chapter 4, consisting of one carbon atom and four hydrogen atoms, and there are four identical C—H bonds. It has been determined that methane (CH_4) has four hydrogen atoms distributed around carbon in the *shape of a regular tetrahedron* (Figure 3.6). All of the H—C—H bond angles have been measured to be 109°20'. The four C—H bond lengths are the same (1.094 Å; 109.4 pm).[5] The tetrahedral array of four atoms attached to a central carbon is explained in large part by repulsion of electrons in the bonds, which pushes the atoms apart. This repulsive energy is at a minimum when the atoms are at the corners of a regular tetrahedron.

The structure of methane is shown as a Lewis dot formula where each covalent bond is represented by two "dots" for the two electrons. A second structure in a tetrahedral replaces ":"with a line (—) to represent the bond. Only the atoms and bonds are shown in this so-called *line drawing*. The line drawing superimposed on the tetrahedron has the closest hydrogen atom projected out of the page, represented by a *solid wedge*. The hydrogen atom that is the most distant in the tetrahedron appears to be projected behind the page, represented by a *dashed line*. The other two hydrogen atoms are connected by *solid lines*, indicating they are in the plane of the page. A three-dimensional *ball-and-stick model* of methane is also shown in Figure 3.6, where "cylinders" represent the bonds and spheres represent the atoms. A "space-filling model" is shown to illustrate the relative size of the atoms.

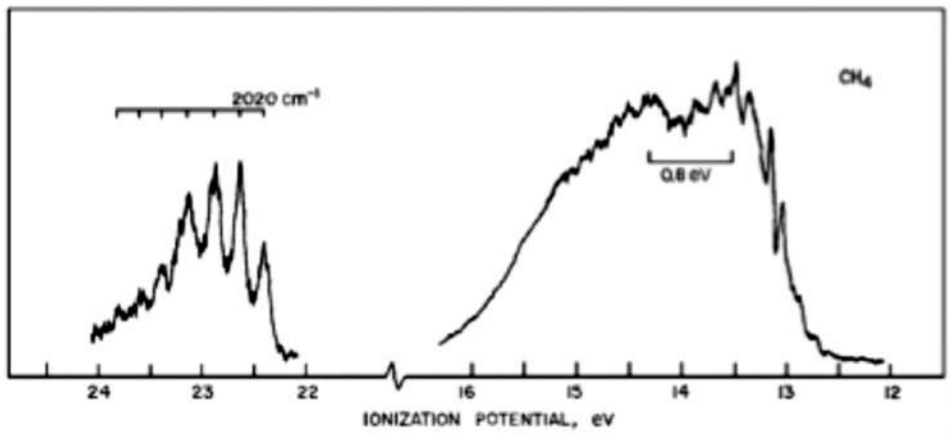


FIGURE 3.7 Photoelectron spectroscopy scan of methane. [Reprinted with permission from Brundle, C.R.; Robin, M.B. *Journal of Chemical Physics*, 1970, *53*, 2196. Copyright 1970, American Institute of Physics.]

What atomic orbitals of carbon are used to form the four bonds in methane? There is an experimental technique called *photoelectron spectroscopy (PES)* that can answer this question. The PES experiment directs an electron beam at the surface of a molecule to "dislodge" electrons in the valence shell. The PES spectrum of methane in Figure 3.7[6] shows two peaks for lower energy electrons. One peak arises from electrons ejected at 13.6 eV and the other arises from electrons ejected at 23.1 eV. An electron volt (eV) = 1.602×10^{-19} J eV^{-1} = 3.883×10^{-20} kcal mol^{-1} eV^{-1}, where 1 kcal = 4.187 kJ. The band at 13.6 eV is due to the electrons in the three degenerate 2p-orbitals.[6] The band at 23.1 eV is due to the 2s electrons. This PES experiment shows that *both* the 2s and the 2p electrons are used for bonding of carbon to the hydrogen

[5] Dean, J.A. *Handbook of Organic Chemistry*, McGraw-Hill, NY, 1987, Table 3–4A, pp. 3–13.

[6] (a) Brundle, C.R.; Robin, M.B. *Journal of Chemical Physics* 1970, 53, 2196–2213; (b) Baker, A.D.; Betteridge, D.; Kemp, N.R.; Kirby, R.E. *Journal of Molecular Structure* 1971, 8, 75–81; (c) Also see, Robinson, J.W., *Practical Handbook of Spectroscopy*, CRC Press, Boca Raton, FL, 1991, p. 178.

atoms. If higher energy is applied to displace electrons, a third band is found at 290 eV, but this band is not shown in Figure 3.6. This third band correlates with the 1s electrons.

3.5.2 ELECTRON PROMOTION AND SP³ HYBRIDIZATION

An atom of elemental carbon cannot be directly converted into a molecule with C—H or C—C bonds by any known chemical reaction. In fact, molecules with covalent carbon-carbon bonds are usually prepared from other molecules with covalent bonds. Mathematical models such as the LCAO model can only approximate bonding in real molecules. It therefore helps to generate a model with prior knowledge of the correct answer. As described in Section 3.5.1, it is known that methane has four identical bonds directed to the corners of a regular tetrahedron, and there are no unshared electrons in the molecule. As noted, the LCAO model does not work for carbon since there are 2p electrons. Another model "promotes" an electron from the 2s orbital of carbon to the empty 2p orbital before they are mixed to generate molecular orbitals. When the electron is "promoted", the result is four *sp³ hybrid molecular orbitals*. Obviously, it is *not* possible to actually "promote" an electron in a real atom of atomic carbon to yield a real organic molecule. It is possible, however, to use a model that visualizes moving electrons from the 2s orbital into the empty 2p orbital to generate four identical atomic orbitals. Using this model, the graphical pictures shown in Figure 3.8 illustrate mixing a 2s-orbital and the three degenerate 2p-orbitals of carbon to transform them into four identical *sp³ hybrid molecular orbitals*. These four hybrid orbitals are mixed with the four s-orbitals of hydrogen atoms to generate the molecule orbitals for the four identical C—H bonds in methane. This *hybridization model* predicts the correct bonding picture of methane. ***It must***, the model was developed based on an understanding of the real bonding in methane.

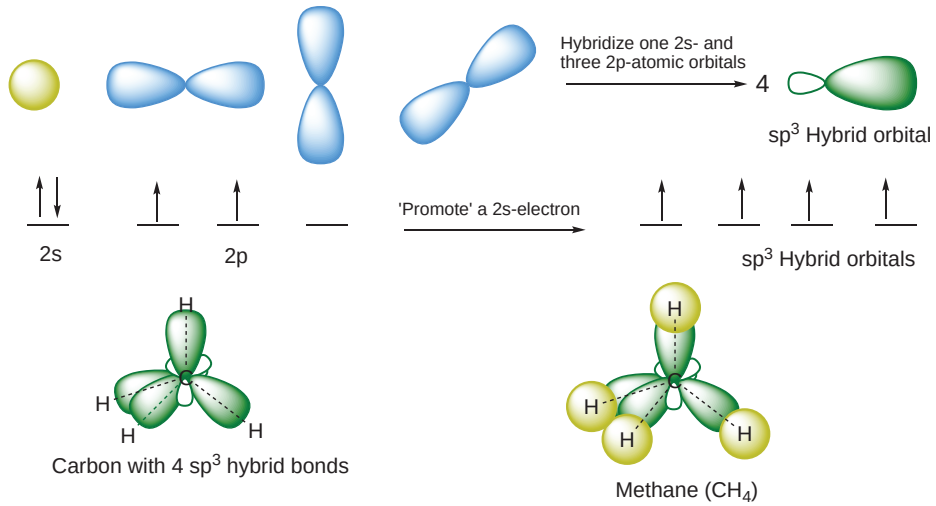


FIGURE 3.8 The predicted bonding in methane by promoting an electron from a 2s orbital to a 2p orbital to generate four sp³ hybrid orbitals.

3.8 Draw the LCAO model for a C—C bond using four sp³-hybrid orbitals for each carbon.
3.9 Predict the hybridization of carbon in the molecule CCl_4 (carbon tetrachloride).

3.5.3 THE HYBRID CARBON MODEL OF SP³-HYBRID ORBITALS

The electron promotion hybridization model is widely used in textbooks, but atomic carbon does not really hybridize and change into something else. In reality, methane and other

organic molecules form the best bonds possible with the atoms, given the three-dimensional requirements of the molecule and the orbitals that are available. This fact is apparent when one examines the PES spectra of methane given in Figure 3.7. In other words, bonds are not formed using four identical hybrid orbitals but they are formed by the best overlap of the s-orbitals of the four hydrogen atoms with the valence orbitals of carbon, 2s, and 2p. A carbon atom with the 2s (gray) and 2p orbitals (blue, green, yellow), is used for the *hybrid-carbon model* shown in Figure 3.9. Based on the known geometry of methane and electronic repulsion of the bonds to be formed, four hydrogen atoms (in red) are positioned at the corners of a regular tetrahedron.

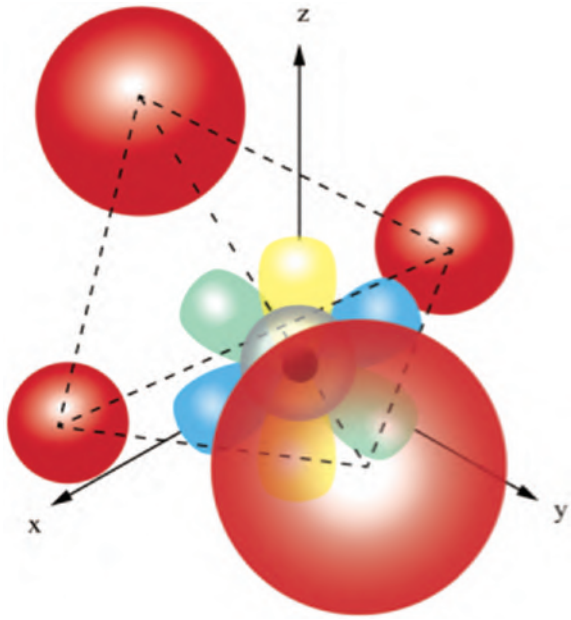


FIGURE 3.9 The hybrid-carbon model for bonding in methane.

The carbon atom uses the 2s orbital and the three degenerate 2p-orbitals to form bonds to each hydrogen. Each hydrogen atom in the model is a red spherically symmetrical s-orbital and will overlap the 2s orbital and all three 2p-orbitals of carbon to form a covalent bond. There is no overlap with the core 1s orbital of carbon. Each carbon and hydrogen covalent bond is therefore formed from *three* 2p-orbitals and *one* 2s-orbital, so sp^3 hybridization is a reasonable description of the bonding. The model in Figure 3.9 is not real, of course, since four hydrogen atoms do not "fly" into a carbon atom to form methane. This model does, however, give a visual representation of the actual bonding in methane. This model is an alternative way to visualize how the sp^3 hybrid bonds are formed.

VSEPR Model

3.6 THE VALENCE SHELL ELECTRON PAIR REPULSION (VSEPR) MODEL

As illustrated by methane, a three-dimensional view of molecules is necessary to truly understand them. Although versions of the sophisticated computer programs used to generate the ball-and-stick and the space-filling models shown in Figure 3.6 are available, a practical alternative is the model kit usually suggested for an organic chemistry course. Using such kits will give useful information not only for the shape of molecules but for many concepts. This option is strongly recommended. In lieu of computer software or a model kit, a method is used for drawing structures that assumes a tetrahedral shape around a central atom to predict the three-dimensional shape of molecules.

The discussion in Section 3.5.1 showed that carbon has a valence of four and forms covalent bonds to four atoms or groups of atoms. Nitrogen is in group 15 has a valence of three

and forms molecules with three covalent bonds. Oxygen is in group 16, has a valence of two and forms molecules with two covalent bonds. Based on this knowledge of real molecules, the *Valence Shell Electron Pair Repulsion or VSEPR model* predicts the shape of molecules. The shape of a given molecule is determined by assuming a tetrahedral array of the atoms attached to a central C, N, or O, including unshared electron pairs. Since electrons exert an influence on the shape of a molecule, they must be included in the tetrahedral array. In all cases, the molecules formed will be neutral: they have no charges. The VSEPR model is most useful for molecules made from second row elements, but it is sometimes used for some molecules that have atoms in other rows of the periodic table.

The molecules chosen to illustrate the VSEPR model are methane, ammonia, and water, as shown in Figure 3.10. These three molecules are drawn first in the Lewis electron dot representations and then again using the wedge-dashed line notation based on the VSEPR model using a tetrahedral array of the attached atoms. The tetrahedral structure of methane is repeated from Section 3.5.1. Ammonia (H_3N) has a tetrahedral array around nitrogen if the electron pair is taken into account. Since the electron pair cannot be seen, the focus is only on the atoms and ammonia has the *pyramidal* shape shown. Water (HOH) has two electron pairs that occupy the corners of a tetrahedral shape, as shown, but if the focus is only the atoms, water is a *bent (angular)* molecule. Ball-and-stick molecular models of each molecule are shown, which confirm the shape predicted by the VSEPR model. This model does a *poor* job of accurately predicting bond lengths and angles since it *underestimates* the importance of electron pairs. It also does not take the *size* of the atoms or groups attached to the central atom into account.

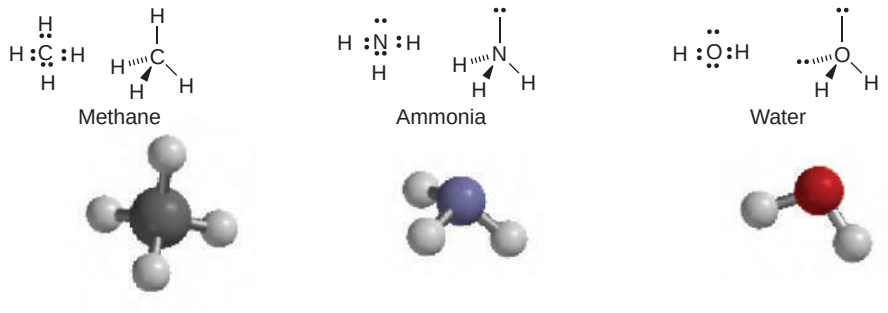


FIGURE 3.10 Three-dimensional shapes of methane, ammonia, and water based on the VSEPR model.

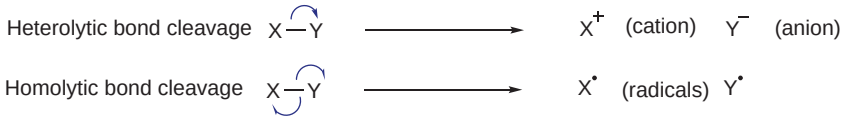
3.10 Estimate the shape of a molecule if it has the structure OF_2.

3.7 BREAKING COVALENT BONDS

Bond Dissociation Energy

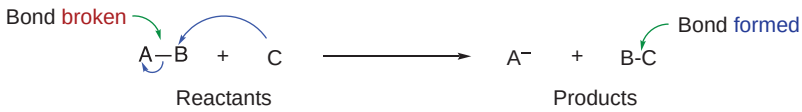
Bond breaking is an endothermic process because it requires energy. Bond forming is an exothermic process, because it releases energy. Endothermic and exothermic processes will be discussed in Sections 7.4 and 7.5. When energy is applied, there are two ways to break a covalent bond X—Y. In one, both electrons in the bond are transferred to one atom leaving none on the other atom. As the X—Y bond breaks, for example, two electrons are transferred to Y generating a cation (X^+) and an anion (X^-). Breaking a bond in this manner is called *heterolytic bond cleavage*. Note the use of the *curved double-headed arrow* to indicate transfer of two electrons as the bond breaks. Another bond cleavage reaction is also shown where the covalent bond is broken with transfer of one electron to each of the atom, generating two *radicals*. This process is known as *homolytic bond cleavage.* A radical is a species with one extra electron (Section 7.2.3). *The* homolytic cleavage of X—Y leads to two radical products, X• and Y•. Note the use of the *curved single-headed arrows* to indicate transfer of one electron to each atom as the bond breaks.

The strength of a covalent bond is directly related to the electron density between the atoms. Energy is absorbed to break a bond. When a bond is broken or formed, the energy stored in the bond is the *bond dissociation enthalpy* or sometimes just *enthalpy* ($D°$, or $H°$) (Section 7.5). It is also called *bond dissociation energy*.



The X—Y bond in the two reactions shown is a covalent bond. Ionic bonds will be ignored for discussions of the bond dissociation energy of bonds. For organic compounds that have C—C bonds, the bond dissociation energy of the C—C bond is reported to be 145 kcal (606.7 kJ) mol^{-1}.[7] Bond dissociation energy is measured by effectively ripping the atoms apart, but this process does not occur in chemical reactions where bonds are made and broken by electron transfer from one atom to another. Indeed, the C—C bonds in organic molecules are formed as another bond is broken in chemical processes in which electrons are transferred from one atom to another. These chemical reactions usually require a much lower energy that the bond dissociation energy for a given bond. Bond dissociation is a useful parameter, however, and it is used to estimate if a reaction is spontaneous or not (Sections 7.4 and 7.5).

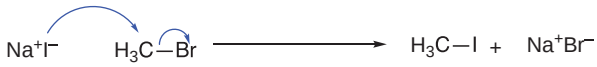
3.11 Is LiCl likely to completely dissociate at a temperature of 600°C? Explain.



As just described, the formation of organic molecules requires bond-making and bond-breaking processes called *chemical reactions*. The molecules in which the bonds are broken are called *reactants*, whereas the molecules in which bonds are made are called *products*. In the generalized example shown, a certain amount of energy is absorbed to break the A—B bond (called $H°_{reactants}$) and a certain amount of energy is required to form the B—C bond (called $H°_{products}$). Therefore, there is a *change* in bond dissociation energy, represented by $\Delta H°$ where the symbol Δ represents *change in*. This value is determined by subtracting the bond dissociation energy for the products ($H°_{BC}$) from the bond dissociation energy for the reactants ($H°_{AB}$). The $H°$ values that are listed in Table 3.1 for various molecules and bonds are reported in kcal and also in kJ mol^{-1} at 298 °C.[8] For this generalized reaction, $\Delta H° = H°_{bonds\ broken} - H°_{bond\ made}$.

For the reaction of A—B + C ⟶ A + B—C, $\Delta H° = H°_{AB} - H°_{BC}$

An example is a reaction between I^- and H_3C—Br to give Br^- and H_3C—I.



In this reaction, the iodide ion of the ionic NaI donates two electrons to the carbon that bears the Br, making a C—I bond in the product ($H°$ = 50 kcal or 209.2 kJ mol^{-1}) in a process that breaks the H_3C—Br bond ($H°$ = 67 kcal or 280.3 kJ mol^{-1}), which is the reactant. The $\Delta H°$ calculation is:

$$\Delta H = H_{C-Br} - H_{C-I} = 67 - 50 = 17\text{kcal}\left(71.1\text{kJ}\right)\text{mol}^{-1}$$

[7] *CRC Handbook of Chemistry and Physics*, 94th ed., CRC Press, Inc., Boca Raton, FL, 2013–2014, $D°_{298}$, pp. 9–66.
[8] *CRC Handbook of Chemistry and Physics*, 94th ed., CRC Press, Inc., Boca Raton, FL, 2013–2014, pp. 9–65 to 9–69.

The negative sign of $\Delta H°$ indicates that this reaction will *absorb* 17 kcal mol^{-1} of energy and is *endothermic* (Sections 7.4 and 7.5). Based solely on bond dissociation energies, this result means that this reaction is expected require more energy than it consumes so it must be continually heated. As noted, the ionic bonds have been ignored in this calculation. There are many different types of organic molecules, with different types of bonds including different C—C bonds. The C—C bond in each type of compound will have a slightly different environment so each will have a different value of H°. In addition to C—C bonds, C—H, C—halogen, C—O, C—N, and C—S bonds are listed in Table 3.1, along with others that are common in organic chemistry.

TABLE 3.1 Bond Dissociation Energies of Common Bonds

Bond	$H°_{298}$, kcal (kJ) mol^{-1}	Bond	$H°_{298}$, kcal (kJ) mol^{-1}
I—I	36.5 (152.7)	Br—H	87.4 (365.7)
F—F	37.5 (156.9)	C—Cl	95 (397.5)
Br—Br	46.3 (193.7)	Cl—H	103.2 (431.8)
C—I	50 (209.2)	H—O	104.2 (436)
Cl—Cl	58 (242.7)	O—O	119.1 (498.3)
C—Br	67 (280.3)	C—C	145 (606.7)
H—I	71.4 (298.7)	C—S	167 (698.7)
N—H	75 (313.8)	C—N	184 (769.9)
C—H	80.6 (337.2)	N—N	225.9 (945.2)
S—H	82.3 (344.3)	C—O	257.3 (1076.5)

3.12 Using data in Table 3.1, calculate $\Delta H°$ for a process with I- and H_3C—Br that breaks a C—Br bond and makes a C—I bond in H_3C—I, generating Br-. Ignore the bromide ion and the iodide ion.

3.8 CARBON BONDED TO HETEROATOMS

This section will describe several bond types that contain single covalent bonds of carbon to atoms other than C or H. Such atoms, including the halogens, O, N, B, P, S, etc., are called *heteroatoms*. The presence of a heteroatom will greatly influence the properties and reactivity of a molecule.

3.8.1 A COVALENT BOND BETWEEN CARBON AND A HETEROATOM: BOND POLARIZATION

Electronegativity was introduced in Section 2.4.1 and defined as the property of an atom to attract electrons. When two identical atoms such as two carbon atoms are connected by a covalent bond, the carbon atoms have equal electronegativities. The electron density is equally and symmetrically distributed between both nuclei. This type of covalent bond is represented in Figure 3.11a, where the black dots represent the atoms connected by a symmetrical covalent bond. A covalent bond for two atoms of different electronegativity is different.

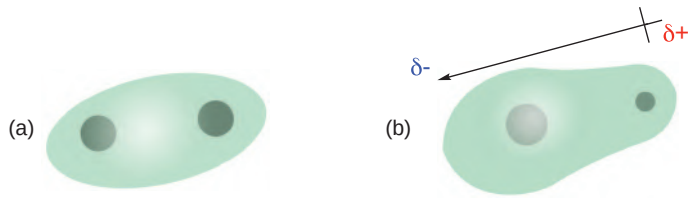


FIGURE 3.11 A nonpolar covalent bond (a) and polar covalent bond (b).

Electronegativity differences of the atoms will distort the electrons in that bond *toward* the more electronegative atom. Therefore, electron density is *not* equally distributed between the nuclei. Such a bond is said to be *polarized*; *a polarized covalent bond*. Structure (b) in Figure 3.11b illustrates a polar covalent bond formed between two atoms that have different electronegativity values. The polarization can be represented as (+)-------(-), by a specialized arrow (+---->), where the + part of the arrow is on the more positive atom and the arrow (⟶) points to the more negative atom. A more simple representation uses δ^- and δ^+. The more electronegative atom is electron rich and marked by δ^- and the less electronegative atom is electron deficient and marked by δ^+. These symbols indicate that the atoms are *partially negative* (δ^-) or *partially positive* (δ^+). It is important to emphasize that these are covalent species and not ionic species and the (δ^+) and (δ^-) do not indicate charges, but rather bond polarization. A "cross-section" of a polarized covalent bond will show that there is less electron density between the nuclei, which is usually indicative of a more reactive bond.

Dipole Moments

3.8.2 BOND POLARITY, BOND MOMENTS, AND BOND STRENGTH

A polarized covalent bond has interesting characteristics that affect both the physical and chemical properties of a molecule. A polarized covalent bond has the property of *bond polarity* due to the distortion of electron density, and this distortion is measured by the parameter called *dipole moment* for that bond.

Dipole moment has a magnitude and a direction. The *magnitude* of bond polarization is measurable and is called the *bond moment*. The bond moment (μ) is measured by the

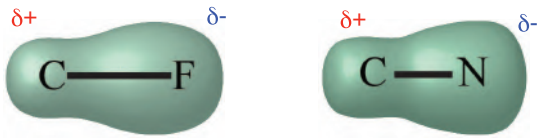


FIGURE 3.12 Polarized C—F versus polarized C—N bond.

charge times the bond distance: $\mu = \delta d$, measured in Debye (D), where 1 Debye = 3.33564 x 10^{-30} coulomb-meters. Examples of polarized bonds include C—F and C—N, as illustrated in Figure 3.12. Both F and N are more electronegative than C. Fluorine is more electronegative than nitrogen, so the C—F bond is more polarized than the C—N bond. Therefore, there is a greater amount of electron density on fluorine in C—F relative to the amount of electron density on nitrogen in C—N. The magnitude of the dipole moment for a typical C—F bond is 1.79 D and 0.45 D for a typical C—N bond.[9] The dipole moments, in Debye, for a number of bonds commonly found in organic molecules include C—C (0.0), C—H (0.3), H—N (1.31), H—O (1.51), C—N (0.45), C=N (1.4), C—O (0.74), C=O (2.4), C—F (1.79), C—Cl (1.87), C—Br (1.82), and C—I (1.65).[9]

The dipole for individual bonds is measured as the dipole moment, but a dipole moment for the entire molecule can be determined. The dipole moment for the molecule is measured by taking the vector sum of each individual bond. A *vector* is an object that has both a magnitude and a direction, so it is a directed line segment, whose length is the magnitude of the vector, and an arrow indicates the direction. A *vector sum* is the result of adding two or more vectors together via vector addition.

In a molecule such as fluoroform (trifluoromethane, HCF_3), the dipole moment is the vector sum of all the individual bond moments. Each bond moment has magnitude and direction. The three dimensional representation of fluoroform is shown in Figure 3.13. The bond moments of the polarized bonds are shown as arrows, and the bond moment is added using the direction of each C—F bond. Vector addition adds all the bond moments to give the magnitude of the molecule's dipole moment and the last arrow gives the direction, shown as a yellow arrow. Only the polarized C—F bonds are used since the C—H bond is not polarized

[9] Dean, J.A. *Handbook of Organic Chemistry,* McGraw-Hill, NY, 1987, Tables 3–6 and 3–7, pp. 3–8 to 3–29.

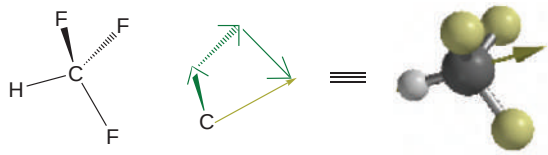


FIGURE 3.13 Vector addition of bond moments to determine the dipole moment for fluoroform.

and therefore does not contribute a bond moment. The molecular model is also shown with the direction of the dipole moment for the molecule, shown as a yellow arrow.

The dipole moments for simple but representative molecules are shown in Figure 3.14. For HF there is only one polarized bond and the direction of the dipole for the molecule is the same as the direction for that polarized bond. For trifluoromethane (F_3CH), the dipole moment for the molecule is the vector sum of the three C—F bond moments, as indicated in Figures 3.13 and 3.14. Similarly in ammonia there are three polarized N—H bonds, and each has a dipole moment directed toward the N. For the molecule, the dipole is the sum of all three N—H bond moments and since ammonia has a pyramidal shape using the VSEPR model, the direction of the dipole for each N—H bond is toward nitrogen. The dipole for ammonia does not lie along an individual bond, but rather bisects the base of the pyramidal shaped molecule. A final example in Figure 3.14 is the molecule $H_3C—NH_2$ (methanamine; Section 5.8.2), which has both polarized C—N and H—N bonds. Note that the dipole moment does not lie along one bond, but is tilted toward the NH_2 unit suggesting that the C—N bond is more polarized than the N—H bonds.

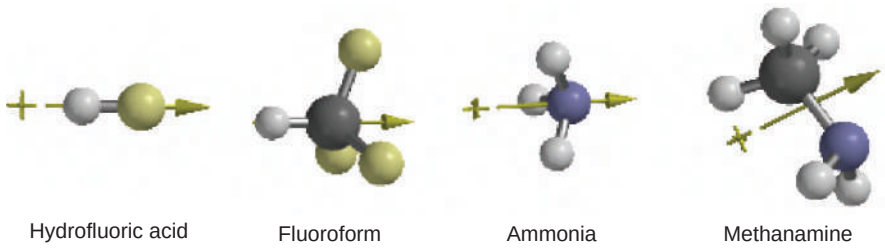


FIGURE 3.14 Dipole moments for hydrofluoric acid, fluoroform, ammonia, and methanamine.

CORRELATION OF HOMEWORK WITH CONCEPTS

- s-Orbitals are spherically symmetrical, p-orbitals are "dumbbell" shaped, and hybrid orbitals are directional: 1, 29.
- Electronic configuration of an atom describes the configuration associated with electrons in atomic orbitals: 2, 3, 5, 8, 9, 14, 15, 28.
- Electrons in the bond of a molecule are located between two nuclei and are at different energy levels than in an unbonded atom: 6.
- Ionic bonds are formed by electrostatic attraction of two atoms that have opposite charges: 4, 17, 18.
- Covalent bonds are made of two electrons that are mutually shared between two atoms: 6, 17, 21.
- Mixing atomic orbitals forms hybrid molecular orbitals (LCAO method); s- and p-orbitals can be mixed to form the hybrid, which determines the hybridization (e.g., sp^3): 14, 15, 25, 27, 45, 46.
- Hybridization models are used to predict the bonding in organic molecules: 10.
- Organic molecules generally have a backbone of carbon-carbon covalent bonds: 8, 29.
- The VSEPR model is used to predict the three-dimensional shape for molecules: 11, 16, 19, 24.

- Polarized bonds are formed when two atoms are bonded together, but one is more electronegative: 22, 23, 24, 27.
- Polarized bonds have a dipole moment and polarized molecules have a dipole moment that is the vector sum of all the individual bond moments: 24, 25, 26
- Reactions are driven by making and breaking bonds, which releases or requires energy: 12, 13, 20, 24.

ANSWERS TO IN-CHAPTER QUESTIONS

3.1 The p-orbital shown in Figure 3.1 has the generic shape of a "dumbbell."

3.2 In the fully filled second row there are 8 electrons (2 for the 2s and 6 for the 2p) + the 2 electrons from the filled first row. Therefore, there are a total of 10 electrons. This atom is neon.

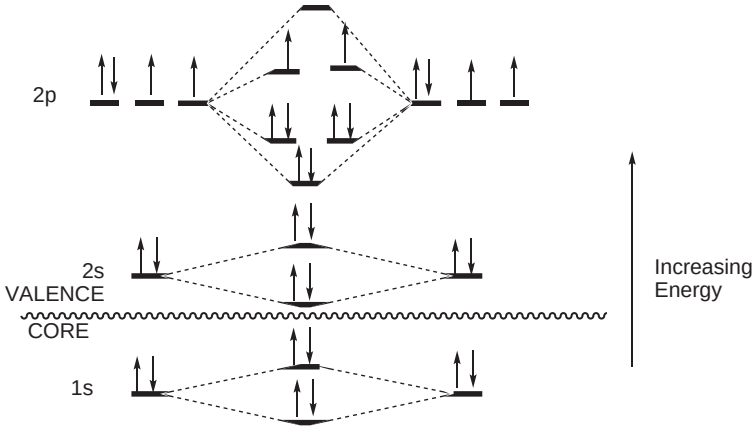
3.3 The electronic configuration of nitrogen is $1s^2 2s^2 2p^3$. The electronic configuration of boron is $1s^2 2s^2 2p^1$. The electronic configuration of phosphorous is $1s^2 2s^2 2p^6 3s^2 3p^3$. The electronic configuration of sulfur is $1s^2 2s^2 2p^6 3s^2 3p^4$.

3.4 Sodium chloride (NaCl) is held together by an ionic bond. Since Na is in group 1 of the periodic table and Cl is in group 17, forming an ionic bond is lower in energy.

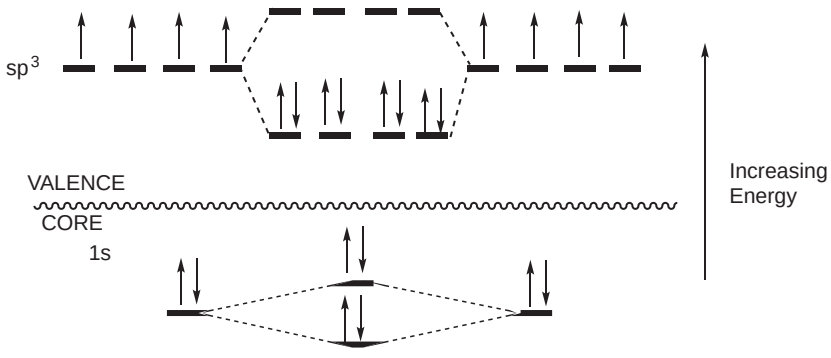
3.5 The electronic configuration of Na^+ is $1s^2 2s^2 2p^6$.

3.6 Rubidium loses one electron since it is in the first row of the periodic table, like Na or Li.

3.7 Using the LCAO model, a carbon–carbon bond is represented by the following diagram: Note that one of the p-molecular orbitals is different from the other two, leading to a prediction of different bonds for the carbon atoms, which is incorrect.



3.8 Using the modified LCAO with four sp^3 hybrid orbitals for each carbon, a carbon-carbon bond is represented by the following diagram.



3.9 Chlorine is monovalent (like a hydrogen atom) so carbon should form four covalent bonds to four chlorine atoms and remain electrically neutral. It is sp^3 hybridized analogous to methane.

3.10 Since F has a valence of 1, like H, it is reasonable to assume that the molecule OF_2 will assume a bent shape analogous to that of water (HOH).

3.11 Lithium chloride is an ionic compound, and the melting point is measured to be 605 °C. The boiling point is measured to be 1325–1360 °C. The dissociation temperature will be much higher and certainly, heating to 600 °C is not quite even up to the melting point much less the required dissociation temperature.

3.12 Ignore the ionic bonds.

$\Delta H°$ for $I^- + H_3C—Br \longrightarrow H_3C—I + Br^-$

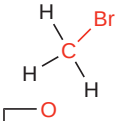
$\Delta H° = H°$ (bonds broken) - $H°$ (bonds made)

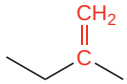
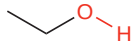
$\Delta H° = H°$ (C—Br) - $H°$ (C—I)

$\Delta H° = 95$ kcal mol^{-1} - 67 kcal mol^{-1} = 28 kcal mol^{-1}, which is an endothermic process

HOMEWORK

13. Give the electronic configuration for the following atoms: Al, He, Be, Mg, Cl, Br, Ti, Cu
14. Based on electron availability in the valence orbital, suggest a simple reason why potassium metal tends to be more reactive than sodium metal.
15. Briefly explain why methane has a tetrahedral shape and ammonia has a pyramidal shape.
16. Indicate whether the highlighted bond (in red) is expected to be covalent or ionic.

(a) $CH_3O^- Na^+$ (b)  (c) $H_3CC{\equiv}C\text{-}H$ (d) $H_3CC{\equiv}C^-Na^+$ (e) NaF

(f) $H_3C\text{-}CH_3$ (g)  (h)  (i) 

17. The first ionization potential of Li is 5.392 eV (124.3 kcal mol^{-1}), Na is 5.139 eV (118.5 kcal mol^{-1}), and K is 4.341 eV (100.1 kcal mol^{-1}), all in the gas phase. What do these numbers indicate about the relative reactivity of each element?
18. Use the VSEPR model to predict the shape for each of the following. Draw each one using line notation.

(a) CCl_4 (b) CH_3OH (c) CH_3OCH_3 (d) $(CH_3)_4N^+$ (e) $CH(CH_3)_3$ (f) $ClCH_2Cl$

19. Calculate $\Delta H°$ for each of the following hypothetical reactions. Determine if they are exothermic or endothermic. Use data from Table 3.1.
    (a) H—Br + C—O → C—Br + H—O (b) C—C + I_2 → 2 C—I
    (c) O—H + C—C → C—O + C—H (d) C—N + H—I → C—I + N-H
20. Draw structures for propane ($CH_3CH_2CH_3$) and butane ($CH_3CH_2CH_2CH_3$).
21. Indicate the more electronegative atom in each of the following.
    (a) C—N (b) N—O (c) C—H (d) Cl—Br (e) B—C
    (f) Li—C (g) C—F (h) N—H (i) H—Cl
22. Indicate if each bond is polarized covalent or non-polarized covalent.
    (a) C—N (b) N—O (c) C—H (d) C—F (e) C—C
    (f) Li—C
23. Draw the structure of each molecule using the VSEPR model and then indicate the general direction of the dipole moment. Indicate if the dipole moment is zero.
    (a) CH_3Cl (b) CH_3OH (c) CCl_4 (d) $C(CH_3)_4$ (e) $ClCH_2Br$
    (f) Cl_3CH
24. Estimate the direction of the dipole moment for the molecule CH_2Cl_2.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-4.php

4

Alkanes, Isomers, and an Introduction to Nomenclature

Carbon is only one atom in the periodic table, so why is it so special? Carbon forms covalent single, double, and triple bonds to a variety of atoms. Carbon can bond with itself, which leads to an almost limitless number of organic molecules. No other atom does this to the same degree. This chapter will discuss the structural features and nomenclature of a class of organic molecules with only carbon and hydrogen (*hydrocarbons*).

To begin this chapter, you should know the following points:

- The fundamental nature of atoms (Section 3.1).
- Covalent bonding between carbon and carbon or carbon and hydrogen (Sections 3.3, 3.6, and 3.8).
- sp^3 Hybridization (Section 3.5).
- Carbon forms four covalent bonds in neutral molecules (Section 3.5).
- The VSEPR model for carbon (Section 3.6).
- How to draw simple structures and the connectivity of atoms (Section 3.6).

4.1 ALKANES

Alkanes

If a molecule contains *only* carbon and hydrogen it is known as a *hydrocarbon*. Hydrocarbons may contain any number of carbon-carbon bonds in linear chains, chains with branches, or rings of carbon atoms. A hydrocarbon with only sp^3 carbons and bonds between sp^3 carbon and hydrogen is known as an *alkane*. Each sp^3 hybridized carbon in a hydrocarbon has a valence of four. In an alkane, there are a total of four covalent bonds to each C must be attached to another carbon. In an alkane, there is a tetrahedral array of hydrogen atoms around each carbon. This leads to a *general formula for acyclic alkanes* (no rings): C_nH_{2n+2} where n is an integer in the series: 1,2,3,4,... When n = 1, for example, the alkane is called methane, CH_4, and when n = 2, the molecule is called ethane $CH_3—CH_3$, C_2H_6. The quantity of each different atom in the formula is indicated by a subscript, so C_6H_{14} means that there are six carbon atoms and fourteen hydrogen atoms**.** While n may be very large, this book will mostly discuss molecules that have linear carbon chains of 2–20 carbon atoms. The alkane general formula defines the *maximum* number of hydrogen atoms that are possible in any organic molecule. There may be fewer hydrogen atoms, but *never* more.

4.1 Is a molecule with the formula $C_{10}H_{22}$ an acyclic alkane. How about $C_{11}H_{18}$?

4.2 STRUCTURAL VARIATIONS OF ALKANE HYDROCARBONS

4.2.1 STRAIGHT-CHAIN AND BRANCHED ALKANES

Initially, the focus will be on alkanes with *linear chains*, which are acyclic alkanes where all of the carbon atoms are connected in a chain with no branching carbon atoms. The example shown is the alkane with a linear chain of four carbon atoms and it is named butane (Section 4.3).

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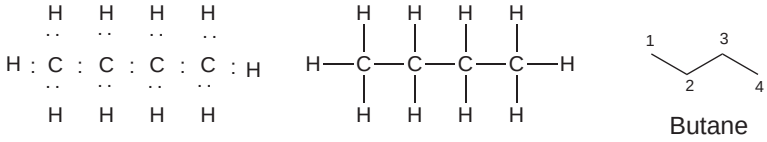
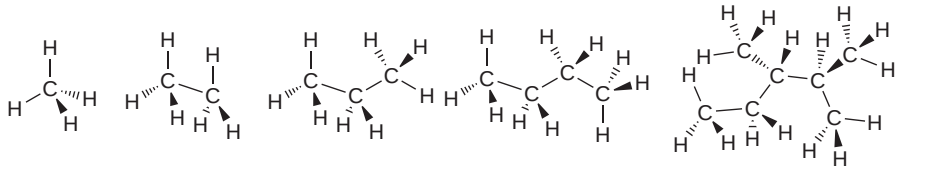
Butane is used as a fuel in "butane lighters." The structure is represented in three different ways. In the Lewis electron dot formula, the two electrons in each covalent bond are shown by ":". Another way to represent the structure uses a line (—) for each covalent bond (two electrons per "line"). A third method is the *line drawing*, introduced in Section 1.1. Each two-electron covalent carbon-carbon σ-bond becomes a "line." When there are more than two carbon atoms, each point where the lines intersect [ ] is a carbon atom. All valences of carbon that are not bonded to another carbon are assumed to be hydrogen atoms. In the line notation drawing of butane, both C1 and C4 are $-CH_3$ units. The "middle" carbon atoms C2 and C3 are $—CH_2—$ units.

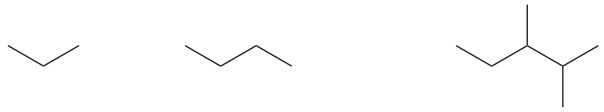


Butane

A fourth way to show a linear chain of carbon atoms in an alkane is as a so-called condensed structural formula $CH_3(CH_2)_nCH_3$ where "*n*" is an integer of the series $n = 0$ to ∞. In a condensed formula the atoms to the right of each carbon atom are assumed to be bonded to that carbon. For example, the carbon of the CH_3 group on the far left has three hydrogen atoms and also an attached carbon. The terminal carbon on the far right is attached to a carbon of the carbon chain and three hydrogen atoms drawn on the right. The $(CH_2)_n$ unit indicates there are *n* CH_2 fragments in the chain that are taken as a unit, where *n* is an integer (1, 2, 3, 4…). Based on the alkane general formula, C_nH_{2n+2}, the one-carbon alkane shown is methane. Nomenclature will not be introduced until Section 4.3. The two-carbon alkane is ethane, the three-carbon alkane is propane, and the four-carbon alkane is butane. The line drawings are also shown for propane and butane.



Methane Ethane Propane Butane 2,3-Dimetxxhylpentane



Propane Butane 2,3-Dimethylpentane

The linear chain of an alkane can have other attached carbon atoms. Such molecules are called "branched alkanes." Carbon branches are known as *alkyl groups.* An example is 2,3-dimethylpentane. It has a five-carbon linear chain with two one-carbon groups attached to a linear chain of five, so there are two branches and a total of seven carbon atoms. This molecule is drawn with all the hydrogen atoms attached to the carbon and also using a line drawing.

4.2 Draw a linear six-carbon alkane and add a one carbon branch at the second carbon from the end, using line notation.

Isomers

4.2.2 ISOMERS

Generating carbon chains of different lengths will lead to many different compounds. Forming alkanes with different numbers of attached carbon branches will generate an even

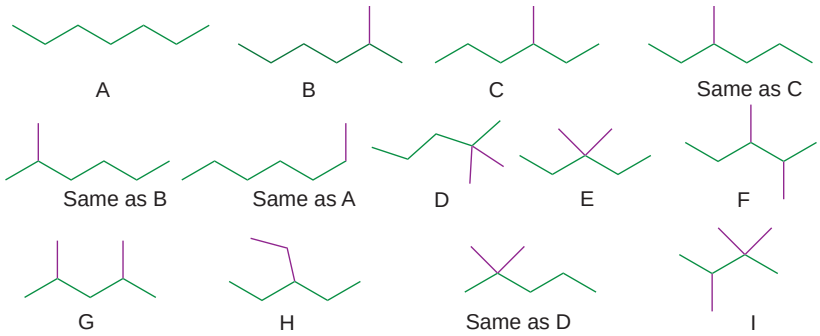


FIGURE 4.1 Structural differences of alkanes with the empirical formula C_7H_{16}.

greater number of molecules. Indeed, many different structures called *isomers* are possible for a given formula. An *isomer* is a molecule with the same empirical formula as another, but with a different structure due to a different connectivity of the atoms. Figure 4.1 shows nine structures labeled **A-I** that have the empirical formula C_7H_{16} but all have a different connectivity. They are isomers of one another, and each is a unique molecule with unique physical properties. It is important to draw the structures of all different isomers with confidence and to recognize them as different molecules. One protocol is to start with the longest possible chain for a given formula and then shorten the chain by removing first one carbon atom and then two, etc. in a stepwise manner. Each time the chain is shortened, the removed carbon atoms are reattached to the shortened chain in as many *different* positions as possible. This protocol can be itemized as follows:

1. Draw the structure with the longest possible linear chain for a given formula.
2. Remove one carbon from the chain and draw the structure with the longest possible linear chain.
3. Attach the removed single carbon to the new chain at as many different positions as possible.
4. Remove two carbons and draw the structure with the longest possible linear chain
5. Attach both removed individual carbons to the new chain in as many different combinations as possible.
6. Attach a two-carbon unit to the new chain in as many different ways as possible.
7. Repeat this protocol one carbon at a time, attaching all remaining carbon atoms in as many different combinations as possible.
8. Check for redundant structures.

For a formula with > 4 carbon atoms, many structures will be generated that are identical to some previous structures. Figure 4.1 shows 13 possible structures for the empirical formula C_7H_{16}. Although 13 structures are shown, there are only *nine different* ways to connect the atoms. Therefore, there are nine different isomers with different constitutions known as *constitutional isomers* (also called *structural isomers*). Since there are only nine different structural isomers, some of the 13 structures in Figure 4.1 are redundant. The first structure is **A**, with a linear chain of seven carbon atoms. If one carbon atom is removed, a chain of six linear carbons is generated plus one extra carbon atom. That one carbon is moved "down the chain" and reattached at as many different positions as possible to generate different structures. Putting the one-carbon unit at the first carbon regenerates **A**. Attaching one carbon to the second carbon and the fifth carbon yields an identical structure (**B**). Similarly, putting a one-carbon unit at the third carbon or the fourth carbon of the six-carbon chain yields identical structures (**C**). Continuing this protocol, removing two carbon atoms from

A yields a linear chain of five carbon atoms. Reattaching those two individual atoms at C2 or C5 on the chain leads to **D**. Structures **E**, **F**, and **G** are generated by attaching the two carbons at different positions. Attaching the two carbons at C2 and C3 or at C3 and C4 gives **F**. Attaching the two carbons as a unit at C3 gives **H**. Attaching the two-carbon unit at C2 or C4 gives **C**. Another isomer with four linear carbon atoms and three carbons to attach is shown as **I**. The redundant structures are discovered by carefully matching the points of attachment (the connectivity) for each structure. Once the nomenclature system in Section 4.3 is known, redundant structures may be discerned from different structures by simply naming each one.

4.3 Using the given protocol, draw all different isomers for the empirical formula C_8H_{18}.

The ability of carbon to form linear and branched chains is a property that leads to hundreds of millions of alkane isomers. The number of possible isomers is directly related to the total number of carbon atoms in the molecule. An alkane with four carbons (C_4H_{10}) will have only three structural isomers. Alkanes with the formula $C_{12}H_{26}$ will have 355 isomers; $C_{15}H_{32}$ alkanes will have 4347 isomers; $C_{25}H_{52}$ alkanes will have about 3.68×10^7 structural isomers, and $C_{40}H_{82}$ alkanes can have 6.25×10^{13} different structural isomers. Estimating the total number of constitutional isomers for a given formula is not trivial, but an algorithm has been developed to assist in this calculation.[1]

4.4 Draw eight different isomers of an alkane with the formula $C_{20}H_{42}$.

IUPAC Nomenclature Rules

4.3 THE IUPAC RULES OF NOMENCLATURE

There are a vast number of alkanes, and each unique structure requires a unique name. The nomenclature system used is based on the number of carbon atoms in the longest continuous chain. Branches are identified by the number of carbon atoms and their position on the longest chain. To accommodate the myriad variations in structure, a set of "rules" have been devised that are universally used to name organic molecules. The organization that supervises these rules is the International Union of Pure and Applied Chemistry, I.U.P.A.C. or just IUPAC.

4.3.1 PREFIXES AND SIMPLE ALKANES

The IUPAC nomenclature rules[2] allow any organic molecule to be named. Once the longest continuous chain is identified, a *prefix indicates the number of carbon atoms,* and a *suffix describes the class of molecules. The* unique *suffix* used for alkanes is *-ane.* The prefix for the number of carbons is based on the first 20 straight-chain alkanes, C_1 to C_{20}, listed in Table 4.1.[2] A one-carbon unit has the prefix meth-; two carbons are eth-; three carbons are prop-; four carbons are but-; five, six seven, eight, nine, and ten are derived from the Latin terms: pent-, hex-; hept-, oct-, non-, dec-. To identify C11-C20 linear alkanes the prefixes use the equivalent of 1+10, 2+10, 3+10, and so on. The prefixes are **undec**- (11), **dodec**- (12), **tridec**- (13), **tetradec**- (14), **pentadec**- (15), **hexadec**- (16), **heptadec**- (17), **octadec**- (18), **nonadec**- (19), and **icos**- (20). The structures and names of the first twenty alkanes are shown in Table 4.1. The structures are drawn as a *condensed formula* $CH_3(CH_2)_nCH_3$.

[1] Paton, R.S.; Goodman, J.M. *Journal of Chemical Information and Modeling 2007, 47,* 2124–2132; de Silva, K.M.N.; Goodman, J.M. *Journal of Chemical Information and Modeling 2005, 45,* 81–87; Goodman, J.M. *Journal of Chemical Information and Computer Sciences 1997, 37,* 876–878.

[2] Fletcher, J.H.; Dermer, O.C.; Fox, R.B. *Nomenclature of Organic Compounds. Principles and Practice,* 1974, American Chemical Society, Washington, D.C., pp. 6–11.

TABLE 4.1 Nomenclature For Alkanes With Linear Chains Of Carbon Atoms

Number of Carbons	Structure	IUPAC Name
1	CH_4	Methane
2	CH_3CH_3	Ethane
3	$CH_3CH_2CH_3$	Propane
4	$CH_3(CH_2)_2CH_3$	Butane
5	$CH_3(CH_2)_3CH_3$	Pentane
6	$CH_3(CH_2)_4CH_3$	Hexane
7	$CH_3(CH_2)_5CH_3$	Heptane
8	$CH_3(CH_2)_6CH_3$	Octane
9	$CH_3(CH_2)_7CH_3$	Nonane
10	$CH_3(CH_2)_8CH_3$	Decane
11	$CH_3(CH_2)_9CH_3$	Undecane
12	$CH_3(CH_2)_{10}CH_3$	Dodecane
13	$CH_3(CH_2)_{11}CH_3$	Tridecane
14	$CH_3(CH_2)_{12}CH_3$	Tetradecane
15	$CH_3(CH_2)_{13}CH_3$	Pentadecane
16	$CH_3(CH_2)_{14}CH_3$	Hexadecane
17	$CH_3(CH_2)_{15}CH_3$	Heptadecane
18	$CH_3(CH_2)_{16}CH_3$	Octadecane
19	$CH_3(CH_2)_{17}CH_3$	Nonadecane
20	$CH_3(CH_2)_{18}CH_3$	Icosane (Eicosane)

When the longest linear (unbranched) chain has an atom or group of atoms attached, that atom or group is called a *substituent*. If the substituent has only sp^3 hybridized carbon atoms, each with attached hydrogen atoms, it is called an *alkyl group*, or an *alkyl substituent*. For a hydrocarbon substituent, the same prefix used in Table 4.1 indicates the number of carbon atoms, meth→icos but *the suffix for the alkyl substituent is -yl*. A one-carbon substituent is methyl, a two–carbon substituent is ethyl, a three–carbon substituent is propyl, and a four-carbon substituent is butyl, etc.

4.5 What is the name of the 12-carbon linear alkane?

An alkyl substituent can be attached to any of the different carbon atoms of the longest linear chain except the terminal carbons because that would simply give a longer continuous chain. If a methyl alkyl group is attached to C2-C5 of a six-carbon chain the name of that compound is methylhexane, but one must ask which methylhexane. A number based on the lowest *locant* is used to identify the position of the methyl group on the longest chain. A *locant* is the location of a structural feature along the chain and in this case the methyl substituent is the locant. The longest carbon chain is numbered so that the locant is assigned the lowest possible number. Attachment at C2 or C3 of the six-carbon chain will give different isomers, each requiring a unique name. Placing the methyl on C2 or C5 gives the same structure and placing the methyl group of C3 or C4 gives the same structure. 3-Methylhexane is the proper name of that isomer rather than "4-methylhexane." Similarly, 2-methylhexane is the proper name rather than "5-methylhexane."

Figure 4.2 shows five additional examples. In the first structure, the longest chain is seven. Although the structure is drawn such that six carbons are in a line and the seventh carbon "looks" like a substituent, the longest chain is seven, so the name is heptane, *not* 1-methylhexane. There is no locant in the continuous chain. The next example is a methylhexane and the longest continuous six-carbon chain is numbered to give the *methyl* group (the one-carbon alkyl substituent) the lower number. Of the two possible numbering sequences, one numbers from right to left to place the methyl group at C3. The other sequence numbers from left to right to place the methyl group at C4. Since the methyl group at C3 is the nearest locant, 3-methylhexane is the proper. In 3-methyldecane, there is a 10-carbon chain (decane) with a one-carbon substituent (methyl). The lowest locant gives the methyl group the lower number of 3. In

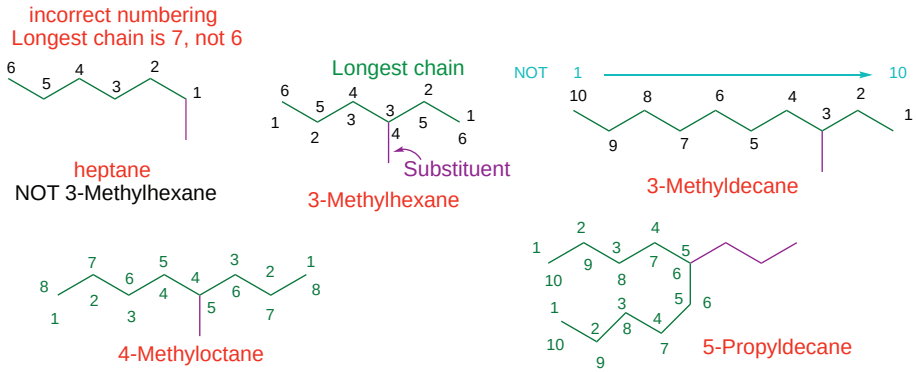


FIGURE 4.2 Assigning position numbers to alkyl substituents.

4-methyloctane, there is an 8-carbon chain (octane) with a one-carbon substituent (methyl). The lowest locant gives the methyl group the lower number of 4. 5-Propyldecane is drawn in such a way that the eye is drawn to an 8-carbon linear chain, but the *longest* linear chain is 10, so it is a decane. The 3-carbon substituent at C5 (the lowest locant) is a propyl group.

4.6 Briefly explain why 3-methylhexane is not named 2-ethylpentane.
4.7 Draw the structure of 4-ethyleicosane.

As shown in the first example in Figure 4.2, putting the alkyl group at C1 of the chain simply extends the chain and does not lead to a new isomer. It is important to reiterate this point. Do not be fooled! The angle at which a substituent is attached is not important in these line drawings. Look at the points of attachment to determine the structure of the molecule. If the atoms are the same and the points of attachment are the same, the structures must be identical.

A summary of the first four IUPAC rules is shown for naming any alkane.

1. Determine the longest, continuous chain of carbon atoms and assign the proper prefix from Table 4.1 to indicate the number of carbon atoms.
2. Determine the class of compounds to which the molecule belongs and assign the proper suffix. For hydrocarbons with only sp^3 hybridized carbons, the class name is alkane and the suffix is -ane.
3. Alkanes that have carbon groups attached to the longest unbranched chain (called substituents) are known as branched chain alkanes. When that branch is an alkane fragment, it is known as an alkyl group or an alkyl substituent where the prefix indicates the number of carbons and the suffix is -yl.

Common Names

4.3.2 COMMON NAMES

Before the IUPAC system of nomenclature was devised, alkyl substituents were given common names. Common names are used today in some situations. The IUPAC names for methyl→butyl substituents are listed in Table 4.2 along with the common names. Note that the IUPAC rules indicate that common names should only be used for the parent alkane, and not for substituents. The three-carbon fragment 1-methylethyl group is called isopropyl; the term *iso-* refers to a carbon at the end of the branch chain that has one hydrogen, and two methyl groups. The four-carbon 2-methylpropyl is called isobutyl and the 3-methylbutyl fragment is called isopentyl (sometimes isoamyl). When a methyl group is attached to the C1 carbon of the branch chain, and there are four or more carbons in the substituent, the common term used is *secondary-* or *sec-*. The 1-methylpropyl fragment is therefore *sec-butyl* and the 1-methylbutyl fragment is *sec-pentyl* or *sec*-amyl. The four-carbon substituent named 1,1-dimethylethyl is known as a *tertiary*-butyl group (or *tert-butyl*). The term *tertiary (tert-)*

TABLE 4.2 Common Alkyl Substituents[a]

Substituent	IUPAC Name	Common Name (Abbreviation)
CH_3–	Methyl	Methyl (Me)
CH_3CH_2–	Ethyl	Ethyl (Et)
$CH_3CH_2CH_2$–	1-Propyl	n-Propyl (n-Pr)
$CH_3CH_2CH_2CH_2$–	1-Butyl	n-Butyl (n-Bu)
$(CH_3)_2CH$–	2-Methylethyl	Isopropyl (iPr)
$(CH_3)_2CHCH_2$–	2-Methylpropyl	Isobutyl
$CH_3CH_2-CH(CH_3)$–	1-Methylpropyl	secondary-Butyl; sec-butyl (s-Bu)
$CH_3CH_2CH_2-CH(CH_3)$–	1-Methylbutyl	sec-Pentyl
$(CH_3)_3C$–	1,1-Dimethylethyl	tertiary-Butyl; tert-butyl (t-Bu)
$(CH_3)_3CCH_2$–	2,2-Dimethylpropyl	Isoamyl (isopentyl)

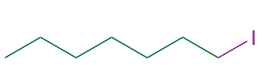
[a] In each structure, the highlighted carbon (C) is the point of attachment to the longest continuous chain

refers to the fact that the carbon attached to the main chain is tertiary (i.e., it bears three carbon entities). The 1,1-dimethylpropyl substituent is called *tertiary-amyl* where amyl is an old term for pentyl. There is a special fragment, the 2,2-dimethylpropyl fragment, which is known as *neopentyl*. These terms become unwieldy if there are more than five carbons, so they are used only for relatively small fragments. It is important to note that common names are not mixed with IUPAC names.

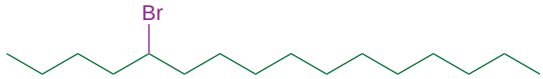
4.8 Draw isobutane and tert-butylhexane using line notation.
4.9 Give the IUPAC prefix for the longest chain in the isopropyl group, the sec-butyl group, and the tert-butyl group.

4.3.3 HALOGENS ARE SUBSTITUENTS

The presence of halogens in organic molecules is common. Halogens are *substituents* so there is no suffix to indicate the presence of a halogen. Since halogens have a valence of 1 they will replace a hydrogen atom one-for-one. When a fluorine, chlorine, bromine, or iodine is attached to a carbon chain, each is assigned the lowest number on the carbon chain, as with any substituent. The identifying name for a halogen substituent drops the -ine ending of each halogen and replaces it with o- (i.e., fluoro, chloro, bromo, iodo). The nearest locant for the halogen substituents in the examples are C1 in 1-iodoheptane and C5 in 5-bromohexadecane.



1-Iodoheptane



5-Bromohexadecane

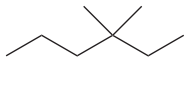
4.3.4 MULTIPLE SUBSTITUENTS

Multiple Substituents

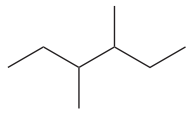
If there are two or more substituents, the lowest sequence of numbers is assigned based on the locant closest to the end of a chain. The substituents can be identical, or they can be different. If the substituents are identical, another prefix is required for the substituent: *di-* for two, *tri-* for three, *tetra-* for four, *penta-* for five, and *hexa-* for six identical substituents. Therefore, two methyl groups are dimethyl, three ethyl groups are triethyl, and five methyl groups will be pentamethyl. First, determine the name and number of the substituents and

then insert the multiplying prefix if needed. Both structures shown have identical methyl substituents, so they are dimethylhexanes. The left structure has two methyl groups on the same carbon (C3), whereas in the right structure the two methyl groups are on different carbons (C3 and C4). The name of the first alkane is *not* 3-dimethylhexane since *all substituents must have a number,* even if they appear on the same carbon atom. There are two methyl groups on C3, so the proper name is 3,3-dimethylhexane. The name for 3,4-dimethylhexane is straightforward. Commas separate the numbers, and a hyphen separates the number from the rest of the name.

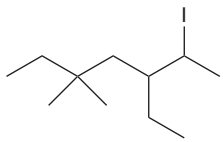
When there are different substituents, they are arranged alphabetically based on the group with their appropriate number based on the closest locant. In the third example there is an ethyl, an iodo, and two methyl substituents. The closest locant is 2. Giving each substituent the lowest number and arranging the substituents alphabetically gives 3-ethyl-2-iodo-5,5-dimethylheptane. The last example has multiple substituents and using the rules just discussed the name is 5-bromo-2-chloro-11-iodo-10-methyl-7-propylhexadecane.



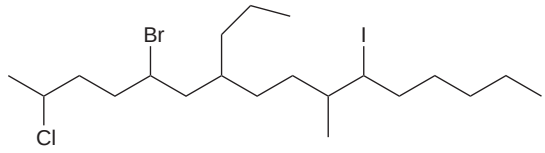
3,3-Dimethylhexane



3,4-Dimethylhexane



3-Ethyl-2-iodo-5,5-dimethylheptane



5-Bromo-2-chloro-11-iodo-10-methyl-7-propylhexadecane

4.10. Give the structure for the following: 3-chloro-5-(2-methylpropyl)-2,4-dimethyl octane, 3,3,8-triethyldecane, and 2,3,4,5,6,7,8-heptabromodecane.

4.11. Draw the structure for 6-ethyl-5-fluoro-12-iodo-2-methyltetradecane using line notation.

4.12. Draw 6,6-dichloro-9-ethyl-2,4,4-trimethyltetradecane.

Complex Substituents

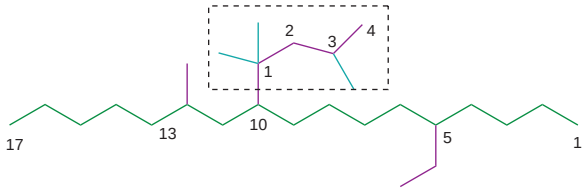
4.3.5 COMPLEX SUBSTITUENTS

There are structures in which the longest unbranched chain has a substituent, but the substituent also has one or more substituents. In other words, the branch has branches. Another rule is required:

If a complex substituent is present on the longest continuous chain, count the number of carbon atoms in the longest continuous part of that "side chain" and use the proper prefix. The name of a complex substituent begins with the first letter of its complete name (take the longest chain of the substituent from the point of attachment to the longest unbranched chain, and ignore di-, tri-, etc.).

Naming molecules with this type of complex substituent is a bit more complicated. An example is 10-(1,1,3-trimethylbutyl)-5-ethyl-12-methylheptadecane, in which the longest unbranched chain is 17, with a methyl substituent and an ethyl substituent. Using the rule that substituents are arranged alphabetically, the molecule is a 5-ethyl-12-methylheptadecane. However, the group at C10, in the box, is a complex substituent and this four-carbon linear chain is a butyl substituent. The butyl substituent has three attached

methyl substituents, however. Note that the butyl substituent is attached to C10 on the heptadecane chain based on the closest locant of the longest chain, which is C5. This assessment leads to 10-butyl-5-ethyl-12-methylheptadecane. The point of attachment of the butyl substituent to the longest chain is the C1 carbon so the three methyl groups on the side chain are attached at C1 and C3. Therefore, the complex side chain is named 1,1,3-trimethylbutyl, and the entire unit is attached to C10 of the heptadecane. The final name is 10-(1,1,3-trimethylbutyl)-5-ethyl-12-methylheptadecane. In order to set the complex substituent apart from the other substituents, parentheses are used. Note that the 1,1,3-trimethylbutyl group is alphabetized by the "*b*" since it is a butyl group, ignoring the tri and the methyl groups.



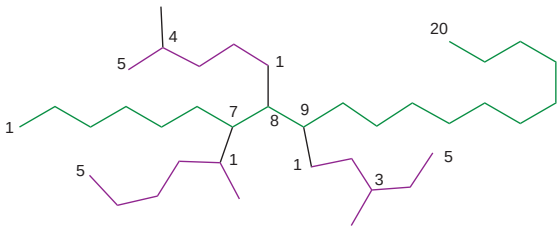
10-(1,1,3-Trimethylbutyl)-5-ethyl-12-methylheptadecane

If chains of equal length are competing for selection as the main chain in a saturated branched acyclic hydrocarbon, the main chain required for naming must be chosen. The main chain can be determined in one of several ways, all of which lead to the same conclusion. Rules 3 and 4 that follow are the most salient.

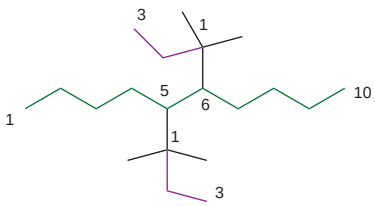
1. The main chain is that with the greatest number of side chains.
2. The main chain is the one whose side chains have the lowest numbered locants.
3. The main chain will have the greatest number of carbon atoms that have smaller side chains (methyl or ethyl rather than a complex substituent).
4. The main chain will have the least branched side chains.

There are cases where the molecule contains two or more complex substituents that have the same number of carbon atoms in the longest chain, but those complex substituents are different. An example is 7-(1-methylpentyl)-9-(3-methylpentyl)-8-(4-methylpentyl)icosane, which has three pentyl groups. This compound is a tripentylicosane, but each of the three pentyl substituents are different. At C7 there is a 1-methylpentyl, there is a 4-methylpentyl at C8 and a 3-methylpentyl group is at C9. In such cases, the rule states that priority for citation is given to that substituent containing the lowest locant at the first cited point of difference. In this case, the 1-methylpentyl, followed by 3-methylpentyl, followed by 4-methylpentyl. The name is 7-(1-methylpentyl)-9-(3-methylpentyl)-8-(4-methylpentyl)icosane.

If there is more than one complex substituent, but they are identical, the number of identical substituents may be indicated by the appropriate multiplying prefix bis-, tris-, tetrakis-, pentakis-, and so on. This protocol is related to the situation where there are two or three methyl groups (dimethyl, trimethyl, etc.). The complete expression denoting such a side chain may be enclosed in parentheses. For 5,6-bis-(1,1-dimethylpropyl)decane, there are two 1,1-dimethylpropyl groups at C5 and C6 so the term bis- is used.

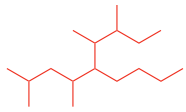
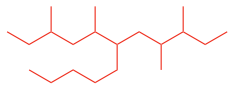


7-(1-Methylpentyl)-9-(3-methylpentyl)-8-(4-methylpentyl)icosane



5,6-bis-(1,1-Dimethylpropyl)decane

4.13 Give the proper IUPAC name:

(a)  (b) 

Cyclic Alkanes

4.4 RINGS MADE OF CARBON: CYCLIC COMPOUNDS

All examples discussed so far have linear chains of carbon atoms with or without substituent branches attached to the linear chain, so they are *acyclic alkanes*. Alkanes that have rings of sp^3 hybridized carbon atoms are *cyclic alkanes*. In a cyclic alkane, two carbon atoms must be joined to form a ring so there are two fewer hydrogen atoms when compared to an acyclic alkane. Because of this, the *general formula for cyclic alkanes* is C_nH_{2n}, where *n* is an integer: 3,4,5.... The smallest possible ring has three carbons (n = 3) so the integer "*n*" in the general formula *must be* ≥ 3. In the absence of substituents, each carbon in a cyclic alkane will have two hydrogen atoms attached, a CH_2 unit known as a *methylene* unit. That carbon will be connected to two other carbons in the ring. Figure 4.3 shows the basic structure and the name of 10 cyclic alkanes that have 3–12 carbon atoms.

How are cyclic alkanes named? The suffix for the name must be *-ane* because they are alkanes. Prefixes for the number of carbons in the acyclic alkanes cannot be used without modification. To distinguish between the acyclic alkenes and the cyclic alkanes, the term *cyclo-* precedes the carbon number prefix. The three-membered ring alkane becomes cyclopropane, and the 12-membered ring alkane becomes cyclododecane, and so on.

4.14 Draw and name the structure of the cyclic alkane that has 15 carbon atoms in the ring.

Cyclic alkanes can have substituents attached, and the position of a substituent attached to a cyclic alkane is assigned the lowest possible number. In methylcyclohexane, this six-membered cyclic alkane is a cyclohexane with one methyl substituent. Since there is only one group attached to the ring the 1- is obvious and it is omitted so the name is just methylcyclohexane. With 1,3-dimethylcyclohexane, however, several isomers are possible so both numbers must be included to specify the position of the methyl groups. The ring is numbered from one methyl group to give the lowest possible combination of numbers. It is 1,3-dimethylcyclohexane. If two different substituents are attached to the ring, the names are listed in alphabetical order and the first cited substituent is assigned to C1. An example is 1-ethyl-3-methylcycloheptane. If there are three or more substituents, the rules are slightly different. List the substituents in alphabetical order, but C1 is chosen so the lowest combination of numbers is obtained. An example is 4-chloro-2-ethyl-1-methylcyclohexane.

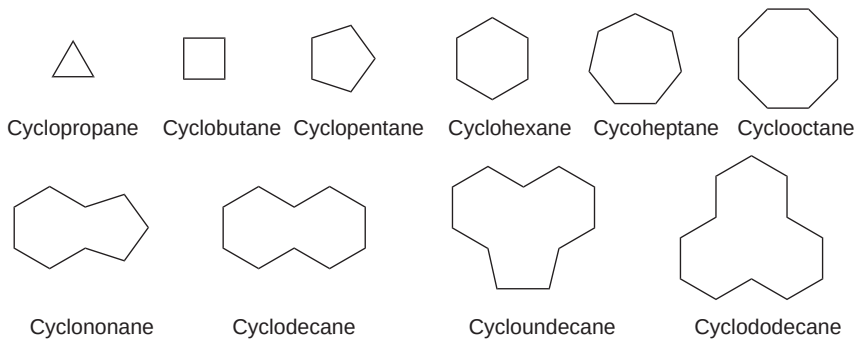
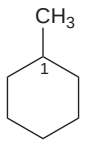
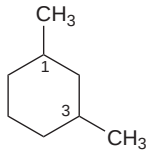


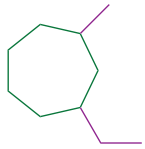
FIGURE 4.3 Cyclic hydrocarbons of 3–12 carbon atoms.



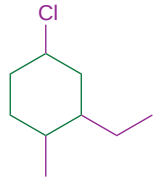
Methyl-
cyclohexane



1,3-Dimethyl-
cyclohexane



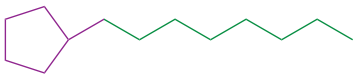
1-Ethyl-3-methyl-
cycloheptane



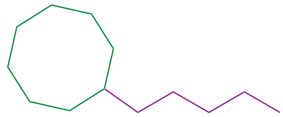
4-Chloro-2-ethyl-
1-methylcyclohexane

4.15 Write a structural isomer of methylcyclooctane that has a nine-membered ring; a six-membered ring; a seven-membered ring, and then name all three compounds.
4.16 Draw the structure of 1-chloro-3-ethyl-4,5,6-trimethylcyclononane.

A subtle naming problem arises when an acyclic carbon chain is attached to a cyclic alkane. Is the molecule named as a cyclic alkane with a substituent or as an acyclic chain with a cyclic substituent? The IUPAC rules state that a hydrocarbon with a small ring attached to a long chain is named as a derivative of the acyclic hydrocarbon. A hydrocarbon with a small alkyl chain attached to a large ring is generally named as a derivative of the cyclic hydrocarbon. A small ring is usually defined as *three to six carbon atoms* and a large ring is usually defined as ≥ *seven carbon atoms*. Therefore, make an assumption. If the number of carbon atoms in the longest acyclic carbon chain is six carbon atoms or less, the compound is named as a cyclic alkane, and the chain is treated as a substituent. If the longest acyclic chain is seven carbons or greater, the molecule is named as an acyclic alkane, with a cyclic substituent. Note that if a ring is named as a substituent, the -ane is dropped and replaced with -yl. Therefore, a cyclopropane unit treated as a substituent is cyclopropyl, a cyclobutane substituent is cyclobutyl, a cyclopentane substituent is cyclopentyl, and so on. Using this rule, the two compounds shown are 1-cyclopentyloctane and pentylcyclooctane.



1-Cyclopentyloctane



Pentylcyclooctane

4.17 Give the IUPAC name for the following compound. 

4.5 THE ACID OR BASE PROPERTIES OF ALKANES

Acid-base theory is used to examine the chemistry of organic molecules throughout this book, so it is reasonable to ask if an alkane is an acid or a base. All electrons in an alkane are "tied up" in covalent bonds, so there are no electrons to donate. In other words, an alkane does not react as a base! If the C—H unit in methane loses a proton as an acid, the conjugate base would be the methide anion, CH_3^-, as shown in Figure 4.4. The K_a for removing the hydrogen atom in an alkane is estimated to be $< 10^{-40}$ so the pK_a is >40. An alkane is therefore a very weak acid and no base has been discussed thus far that is strong enough to remove a proton from an alkane. If methide were to form, it would be a remarkably strong base, very reactive and an unstable entity. Alkanes are not used as acids in this book. However, identifying the pK_a of methane is a useful starting point for a discussion of very weak acids in later chapters.

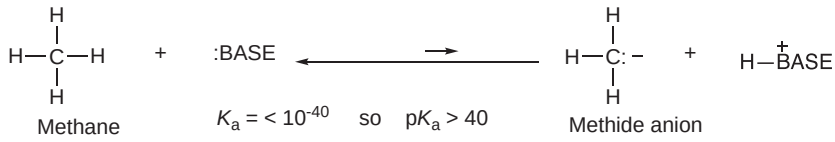


FIGURE 4.4 The acid-base reaction of methane.

Combustion Analysis

4.6 COMBUSTION ANALYSIS AND EMPIRICAL FORMULAS

An alkane is identified by its hydrocarbon formula. How is the formula for an unknown determined? There is an experimental procedure that will verify a hydrocarbon has the formula, C_nH_{2n+2}. An unknown compound is burned in the presence of oxygen (Section 1.2), making use of a discovery by Antoine Lavoisier (France; 1743–1794). Burning (combusting) an organic molecule in oxygen converts the carbon in that molecule to carbon dioxide (CO_2). This gas can be trapped and weighed. Similarly, the hydrogen atoms in the molecule react with oxygen to form water vapor, which can also be trapped and weighed. Experimentally, the unknown organic compound is accurately weighed before combustion, and the trapped water and CO_2 are accurately weighed after combustion. It is then possible to calculate the percentage of carbon and hydrogen in the original molecule that was burned. This data is used to calculate the number of carbon and hydrogen atoms. For a hydrocarbon, knowing the number of carbon and hydrogen atoms by this procedure allows one to calculate the *empirical formula*.

An example of this process takes 0.36 g of an unknown organic compound. When burned, trapping and weighing of the products gives 0.594 g of H_2O and 1.078 g of CO_2. In the CO_2 product, with knowledge that the molecular weight of CO_2 is 44 and the atomic weight of carbon is 12, the ratio of carbon/carbon dioxide $\left(\frac{C}{CO_2}\right)$ is $\frac{12}{44} = 0.2727$. This number means that 27.27% of the weight of CO_2 is due to carbon. If the weight of CO_2 trapped in this experiment is 1.078 g, then the weight of carbon in the CO_2 is 1.078 x 0.2727 = 0.294 g. Similarly, the molecular weight of water is 18, and the atomic weight of hydrogen is 1. Since there are two hydrogen atoms in water, the ratio of hydrogen to water $\left(\frac{H}{H_2O}\right)$ is $\frac{2}{18} = 0.1111$. In other words, 11.11% of the weight of water is due to hydrogen. Since the weight of water trapped in this experiment is 0.594 g, the weight of hydrogen in the water is 0.594 x 0.1111 = 0.066 g. Based on the amount of CO_2 and H_2O trapped, the 0.36 g sample contained 0.294 g of carbon. The original weight of the unknown was 0.36 g, so the percentage of each element in the unknown can be calculated.

The % carbon is $^{0.294}/_{0.36} = 0.817 = 81.7\%$ and the % hydrogen is $^{0.066}/_{0.36} = 0.183 = 18.3\%$.

How can this percentage be translated to a formula? Make the arbitrary assumption that there are 100 g of the unknown just to make it easy. If the sample contained 81.7% of carbon and 18.3% of hydrogen, a 100 g sample has 81.7 g of carbon and 18.3 g of hydrogen. The atomic mass of carbon is 12 and the atomic mass of hydrogen is 1. With the weight of each element and the atomic mass, the number of moles of carbon and hydrogen in the sample can be calculated. The moles of carbon in 100 g of unknown is $^{81.7}/_{12} = 6.81$. The moles of hydrogen in 100 g of unknown is $^{18.3}/_{1} = 18.3$. Dividing the smaller number into both numbers will give the molar ratio of each element. This calculation yields $^{6.81}/_{6.81} = 1$ and $^{18.3}/_{6.81} = 2.69$ or 2.69H/1C. This ratio can also be expressed as 2.69 H:1 C or $C_1H_{2.69}$. Clearly, there are no fractional atoms, so simply multiply this ratio by a whole number to obtain a whole number value for all elements. In this case, a multiplication factor of 2 yields fractional hydrogen atoms, but the multiplication factor of 3 leads to 2.69 H x 3 and 1 C x 3 or $C_3H_{8.07}$. Given experimental error, a reasonable empirical formula is C_3H_8. If the molecule is an alkane, propane is the only possibility. If the formula shows a large number of carbon atoms, then isomers are possible,

and more information must be obtained to identify the specific sample. This overall process of burning a sample to trap the CO_2 and water, determining empirical formula, and thereby molecular formula, is known as *combustion analysis*.

4.18 Calculate the %C and %H for the formula $C_{16}H_{30}$.
4.19 Determine the grams of CO_2 and H_2O from combustion of 0.348 g of a sample that has 94.34% C and 5.66% H.

4.7 COMMERCIAL AND BIOLOGICAL RELEVANCE

Alkanes are generally unreactive. However, they are burned every day in the form of gasoline, which is mainly a complex mixture of hydrocarbons. Long straight-chain and branched-chain alkanes are major components of crude oil, accounting for their presence in gasoline and fuel oil. The process of "cracking" petroleum heats the crude oil to break down long complex hydrocarbons into a mixture of hydrocarbons that have simpler structures, with lower boiling points and vapor pressures. Subsequent fractional distillation separates the mixture into its component parts, or fractions. On an industrial scale, various fractions are obtained based on boiling point ranges, including gasoline (20–200 °C), kerosene (175–275 °C) and heating oil, otherwise known as diesel fuel (250–400 °C). Distillation of the residue obtained after distillation of these fractions, under reduced pressure, gives lubricating oils and waxes. The tarry residue is asphalt.

The low-melting solid (about 37 °C) known as Vaseline is a mixture of alkanes, generally greater than C_{25}. Mineral oil is a liquid derived from petroleum that is primarily a mixture of alkanes with a boiling point range of 260–330 °C. This mixture includes alkanes ranging from tetradecane (bp, 253–357 °C) to nonadecane (bp 330 °C). Both Vaseline and mineral oil probably contain branched chain alkanes as well as linear alkanes.

Due to their remarkably poor chemical reactivity, it may be surprising that alkanes have a place in biological systems. It is known that the waxy coating on cabbage leaves contains nonacosane ($C_{29}H_{60}$) and the wood oil of the Jeffrey Pine (Sierra Nevada) contains heptane. The needle wax of the Pinaceae *Picea omorika* contains 11–19% C_{27}, C_{29}, and C_{31} straight chain alkanes.[3] It has been reported that alkanes are formed by peroxidation (see Chapter 16 for oxidation reactions) of unsaturated fats (Section 18.14). Peroxidation leads to fatty acid hydroperoxides (alkyl-O-OH) that decompose.[4] In one study, the levels of ethane and pentane in human breath are measured as markers of lipid peroxidation in patients who smoked, suffered from human immunodeficiency virus (HIV) infection, or suffered from inflammatory bowel disease.[5]

Methane has an interesting relationship with biology. It is a greenhouse gas known to be 10 times more effective than CO_2 in contributing to global warming. Methane is produced by decaying vegetation and is referred to as swamp gas in some regions. Methane is a byproduct of the digestion of mammals, such as cows. Methane is also known to be trapped in marine sediments (e.g., methane hydrate), which is a crystalline solid consisting of methane molecules surrounded by a cage of water molecules. Methane hydrate is stable in ocean floor sediments at depths of > 1000 feet, where the methane hydrate is kept very cold and under high pressure.

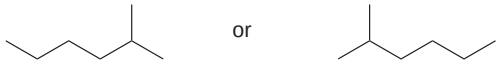
[3] Nikolic, B.; Tesevic, V.; Djordjevic, I.; Jadranin, M.; Bojovic, S.; Marin, P.D. *Chemisty of Natural Compounds*, 2009, 45, 697–699.
[4] (a) Mounts, T. L.; McWeeny, D. J.; Evans, C. D.; Dutton, H. J. *Chemistry and Physics of Lipids*, 1970, 4, 197–202; (b) Dumelin, E. E.; Tappel, A. L. *Lipids*, 1977, 12, 894–900.
[5] Aghdassia, E.; Johane P. Allard, J.P. *Free Radical Biology and Medicine*, 2000, 28, 880–886.

CORRELATION OF HOMEWORK WITH CONCEPTS

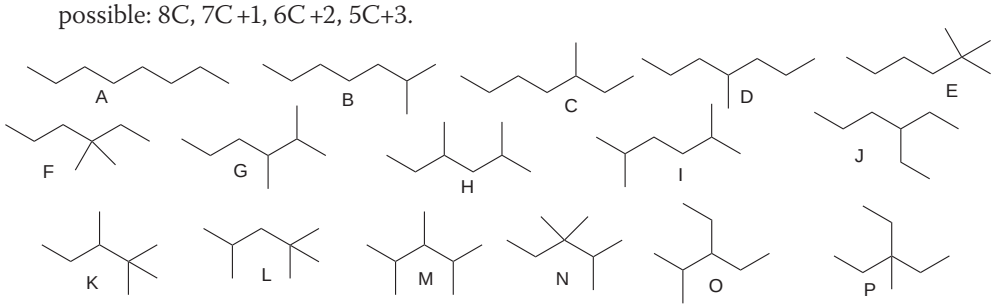
- Hydrocarbons are molecules that contain only carbon and hydrogen, and alkanes are hydrocarbons that have only carbon-carbon single bonds and carbon-hydrogen bonds with the generic formula C_nH_{2n+2}: 1, 2, 3, 4, 5, 6, 7, 24, 27, 32.
- Each carbon atom in an alkane has a tetrahedral array of attached atoms: 2, 3, 4, 5, 6, 32.
- Molecules with different connectivity are different molecules. Isomers are molecules with the same empirical formula and the same number of atoms, but the atoms are attached in different ways: 3, 4, 5, 6, 7, 8, 27, 30, 31, 39, 40.
- The IUPAC rules of nomenclature identify the longest continuous carbon chain and assign a prefix that correlates with the number of carbon atoms. The class name for a molecule is designated by a suffix, which is -ane for alkanes. Rules are established based on number of carbons, assignment of the lowest number(s), and position on the longest carbon chain for naming substituents. Groups attached to the longest continuous chain are known as substituents and given the suffix -yl for alkane base substituents. Complex substituents are treated as a substituent-on-a-substituent: 8, 9, 10, 12, 13, 14, 15, 16, 17, 25, 26, 28, 29, 32, 34, 35, 37, 38, 40, 41.
- There are common names for some alkyl substituents: 11, 12, 13, 29.
- Cyclic alkanes, use the prefix cyclo-: 18, 19, 20, 21, 22, 29, 35, 37, 38.
- Combustion analysis is used for determining the %C and %H in an alkane, which is then used to calculate the empirical formula: 5, 6, 23, 24, 33, 36.

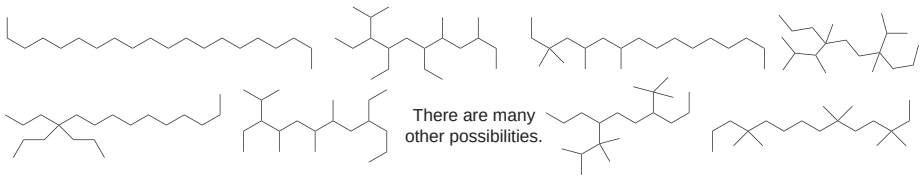
ANSWERS TO IN-CHAPTER QUESTIONS

4.1 A molecule with the formula $C_{10}H_{22}$ is an alkane since it fits the general alkane formula, C_nH_{2n+2}. A molecule with the formula $C_{11}H_{18}$ does *not* fit the alkane general formula so it is *not* an alkane.

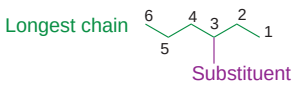
4.2 

4.3 Use the eight-carbon chain parent alkane. Shorten the carbon chain one carbon at a time and then attach those carbons to the new chain in as many different ways as possible: 8C, 7C +1, 6C +2, 5C+3.

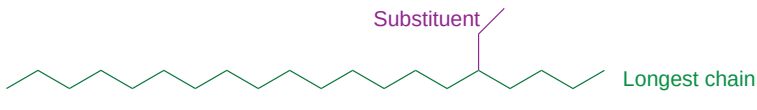


4.4 

4.5 Dodecane

4.6 

This alkane is not 2-ethylpentane because the longest continuous chain in this molecule is a 6-carbon chain (numbered 1-6) and that is used as the base name (hexane).
It is 3-methylhexane.

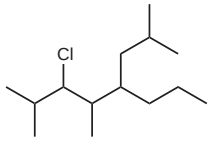
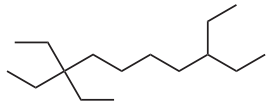
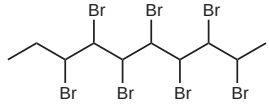
4.7 

4-ethylicosane

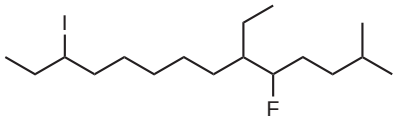
4.8  Isobutane (2-methylpropane)  *tert*-Butylhexane (2,2-dimethylbutane)

4.9  2 carbons (ethyl)  3 carbons (propyl)  2 carbons (ethyl)

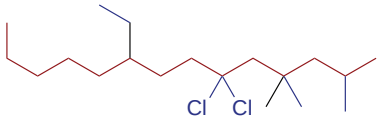
Isopropyl *sec*-Butyl *tert*-Butyl

4.10   

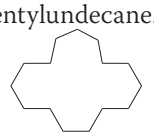
3-Chloro-5-(2-methylpropyl)-2,4-dimethyloctane 3,3,8-Triethyldecane 2,3,4,5,6,7,8-Heptabromodecane

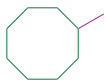
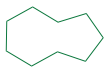
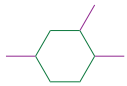
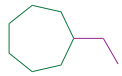
4.11 

6-Ethyl-5-fluoro-12-iodo-2-methyltetradecane

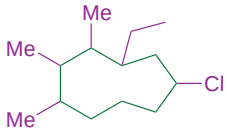
4.12  6,6-Dichloro-9-ethyl-2,4,4-trimethyltetradecane

4.13 (a) The name is 5-butyl 2,4,6,7-tetamethylnonane. (b) The name is 3,4,7,9-tetramethyl-6-pentylundecane.

4.14  Cyclopentadecane

4.15    

Methylcyclooctane Cyclononane 1,2,4-Trimethylcyclohexane Ethylcycloheptane

4.16  1-Chloro-3-ethyl-4,5,6-trimethylcyclononane.

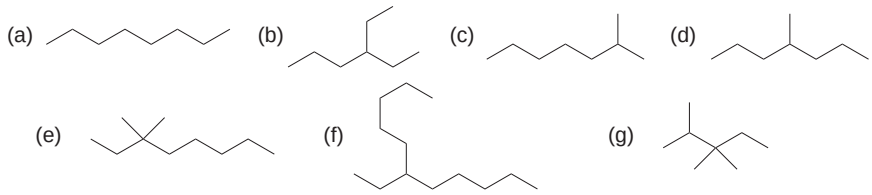
4.17 There are three carbons in the ring, which is more than either of the two-carbon substituents. The name is 1,1-diethylcyclopropane. This alkane *cannot* be cyclopropylpentane. One carbon of the ring is part of the "chain" whereas cyclopropyl is a three-carbon substituent.

4.18 For the formula $C_{16}H_{30}$, the formula weight is 222.41, rounded to 222. The $\%C = \frac{1612}{222} = \frac{192}{222} = 0.865 = 86.5\%$; Similarly, the $\%H = \frac{301}{222} = \frac{30}{222} = 0.135 = 13.5\%$. These percentages have a slight rounding error.

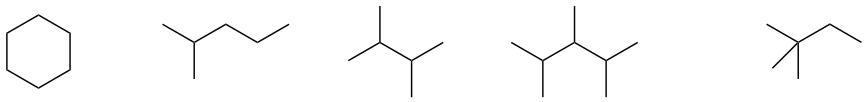
4.19 For a 0.348 g sample, there are 0.9434 (0.348) = 0.3299 g of C and 0.0566 (0.348) = 0.0197 g of H in that sample. Since the mass of CO_2 is 44 and that of C is 12, 0.3299 g of C will correspond to $\frac{44}{12} \bullet 0.3299 = 1.2096$ g of CO_2. Similarly, since water has a mass of 18 and there are 2 H, 0.0197 g of H for the sample, which will correspond to $\frac{18}{2} \bullet 0.0.0197 = 0.1773$ g of H_2O.

HOMEWORK

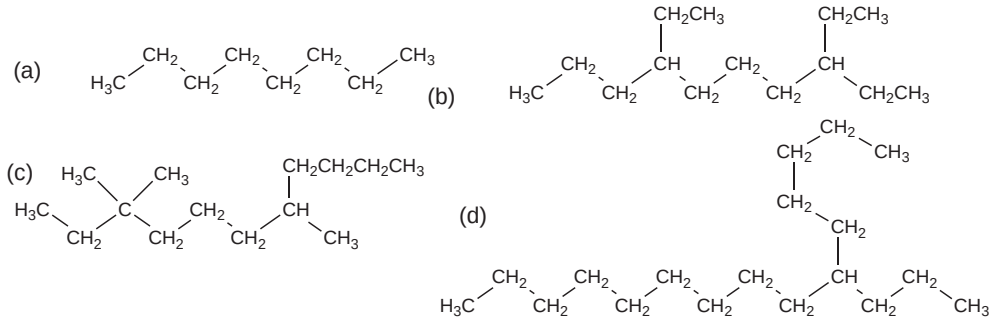
20. Draw the structure of butane, decane, and tridecane using line notation for making chemical structures.
21. (a) Indicate by letter, which of the following molecules are isomers with the empirical formula C_8H_{18}:



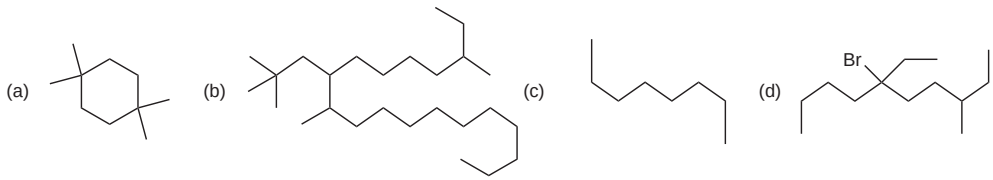
(b) Identify which molecules are isomers of the formula C_6H_{14}.



22. Give the correct IUPAC name (no common names) for each of the following.



23. For each of the following, give the correct IUPAC name (no common names):

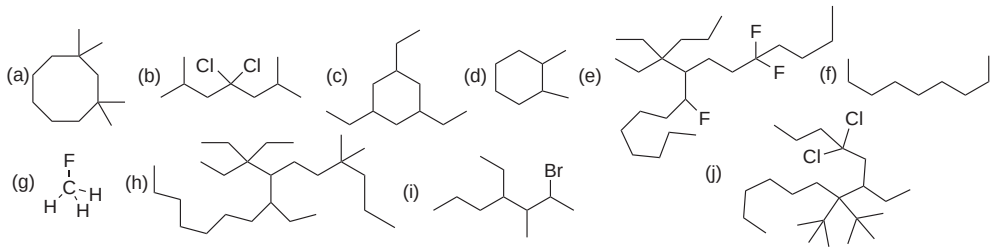


24. (a) Draw six *different* isomers of 1-bromooctane using line notation. Give the IUPAC name for each isomer you draw. (b) Draw the structure for five *different* isomers of the formula C_6H_{12} using line notation. Name each structure, and do *not* use common names.
25. (a) Identify all *isomers* of 3,5-dimethylheptane.

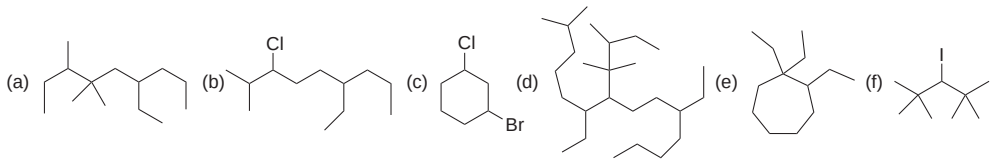
2. (b) Identify all isomers of cycloheptane.

26. Draw the structure for each of the following using line notation:
    (a) 1,2,3-Triethylcycloheptane (b) 3,4-Dichloro-5-(3-methylbutyl) hexadecane
    (c) 1-Chloro-2,2,4,4-tetramethylhexane (d) 2,2-Dibromo-3-methyloctane
    (e) 1,1-Diethylcyclohexane (f) 5-(1-Methylpropyl)decane

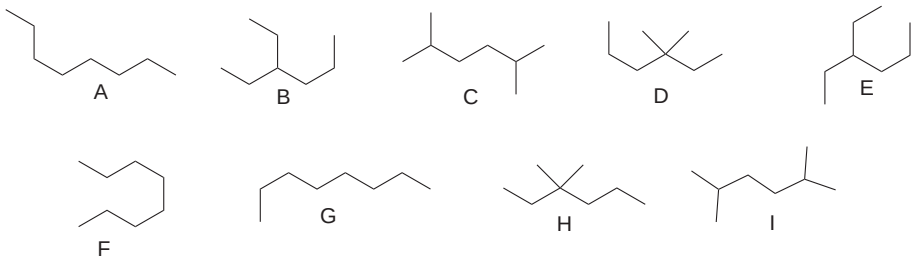
27. Calculate the *empirical formula* for a molecule having only C and H with the following combustion analysis. A sample weighing 0.6000 g was burned in the presence of oxygen to give 0.7692 g of water and 1.8827 g of CO_2.
28. Calculate the % C and % H as well as an empirical formula using the combustion analysis provided: Combustion of 0.81 g of an unknown organic compound yields 0.8578 g of H_2O and 2.6208 g of CO_2.
29. Give the proper IUPAC name for each of the following. Do *not* use common names.



30. Give the proper IUPAC name for each of the following:



31. Determine which of the following structures are isomers and which are identical.



32. Draw the correct structure for each of the following alkyl halides:
    (a) 3,3,5-trichlorodecane (b) 2,6-dimethyl-3-fluoroheptane
    (c) 2,2-dichloro-4,4-dibromooctane

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-5.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

5

Functional Groups

Discreet units of atoms with special physical and/or chemical properties are known as *functional groups*. They are remarkably important in organic chemistry. Although the C—C unit of an alkane is ***not*** considered to be a functional group, the C=C unit of alkenes and the C≡C unit of alkynes are examples of hydrocarbon functional groups. Several functional groups include atoms other than carbon or hydrogen, *heteroatoms*.

To begin this chapter, you should know the following points:

- Covalent bonding between carbon-carbon and carbon-hydrogen (Sections 3.3 and 3.5).
- The definition of a heteroatom (Section 3.8).
- Polarized covalent bonds between carbon and heteroatoms (Section 3.8.1).
- The characteristics of σ-orbitals, p-orbitals,σ-bonds and π-bonds (Sections 3.1, 3.3, 3.4, 3.5, and 2.6).
- The valence of atoms in the first and second row of the periodic table to form covalent bonds in neutral molecules (Sections 3.1.2, 3.2, 3.3, and 3.5).
- The VSEPR model (Section 3.6).
- The nomenclature of any alkane with alkyl or halogen substituents (Section 4.3).

5.1 Π-BONDS. THE C=C UNIT AND ALKENES

π-Bonds were introduced in Section 2.6 for the S=O unit of sulfuric acid and the Cl=O unit of perchloric acid. Both the S=O and the Cl=O double bonds have a strong single σ-bond and a weak π-bond formed by the overlap of adjacent p-orbitals. One π-bond between two carbon atoms gives the C=C functional group. Two π-bonds between two carbon atoms gives the C≡C functional group.

Chapters 3 and 4 examined the structure of molecules that contain only covalent σ-bonds between two sp^3-hybridized carbon atoms. It is also possible to have two bonds between adjacent sp^2 carbon atoms, forming a so-called carbon-carbon double bond, C=C. One is a strong σ-bond and the other is a weaker π-bond. Each sp^2-hybridized carbon forms three σ-bonds to other atoms, as illustrated for CH_2=CH_2 (ethene) in Figure 5.1. After formation of the C—C σ-bond and two C—H σ-bonds on each carbon using the sp^2 hybrid orbitals, there is an unhybridized p-orbital on each carbon that is perpendicular to the plane of the atoms. Each p-orbital contains an electron. When two sp^2 hybridized carbon atoms are connected, the p-orbitals are adjacent and parallel. The two electrons are shared (dispersed) over both p-orbitals to generate a new type of covalent bond, a *π-bond*. The *π-bond* is orthogonal to the σ-bonds with all four hydrogen atoms and the two carbon atoms in the same plane. The two adjacent orbitals share electron density by "sideways" overlap so there is less electron density between the carbon atoms, and it is weaker than a σ-bond. The probability of finding electron density is equal for *both* lobes of the π-bond, so the electrons do not "travel" from top and part on the bottom. Hydrocarbons that contain at least one π-bond and a C=C unit are called *alkenes*.

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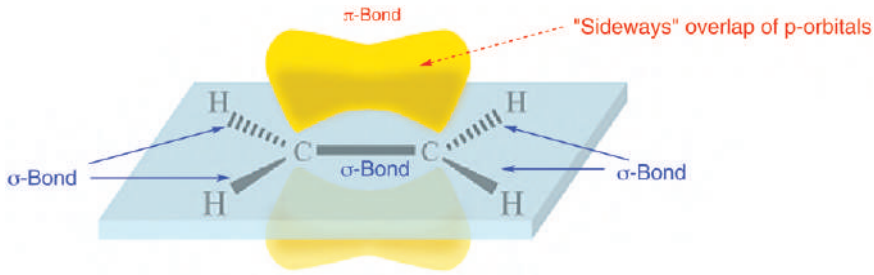


FIGURE 5.1 Interaction of two sp^2 hybridized carbon atoms to form three σ-bonds to each carbon and a π-bond in an alkene.

Since both carbon atoms in a C=C bond have only three σ-covalent bonds, there is trigonal planar geometry for the H—C—C unit with bond angles about 120°. The hybrid carbon model (Section 3.5.3) can be used to visualize a sp^2 hybridized carbon, as shown in Figure 5.2. To form three σ-bonds, three atoms (two H and a C) are arranged around a central carbon atom in a *trigonal planar geometry*. This arrangement will minimize repulsive forces. Each of the three atoms overlap *only* with the 2s, and the $2p_x$ and $2p_y$-orbitals on carbon, generating three coplanar *sp^2-hybrid molecular orbitals* used to form σ-bonds. There is no overlap with the $2p_z$-orbital The sp^2-hydrid orbitals are used to form three covalent σ-bonds to carbon and the two hydrogen atoms. The 2p-orbital *not* used for the σ-bonds (the p_z-orbital in Figure 5.2) has one electron and is perpendicular to the plane formed by the three atoms connected to carbon. If a carbon-carbon σ-bond is formed to another sp^2-hybridized carbon, each has one unused sp-hybrid orbitals and overlap will generate a π-bond.

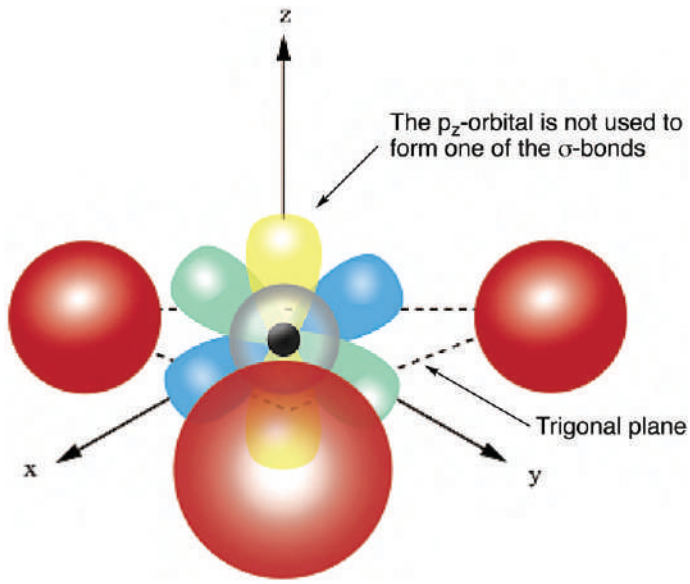


FIGURE 5.2 Covalent σ-bonding for a sp^2-carbon atom.

π-Bonds and Alkenes

5.1 Describe the hybridization of O in the C=O unit.
5.2 If an alkene π-bond were to undergo a chemical reaction, which bond would donate electrons, the σ- or the π-bond? Briefly explain your choice.

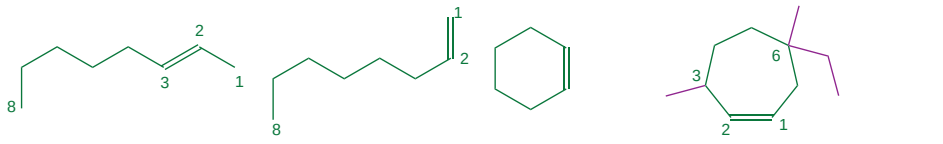
An alkene is a molecule that has at least one carbon-carbon double bond (C=C) and there are two fewer hydrogen atoms relative to an alkane. The *general formula for an alkene* is C_nH_{2n}, where *n* is an integer: 2,3,4. The integer "*n*" *cannot* be 1. When $n = 2$, the formula becomes C_2H_4; when $n = 3$ it is C_3H_6; and when $n = 100$ it is $C_{100}H_{200}$, and so on. Note that the general formula for an alkene with one C=C unit is the same as the general formula for a cyclic alkane with one ring (Section 4.4). As noted, the molecule $H_2C{=}CH_2$ in Figure 5.1

is an alkene named ethene (the common name is ethylene). Since both carbon atoms are sp^2-hybridized, they have a trigonal planar geometry, with the π-bond perpendicular to that plane. The H—C—H and the H—C=C bond angles are close to 120°. The bond lengths for a typical C=C bond distance is 133.7 pm (1.337 Å) whereas that for a typical singly bonded C—C bond distance is 154.1 pm (1.541 Å).[1]

Alkene Nomenclature

5.3 Draw eight different isomers with the formula C_7H_{14}, where one-half of the structures are alkenes and the remainder are cyclic alkanes.

The C=C unit in an alkene is the functional group. Nomenclature for alkenes uses the appropriate prefix to indicate the number of carbon atoms (Section 4.3.1). The suffix for the C=C functional group is taken from *the class name for an alkene (-ene).* The longest linear chain must contain the C=C unit, which is the locant. The first carbon of the C=C unit is given the lowest number. All substituents are assigned a number after the C=C unit is assigned the smallest number.



Oct-2-ene Oct-1-ene Cyclohexene 6-Ethyl-3,6-dimethylcyclohept-1-ene

The first example shown has a C=C unit that is part of an eight-carbon chain (oct-). Since the C=C unit can be at different positions along the eight-carbon chain, there are several possible isomers. Each requires a different name. The name must designate the position of the π-bond, and the *first carbon of the* π-bond receives the lowest possible number. The example shown is named oct-2-ene. Note that the number is placed immediately in front of the -ene term. Oct-1-ene, oct-3-ene and oct-4-ene are the unbranched isomers of oct-2-ene, where the position of the C=C unit is different.

5.4 Draw the structures of both oct-3-ene and oct-4-ene.
5.5 Name an acyclic alkene and a cyclic alkane that are isomers with the formula C_5H_{10}.

Cyclic alkenes are known. *The general formula for a cyclic alkene is* C_nH_{2n-2}. As with cyclic alkanes, the parent name for cyclic alkenes is based on the number of carbon atoms in the ring but the prefix cyclo- is added to the name. The six-carbon cyclic molecule that contains a C=C unit is called cyclohexene. There is only one possibility, so the number is omitted. Cyclic alkenes may have substituents attached to the ring. The C=C unit is the locant in the ring, so the carbon atoms of the double bond are numbered "1" and "2" in the direction that gives the substituent first encountered *the smaller number.* 6-Ethyl-3,6-dimethylcyclohept-1-ene is a seven-membered ring alkene with a methyl and ethyl substituent. The ring is numbered to give the lowest combination of numbers. Since the first encountered C=C carbon could be numbered either 1 or 2, the number must be included in the name.

5.6 Draw the structures of cyclobutene, cycloheptene, and cyclopentadecene.

5.2 Π-BONDS. THE C≡C UNIT AND ALKYNES

Alkynes

A C≡C unit constitutes a new functional group. A carbon-carbon triple bond has two σ-bonds and two π-bonds that are mutually perpendicular. Hydrocarbons that have a carbon-carbon

[1] Haynes, W.M. *CRC Handbook of Chemistry and Physics, 94th ed.*, CRC Press, Inc., Boca Raton, FL, 2013–2014, pp. 9–38.

triple bond are known as *alkynes*. An alkyne has four fewer hydrogen atoms than an alkane and two fewer than in an alkene so the general formula is C_nH_{2n-2}, where n is an integer: 2,3,4,... The integer n *cannot* be 1, but when $n = 2$, the formula is C_2H_2; when $n = 3$, the formula is C_3H_4; and when $n = 100$, the formula is $C_{100}H_{198}$, and so on. Cyclic alkynes are known, and they have the *empirical formula* C_nH_{2n-4}.

As with sp^3 hybridization and sp^2 hybridization, sp hybridization can be examined using the hybrid carbon model (Section 3.5.3). To form two σ-bonds, two hydrogen atoms are arranged around a central carbon on either side, in a straight line, as seen in Figure 5.3. This linear geometry is the lowest energy arrangement of all atoms. Each hydrogen atom overlaps with the 2s-orbital and the 2p-orbital ($2p_x$) of carbon to form a *sp-hybrid orbital*. The sp-hybrid orbitals are used to form C—H σ-bonds. Two of the 2p-orbitals on carbon are not used. If a carbon-carbon σ-bond is formed to another sp-hybridized carbon, each has two unused sp-hybrid orbitals and overlap will generate two π-bonds.

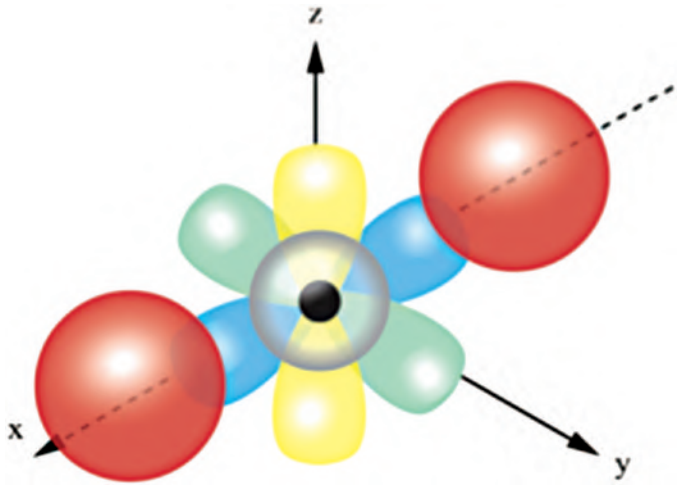


FIGURE 5.3 Covalent σ-bonding for a sp hybridized carbon.

The simplest alkyne is ethyne (the common name is acetylene) with the formula C_2H_2. As shown in Figure 5.4, the unused p-orbitals overlap in a sideways manner to form two π-bonds that are mutually perpendicular. The carbon atoms and all the σ-bonds form a linear array, which is clearly shown in the ball-and-stick model of ethyne. An electron density map of acetylene is also shown, where the higher concentration of red corresponds to higher electron density. It is apparent that the region between the carbon atoms and *surrounding* the molecule has the most red, consistent with two mutually perpendicular π-bonds.

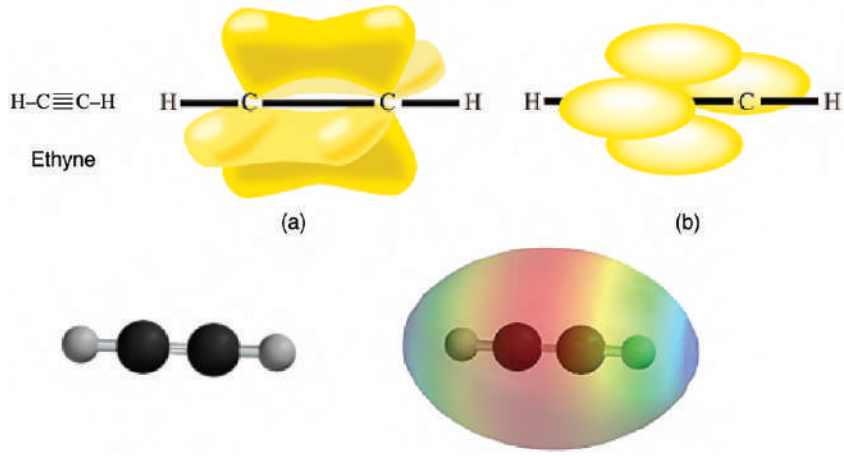
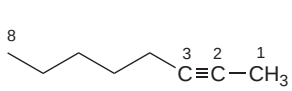


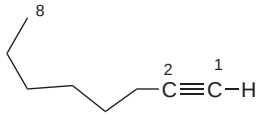
FIGURE 5.4 Two π-bonds in a sp hybridized carbon–carbon bond.

Alkyne Nomenclature

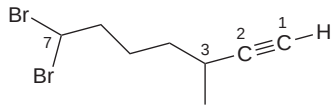
As with alkanes and alkenes, alkynes have linear and branched carbon chains, and a molecule can have more than one triple bond. The nomenclature requires that the prefix indicate the number of carbon atoms and the suffix is taken from the class name for an alkyne, *-yne.* The C≡C unit receives the lowest possible number since the C≡C unit is the closest locant. An example is oct-2-yne, which has a linear eight- carbon chain containing the triple bond. Since the triple bond can be at several different positions, there are several possible isomers. The first carbon of the triple bond receives the lowest possible number. *Oct-1-yne is an isomer of oct-2-yne.* Carbon chains that contain the alkyne unit can have substituents, of course, and in 7,7-dibromo-3-methylhept-1-yne there is a methyl substituent and two bromine substituents. The first carbon of the triple bond receives the lowest number, which dictates the numbering of the substituents.



Oct-2-yne



Oct-1-yne



7,7-Dibromo-3-methylhept-1-yne

There is an important structural difference between oct-2-yne and oct-1-yne that is apparent by examining the first three carbons of the chain containing the triple bond. In oct-1-yne, a hydrogen atom is attached to the first carbon of the triple bond. In oct-2-yne, an alkyl group (methyl) is attached to the first carbon of the triple bond. Oct-1-yne is an example of a *terminal alkyne* where the triple bond is at the end of the chain and a H atom is attached (C—C≡C—H). Oct-2-yne is an *internal alkyne* where both carbon atoms of the triple bond are attached to another carbon (C—C≡C—C).

5.7 Draw the structure of dec-3-yne; draw an isomer that has a linear chain of only eight carbons and name it.
5.8 Draw the structure of 5-chloro-3,3,6-trimethyl-oct-1-ene and of 6,6-diethyl-9-iododec-3-yne.

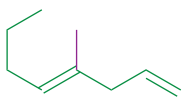
Cyclic alkynes are known, but the linear nature of the C—C≡C—C unit will severely distort any attached carbon atoms in the ring. The distortion is severe in C3-C6 ring compounds so the formation of cyclobutyne, cyclopentyne, or cyclohexyne is virtually impossible. When a ring has eight or more carbon atoms, however, it is usually possible to isolate cyclic alkynes.

5.9 Draw the structure of 4-ethylcyclopentadecyne.

5.3 HYDROCARBONS WITH SEVERAL Π-BONDS

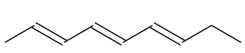
Dienes, Diynes, and Allenes

More than one double bond or triple bond can be incorporated into organic molecules. The terms di-, tri-, tetra-, penta-, and so on are used when multiple unsaturated units are present. The prefix *di-* should be used when there are two alkene units or two alkyne units in one molecule. A molecule with two C=C units is called a *diene* and a molecule with two C≡C units is called a *diyne*. Molecules with both an alkene and an alkyne unit are known. A molecule with one C=C unit and one C≡C is called an *en-yne*.


4-Methylocta-1,4-diene


3,3-Diethylhepta-1,6-diyne


Cyclohepta-1,3-diene


Nona-2,4,6-triene


Tetradeca-2,5,7,10-tetrayne

For a diene, the nomenclature rules require that both C=C units be included in the longest chain. The eight-carbon diene shown is an octadiene. When there is more than one C=C unit or more than one C≡C unit the longest chain is numbered so that each π-bond unit receives the lowest combination. In this example, the lowest combination is C1 and C4 so the name is 4-methylocta-1,4-diene. In diynes, both C≡C units are part of the longest chain. The C≡C units have the lowest combination of numbers as in 3,3-diethylhepta-1,6-diyne. Substituents are numbered based on the numbering of the C=C or C≡C units. Cyclic molecules are named using standard protocols, where both C=C units are within the ring as in cyclohepta-1,3-diene. Polyenes and polyynes are known. Examples are nona-2,4,6-triene and tetradeca-2,5,7,10-tetrayne.

When an alkene and an alkyne are in the same molecule, the nomenclature is a little different. An alkene-alkyne is usually referred to as an en-yne. The numbering is chosen to give the triple bond(s) the lowest number(s) in preference to the double bond(s). Therefore, "yne" is used for the suffix. When the position number of the ene or yne unit closer to the end of the chain, the "ene" takes the lower number. A comparison of 3-ethyldec-2-en-6-yne with 6-ethyldec-6-en-2-yne illustrates this point. In the former example, the C=C unit is closest to the end of the chain, whereas in 6-ethyldec-6-en-2-yne the C≡C unit is closer to the end of the chain. For 3-ethylhex-1-en-5-yne, the "ene" and "yne" have the same position number so the C=C unit receives the lower number.

3-Ethyldec-2-en-6-yne

6-Ethyldec-6-en-2-yne

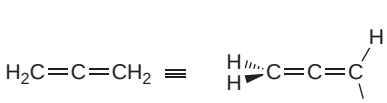
3-Ethylhex-1-en-5-yne

5.10 A molecule has a formula $C_{12}H_{22}$, but it is not an alkyne. Offer an explanation.

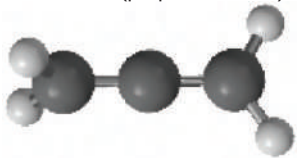
5.11 Draw the structure of cyclopenta-1,3-diene? of 3-ethylhexa-1,5-diene? of 6-bromohexa-1,3-diyne.

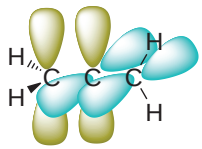
5.12 Draw the structures of octa-1,3,6-triene, octa-1,4,7-triyne, and hex-4-en-1-yne.

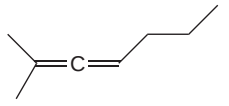
There is another class of dienes known as the *allenes*. The parent compound is named *allene*, but it is a diene and the IUPAC name is propan-1,2-diene, as shown in Figure 5.5. Allene is an example of a *cumulene*, which is a molecule that has cumulative π-bonds. Cumulenes have three or more adjacent sp^2 or sp hybridized carbon atoms. The central carbon of an allene, for example, has two π-bonds and is sp hybridized whereas the two flanking carbons are sp^2 hybridized. This arrangement requires that the two π-bonds are perpendicular one to the other, which positions the methylene units (the $-CH_2-$ units) in different planes. The ball-and-stick model of propa-1,2-diene confirms the fact that the two hydrogen atoms on one terminal carbon (the CH_2 unit) are perpendicular to the two hydrogen atoms on the other terminal carbon (the other CH_2 unit). Substituted allenes are named as dienes.



Allene (propa-1,2-diene)







2-Methylhepta-2,3-diene

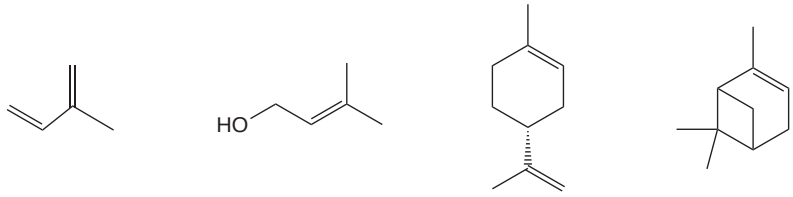
FIGURE 5.5 Allenes.

2-Methylhepta-2,3-diene, for example, has the C=C=C unit as part of a seven-carbon chain, so it is a heptadiene and the C=C=C unit receives the lower numbers.

5.4 TERPENES

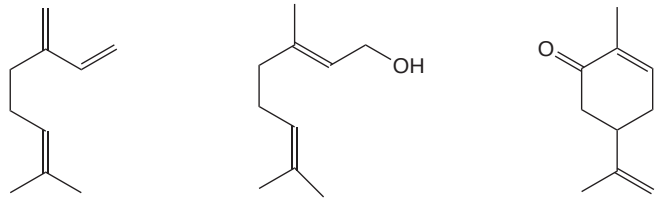
Terpenes

Many naturally occurring compounds in nature have double or triple bonds. *Terpenes* are cyclic and acyclic compounds with the formula $(C_5H_8)_n$ that are usually found in plants. There are several classes of terpenes organized by the number of carbon atoms. The classes include hemiterpenes, (C_5) monoterpenes, (C_{10}) sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), and triterpenes (C_{30}). Terpenes are further classified by the number of isoprene units in the molecule; a prefix in the name indicates the number of isoprene pairs needed to assemble the molecule. For the most part, terpenes contain 2, 3, 4, or 6 isoprene units. *Terpenoids* are heteroatom containing terpenes.



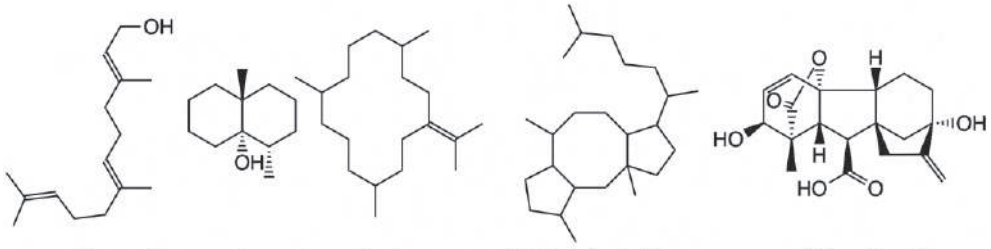
Isoprene | 3-Methylbut-2-en-1-ol (Prenol) | Limonene | Pinene

Hemiterpenes consist of one isoprene unit. Isoprene itself is the only hemiterpene, but oxygen-containing derivatives are hemiterpenoids. Prenol is an example. Monoterpenes have two isoprene units and have the formula $C_{10}H_{16}$. *Limonene* is an example that is found in lemon rind. *Pinene* is a constituent of pine resins and is a major component of the oil obtained from giant Sequoia trees (*Sequoiadendron giganteum*). *Myrcene* is one of the essential oils found in parsley and in hops (used to make beer), the female flowers of the hop plant, *Humulus lupulus*. *Geraniol* is part of the essential oil of roses and is found in citronella oil. *Carvone* is found in the seeds of caraway and in dill.



Myrcene | Geraniol | Carvone

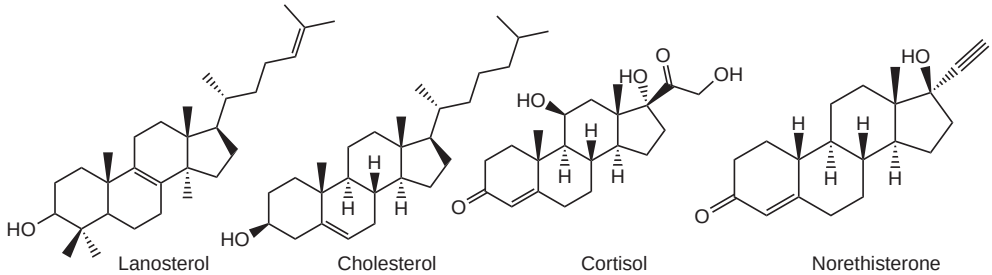
Sesquiterpenes consist of three isoprene units and have the molecular formula $C_{15}H_{24}$. Examples are *farnesol* and *geosmin*. Farnesol is produced from isoprene compounds in both plants and animals. It is present in many essential oils and is used in the perfume industry to emphasize the odor of sweet, floral perfumes. Farnesol is a natural pesticide for mites but acts as a pheromone for some insects. Geosmin has a distinct earthy or musty odor, and it is responsible for the earthy taste of beetroots. It contributes to the scent that is detected when soil is disturbed. Geosmin is responsible for the muddy smell in many freshwater fish such as carp and catfish.



Farnesol | Geosmin | Cembrene | Ophiobolin skeleton | Gibberellic acid

Diterpenes consists of four isoprene units and have the molecular formula $C_{20}H_{32}$. An example is *cembrene*, which has a faint wax-like odor and is a trail pheromone for termites. Sesterterpenes have five isoprene units and 25 carbons. Examples are the *ophiobolins*, a group of tricarbocyclic sesterterpenoids. At least 49 natural ophiobolins have been reported and assigned into A-W subgroups in order of discovery. Some investigations demonstrated that these compounds display a broad spectrum of biological and pharmacological characteristics such as phytotoxic, antimicrobial, nematocidal, cytotoxic, anti-influenza, and inflammation-promoting activities. They are promising drug candidates with anti-proliferative activity against many cancer cell lines. Usha Ranjan Ghatak (India; 1931–2005) was a synthetic organic chemist known for his work in developing novel protocols of stereoselective synthesis of diterpenoids. Dr. Ghatak's contributions were primarily on stereochemically controlled organic synthesis, and he was known for developing synthetic methodologies for diterpenoids and bridged-ring compounds. He demonstrated total synthesis of compounds related to gibberellins, a group of growth-regulating plant hormones. The gibberellins regulate stem elongation, germination, dormancy, flowering and other processes in plants. All known gibberellins are diterpenoid acids. *Gibberellic acid* was the first gibberellin to be structurally characterized.

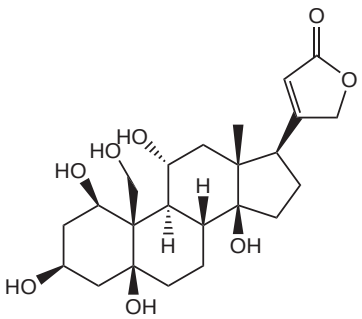
Triterpenes consist of six isoprene units and a molecular formula $C_{30}H_{48}$. Examples are the *steroids lanosterol* and *cholesterol*. The fundamental steroid structure is typically composed of four "fused" rings: three six-membered cyclohexane rings and one five-membered cyclopentane ring. Steroids have two principal biological functions. Steroids are biologically active triterpenes. They are important components of cell membranes that alter membrane fluidity, and they act as signaling molecules. Lanosterol is the compound from which all animal steroids are derived. *Sterols* are forms of steroids with a hydroxy group and a skeleton derived from cholestane. Cholesterol is the principal sterol produced by all animals and is found in all animal cell membranes. Cholesterol is the biosynthetic precursor of steroid hormones, bile acids and vitamin D. Note that triterpenes that possess heteroatoms are known as triterpenoids. *Cortisol* is a steroid hormone and classified as a glucocorticoid hormone. It is released in response to stress and low blood-glucose and functions to increase sugar, suppress the immune system and assist in metabolism. Many synthetic steroids are designed to act like hormones to reduce inflammation. They're known as corticosteroids. They are different from anabolic steroids, which increase protein within the cells of skeletal muscles and have some virilizing effects. Virilization or masculinization is the biological development of adult male characteristics in young males or females. *Norethisterone* was one of the first progestin medications to be developed. It is used in birth control pills, menopausal hormone therapy, and for the treatment of gynecological disorders. Norethisterone is used as a hormonal contraceptive in combination with an estrogen.



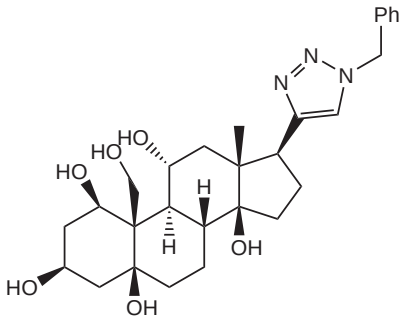
Lanosterol Cholesterol Cortisol Norethisterone

Gunda I. Georg

Professor Gunda I. Georg (USA) at the University of Minnesota does research into the total synthesis and semisynthesis of biologically active agents. She is a leading researcher in male contraception and conducts research on Alzheimer's disease, epilepsy and cancer experimental therapeutics. Cardenolides are a group of cardiac-active steroids that have a five- or six-membered lactone ring and often a sugar moiety. Professor Georg has synthesized new cardenolides with improved selectivity for inhibition of the Na,K-ATPase α4 isoform, which interfere with sperm motility and sperm hyperactivation. They are an attractive target for further development of a male contraceptive.[2] The *N*-benzyltriazole derivative shown was synthesized and shown to be a picomolar inhibitor of Na,K-ATPase *a*4 and sperm function. The activity included a decrease in sperm motility in vitro and in vivo, affected sperm membrane potential, intramolecular Ca^{2+}, pH and hypermotility.[2] Triazoles are discussed in Section 23.1.



Ouabagenin



Triazole analog of Ouabagenin

5.13 Draw the structures of cholestane and of cortisone.

[2] Syeda, S.S.; Sánchez, G.; Hong, K.H.; Hawkinson. J.E.; Georg, G.I.; Blanco, G. *Journal of Medicinal Chemistry* 2018, 61, 1800–1820.

Alkyl Halides

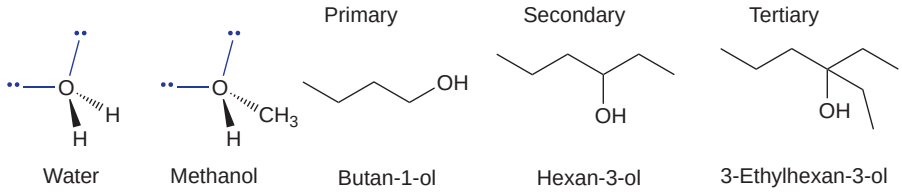
5.5 HETEROATOM FUNCTIONAL GROUPS

Functional groups are collections of atoms that impart unique physical and chemical characteristics to a molecule. Apart from alkenes and alkynes, there are several functional groups that include oxygen, sulfur, or nitrogen atoms. As noted in Section 4.3.3, many molecules have carbon-halogen bonds, but halogen units are treated as substituents and are not considered to be functional groups.

5.5.1 ALCOHOLS AND THIOLS

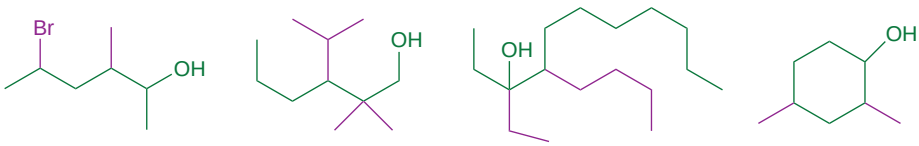
Oxygen is in group 16 of the periodic table and has six electrons in its valence shell, so it requires only two shared electrons to complete the octet. Oxygen has a valence of two and it forms two covalent bonds, with two unshared electron pairs on oxygen. There are several functional groups that contain oxygen. When a molecule has a carbon atom attached to an OH it is called an *alcohol*. The OH functional group is called a *hydroxyl group*. The O—H bond in an alcohol is polarized such that oxygen is δ^- and the hydrogen is δ^+. Alcohols react as a weak Brønsted-Lowry acid *(pK_a about 15–18).* This important chemical reaction of alcohols will be discussed in Section 6.4. Water is H—O—H and the VSEPR model predicts an angular shape (Section 3.6). Imagine that one hydrogen atom of water is replaced with an alkyl group. The result is an alcohol. If the alkyl group is methyl the molecule is CH_3OH, methanol. The H—O—C atoms in methanol assume an angular shape analogous to water. There are three structural variations for alcohols. A primary alcohol is characterized by a RCH_2–OH unit, a secondary alcohol has the OH unit attached to a carbon atom that has one H and two carbon groups (R_2CH–OH), and a tertiary alcohol has the OH unit attached to a carbon atom with three carbon groups (R_3C–OH). Note that "R" is any carbon group.

In the IUPAC nomenclature system for alcohols, the carbon bearing OH is the locant and that carbon is part of the longest linear carbon chain. The carbon bearing the oxygen of the OH unit has the lowest possible number. Alcohols use the familiar carbon prefix, and the suffix is *-ol*, taken from the generic name alcoh***ol***. The hydrocarbon chain is identified, the final *-e* of the hydrocarbon name is dropped and replaced with -ol.



Water Methanol Butan-1-ol Hexan-3-ol 3-Ethylhexan-3-ol

Butan-1-ol is an example of a primary alcohol in which the OH unit is attached to C1. Hexan-3-ol is an example of a secondary alcohol and 3-ethylhexan-3-ol is a tertiary alcohol. Alcohols that have relatively simple structures are found in daily life. Methanol (CH_3OH) is also called wood alcohol since it was once obtained by the distillation of wood. Ethanol (CH_3CH_2OH) is obtained by fermentation of grain and found in liquors, wines, and so on; and propan-2-ol, $(CH_3)_2CHOH$, is rubbing alcohol.



5-Bromo-3-methyl-hexan-2-ol 3-(1-Methylethyl)-2,2-dimethylhexan-1-ol 4-Butyl-3-ethyl-undecan-3-ol 2,4-Dimethyl-cyclohexanol

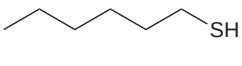
Substituents are common in alcohols and the nomenclature follows the now familiar procedure. Substituents are assigned numbers based on the position of the oxygen of the OH group on the longest chain. The first example is a secondary alcohol with the OH unit

connected at C2 of a six-carbon chain, a hexan-2-ol. The methyl group and the bromine are then assigned a number and the name is 5-bromo-3-methylhexan-2-ol. In 3-(1-methylethyl)-2,2-dimethylhexan-1-ol, there are two methyl substituents at C2 and a 1-methylethyl at C3. The 1-methylethyl unit is also called an isopropyl group. In 4-butyl-3-ethylundecan-3-ol, there is a 12-carbon hydrocarbon chain that does *not* contain the OH unit. The longest unbranched carbon chain bearing the OH group at C3, however, is eleven. Cyclic alcohols are also possible, and the example shown has the OH group attached to a cyclohexene ring, so it is a cyclohexanol. The carbon of the ring that bears the OH is always C1, and the ring is then numbered to give the substituents the lowest numbers, as in 2,4-dimethylcyclohexanol. Since the oxygen-bearing carbon is always C1, the 1- is omitted.

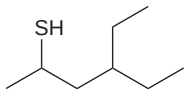
When two hydroxyl units are incorporated into the same molecule it is called a diol. When there are three hydroxyl units, it is a triol, and tetraols, pentaols, and so on are known. The nomenclature for a diol identifies the longest chain that bears *both* OH units and gives *both* C—OH units their lowest possible number. For example, $CH_3CH(OH)CH_2CH(CH_3)CH_2CH_2CH_2OH$ is 4-methylheptane-1,6-diol and $HOCH_2CH_2CH_2CHOH$ is butane-1,4-diol.

5.14 Draw the structure of 3,3,5-trichlorodecane-1,7-diol.

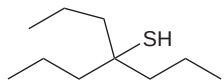
Sulfur is in group 16 of the periodic table, immediately under oxygen. Analogous to oxygen, molecules that have a sulfur atom can form with two σ-bonds to sulfur and two unshared electron pairs on sulfur. Sulfur has d-orbitals, and it can expand its valence to form molecules with multiple bonds to sulfur. Such structures are not possible with oxygen. The discussion in this section is limited to divalent sulfur molecules that are oxygen analogs. Forming two hydrogen σ-bonds to sulfur generates H—S—H, hydrogen sulfide. Hydrogen sulfide is formed by the decomposition of organic matter by bacteria in the absence of oxygen (anaerobic digestion). This type of decomposition typically occurs in swamps and in sewers. Hydrogen sulfide is also found in volcanic gases, and it is a poison comparable to hydrogen cyanide or carbon monoxide.



Hexane-1-thiol



4-Ethylhexane-2-thiol



4-Propylheptane-4-thiol

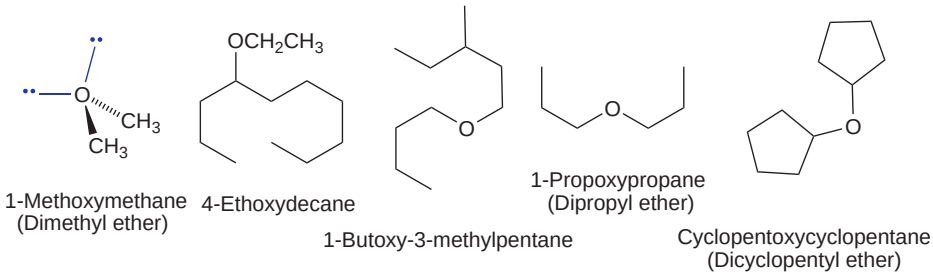
Imagine that the oxygen atom of an alcohol is replaced with sulfur. The result is a *thiol*, R—S—H. Thiols are named using the hydrocarbon portion of the alkyl unit with the suffix *-thiol*. Examples are methanethiol, CH_3SH, and butanethiol, $CH_3CH_2CH_2CH_2SH$. The C—SH unit is the locant so that carbon receives the lowest number. *Mercaptan* is the common name for a thiol so methanethiol is also known as methyl mercaptan. Low molecular weight thiols are foul smelling compounds. The smell of "natural gas" is usually about 1 part per million (ppm) of methanethiol in the gaseous hydrocarbon propane. Methanethiol occurs naturally in humans, in some plant tissues, and in some foods (e.g., some nuts and cheese). It has a putrid smell associated with the odor of bad breath, the smell of flatus, and the smell of decaying organic matter in swampy wetlands. Thiols are common in organic chemistry and there are primary, secondary and tertiary thiols. Hexane-1-thiol is a primary thiol, 4-ethylhexane-2-thiol is a secondary thiol and 4-propylheptane-4-thiol is a tertiary thiol.

Many of the chemical reactions of thiols are similar to those of alcohols. There are differences since sulfur is a larger atom when compared to oxygen and it has d-orbitals whereas oxygen does not. The hydrogen on sulfur in a thiol is acidic. Thiols are generally more acidic than an alcohol. The pK_a of a typical thiol is ~ 10, whereas the pK_a of a typical alcohol is ~ 15–18. An example is the acid-base reaction of methanethiol with sodium amide, which gives the conjugate base, sodium methanethiolate (sodium mercaptide, $CH_3S^-Na^+$) and ammonia as the conjugate acid. Just as there are diols, there are dithiols. Ethanedithiol is $HSCH_2CH_2SH$ and butane-1,4-dithiol is $HS(CH_2)_4SH$. Dithiols are used in reactions with aldehydes and ketones (Section 16.5.4).

Alcohols and Ethers

5.5.2 ETHERS AND DITHIOETHERS (SULFIDES)

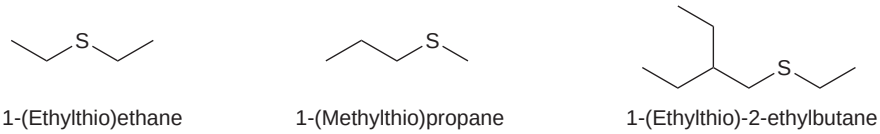
Organic molecules that contain a C—O—C unit are called *ethers*, characterized by an oxygen atom with two attached alkyl groups. Using the VSEPR model, ethers are predicted to be angular, as illustrated with 1-methoxymethane (also called dimethyl ether). Ethers are characterized by their poor reactivity in a variety of reactions and are commonly used as solvents in which organic chemical reactions take place. Ethers are not Brønsted-Lowry acids, but they are weak Brønsted-Lowry bases. Ethers *are* good Lewis bases (Sections 5.5.2. and 6.7.3).



The IUPAC nomenclature rules for naming ethers identifies the longer chain and a shorter linear chain attached to the oxygen, which is the locant. The longer chain is the parent. The oxygen bearing the shorter chain is therefore a substituent named as an alkoxy group: OCH_3 is methoxy, OCH_2CH_3 is ethoxy, and so on. 1-Ethoxyethane (diethyl ether, $CH_3CH_2OCH_2CH_3$) is often used as a solvent, but some care must be exercised since it has a high vapor pressure and air/diethyl ether mixtures are extremely flammable. Diethyl ether was used as a general anesthetic many years ago, but the patients often suffered from convulsions. These side effects are due in part to the fact that diethyl ether is metabolized to acetaldehyde (Section 5.6.2) and ethanol. Diethyl ether was abandoned when better and safer anesthetics were discovered.

Using the IUPAC nomenclature, typical ethers are 1-methoxymethane and 4-ethoxydecane. In 1-butoxy-3-methylpentane, the longest chain is five, with a branching methyl group. The four-carbon chain bearing the oxygen is at C1 is butoxy. Note that 1-propoxypropane has one propyl group bearing the oxygen attached to C1 of the other propyl chain. 1-Propoxypropane is classified as a *symmetrical ether* because there are two propyl groups flanking the oxygen. For symmetrical ethers, each alkyl group can be identified, followed by the word *ether* so 1-propoxypropane is dipropyl ether. The IUPAC name of the next example is 1-cyclopentoxycyclopentane, but it is a symmetrical ether and can be called dicyclopentyl ether. Since they are symmetrical ethers, dimethyl ether is another name for 1-methoxymethane and diethyl ether is another name for 1-ethoxyethane.

5.15 Draw the structures of dibutyl ether and 3-(methylthio)hexane.



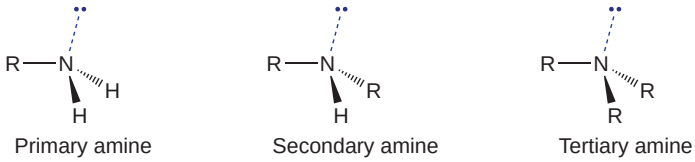
Imagine replacing the oxygen of an ether with sulfur. The product is a *thioether* (R—S—R), also known as a *sulfide*. In the IUPAC system the suffix used for thioethers is *sulfane*. Thioethers are named by identifying the two groups flanking the sulfur. The IUPAC names for the examples shown are diethylsulfane, methyl(propyl)sulfane and ethyl(2-ethylbutyl) sulfane. Another nomenclature system is similar to that of ethers in that the shorter chain is considered an SR group named as an alkylthio unit and the C—SR unit is the locant. The longer chain is the base name. Examples are 1-(ethylthio)ethane, 1-(methylthio)propane, and 1-(ethylthio)-2-ethylbutane. An older method for naming sulfides identifies the two groups

flanking the sulfur followed by sulfide. The examples named diethyl sulfide, methyl propyl sulfide and ethyl 2-ethylbutyl sulfide.

5.5.3 AMINES

Amines

Nitrogen is in group 15 of the periodic table, has five electrons in its valence shell and requires only three shared electrons to complete the octet. It has a valence of three. In neutral organic compounds, nitrogen forms three covalent bonds to other atoms and one unshared electron pair remains on nitrogen.



The structure of ammonia (NH_3) is characterized by three N—H σ-bonds. Imagine replacing the hydrogen atoms of ammonia with carbon groups. The result is an organic molecule called an *amine*, which has N—H σ-bonds and/or N—C σ-bonds. Using the VSEPR model (Section 3.6), amines are predicted to have a pyramidal shape with respect to nitrogen, similar to that of ammonia. The unshared electron pair projects from the apex of the pyramid (see Figure 5.6). The C—N—C or C—N—H bond angles will vary with the size of the alkyl groups. The number of N—H and N—C bonds leads to a structural classification of amines as *primary, secondary, and tertiary*. A primary amine has one carbon and two hydrogen atoms on nitrogen (RNH_2) and a secondary amine has two carbons and one hydrogen atom on nitrogen (R_2NH). A tertiary amine has three carbon and no hydrogen atoms on nitrogen (R_3N).

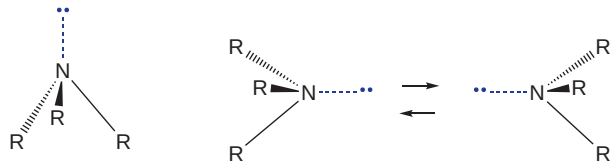


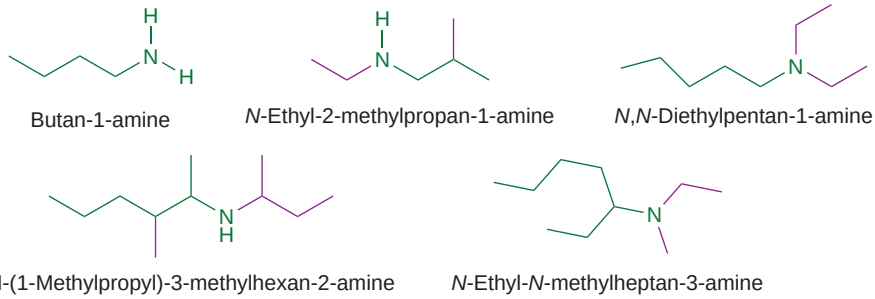
FIGURE 5.6 Pyramidal shape of amines and fluxional inversion.

An amine, such as the generic structure shown in Figure 5.6, flips like "an umbrella in the wind." The nitrogen is at the center of a "flipped" umbrella and the electron pair is at the "handle." This phenomenon is known as *fluxional inversion*, which leads to the two structures shown. Fluxional inversion is remarkably rapid, about $2x10^{11}$ inversions per second for ammonia,[3] although it is slower in amines. Tertiary amines undergo 10^3–10^5 inversions per second.

5.16 Draw a four-carbon primary amine, a five-carbon secondary amine, and a six-carbon tertiary amine using line notation.

The amine-bearing carbon is the locant and must be part of the longest hydrocarbon chain. The name is generated by dropping the -e ending of the hydrocarbon chain and replacing it with the suffix *-amine*. The one-carbon primary amine is methanamine, the two-carbon primary amine is ethanamine, the five-carbon primary amine is pentanamine, and so on. A substituent on the longest carbon chain is assigned a position number relative to the position of the nitrogen locant. A substituent on the nitrogen atom, however, is assigned an *N*- to indicate its position.

[3] Smith, M.B. *March's Advanced Organic Chemistry*, 8th ed., 2019, John Wiley & Sons, Hoboken, NJ, p. 138.



Any group attached to nitrogen other than the longest hydrocarbon chain, is indicated by the terms *N*-alkyl, *N,N*-dialkyl, or *N*-alkyl$_1$-*N*-alkyl$_2$. In other words, groups could be *N*-methyl, *N,N*-diethyl, or *N*-ethyl-*N*-methyl. Using this system, CH_3NHCH_3 is called *N*-methylmethanamine. Butan-1-amine has the NH_2 unit on C1 so it is a primary amine. *N*-Ethyl-2-methylpropan-1-amine has an ethyl group attached to the nitrogen and it is a secondary amine. *N,N*-Diethylpentan-1-amine is a tertiary amine. The longest carbon chain is pentane and the two ethyl substituents on nitrogen are indicated by *N,N*- as shown. In the secondary amine *N*-(1-methylpropyl)-3-methylhexan-2-amine, the nitrogen is attached to C2 of a six-carbon chain. A 1-methylpropyl unit is attached to the nitrogen atom as a substituent. The tertiary amine *N*-ethyl-*N*-methylheptan-3-amine has a seven-carbon chain, with the nitrogen attached to C3. In this amine, both ethyl and methyl are attached to nitrogen as substituents.

Amines can also be named using common names. Some appear so often that the system must be mentioned; however, common names are usually reserved for relatively simple amines. In this system, the alkyl groups are identified followed by the word amine. Therefore, methanamine is methylamine, butan-1-amine is butylamine; *N,N*-diethylpentan-1-amine is diethylpentylamine; *N*-ethyl-2-methylpropan-1-amine is ethylisobutylamine.

5.17 Draw the structure of 3,4-diethyl-*N*-methyldecan-2-amine.

5.6 FUNCTIONAL GROUPS WITH POLARIZED Π-BONDS

A π-bond can form between carbon and oxygen (C=O) or carbon and nitrogen (C=N). As with all double bonds, there is with one strong σ-bond and one weaker π-bond. In addition, molecules that contain N=N bonds, N=O bonds, and O=O bonds will be encountered from time to time. It is also possible to form triple bonds between carbon and nitrogen (C≡N) with one strong σ- and two weaker π-bonds.

5.6.1 THE CARBONYL FUNCTIONAL GROUP, C=O

The structural unit with one π- and one σ-bond between a carbon and oxygen, C=O, is called a *carbonyl*. Both the carbon and the oxygen are sp^2 hybridized. Formaldehyde, $H_2C{=}O$, is the simplest example with two hydrogen atoms attached to the carbonyl carbon. As seen in Figure 5.7, the unshared electrons are orthogonal to the π-bond and coplanar with the atoms. The H—C=O bond angle is ~120°, consistent with sp^2 hybridization, making the carbon, oxygen, and the hydrogen atoms all coplanar. Since the oxygen of the C=O unit is more electronegative than carbon the carbonyl is polarized such that the carbon is δ^+ and the oxygen is δ^- as shown,

Aldehydes and Ketones

5.6.2 ALDEHYDES AND KETONES

Aldehydes or ketones have a C=O unit with an attached hydrogen atom or carbon groups. If at least one of the groups is a hydrogen atom the functional group is called an *aldehyde* with

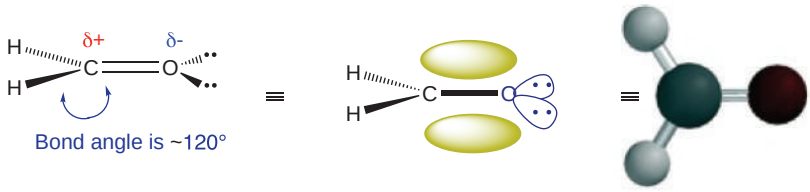


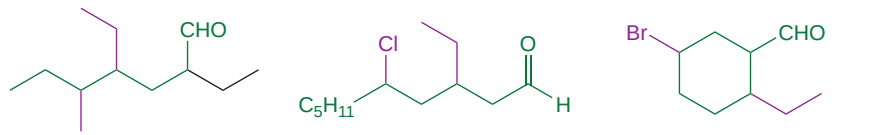
FIGURE 5.7 The carbonyl group in formaldehyde.

a H–C=O unit (see the red box). This group is abbreviated as CHO. All aldehydes except formaldehyde have one hydrogen and one carbon group attached to the carbonyl carbon. If two carbon groups (two alkyl groups) are attached to the carbonyl carbon, the generic formula is $R_2C{=}O$ and the functional group is called a *ketone.*

The nomenclature systems for an aldehyde and a ketone are slightly different. Aldehydes use a suffix derived from the first two letters of ***al***dehyde, *-al*. The carbonyl carbon is the locant and takes priority so *in all cases* the lowest number is 1 because all aldehydes have a hydrogen attached to the carbonyl unit. Therefore, the number is omitted. Substituents attached to the aldehyde chain are named in the usual manner relative to the carbonyl carbon. The nomenclature rules concerning substituents are the same as for other functional groups. The two most simple aldehydes are formal (the common name is formaldehyde, HCHO) and ethanal (the common name is acetaldehyde, CH_3CHO). Formaldehyde has been detected in interstellar space and many products are manufactured using formaldehyde, including many useful polymers and resins. Formaldehyde is a bactericide and a fungicide and it is used for tissue preservation, for embalming and as a disinfectant. Acetaldehyde is produced by the partial oxidation of ethanol (Section 15.2) and may contribute to hangovers.

An example that illustrates the nomenclature of more structurally complicated aldehydes is 2,4-diethyl-5-methylheptanal, where the longest chain that contains the aldehyde C=O with two ethyl groups and a methyl group. Note the shorthand notation of CHO for the aldehyde. 5-Chloro-3-ethyldecanal is another example. Note that five of the carbon atoms in the longest chain are shown in condensed notation, C_5H_{11}. When a carbonyl unit is in a chain of carbon atoms that contains a C=C or a C≡C unit, the carbonyl has a higher priority, and the carbonyl carbon is the locant and receives the lowest number.

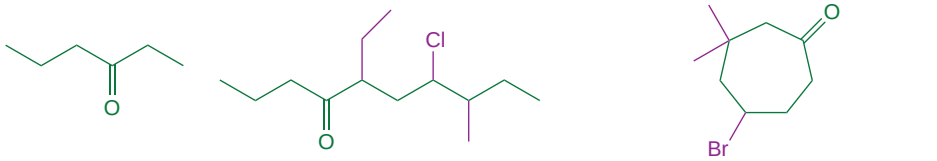
5.18 Draw the structure of 2,2,4,4-tetramethyl-5-(2-chloro-1-propyl)-decanal.



When the aldehyde unit (-CHO) is attached to a ring, a major modification in the name is required. Rather than name such compounds as the *incorrect* "cycloalkylmethanal," the IUPAC rules first name the ring and then add the word *carbaldehyde*. Substituents are numbered relative to the CHO unit at C1, and different substituents are arranged alphabetically. An example is 5-bromo-2-ethylcyclhexane-1-carbaldehyde. This nomenclature rule should be used for all aldehydes where the CHO unit is attached to a ring.

5.19 Draw the structure for hex-4-ynal.
5.20 Draw the structure of 3-chlorocyclopentanecarbaldehyde.

A ketone contains a carbonyl group attached to two alkyl groups and the suffix for ketones derives from the last three letters of ket**one**, *-one*. When numbering the longest chain, the carbonyl is the locant, so the *carbonyl carbon* receives the lowest possible number. The six-carbon straight-chain ketone with the carbonyl carbon at C3 is hexan-3-one.



Hexan-3-one 7-Chloro-5-ethyl-8-methyldecan-4-one 5-Bromo-3,3-dimethylcycloheptanone

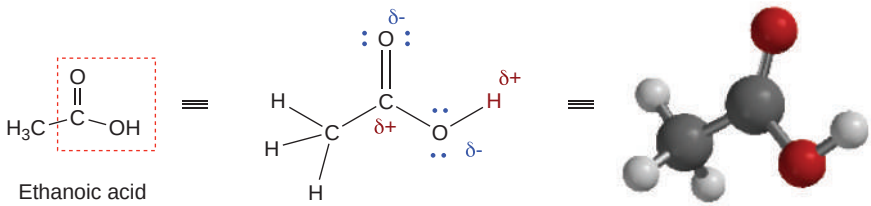
Substituents are handled in the usual manner and they are given the lowest number relative to the position of the carbonyl carbon, as in 7-chloro-5-ethyl-8-methyldecan-4-one. Cyclic ketones are possible, but contrary to aldehydes, *the carbonyl carbon is part of the ring* and is always numbered 1. Substituents are numbered accordingly. In 5-bromo-3,3-dimethylcycloheptanone, the carbonyl unit is part of a seven-membered ring. The ring is numbered toward the bromine atom, which is listed before the methyl groups (*b* before *m*).

5.21 Draw 3,6-dibromo-5-ethyldecan-4-one.

Carboxylic Acids

5.6.3 CARBOXYLIC ACIDS, CARBOXYLIC ANIONS, AND RESONANCE

An important functional group has a carbon atom (alkyl group) attached to a carbonyl (C=O) but an hydroxyl (OH) group is attached to the carbonyl carbon. This unit is known as a *carboxyl group*, which is the functional group for the class of organic molecules known as



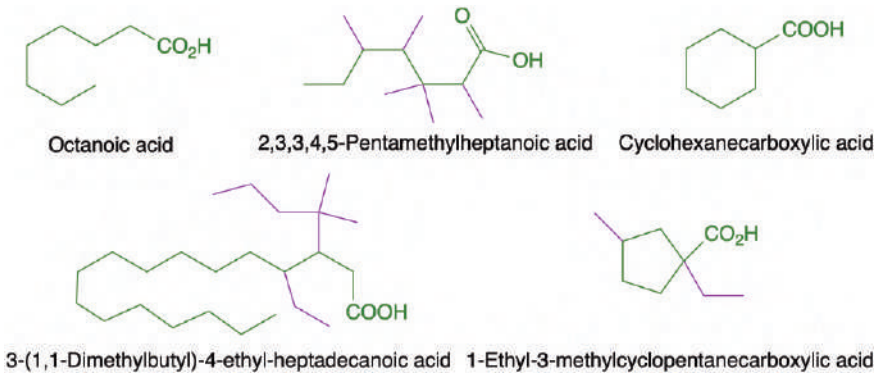
Ethanoic acid
(Acetic acid)

FIGURE 5.8 Structure of ethanoic acid.

carboxylic acids. The carboxyl unit for ethanoic acid (the common name is acetic acid) is shown in a box in Figure 5.8. The *carboxyl* functional group can also be written as –COOH or $-CO_2H$. The carboxyl group has an O—H unit attached to a carbonyl, and the two oxygen atoms and two carbon atoms are coplanar due to the presence of sp^2 hybridized carbonyl carbon. Ethanoic acid has the highly polarized carbonyl with an induced dipole of the $^{\delta-}O—H^{\delta+}$ unit. Because of this polarization the proton is acidic (Section 6.2.1). Ethanoic acid is also drawn as a ball-and-stick model.

Nomenclature for carboxylic acids identifies the longest continuous chain for the acid, which *must* contain the CO_2H unit. The carboxyl carbon is always C1 so it is omitted from the name. The suffix for carboxylic acids is *-oic acid*, and the word "acid" is separated from the first part of the name. Carboxylic acid nomenclature is first illustrated by the 8-carbon acid, octanoic acid. All substituents are assigned numbers based on C1 for the carboxyl group, as

in 2,3,3,4,5-pentamethylheptanoic acid. Complex substituents are accommodated as with all other compounds, illustrated by 3-(1,1-dimethylbutyl)-4-ethyl-heptadecanoic acid. Note that the substituted butyl group (b) group precedes the ethyl group (e) in the 17-carbon chain.



Naming a cyclic carboxylic acid in which a COOH unit is attached to a ring uses the same the protocol as aldehydes. The ring is named, followed by the term *-carboxylic acid*. One example is cyclohexanecarboxylic acid, where the carboxylic group is attached to the six-membered ring. Substituents are numbered relative to the point of attachment of the carbonyl carbon of the COOH unit, which is always 1, as in 1-ethyl-3-methylcyclopentane-carboxylic acid. A carboxylic acid with two COOH units is known as a dicarboxylic acid, or a dioic acid. The molecule $HO_2C(CH_2)_3CO_2H$, for example, could be named 1,5-pentanedioic acid but the two carbonyl units must be at the ends of the molecule to be carboxyl units, so the 1- and 5- are redundant. The name is just pentanedioc acid. A discussion of these compounds, and more about the nomenclature of carboxylic acids is presented in Section 18.1.

5.22 Draw the structure of 1-methylcyclohexanecarboxylic acid.

5.23 Draw the structure of 3-chloro-4-methylheptanoic acid.

5.24 Draw the structure of 3,4-diethylhexanedioic acid.

A carboxylic acid is much stronger Brønsted-Lowry acid (pK_a 1–5) than an alcohol (pK_a 16–18). The greater acidity of the carboxylic acid is largely due to the stability of the resonance-stabilized conjugate base that is formed (Sections 6.2,3). The reaction of formic acid and a base, for example, gives a carboxylate anion (the formate anion) as the conjugate base (see Figure 5.9). Note that the formate anion has one atom (O) with a negative charge adjacent to the p-orbitals of a π-bond (C=O). In the formate anion, the p-orbital of the negatively charged oxygen atom and the p-orbitals of a π-bond are adjacent and parallel. Those three orbitals overlap, and the electron density is delocalized to generate a resonance stabilized anion. In other words, when three orbitals are on adjacent atoms and are parallel, electron density is shared and dispersed (delocalized) over all three atoms. Due to resonance, there are four electrons (two from the π-bond and two from the negative charge) dispersed over the larger surface area of three atoms (delocalized) as represented in Figure 5.9 rather than localized on a single negatively charged oxygen. In the methoxide anion, which is the conjugate base of methanol, the charge is localized on the oxygen atom as shown. The delocalized structure of the formate anion is lower in energy than a structure that has the charge localized on a single oxygen atom. Dispersal of a charge over a larger area makes the anion (the conjugate base) less reactive (more stable) so it is a weaker base, and the K_a is larger, so the species is more acidic, as noted in Sections 2.6 and 6.3.

5.25 Draw all reactants and final products formed when 4-methylhexanoic acid reacts with $NaNH_2$.

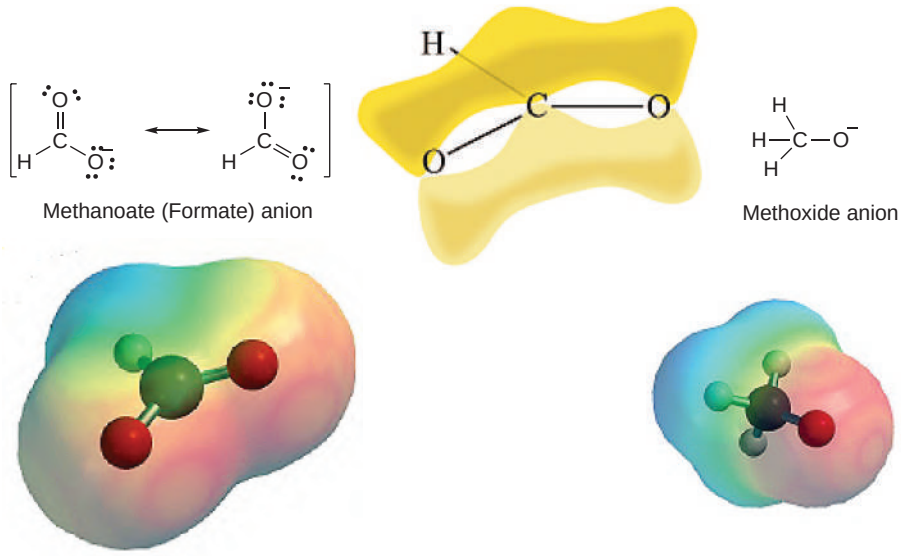


FIGURE 5.9 The methoxide anion and resonance delocalization in the methanoate (formate) anion.

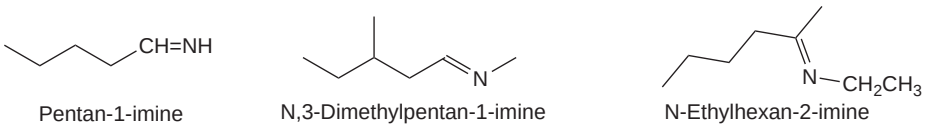
The formate anion has two *resonance contributors. A double-headed arrow is used to indicate resonance.* The two resonance contributors represent *one* resonance-stabilized anion, not two different molecules. In the two resonance contributors for the formate anion, the oxygen atoms are more electronegative than the carbon atom. In other words, there is more electron density on the oxygen atoms rather than on the carbon. This fact is represented by the δ^+ and δ^- in the structures in Figure 5.9. The localized charge is shown in the electron density map of the methoxide anion, and when compared to the electron density map of the formate anion, charge dispersal is clear in the latter as shown by the higher electron density (red) on the two oxygen atoms.

5.26 The species $H_2C{=}CH\text{-}CH_2^+$ is resonance stabilized. Using Figure 5.9 as an example, draw a similar picture to show the resonance contributors and indicate on which atoms the positive charge is higher.
5.27 Is the neutral acid HCOOH resonance stabilized? Briefly explain.

Imines (C=N) and Nitriles (C≡N)

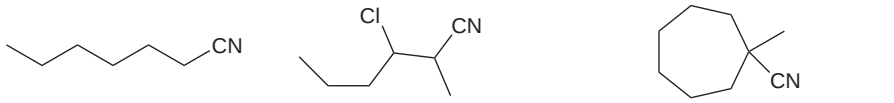
5.6.4 DOUBLE AND TRIPLE BONDS TO NITROGEN

Just as there are functional groups with a C=C or a C=O unit, there is a class of compounds with a C=N unit. These compounds are known as *imines*, and an example is pentan-1-imine. Both the carbon and the nitrogen atoms of imines are sp^2 hybridized. The nomenclature uses *-imine* as the suffix and the C=N unit is part of the longest continuous chain. In pentan-1-imine, the carbon of the C=N unit is part of a five-carbon chain, and it is the locant, so it is given the lowest number. Substituents attached to carbon are assigned a number in the usual manner, but substituents attached to nitrogen are given the designation *N-*, as with amines (Section 5.6.3). Another example is *N*,3-dimethylpentan-1-imine. The carbon of the C=N unit can be attached to a carbon further down the longest chain, as in *N*-ethylhexan-2-imine, where the carbon of the C=N unit is attached to C2 of a six-carbon chain, and there is an ethyl substituent on nitrogen. Since *N*-ethylhexan-2-imine is derived from a ketone, it is generically called a *ketimine*, whereas pentan-1-imine and *N*,3-dimethylpentan-1-imine are derived from aldehydes, and each is an *aldimine*. Chemical reactions that produce imines will be discussed in Section 16.4.3.



Pentan-1-imine N,3-Dimethylpentan-1-imine N-Ethylhexan-2-imine

Triple bond units are found in molecules other than alkynes. A carbon-oxygen triple bond is possible ($C{\equiv}O^+$), but the oxygen must take on a charge of +1 (Section 7.3). This cation is considered to be a reactive intermediate (Section 7.2). Compounds that have a carbon-nitrogen triple bond (C≡N; known as a *cyano group*) are common and they are known as *nitriles*. Both the carbon and the nitrogen atoms are sp hybridized. Heptanenitrile has the C≡N unit attached to a six-carbon chain, so it is a seven-carbon molecule and the prefix *hepta-* is used. In other words, the C≡N carbon is part of the longest chain but cyano is the locant and the carbon of the CN is always 1. Substituents are numbered relative to the CN carbon, as in 3-chloro-2-methylhexanenitrile. As with aldehydes and carboxylic acids, the CN unit can be attached to a ring, and the proper nomenclature term is *carbonitrile*. The example shown is 1-methylcycloheptanecarbonitrile. Reactions that give nitriles will be discussed in Section 11.3. All examples shown use the shorthand CN for C≡N. This abbreviation is used throughout the book, and the triple bond is understood to be between carbon and nitrogen.



Heptanenitrile 3-Chloro-2-methylhexanenitrile 1-Methylcycloheptane-1-carbonitrile

5.7 ACID-BASE PROPERTIES OF FUNCTIONAL GROUPS

Acid-Base Properties of Functional Groups

The functional groups alkenes, alkynes, alkyl halides, amines, alcohols, thiols, and ethers were introduced in the previous sections. Consistent with the acid-base theme of this book, the acid-base properties of these functional groups will be introduced in this section. Carboxylic acids are clearly Brønsted-Lowry acids, as introduced in Section 5.6.3. Terminal alkynes, alcohols, and thiols are weak Brønsted-Lowry acids.

The pK_a of a terminal alkyne such as prop-1-yne is about 25, the pK_a of methanol is 15.5 and methanethiol has a pK_a of about 10.4. As shown in Figure 5.10, prop-1-yne reacts with

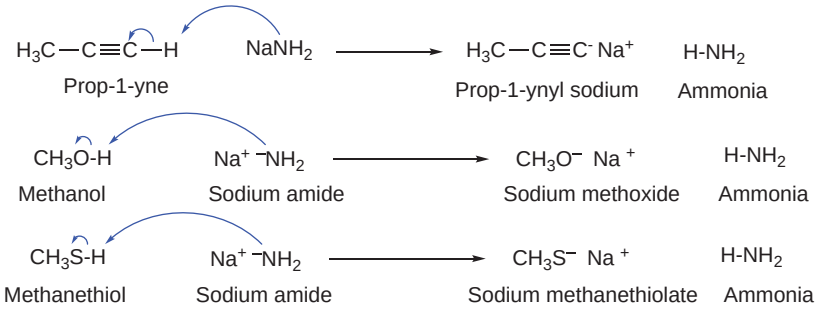


FIGURE 5.10 Acid-base reactions of prop-1-yne methanol and methanethiol with sodium amide.

sodium amide to generate the conjugate base prop-1-ynyl sodium and ammonia is the conjugate acid. The reaction with methanol generates sodium methoxide as the conjugate base and ammonia as the conjugate acid. Likewise, methanethiol reacts to give sodium methanethiolate, the conjugate base and ammonia as the conjugate base. The hydrogen atoms on the carbon atom adjacent to the carbonyl in ketones, aldehydes and carboxylic acids are weak acids, as will be discussed in Section 20.1.

All the functional groups shown in Figure 5.11 can react as Brønsted-Lowry bases. If an amine reacts as a base with a Brønsted-Lowry acid (H^+), the N donates two electrons to form a new covalent bond in the conjugate acid, an ammonium salt. Ammonium

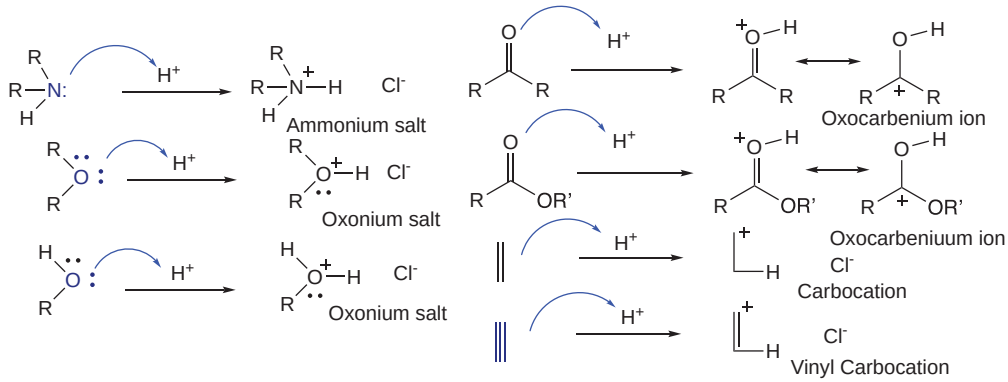


FIGURE 5.11 Reactions of functional groups as Brønsted-Lowry bases.

salts are rather stable, and they are weak acids. Ethers and alcohols are weaker electron donors than the amine and in a reaction with H^+, and the conjugate acid is an oxonium salt. Oxonium salts usually react as intermediates (Section 7.2). With two carbon groups on oxygen the oxygen of an ether is expected to be more electron-rich oxygen relative to the oxygen of the alcohol, which has only one electron-releasing carbon group. Therefore, ethers are stronger bases than alcohols also generate an oxonium ion as a reactive intermediate. The carbonyl of both an aldehyde and a ketone will react with a strong acid to generate a reactive resonance stabilized oxocarbenium ion. Carboxylic acid derivatives (Sections 18.2,4) react with a strong acid to give a reactive resonance stabilized oxocarbenium ion. Alkenes are rather weak bases, but they react with acids (H^+) to yield a carbocation, a reactive intermediate that will be introduced in Section 7.2. An alkyne reacts similarly with H^+, to yield a so-called vinyl carbocation, to be discussed in Section 10.8.1. The reaction of alkenes and alkynes as bases is the basis for the chemical reactions presented in Chapter 10. In terms of base strength, amines > ethers > aldehyd e,ketones ~ carboxylic acid derivatives > alkenes > alkynes.

The functional groups just described also react as Lewis bases with Lewis acids such as boron trifluoride (BF_3). An amine is a good electron donor and reacts readily with BF_3 to form the corresponding ammonium salt "ate" complex (Sections 2.7 and 6.8). Both ethers and alcohols react readily with BF_3 to form oxonium salt ate complexes, but both are weaker Lewis bases when compared to amines. Aldehydes, ketones and carboxylic acids are reasonably good Lewis bases with BF_3.

5.28 Draw the product for when diethyl ether reacts with boron trifluoride.

Physical Properties

5.8 PHYSICAL PROPERTIES AND INTERMOLECULAR FORCES

A *physical property* of an organic compound is characteristic of that molecule and can be measured experimentally. The temperature at which a compound boils or melts, for example, is a physical property of the molecule. Physical properties can be used to characterize and identify a compound since the complete set of physical properties of an individual molecule are usually unique. Bond polarization has a profound influence on physical properties and chemical properties. Functional groups therefore exert a great influence on the physical properties of a molecule. An alcohol has different physical properties than an amine, for example, and both are different than a carboxylic acid.

5.8.1 BOILING POINT

Boiling point is defined as the temperature at which a liquid and the vapor (gas) above it are in equilibrium. Most boiling points are recorded at normal atmospheric pressure, which is 101,325 Pa (1,013.25 mbar), equivalent to 760 mm Hg (29.9212 inches Hg,) or 14.696 psi. Several structural factors are important in determining the boiling point of a liquid including the non-bonded interactions of the atoms in the molecule. Heating is required to disrupt these intermolecular interactions. In addition, the boiling point generally increases with an increase in the number of atoms, which increases the mass. The number and type of heteroatom functional groups play an important role. Liquids boil at a lower temperature under vacuum.

5.29 Which has the higher boiling point, an eight-carbon alcohol or an eight-carbon ether? Briefly explain.

The boiling point of molecules is influenced by forces that lead to attraction between molecules, even when there are no polarized bonds. When two ethane molecules come close together, the molecules are attracted to one another as illustrated by Figure 5.12. There is no dipole in ethane. However, electrons are constantly moving, and an atom or molecule can develop a temporary dipole when its electrons are unsymmetrically distributed about the

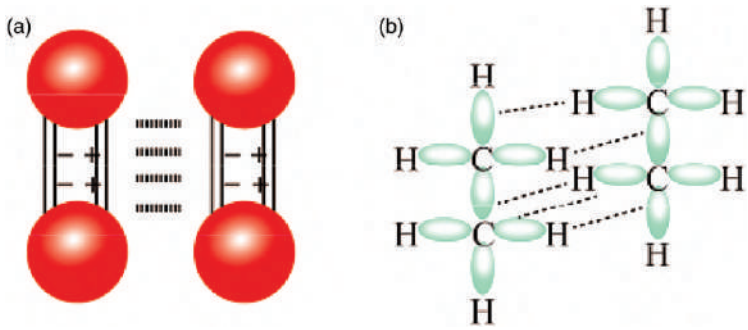


FIGURE 5.12 Attractive London Forces in ethane.

nucleus. In other words, the electron cloud around a nonpolar atom will fluctuate to generate a transient shift in electron density that leads to a dipole. This dipole will induce a dipole in an oppositely polarized nearby atom (Figure 5.12a). This is an extremely weak attraction between molecules known as a *London force* after Fritz Wolfgang London (Germany-USA; 1900–1954). This attractive force is also known as *van der Waal's force* after Johannes Diderik van der Waals (Netherlands; 1837–1923). The induced dipole results from close contact, so the larger the surface area of the molecule the greater the van der Waal's interaction. Branched alkanes have a smaller surface area and a lower boiling point than their straight-chain isomers. In general, this weak force is easily disrupted by application of small amounts of energy, so the boiling point of alkanes is low.

A molecule with polarized bonds (Section 3.8.2) has a dipole moment and it is considered to be polar. For molecules with similar molecular weights, those with polarized bonds have a higher boiling point when compared to a nonpolar molecule. When the polarized atoms in an alkyl halide (e.g., fluoromethane) come into close proximity with another molecule of fluoromethane, illustrated in Figure 5.13, the δ^+ carbon of one molecule is attracted to the δ^- fluorine of the second molecule. This electrostatic attraction is called a *dipole-dipole interaction*. It is much ***stronger*** than London forces, which are also present. Indeed, more energy (heat) is required to overcome dipole-dipole interactions and the boiling point is higher. The change in boiling point is large when comparing molecules with similar mass. The boiling point of fluoromethane (34 g mol^{-1}) is -37.1 °C and that of ethane (30 g mol^{-1}) is -89 °C. Dipole-dipole interactions occur between any two molecules that have a polarizing atom or group.

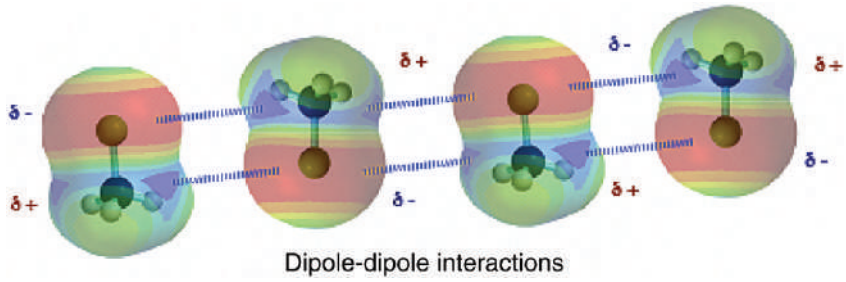


FIGURE 5.13 Attractive dipole-dipole interactions in fluoromethane.

A special type of dipole-dipole interaction occurs between molecules when one atom of the dipole is a hydrogen, as in the O—H bond of an alcohol. When the O—H of one methanol molecule comes into close proximity with the O—H unit of a second molecule of methanol there is a strong dipole-dipole attraction. The positively polarized hydrogen is attracted to the negatively polarized oxygen. This $O^{\delta-}$------$H^{\delta+}$ interaction leads to a large dipole. This attractive force is much stronger than a common dipole-dipole interaction and is called a *hydrogen bond*. Figure 5.14 shows an array of *several* methanol molecules attracted to each other by hydrogen bonds. A hydrogen bond is strong, much more energy is required to disrupt it, and the boiling point is expected to be high. The boiling point of methanol (32 g mol^{-1}; 64.7 °C), for example, is much higher than that of fluoromethane (34 g mol^{-1}; -37.1 °C), which is higher than that of ethane (30 g mol^{-1}; -89 °C). The hydrogen bonding of a more acidic hydrogen atom in an OH unit is greater and makes the boiling point higher. Formic acid (46.03 g mol^{-1}; 100.8 °C) has a higher boiling point than ethanol (46.07 g mol^{-1}; 78.4 °C).

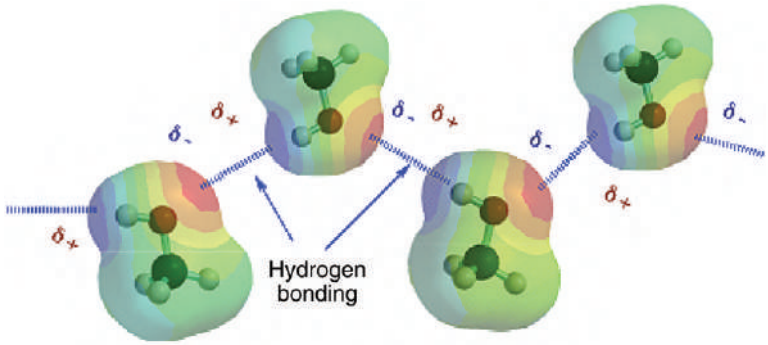


FIGURE 5.14 Hydrogen bonding in methanol.

Water is a common solvent and frequently used in reactions with organic molecules. It is therefore important to mention that water can form strong hydrogen bonds to itself as well as to molecules that contain a polarized X—H bond (X is usually, O, S, N, etc.). Examples are water with alcohols, water with amines, and water with carboxylic acids. Hydrogen bonding is *not* possible with alkane or alkenes since there are no polarized bond in those molecules. Indeed, water and hydrocarbons are usually insoluble (Section 5.8.2)

5.30 Which molecule will form the stronger hydrogen bond to the water hydrogen bond, methanamine (CH_3NH_2) or methanol (CH_3OH)?

5.8.2 SOLUBILITY

"Like-dissolves-like" is an old axiom in chemistry. The term *dissolve* is formally defined as "to cause to pass into solution" or "to break up." The term "solubility" refers to one molecule *dissolving* in another, so the molecules mix together such to give one phase (one layer). If

two things are not mutually soluble (like oil and water), two phases (two layers) are formed. Solubility differs with different compounds and with the amount of material. The formal definition of solubility is the "mass of a substance contained in a solution that is in equilibrium with an excess of the substance." The accepted definition defines the number of grams of one molecule (the *solute*) that can be dissolved in 100 g of the second compound (identified as the *solvent*). This definition is dependent upon the temperature since more solute can usually be dissolved in a hot solvent than in a cold solvent. One molecule can be *partially soluble* in another so that some of it dissolves in 100 g, but two phases are formed. The word *miscible* is often used interchangeably with complete solubility.

In the context of the solubility definition, a polar compound will dissolve in another polar compound, but not very well in nonpolar compounds and vice-versa. An alkane should therefore dissolve in another alkane, or in most hydrocarbons, but not in the polar molecule water. Solubility is influenced by the polarity of the functional group. A heteroatom functional group in a molecule of less than five carbons is considered polar and soluble. A molecule with more than eight carbons and one polar functional group may be considered nonpolar. Compounds of 5–7 carbon atoms are difficult to categorize using this simplistic criterion.

5.8.3 MELTING POINT

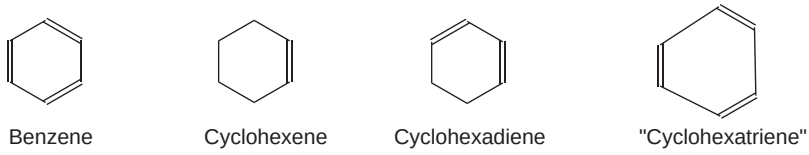
The *melting point* is defined as the temperature at which the solid phase of a molecule and the liquid phase of that molecule are in equilibrium. In general, the melting point of a compound increases as the molecular weight of that compound increases. A molecule in the solid phase can exist as a regular array of atoms called a crystal lattice. Such molecules will have a higher melting point since it takes more energy to disrupt these intermolecular forces. The shape, geometry, and "packing" of molecules within this lattice has a great effect on melting point. Sodium chloride, an inorganic compound, packs into a regular and rigid crystal array to form rectangular crystals. An organic molecule such as the alkane tetradecane is rather flexible and packing tetradecane molecules into a regular array is much like trying to pack worms into a can. The flexibility is due to rotation about each of the C—C covalent bonds, as will be discussed in Section 8.1. Since tetradecane does not pack into a regular crystal array, it is expected to have a lower melting point. This effect is perhaps best illustrated by comparing two organic molecules of similar mass. An "irregular" compound (e.g., undecane) is compared with a "compact" molecule (e.g., carbon tetrachloride). Compact molecules may pack into a regular array to form a rigid and strong structure, but an irregular compound cannot. For molecules that have relatively close masses, more energy is required to disrupt a rigid structure, so it is expected to have a higher melting point. Indeed, undecane (156.3 g mol^{-1}) has a melting point of -26.5 to -25°C but carbon tetrachloride (153.8 g mol^{-1}) has a melting point of -9.3°C.

5.31 Which compound should have the higher melting point, CCl_4 or CH_3Cl? Briefly explain.

5.9 BENZENE: A SPECIAL CYCLIC HYDROCARBON

Benzene

Sections 5.1 and 5.3 discuss the structure of alkenes and alkynes, which are hydrocarbons that have localized π-bonds. In those sections, cyclic alkenes and cyclic dienes are discussed. The molecule known as *benzene* is a hydrocarbon derived from petroleum distillates and has the formula C_6H_6. Although the structure shown for benzene looks like a cyclic triene, it is very different from alkenes or alkynes in its chemical properties (see Chapter 19). Benzene is the parent compound for a class of compounds known as *aromatic hydrocarbons*, where the term *aromatic* refers to the special stability imparted by the six π-electrons in benzene when they are confined to a ring (Sections 19.1 and 19.7).



In cyclohexene and cyclohexadiene the structures have one or two π-bonds where the electrons are localized between the sp^2-hybridized carbons. The bond length of a standard C=C unit is ~133 pm (1.33 Å) and that of a standard C—C unit is ~ 148 pm (1.48 Å). If "cyclohexatriene" exists, it should have a "long-short" bonding pattern illustrated by a structure with exaggerated bond lengths for the C=C and C—C units. It is *not* cyclohexatriene since the measurements for benzene show that all C—C bond lengths are *identical*, ~ 139 pm (1.39 Å). The bonds are not localized as shown in the structure but rather delocalized. The structure of benzene is different than cyclic alkenes, with different chemical proprieties.

Examination of benzene shows that all six carbons of benzene are sp^2 hybridized. Each carbon has a trigonal planar geometry with a p-orbital that is perpendicular to the plane of the carbon atoms as shown in Figure 5.15. A π-bond is defined as the "sideways" overlap of two adjacent p-orbitals (Section 5.1), so it is reasonable to expect that the six parallel and contiguous sp^2 hybridized carbons with p-orbitals in the ring will share the electron density

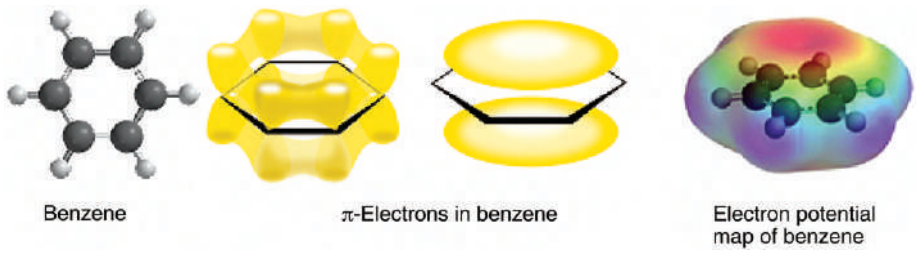
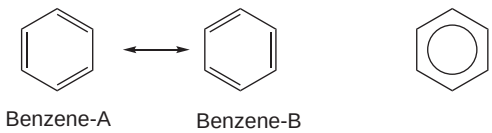


FIGURE 5.15 Electron delocalization in benzene.

of six π-electrons. In other words, *the electron density is delocalized.* Delocalization in this type of cyclic π-system is *resonance*, and when confined to a ring it is known as *aromaticity*. An electron potential map is shown that clearly shows electron density (intense red) above and below the plane of the atoms, consistent with the aromatic π-cloud.

5.32 Is cyclohexadiene resonance stabilized? Briefly explain.

Two structures called *resonance contributors* are drawn for benzene to represent a resonance stabilized compound and delocalization of electrons. If drawn as *benzene-A*, all the π-bonds are localized. This single structure does *not* adequately represent the structure of benzene. If the double bonds are "moved" from their position in *benzene-A* to generate *benzene-B*, *benzene-B* is a different structure.

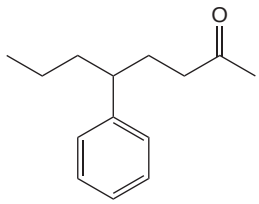


However, it is also inadequate since all the bonds are again localized. The actual structure of benzene is represented by *both* structures. They are resonance contributors that show the six π-electrons are delocalized over all six carbon atoms of the ring. A *double-headed arrow* is used to show the two resonance contributors. Note that the term resonance stabilized indicates that benzene is expected to be more stable. Benzene is sometimes represented as a six-membered ring with a circle in the middle to indicate the resonance. This circle represents the movement of electrons in aromatic ring. However, it is easier to show the movement

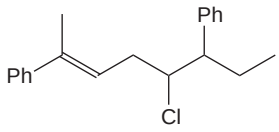
of electrons in chemical reactions (Sections 19.3,4,10–12) using benzene-A or benzene B structures. Therefore, the use of this "circle" representation is discouraged.

5.33 Which is likely to be more stable, benzene or cyclohexane? Briefly explain your answer.

Benzene is the parent of an entire class of molecules called *aromatic hydrocarbons* that will be discussed in detail in Chapter 19. Naming benzene derivatives is different from naming other types of molecules and will be discussed in Section 19.2. However, the benzene unit can be attached by one of the ring carbons to an alkyl chain. The benzene is then a substituent and the C_6H_5 unit is called *phenyl*. An example is 5-phenyloctan-2-one. A final note about nomenclature is required when a benzene ring is a substituent (a phenyl group). Drawing a benzene ring occupies more space that many other groups so the shorthand representation "Ph" is used to represent a phenyl substituent, as in 5-chloro-2,6-diphenyloct-2-ene.



5-Phenyloctan-2-one

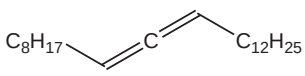


5-Chloro-2,6-diphenyloct-2-ene

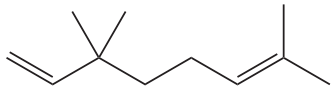
5.34 Draw the structure of 3,5-diphenyloctan-2-one; tetraphenylmethane.
5.35 Draw the structure of 3-phenylpentan-1-ol using the symbol Ph for the phenyl substituent.

5.10 BIOLOGICAL RELEVANCE

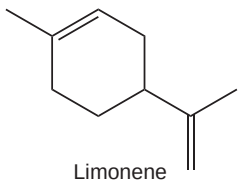
The structure and the biological importance of some terpenes was discussed in Section 5.4. Terpenes are major biosynthetic building blocks. They are the primary constituents of the essential oils of many types of plants and flowers. Many terpenes have direct physiological effects on the body, including linalool and limonene. Plants that contain linalool may have a calming effect and provide pain relief. Plants that contain limonene may be mood-elevating. Terpenes play a role in plant defense, disease resistance, the attraction of insects that are important for pollination, and many are antifeedants. Terpenoids are important in cell growth modulation and plant elongation, light harvesting and photoprotection, and membrane permeability and fluidity control. Some insects use some terpenes as a form of defense. In addition to terpenes, other π-bond-containing molecules are found in nature. The allene group, for example, is found in some insects. 9,10-Tricosadiene, for example, was isolated from a class of Australian insects (melolonthine scarab beetles).[4]



9,10-Tricosadiene



Linalool



Limonene

[4] See McGrath, M.J.; Fletcher, M.T.; König, W.A.; Moore, C.J.; Cribb, B.W.; Allsopp, P.G.; Kitching, W. *Journal of Organic Chemistry* 2003, 68, 3739–3748.

Ethene (common name ethylene) is introduced in Section 5.1. It has been used as an inhalation anesthetic to induce general anesthesia and it is a widely known alkene. What remains of the Oracle of Delphi is found in the ruins of the temple of Apollo on Mount Parnassus, near the ancient city of Delphi in Greece. Many in the ancient world consulted the oracle about important matters, from farmers planting their crops to Alexander the Great. The oracle was a priestess, known as a Pythia, who was believed to communicate with the gods while in a trance-like state. The Pythia sat in a small room as vapors, which reportedly had a sweet smell, issued from cracks in the floor and washed over her, causing her to fall into a trance. A priest would take money from a visitor, who would ask a question of the Pythia. The answer was usually very obscure, but the priest would translate the Pythia's words.[5] In recent times, geologists discovered that water in a spring near the ancient site of the oracle contains the hydrocarbons methane, ethane, and ethylene (ethene).[5] These gases were found in pieces of travertine, a limestone stalactite deposited by an ancient spring.[5] In the days of the Pythia, colliding tectonic plates near the Temple of Apollo are believed to have generated sufficient heat to vaporize the hydrocarbons, which were extruded as vapors in the chamber of the Oracle. The Pythia may have been in a state of ethylene narcosis,[6] known to produce states of euphoria and memory disturbances. Overexposure can lead to loss of consciousness and even death due to hypoxia.[7]

Ethene (ethylene) acts physiologically as a hormone in plants and plays a major role in the ripening process of climacteric fruit such as apples, tomatoes, etc.[8] Ethene exists as a gas and acts at trace levels throughout the life of the plant by stimulating or regulating the ripening of fruit, the opening of flowers, and the abscission (or shedding) of leaves.[9] Ethene biosynthesis begins from methionine and 1-aminocyclopropane-1-carboxylic acid (Sections 24.3,4) is formed as a key intermediate." [10]

Polarity and solubility are critical to the design and delivery of the drugs used as medicines, an area of chemistry known as medicinal chemistry. The so-called *partition coefficient* (distribution coefficient) is used as a measure of the ability of the drug to pass through relatively nonpolar lipid membranes from the highly polar environment of blood serum. This correlation has been used to predict the activity of potential drugs but is valid only when solubility and transport by diffusion though a membrane are important. The partition coefficient P is defined as[11]

$$P = \frac{\text{Drug in the Organic Phase}}{\text{Drug in an Aqueous Phase}}$$

[This equation is taken from Thomas, G. *Medicinal Chemistry, An Introduction*, John Wiley & Sons, Ltd., Chichester, NY, ***2000***, p. 123. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.]

The values of the partition coefficient are usually measured using water or a phosphate buffer at pH 7.4 (the pH of blood) against octan-1-ol.[11] A large value of P is taken as an indication that the compound will diffuse into lipid membranes and fatty tissue, whereas a low value of P indicates that it will not easily diffuse. A large value of P is associated with more water insoluble compounds, usually caused by a higher percentage of nonpolar organic fragments. Pharmacokinetics is the science that concerns itself with what the body does to a drug. The distribution coefficient is an important factor since a drug must first pass through lipid bilayers in the intestinal epithelium in order to be absorbed after oral ingestion. Pharmacodynamics is the science of what a drug does to the body. It is known that

[5] de Boer, J.Z.; Hale, J.R.; J. Chanton, J. *Geology* 2001, 29, 707–710.
[6] John Roach *National Geographic*, August 14, 2001.
[7] Clayton, G.D.; Clayton, F.E. (Eds.) *Patty's Industrial Hygiene and Toxicology: Volumes 2A, 2B, 2C: Toxicology*, 3rd ed. John Wiley & Sons, NY, 1981–1982, p. 3199.
[8] Pech, J.C.; Sharkawi, I.; Chaves, A.; Li, Z.; Lelièvre, J.M.; Bouzayen, M.; Frasse, P.; Zegzouti, H.; Latché, A. *Acta Horticulturae* 2002, 587, 489–495.
[9] Chow, B.; McCourt, P. *Gene Development* 2006, *20*, 1998–2008. (b) De Paepe, A.; Van der Straeten, D. *Vitamins and Hormones* 2005, 72, 399–430.
[10] Van Doom, W.G. *Annals of Botany* 2002, 89, 689–693.
[11] Thomas, G. *Medicinal Chemistry, An Introduction*, John Wiley & Sons, Ltd., Chichester, NY, 2000, p. 123.

hydrophobic drugs tend to be more toxic because they tend to be retained longer, have a wider distribution within the body, are somewhat less selective in their binding to proteins. In addition, they are often extensively metabolized.

CORRELATION OF HOMEWORK WITH CONCEPTS

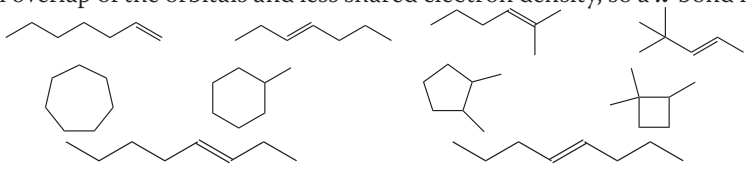
- A π-bond is formed by "sideways" overlap of p-orbitals on adjacent sp^2 hybridized atoms, is composed of a strong σ-bond and a weaker π-bond: 1, 2.
- Alkenes are hydrocarbons with a C=C unit. The generic formula is C_nH_{2n}: 3, 4, 8, 36, 45, 46, 49.
- Cyclic alkenes have the generic formula C_nH_{2n-2}: 5, 6, 47, 48.
- Alkynes are hydrocarbons with a C≡C unit, and the generic formula is C_nH_{2n-2}. 7, 8, 9, 45, 46, 49.
- Hydrocarbons with multiple bonds include dienes, diynes and allenes: 10, 11, 12, 45, 49.
- The structures of the functional groups for alcohols, amines, ethers, ketones, aldehydes, and carboxylic acids: 14, 15, 16, 17, 18, 19, 20. 21, 22, 23. 24, 44, 50, 51, 52, 53, 54.
- Amines contain a covalent bond to nitrogen and undergo fluxional inversion: 38.
- Each functional group has a unique suffix. 14, 15, 16, 17, 18, 19, 20. 21, 22, 23. 24, 44, 50, 51, 52, 53, 54
- Terpenes are cyclic and acyclic compounds with the formula $(C_5H_8)_n$. 13, 42.
- Several functional groups are Brønsted-Lowry acids: 24, 55.
- Several functional groups are Lewis bases or Brønsted-Lowry bases: 28, 56.
- Many physical properties result from the presence of polarized bonds: 29, 30, 31, 39, 40, 57.
- Dispersal of charge over several atoms via aligned p-orbitals is called resonance, and leads to greater stability: 26, 278, 32 37, 41, 43, 55, 56.
- Benzene is a unique cyclic hydrocarbon that is more stable than expected due to resonance delocalization. When benzene is a substituent in a molecule, it is called phenyl: 33, 34, 35, 47, 49, 50, 51, 53, 54.

ANSWERS TO IN-CHAPTER QUESTIONS

5.1 The hybridization of O in the C=O unit is sp^2 since it is one atom of a π-bond.

5.2 In an alkene, the electrons in the π-bond react since they are weaker (held less tightly) than the electrons in the σ-bond. The electrons in the σ-bond are localized along a line between the C nuclei, whereas the electrons in the π-bond are shared between the two carbon atoms above and below the plane of the C—C σ-bond. There is only partial overlap of the orbitals and less shared electron density, so a π-bond is weaker.

5.3

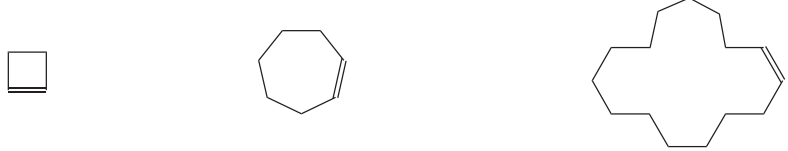


5.4

Oct-3-ene Oct-4-ene

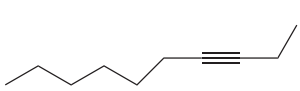
5.5 Two isomers with the formula C_5H_{10} are cyclopentane and pent-1-ene.

5.6

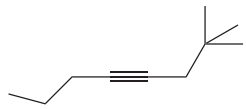


Cyclobutene Cycloheptene Cyclopentadecene

5.7

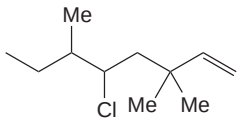


Dec-3-yne

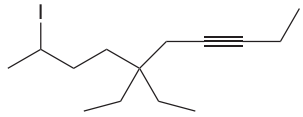


2,2-Dimethyloct-4-yne

5.8

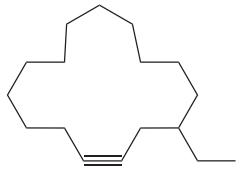


5-Chloro-3,3,6-trimethyloct-1-ene



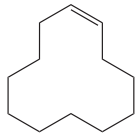
6,6-Diethyl-9-iododec-3-yne

5.9

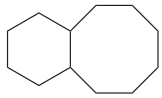


4-Ethylcyclopentadecyne

5.10



Cyclododecene

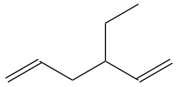


Bicyclo[6.4.0]dodecane

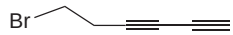
One molecule with the formula $C_{12}H_{22}$ is cyclododecene, a cyclic alkene with a ring and a π-bond. A second possilbity has two saturated rings fused together, as in bicyclo[6.4.0]dodecane.

5.11

Cyclopenta-1,3-diene

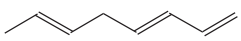


3-Ethylhexa-1,5-diene



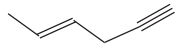
6-Bromohexa-1,3-diyne

5.12



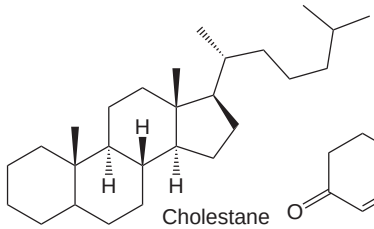
Octa-1,3,6-triene

Octa-1,4,7-triyne

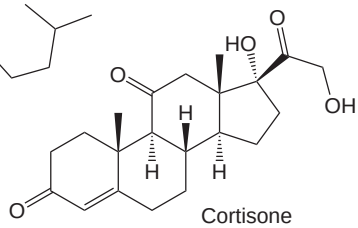


Hex-4-en-1-yne

5.13

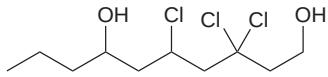


Cholestane



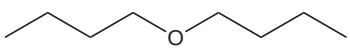
Cortisone

5.14

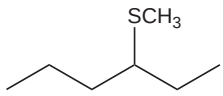


3,3,5-Trichlorodecane-1,7-diol

5.15

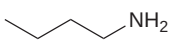


Dibutyl ether

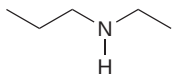


3-(Methylthio)hexane

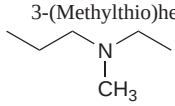
5.16



C_4 Primary amine

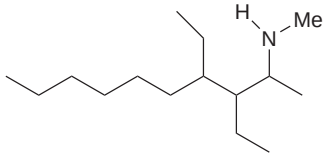


C_5 Secondary amine



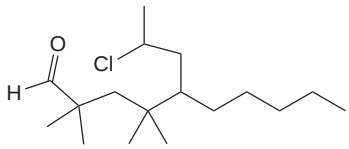
C_6 Tertiary amine

5.17



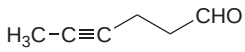
3,4-Diethyl-*N*-methyldecan-2-amine

5.18



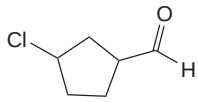
2,2,4,4-Tetramethyl-5-(2-chloro-1-propyl)-decanal

5.19



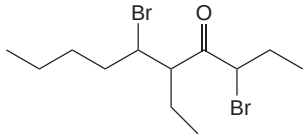
Hex-4-ynal

5.20



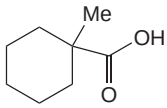
3-Chlorocyclopentanecarbaldehyde

5.21



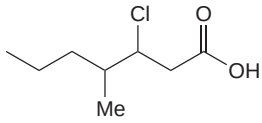
3,6-Dibromo-5-ethyldecan-4-one

5.22



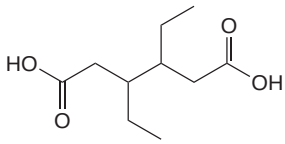
1-Methylcyclohexane-1-carboxylic acid

5.23



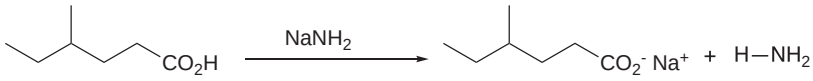
3-Chloro-4-methylheptanoic acid

5.24



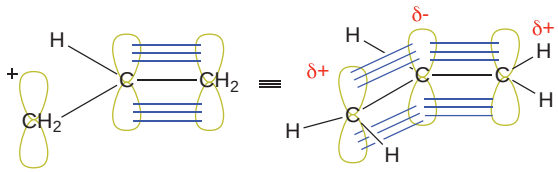
3,4-Diethylhexanedioic acid

5.25



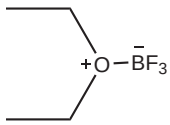
Sodium 4-methylhexanoate

5.26 The positive charge is greatest on the two terminal carbon atoms of this cation due to resonance. This is called an allyl cation.



5.27 No! There is no opportunity for resonance since there is no vacant p-orbital as in the carboxylate anion.

5.28



5.29 The eight-carbon alcohol with a H—bonding O—H unit will have a higher boiling point than an eight-carbon ether which has only dipole-dipole interactions. Octan-1-ol has a boiling point of 194.45 °C and dibutyl ether has a boiling point of 52 °C.

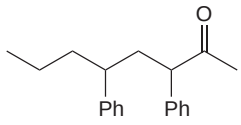
5.30 Since O is more electronegative than N, the O—H bond is more polarized than the N—H bond. The δ^+ dipole on H in an O—H unit is greater than that in a N—H unit and the H of OH is more acidic. There will be greater hydrogen bonding with the OH unit, which means that methanol will form stronger hydrogen bonds.

5.31 Carbon tetrachloride, CCl_4 is more symmetrical when compared to CH_3Cl, and those molecules should pack into a crystal lattice more efficiently. Therefore, CCl_4 has the higher melting point. It also has a higher formula weight. At -23 °C, CCl_4 melts at a much higher temperature than chloromethane at -97 °C.

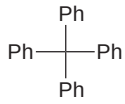
5.32 Cyclohexadiene is ***not*** resonance stabilized. There are π-electrons but there is not a continuous array and it is not possible for one "end" of the π-system to interact (delocalize electrons) to the other "end."

5.33 Benzene is more stable than cyclohexane. Benzene is stabilized by electron delocalization of the π-electrons. Cyclohexane has no π-electrons, so electron delocalization is impossible.

5.34

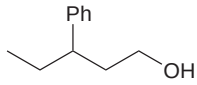


3,5-Diphenyloctan-2-one



Tetraphenylmethane

5.35



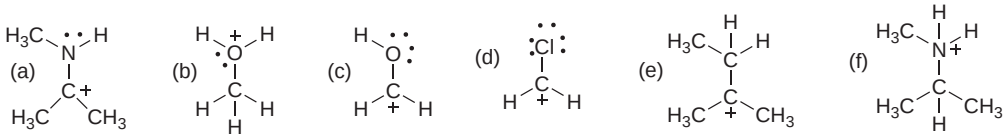
3-Phenylpentan-1-ol

HOMEWORK

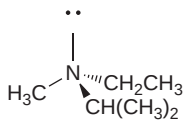
36. Categorize each of the following formulas as consistent with an alkane, alkene or alkyne:

(a) CCl_4 (b) CH_3OH (c) CH_3OCH_3 (d) $(CH_3)_4N^+$ (e) $CH(CH_3)_3$ (f) $ClCH_2Cl$

37. Examine each of the following cations and draw a resonance contributor with an X=X bond where it is appropriate. If no X=X structure is possible, briefly explain why not.

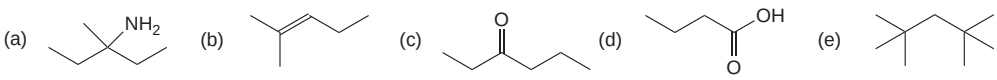


38. Draw both fluxional isomers for the amine shown. Are they the same? Explain your answer.

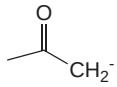
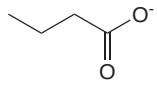


39. Rank order each of the following lists according to their boiling point, lowest to highest.
    (a) 2,4,5,5,6,6-Hexamethylheptan-2-ol, pentan-3-ol 2,3,4-trimethylpentan-3-ol
    (b) Butan-2-amine, 2-methylbutaonic acid, butan-2-ol
    (c) Chloromethane, methanamine, ethanoic acid

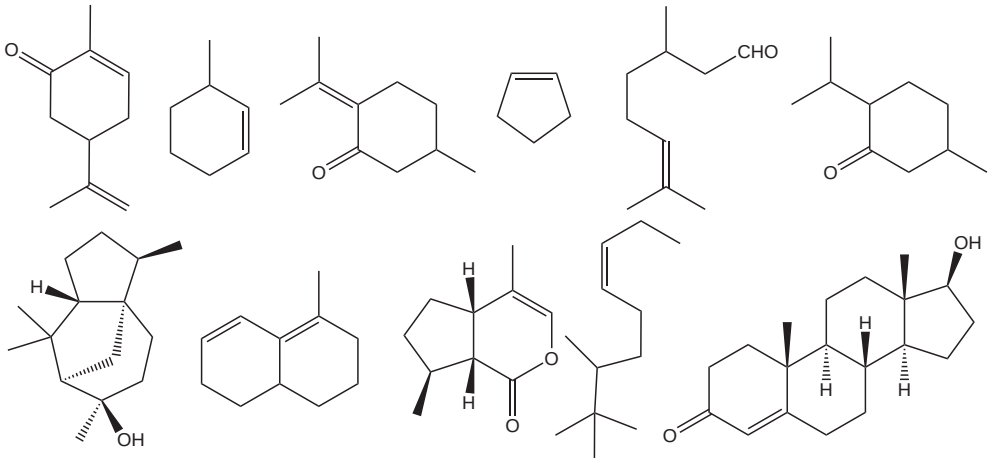
40. Indicate whether the boiling point of the following molecules is most influenced by London forces, dipole–dipole interactions, or by hydrogen bonding.



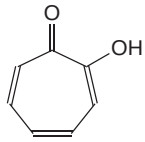
41. Indicate which of the following anions might be stabilized by resonance. Explain.

(a) CH_3O^- (b)  (c)  (d) 

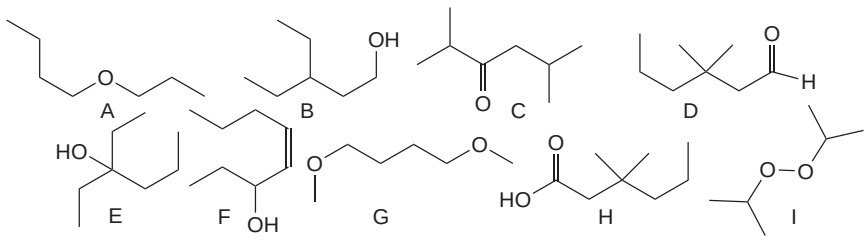
42. Classify the following as terpenes and/or terpenoids:



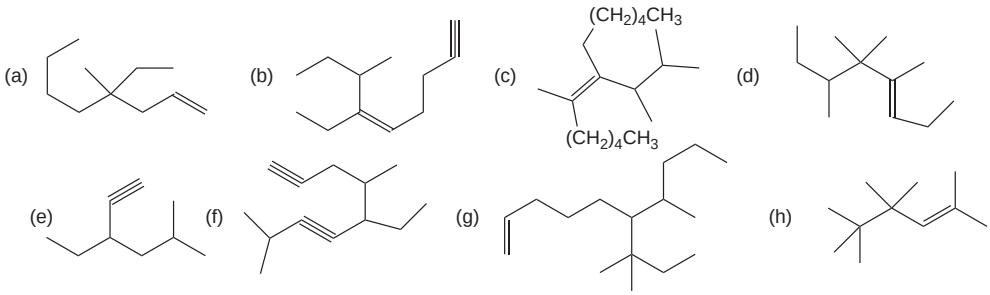
43. The following molecule is called tropolone and it reacts very similarly to a carboxylic acid to form a conjugate base when exposed to base. Offer an explanation.



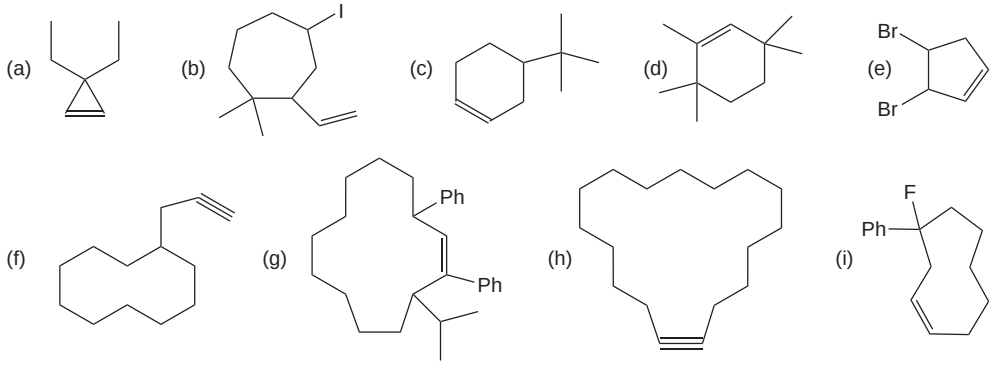
44. Determine which of the following structures are isomers:



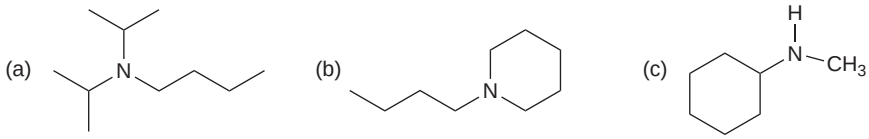
45. Draw the correct structure for each of the following:
    (a) 5-(2,2-Dimethylbutyl)hexadec-2-ene (b) 4,5,6,7-Tetraethyldodec-2-yne
    (c) 7,8-Di(1,1-dimethylethyl)pentadeca-1,3-diene
    (d) 1,3,3,5,5,6-Hexamethylcyclohexene
    (e) 1-Cyclopropyl-2-ethylcycloheptene (f) 5,5-Diethylnon-3-yne
46. Give the IUPAC name for each of the following:



47. Give the correct IUPAC name for each of the following cyclic alkenes:



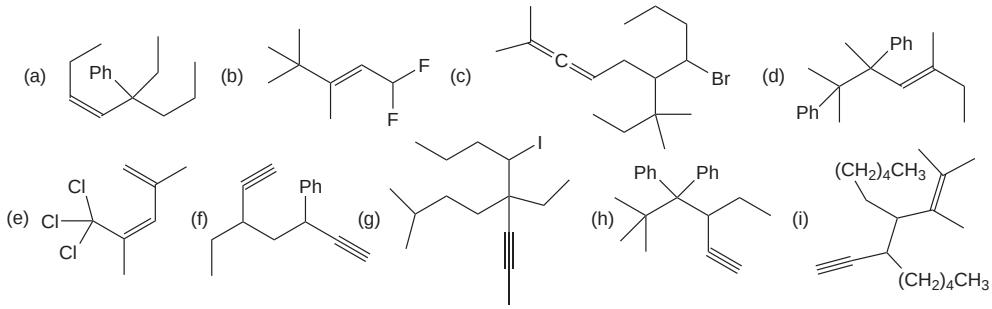
48. Draw the structure and provide the IUPAC name for 12 different molecules that have the empirical formula $C_{10}H_{20}$. Only *five* of these structures can contain a C=C unit.
49. Give the correct IUPAC name for the following amines:



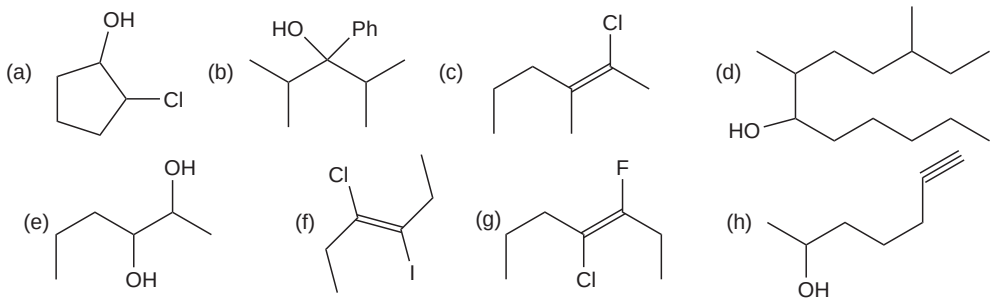
50. The methanesulfonate anion ($CH_3SO_3^-$) is *less basic* than the methoxide anion (H_3CO-).

    Draw *all* resonance structures for *all* molecules that exhibit resonance. Use the structures you have drawn to explain why the methanesulfonate anion is less basic.
51. Which of the following alkanes is likely to have the *highest* boiling point? Justify your answer.

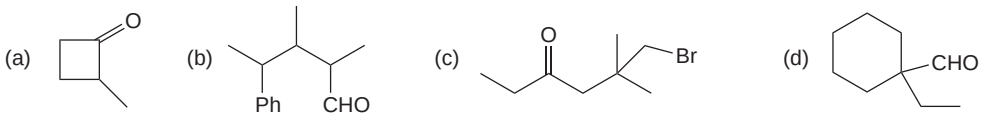
    CH_3CH_3 $CH_3CH_2CH_3$ $CH_3CH_2CH_2CH_2CH_3$
    $CH_3CH_2CH_2CH_2CH_2CH_3$
52. Provide the unique IUPAC name for each of the following molecules:



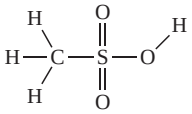
53. Give the name for each of the following molecules:



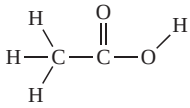
54. Draw the structure for each of the following:
    (a) 2-Methylcycloheptan-1-ol (b) 5,6-Diphenylheptan-2-ol
    (c) Hex-2-en-1-ol
    (d) 5-(3-Ethylhexyl)-8-chloropentadecan-1-ol (e) 3,4,5-Heptanetriol
    (f) 1,2,3,4,5,6-Hexamethylcyclohexanol (g) 4-Phenyloctane-1,8-diol
    (h) 3-Chlorononon-8-en-1-ol
55. Name the following ketones and aldehydes:



56. Draw the structure of the following molecules:
    (a) 8-Phenyloctanoic acid (b) 3,3,6,6-Tetrabromohexadecanoic acid
    (c) 2,5-Dimethylhexanedioic acid (d) 3-Chlorocyclohexane-1-carboxylic acid
57. Methanesulfonic acid has a much lower pK_a when compared to acetic acid.



Methanesulfonic acid



Acetic acid

(a) Draw the products expected of the acid–base reaction between methanesulfonic acid and NaOH, and also for the reaction of acetic acid and NaOH.
(b) Discuss why methanesulfonic acid has a lower pK_a relative to acetic acid. There is no need to do a calculation here. The answer should be a discussion-type answer.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-6.php

6

Acids, Bases, and Nucleophiles

The acid-base reaction is one of the most common reaction types in all of organic chemistry. Acid-base chemistry was reviewed in Chapter 2 in an effort to bridge the concepts learned in general chemistry with those in organic chemistry. Most of the reactions encountered in organic chemistry involve acid-base chemistry in one form or another. This chapter will discuss acid-base reactions and reactivity of organic molecules.

To begin this chapter, you should know the following points:

- Covalent σ-bonds (Section 3.3).
- Polarized covalent bonding (Section 3.8).
- π-Bonds (Sections 5.1, 5.3, and 5.6).
- Factors that influence bond strength. (Sections 3.7 and 7.5).
- K_a and pK_a (Sections 2.2, 2.4, 2.5, and 2.6).
- Lewis acids and Lewis bases (Sections 2.7).
- Structures and names of functional groups. (Sections 5.1, 5.3, 5.5, and 5.6).
- Acid-base properties of functional groups. (Section 5.7).
- Resonance (Sections 2.6 and 5.6.3).

6.1 ACID-BASE EQUILIBRIA

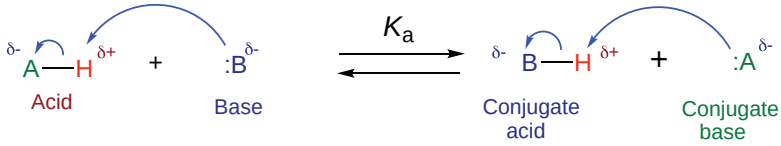
Acid-Base Equilibria

As discussed in Section 2.3, a generic Brønsted-Lowry acid-base reaction involves the reaction of an acid (A—H) with a base (B:) to yield a conjugate acid (B—H) and a conjugate base (A:) as the products. This is an equilibrium reaction, and the acidity constant K_a is a measure of the position of the equilibrium and the strength of an acid. The equilibrium constant K_a is also represented by pK_a = -log K_a. The pK_a and K_a are inversely proportional, so $K_a = 10^{-pKa}$. A Brønsted-Lowry acid-base reaction is simply a chemical reaction in which a base, which is electron-rich, donates two electrons to a proton, which is electron-deficient. This reaction forms a new covalent bond. Brønsted-Lowry acids have an electron deficient proton and take the form A—H. Such acids include molecules with a O—H, S—H, or N—H unit, where each bond is polarized with a δ^+ hydrogen atom.

The curved, double-headed arrow in the generic reaction shows electron donation *from* the electron rich base *to* the electron deficient hydrogen atom. When the A—H bond is broken, the two electrons in that bond are transferred to the more electronegative atom A, as indicated by the second curved arrow. By definition, the acid-base pair (the reactants) is written on the left and the conjugate acid-conjugate base pair (the products) is written on the right. By definition, the acidity constant $K_a = [\frac{\text{products}}{\text{reactants}}] = \frac{[BH][A]}{[AH][B]}$, where the *products* are the conjugate acid (BH) and conjugate base (A) and the *reactants* are the initial acid (AH) and base (B). If A—H reacts with the base to a greater extent than B—H reacts with the conjugate base, the equilibrium lies to the right. If there is more product, K_a is large (small pK_a), which indicates a stronger acid. If K_a is large A—H reacts with the base, B, to a greater extent than the conjugate acid reacts with the conjugate base. If there is less product, K_a is small

DOI: 10.1201/9781003174929-6

(large pK_a), which indicates a weaker acid. If K_a is small the conjugate acid reacts with the conjugate base to a greater extent than A—H reacts with the base, B.



There is an old axiom in acid-base chemistry: a strong acid gives a weak conjugate base and a weak acid gives a strong conjugate base. It is therefore important to examine the stability and reactivity of the conjugate base derived from HA, as well as the relative bond strength and reactivity of A—H. A strong acid will give a weak conjugate base, which is more stable and less reactive. If the conjugate base (A^-) is more stable, it is *less reactive* and a weaker base. If A^- is a weaker base, it does *not* react with the conjugate acid HB and there will be a higher concentration of A^- and HB (products) and a lower concentration of AH and B^- (reactants). In other words, K_a is larger, and HA is a stronger acid. A weak acid will give a strong conjugate base, which is less stable and more reactive. If the conjugate base (A^-) is *more reactive*, it is a stronger base and the K_a is smaller. If A^- is a stronger base, it reacts well with the conjugate acid HB and there will be a lower concentration of A^- and HB (products) and a higher concentration of AH and B^- (reactants). In other words, K_a is smaller, and HA is a weaker acid. A moderately strong acid may have close to the same concentrations of acid:base and conjugate acid:conjugate base. For example, if the pK_a of A:H is 4.6 and the pK_a of B:H is 4.7. In such a case, K_a is close to unity which means there will be close to a 1:1 mixture of both reactants and both products.

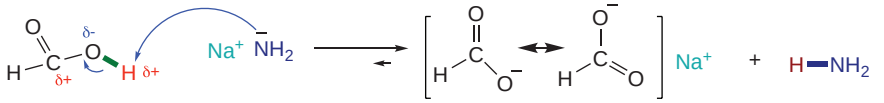
6.1 If $K_a = 6.34 \times 10^{-8}$, determine the pK_a; if the $pK_a = 11.78$, determine K_a.

Carboxylic Acids and Sulfonic Acids

6.2 CARBOXYLIC ACIDS AND SULFONIC ACIDS

6.2.1 CARBOXYLIC ACIDS

Carboxylic acids have a polarized carbonyl group (C=O) as part of the carboxyl group, and inductive effects lead to δ^+ polarization for the proton (Section 5.6.3). An *inductive effect* is the transmission of unequal sharing of bonding electrons by adjacent atoms through a chain of atoms, bond polarization, that leads to a permanent dipole in a bond. Due to this polarization of the OH bond, carboxylic acids react as Brønsted-Lowry acids. The pK_a of carboxylic acids is usually in the 2–5 range. The pK_a of formic acid is 3.75 and that of acetic acid is 4.75.



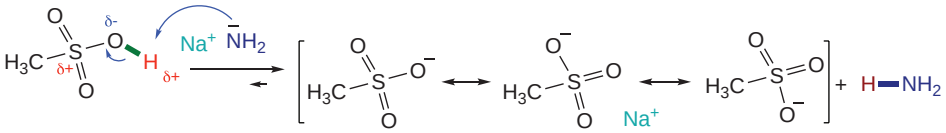
Bond polarization of the hydroxyl group does not completely explain the acidity of a carboxylic acid such as formic acid, however. The stability of the conjugate base in the reaction of formic acid and indeed all carboxylic acids is a major contributing factor to K_a. When formic acid reacts with sodium amide (the base), removal of the proton gives the resonance-stabilized formate anion as the conjugate base, with two resonance contributors. The electrons are not localized on one oxygen atom, but rather delocalized over three atoms by resonance as shown (also see Figure 5.9). There is a higher concentration of electron density on both oxygen atoms, however. The resonance-delocalized formate anion is lower in energy and more stable, so it is a poor electron donor and *less reactive as a base with the conjugate acid, ammonia*. This poor reactivity means that the equilibrium for the reaction with formic acid

shifts to favor products (larger K_a). The resonance stability of the carboxylate anion is a major contributor to the acidity of carboxylic acids.

6.2 Draw the two resonance forms for the anion derived from propanoic acid.

6.2.2 SULFONIC ACIDS

Sulfonic acids have the general structure RSO_3H, where R is a carbon group. Sulfonic acids are named by identifying the name of the "R" group followed by *-sulfonic acid*. Examples are $CH_3CH_2CH_2SO_3H$ (propanesulfonic acid) and $CH_3CH_2CH(CH_2CH_3)CH_2SO_3H$ (2-ethylbutanesulfonic acid). It is known that sulfonic acids are more acidic than the corresponding carboxylic acid. The greater acid strength of a sulfonic acid is clearly seen by the comparison of acetic acid (ethanoic acid, MeCOOH, $pK_a = 4.76$) with methanesulfonic acid ($MeSO_2OH$) ($pK_a = -1.9$).[1] Just as the C=O group of a carboxylic acid polarizes the adjacent O—H bond, the S=O bond of a sulfonic acid will polarize the adjacent OH group via an inductive effect that enhances the acidity.



Perhaps more importantly is the structure of the alkyl sulfonate anion, the conjugate base formed from a sulfonic acid. The alkyl sulfonate anion is resonance stabilized so it is very stable, a poor electron donor, less reactive and it is a weak base. Methanesulfonic acid with sodium amide, for example, to give the resonance stabilized sodium methanesulfonate as the conjugate base and ammonia as the conjugate acid. The methanesulfonate anion has three resonance contributors whereas a carboxylate anion has only two resonance contributors so the methanesulfonate anion is more stable, less reactive and a weaker base than the acetate anion. The K_a is larger and methanesulfonic acid is a stronger acid.

6.3 Draw out the reaction of pentanesulfonic acid with sodium amide, including reactants and products.
6.4 Draw all resonance contributors to the butanesulfonate anion.

6.3 FACTORS THAT INFLUENCE THE STRENGTH OF A CARBOXYLIC ACID

Since carboxylic acids are the most common organic acids, they will be used to examine structural variations that contribute to variations in acid strength. Both the strength of the O—H bond and the stability (reactivity) of the conjugate base have been identified as important factors that influence the relative strength of an acid. These factors will be discussed in more detail.

6.3.1 STABILITY OF THE CONJUGATE BASE

As seen in the previous section and in Sections 2.4 and 2.6, electronegativity of the basic atom, the size of the conjugate base and whether or not it is stabilized by dispersal of charge are important factors that influence basicity. If the charge on a conjugate base is dispersed

[1] Stewart, R. *The Proton: Applications to Organic Chemistry* Academic Press, Orlando, FL, 1985, p. 17.

over a greater area it is less able to donate electrons, so it is more stable and less reactive. It is a weaker base. The size of an anion is one contributing factor, as when two different size conjugate bases are compared. In Section 2.5 it was shown that HI is more acidic than HF, in large part because the much larger iodide anion disperses the charge over a larger area relative to fluoride ion. Since the iodide ion is more stable and therefore less reactive it is a weaker base.

Resonance stabilization of the conjugate base leads to dispersal of charge and it is another important factor that lowers the basicity. Both carboxylate anions and sulfonate anions are resonance stabilized. The dispersal of charge over several atoms due to resonance diminishes the ability to donate electrons and so the basicity. Therefore, the K_a is larger consistent with a stronger acid.

6.5 Compare the conjugate bases of methanesulfonic acid (CH_3SO_3H) and methanol (CH_3OH). Which is the stronger base and why? Compare the relative acidity of nitromethane and methanol.

Structural Variations in Carboxylic Acids

6.3.2 INDUCTIVE EFFECTS

The influence of different groups attached to the carbonyl carbon of carboxylic acids can be examined by comparing carboxylic acids with different groups attached to the carbonyl carbon. Formic acid (pK_a of 3.75) can be compared with acetic acid (pK_a of 4.76). Acetic acid has a sp^3 hybridized carbon attached to the carbonyl carbon, the α-*carbon*, whereas formic acid has a hydrogen atom attached. The electronegative oxygen atom of the carbonyl induces a δ^+ dipole at the carbonyl carbon. This in turn induces a δ^- dipole on the α-carbon of acetic acid. Due to a so-called *through-bond inductive effect*, that methyl carbon "releases" electrons toward the δ^+ carbonyl carbon, which extends to the O—H unit. The through-bond inductive effect for acetic acid is illustrated in Figure 6.1. Formic acid has a hydrogen atom attached to the carbonyl carbon rather than an electron releasing carbon group, so there is no possibility of an inductive effect to decrease the

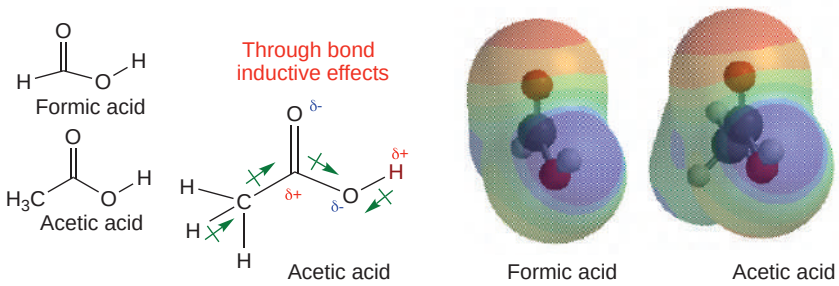


FIGURE 6.1 Inductive effects in acetic acid relative to formic acid.

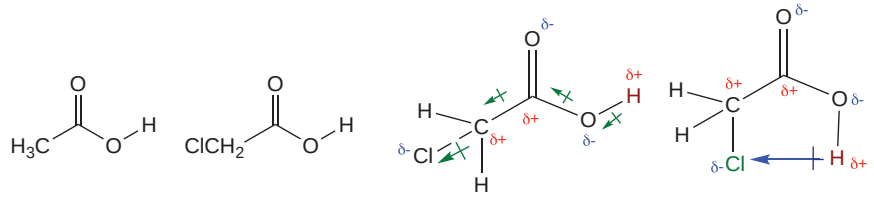
acidity. If the carbonyl carbon is less polarized the acidic hydrogen is less polarized, so acetic acid is *less* acidic than formic acid. Figure 6.1 also shows electron potential maps for formic and acetic acid to illustrate the effects on the acidic proton. The blue area over the acidic hydrogen atom of formic acid is slightly larger when compared to the hydrogen atom in acetic acid. This difference is an indication that formic acid is more acidic, consistent with the presence of the methyl group in acetic acid. In addition, the carbonyl oxygen in the electron potential map of acetic acid has a greater area of red, indicative of more electron density pushed toward the carbonyl.

When electron releasing alkyl groups are attached to the α-carbon the inductive effect will diminish the acidity. Acetic acid, for example has a pK_a of 4.76 but the pK_a of propanoic acid is 4.87 and butanoic acid has a pK_a of 4.82. Clearly, the presence of an alkyl group on the α-carbon makes the acid slightly weaker. The presence of a second methyl group on the

α-carbon (dimethylacetic acid) has minimal effect (pK_a 4.85). The presence of three methyl groups on the α-carbon (trimethylacetic acid; the common name is pivalic acid), however, leads to diminished acidity, pK_a 5.03.

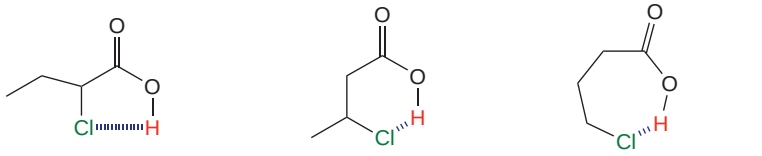
An *electron-releasing group* attached the α-carbon to a polarized carbonyl carbon leads to a stronger O—H bond via an inductive effect and a larger pK_a. Conversely, an *electron-withdrawing group* on the α-carbon has the opposite effect and leads to a weaker O—H bond, a smaller pK_a and greater acidity. This difference can be probed by examining structural differences between acetic acid (pK_a 4.76) and chloroacetic acid (pK_a 2.87). Chloroacetic acid has a more electronegative chlorine on the α-carbon. Due to through-bond inductive effects, the C—Cl bond is polarized with a δ^- Cl and a δ^+ C. Both the carbon of the C—Cl unit and the carbonyl carbon are polarized δ^+. The net inductive effect of two electron-withdrawing entities favors distortion of the electron density toward the chlorine rather than toward oxygen. To compensate for the effect of the electron-withdrawing chlorine, the carbonyl carbon draws more electron density from oxygen of the OH unit. The hydrogen atom of the O—H bond is therefore more δ^+ and chloroacetic acid more acidic.

Another inductive effect is seen if chloroacetic acid is drawn differently. There is rotation about *all* of the covalent single bonds in the molecule. Such rotation is explained in Section 8.1. Due to this rotation, one arrangement of atoms brings the chlorine and the acidic proton close together in space. In this arrangement of the atoms, called a *conformation*, the δ^- chlorine is attracted to the δ^+ hydrogen in what constitutes an *intramolecular hydrogen bond* (Section 5.8.1). The H and Cl are *not* connected, simply close together, but the attraction between the two atoms will "pull" the proton closer to chlorine. This attraction elongates the O—H bond so it is weaker. The O—H bond is more polar and H is more δ^+, so chloroacetic is more acidic than acetic acid. This effect is described as a *through-space inductive effect,* and it is possible *only* if the two polarized atoms (with opposite charges) can be brought into close proximity. A through-space effect generally has a greater influence on acidity than the through-bond effect. Bromoacetic acid is slightly less acidic than chloroacetic acid, as seen in Table 6.1. The is a slight increase in acidity when two halogens are attached, as seen in dichloroacetic acid and dibromoacetic acid.



6.6 Predict if 2-nitroethanoic acid ($HOOCCHNO_2$) is stronger or weaker than ethanoic acid (acetic acid). Briefly explain.

The closer an attached electron withdrawing halogen atom is to the carbonyl, the more polarized the O—H unit. Conversely, if the attached electron-withdrawing atom is further away the effect is weaker. The pK_a of 2-chlorobutanoic acid is 2.86. The acidic proton and the δ^- chlorine atom can be relatively close in space, approximating a five-membered ring. The intramolecular through-space interaction coupled with the through-bond effect enhances the acidity. In 3-chlorobutanoic acid the chlorine atom is on C3 and a through-space hydrogen-bonding effect requires a conformation that mimics a six-membered ring. In other words, the chorine atom is further away from the OH proton. The diminished inductive effects relative to 2-chlorobutanoic acid lead to a pK_a is 3.99, so it is a weaker acid. In 4-chlorobutanoic acid, the chlorine atom is still further away.



A through-space interaction demands an arrangement that approximates a seven-membered ring. The diminished inductive effects lead to a pK_a of 4.50, which is only slightly more acidic than butanoic acid (4.82). Table 6.1[2] correlates several carboxylic acids with pK_a to show how structural changes and the presence of carbon groups or heteroatom groups influence acidity. The chlorinated butanoic acid derivatives suggest that the practical "limit" of inductive effects is reached when the electron-withdrawing group is on the third or fourth carbon atom away from the carbonyl carbon. Note also that chloroacetic acid is stronger than bromoacetic acid. The electron-withdrawing ability of the halogens is Cl > Br > I.

TABLE 6.1 The pK_a Values of Common Carboxylic Acids

Acid	pK_a	Acid	pK_a
Formic acid	3.75	Chloroacetic acid	2.87
Acetic acid	4.76	Bromoacetic acid	2.90
Propanoic acid	4.87	Iodoacetic acid	3.18
Butanoic acid	4.82	Dichloroacetic acid	1.26
2,2-Dimethylpropanoic acid (Pivalic acid)	5.03	Dibromoacetic acid	1.39
4-Methylpentanoic acid	4.79	2-Methylpropanoic acid	4.85
Phenylacetic acid	4.31	2-Methylbutanoic acid	4.76
Benzoic acid[a]	4.20	2-Chloropropanoic acid	2.84
4-Methylbenzoic acid[a]	4.36	3-Chloropropanoic acid	3.99
3-Chlorobenzoic acid[a]	3.99	2-Chlorobutanoic acid	2.88
4-Methoxybenzoic acid[a]	4.49	3-Chlorobutanoic acid	3.83
4-Nitrobenzoic acid[a]	3.44	4-Chlorobutanoic acid	4.50

[a] See section 19.2

6.7 Discuss the relative acidity of 2-methoxybutanoic acid and 4-methoxybutanoic acid.

6.3.3 SOLVENT EFFECTS

With the exception of a brief introduction in Section 2.3, the role of the solvent has been largely if not completely ignored. In fact, the solvent plays a major role in the ionization, the solubility of all species, and in acid strength. The ability to separate ions and "drive" the reaction to the right is important in acid-base reactions. The pK_a values given for all organic molecules in this chapter are based on their reaction in water, which means that water is the base in those reactions (Section 2.3). If a different solvent is used, the pK_a is different. If a different base is added, the acid strength depends on the strength of the base and the pK_a is different. In the reaction of acetic acid (ethanoic acid) and water, the conjugate acid is H_3O^+ and the conjugate base is the acetate anion. As the proton of the O—H bond of acetic acid is pulled away by the water ($H_2O^{\delta-}$------$H^{\delta+}$----$^{\delta-}O_2CH_3$), the new H—O bond to water begins to form, generating the hydronium ion (H_2O--$H^{\delta+}$). Since water has a δ^+ proton and a δ^- oxygen atom, it is very effective at stabilizing both ions once they form. Such stabilization is called *solvation*. The solvent surrounds each ion, separating and stabilizing the ions as they form. Water is a very polar molecule, and it is capable of solvating and separating ions (Sections 12.7,8). Separation of the ions in this manner leads to a higher concentration of products and a larger K_a. The net result is that acetic acid is a stronger acid in water than in a solvent that cannot generate a polarized transition state to assist the ionization.

[2] *CRC Handbook of Chemistry*, 94th ed., CRC Press, Boca Raton, FL, 2013–2014, pp. 5–94 to 5–103.

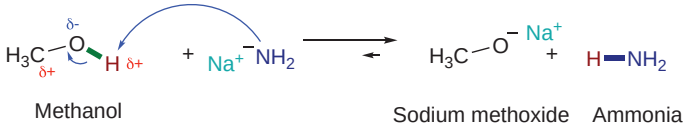
If diethyl ether is used as a solvent in a reaction of *one molar equivalent of water* with acetic acid, the acid is a weaker relative to the reaction in water as a solvent. Diethyl ether is much less effective with respect to solvation so there is less ionization. The ether can coordinate with an electron poor species via the electron rich oxygen. While diethyl ether has $C^{\delta+}$—$O^{\delta-}$ units, the carbon atoms have hydrogen or alkyl units attached. Therefore, coordination of $C^{\delta-}$ with an electron rich species is difficult due to steric repulsion. As a practical matter, ether *cannot* separate ions the way water does, so ionization of acetic acid to form acetate and the hydronium ion is less favorable than in water. This is reflected by a smaller K_a. Based on this discussion, it is clear that solvents may participate in a reaction although they do not appear in the final product.

6.8 Both water and methanol are solvents that contain an acidic OH unit. With this in mind, briefly explain why acetic acid is a stronger acid in water than in methanol.

6.4 ALCOHOLS ARE AMPHOTERIC

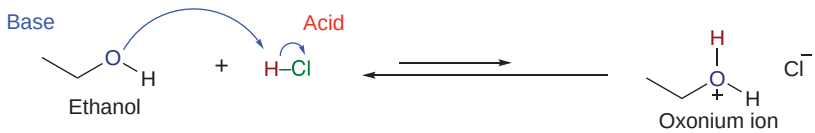
Alcohols Are Acids

An $O^{\delta-}$—$H^{\delta+}$ unit is found in alcohols as well as in carboxylic acids but alcohols are much weaker acids. Methanol, for example, has a pK_a of 15.2 so it is a slightly stronger acid than water (pK_a of 15.7). Alcohols are relatively weak Brønsted-Lowry acids and the conjugate base of an acid-base reaction is an *alkoxide*, RO^-. The conjugate base of methanol is the methoxide anion. The charge is localized on the oxygen atom rather than dispersed by resonance as in the conjugate base derived from a carboxylic acid. Therefore, the methoxide ion is a better electron donor and more basic than a carboxylate anion. The somewhat greater acidity of methanol relative to water probably results from greater stabilization of the methoxide ion in water relative to the hydroxide ion. Ethanol has a pK_a of 15.9 but most alcohols have pK_a values of 16–18. The base chosen to react with the alcohol should be a stronger base than the alkoxide product. The conjugate acid should be a weaker acid than the alcohol. In other words, the base that reacts with the alcohol should generate a conjugate acid with a pK_a that is > 16–18.



In this reaction, methanol reacts with sodium amide ($NaNH_2$) to the δ^+ hydrogen of the O—H unit. The conjugate acid is H—NH_2 (ammonia) and the conjugate base is sodium methoxide. Note that the sodium counterion is transferred from NH_2^- to the negatively charged alkoxide anion. The conjugate acid in this reaction is ammonia, with a pK_a of ~ 38, so the equilibrium should shift to the right (larger K_a), favoring a large equilibrium concentration of methoxide.

6.9 Which is more acidic, water or ammonia. Discuss and justify your choice.



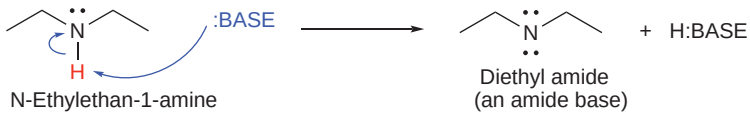
Some molecules are classified as both an acid and a base. They react as an acid in the presence of a suitable base or as a base in the presence of a suitable acid. The property of a compound to react as either an acid or a base is called *amphoterism*. Alcohols, water, and other compounds that react in this manner are referred to as *amphoteric compounds*. An alcohol will react as a base in the presence of an acid with a pK_a significantly lower than itself. An

alcohol will react as an acid reacts with a base that is a stronger base than its own conjugate base ethoxide, as shown by the reaction with sodium amide. The reaction of the oxygen of ethanol as a base with HCl (pK_a -6.1) forms an oxonium salt (pK_a of ~ –2.3) as the conjugate acid and the chloride ion as the conjugate base.

6.10 Draw the products of a reaction between butan-1-ol and HCl.

6.5 AMINES

The N—H bond of an amine is polarized because nitrogen is more electronegative than carbon. Since the hydrogen is polarized δ^+, amines are very weak acids (pK_a, 36–40) and they react as acids only with very strong bases. An example is the deprotonation of diethylamine (*N*-ethylethan-1-amine) to give an amide base (the conjugate base). Most of the strong bases used in this reaction will not be introduced and used until Sections 14.2,3 and 20.2.



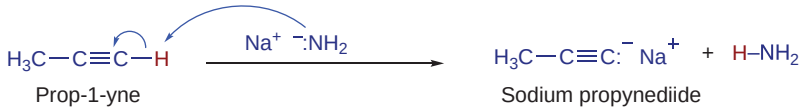
6.11 Draw the product when *N*-(1-methylethyl)propan-2-amine reacts as an acid with a suitable base.

6.6 CARBON ACIDS

C—H Acids

6.6.1 TERMINAL ALKYNES ARE WEAK ACIDS

Alkynes (Section 5.2) can be categorized as internal alkynes (RC≡CR) or terminal alkynes (RC≡CH). The hydrogen atom of a terminal alkyne is a weak acid ($pK_a \sim 25$) and undergoes an acid-base reaction with a strong base such as sodium amide, $NaNH_2$. The conjugate base is an *alkyne anion* ($RC{\equiv}C:^-$), although they are commonly known as *acetylides*. When prop-1-yne reacts with sodium amide, for example, the products are the alkyne anion sodium propynediide (the conjugate base) and ammonia (the conjugate acid). An alkyne anion is a carbanion (Section 7.2.2), and a useful nucleophile in many reactions (Section 11.3).

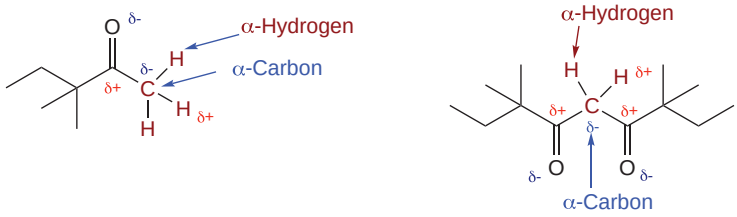


6.12 Draw the product formed when pent-1-yne reacts with $NaNH_2$, and draw the corresponding conjugate acid and base.

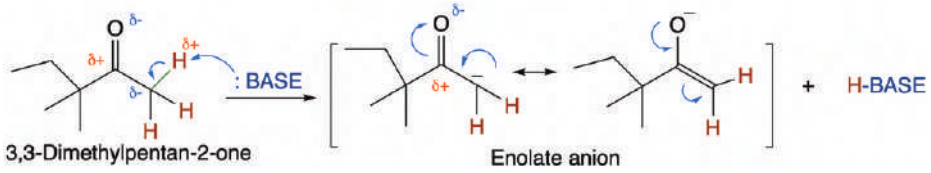
6.6.2 α-HYDROGEN ATOMS AND CARBONYLS

In aldehydes, ketones or carboxylic acid derivatives, a C—H unit of an α-carbon atom is polarized with a δ^+ dipole on the hydrogen due to the presence of a carbonyl (C=O).

This bond polarization is induced by the carbonyl oxygen. The δ+ polarized hydrogen atom attached to the α-carbon is the so-called α-hydrogen. The α-hydrogen atom in 3,3-dimethylpentan-2-one, for example, is weakly acidic and the pK_a is ~ 19–20 (Section 20.1). Ketones are weaker acids than alcohols, and the base required for an acid-base reaction must be strong (Section 20.2).



If two electron-withdrawing groups are present in a molecule, such as the two carbonyl groups in 3,3,7,7-tetramethylnonane-4,6-dione, the indicated hydrogen is more polarized than in a mono-ketone. The α-proton is more acidic and the pK_a is ~ 8.5–9.5. When 3,3-dimethylpentan-2-one reacts with a strong base the conjugate base is a carbanion known as an enolate anion. Enolate anions are resonance stabilized, as shown and the charge is delocalized on carbon and on oxygen (Sections 20.1,2). Enolate anions are important nucleophilic species that are used for the formation of carbon-carbon bonds using chemical reactions presented in Sections 20.3,4,9. In the context of this chapter, the key point is that bond polarization, induced by the carbonyl, leads to an acidic proton that reacts as an acid with a suitable base.



6.13 Draw the enolate anion formed when cyclopentanone reacts with a suitable base. Draw both resonance contributors for the enolate anion

6.7 ORGANIC BASES

Organic Bases

Just as there are "organic acids," there are also "organic bases." Perhaps the most common organic base is an amine, R_3N. Both alcohols and primary or secondary amines react with a suitable base to give a basic anion as the conjugate base. Deprotonation of an alcohol gives an alkoxide RO^- and deprotonation of an amine gives an amide anion, R_2N^-. Anions have a negative charge localized on an oxygen or nitrogen and are stronger bases than the neutral precursor.

6.7.1 AMINES

Amines and pK_{BH}

Amines are commonly used as bases in organic chemical reactions. The lone electron pair on the nitrogen atom of an amine is easily donated to a Bronsted-Lowry acid to generate an ammonium ion as the conjugate acid. Common amine bases are diethylamine, pyrrolidine (Section 23.5) and pyridine (Section 23.1). The reaction of propanoic acid and diethylamine to give the propanoate salt and diethylammonium is an example, shown in Figure 6.2. Ammonium salts are weak acids and the pK_a of an ammonium salt is ~ 10–11.

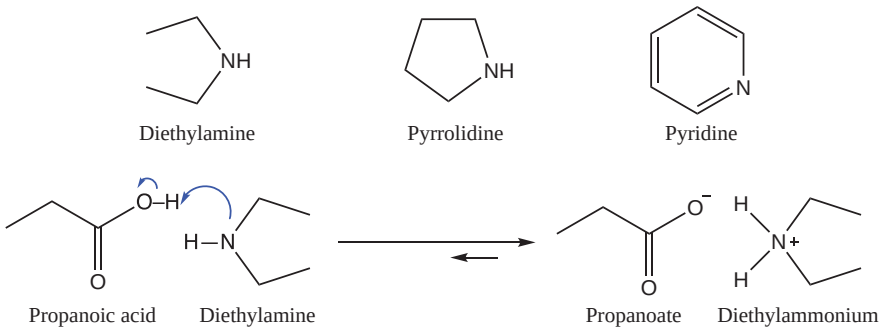


FIGURE 6.2 Common amine bases and the reaction of propanoic acid and diethylamine.

As described in Section 5.5.3, there are three structural types of amines, primary amines RNH_2, secondary amines R_2NH, and tertiary amines R_3N. Differences in basicity between primary, secondary and tertiary amines can be attributed to inductive effects. In the discussion of *inductive effects* for differences in acid strength for carboxylic acids, alkyl groups are classified as electron-releasing groups. A similar inductive effect is observed for amines. The electron-releasing inductive effect of an alkyl substituent attached to nitrogen should increase the electron density on nitrogen, thereby increasing the basicity of the amine. Ammonia has no substituent to give an inductive effect. Therefore, the inductive effects induced by carbon substituents on nitrogen in an amine can be compared to ammonia. In methylamine, the methyl electron releasing carbon distorts electron density toward nitrogen. Since the electron density on nitrogen is greater in methanamine than in ammonia (Figure 6.3) methanamine is a stronger base.

If the presence of one electron-releasing alkyl group makes a primary amine a stronger base than ammonia, then two alkyl groups should make a secondary amine an even stronger base. A secondary amine is indeed more basic than a primary amine. However, the presence of three alkyl groups does not enhance basicity. Trimethylamine is a *weaker* base than dimethylamine or methylamine. The three methyl groups on nitrogen take up quite a bit of space and effectively block nitrogen from approaching another atom. The space-filling molecular models in Figure 6.3 illustrate the "steric blocking effect" of the methyl groups.

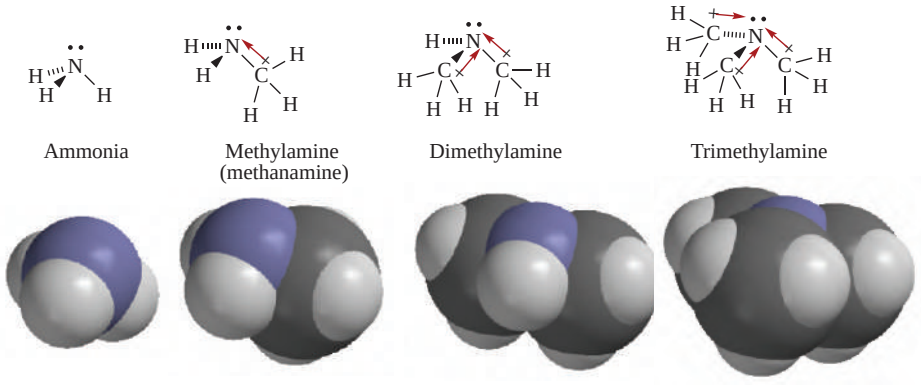


FIGURE 6.3 Inductive effects in amines.

Nitrogen is the blue atom. It is clear that less of the nitrogen atom is exposed in trimethylamine due to the presence of the three methyl groups. For an acid-base reaction, anything that makes it more difficult for nitrogen to approach another atom diminishes the base strength of the amine and based on accessibility to the nitrogen. Therefore, the tertiary amine is less basic. This observation contrasts with the greater amount of nitrogen that is exposed in the secondary amine or the primary amine, consistent with greater basicity. It is important to note that this effect is described for amines that are in solution, not in the gas phase. However, all the reactions of amines in this book will be done in a solvent. Based on

inductive and substitution effects at nitrogen in amines, it is possible to categorize the base strength of amines and the trend in solution is $NH_3 < R_3N < RNH_2 < R_2NH$, where secondary amines are the strongest bases and ammonia is the weakest base.

The basicity of an amine can be compared to that of ammonia. A putative acid-base reaction of ammonia with water gives the ammonium ion and the hydroxide ion. Similarly, the reaction of methanamine with water gives methylammonium hydroxide and the hydroxide ion. The ammonium salt products are weak acid. The pK_a of the ammonium ion (from ammonia) is 9.2 whereas the pK_a for the methylammonium ion (from methylamine) is 10.64.[3] With this knowledge, the equilibrium reaction that converts the ammonium salts to ammonia or amine can be used to measure the basicity of ammonia or the amine. The ammonium ion has a lower pK_a, so it is a stronger acid than the methylammonium ion. It is known that a stronger acid will generate a weaker conjugate base and a weaker acid will generate a stronger conjugate base. Methanamine generates the weaker conjugate acid so it must be more basic than ammonia. Comparing the acidity of the conjugate bases can therefore be used to determine the relative basicity of a variety of amines.

The position of the equilibrium for the acid-base reaction with the ammonium salt as the acid and the amine as the conjugate base is measured by K_B: K_B = [conjugate base][conjugate acid]/[acid][base]

$$pK_B = -\log K_B \text{ and } pK_B \text{ is determined by the formula } K_B = 10^{-pK_B}$$

The value of K_B is used as a measure of the reactivity of the amine as a base. If K_B is large (small pK_B) the concentration of the conjugate base and conjugate acid is large. The equilibrium favors a higher concentration of the ammonium salt relative to the amine, so the amine is a strong base. Alternatively, if K_B is small (large pK_B) there is a lower concentration of the ammonium salt, consistent with a weak base. The pK_B of methanamine is 3.36[4] whereas that of ammonia is 4.75 so the amine is the stronger base.

$$R_3N + HOH \rightleftharpoons R_3NH^+ \ ^-OH \qquad K_B = \frac{[R_3NH^+]\ [^-OH]}{[R_3N]}$$

6.14 Calculate the pK_B for an amine with a $K_B = 3.92 \times 10^6$.

As noted previously, the solvent has an important effect on the strength of a base. In the reaction of methylamine and HCl, shown in Figure 6.4, the product is methylammonium chloride. As the reaction between the amine and HCl progresses, the hydrogen atom is transferred to nitrogen and the neutral amine begins to develop charge (see transition states in Section 7.6). As the H—Cl bond begins to break, more electron density is transferred to the chlorine, which begins to develop a negative charge. When water is the solvent, it plays an important role. Water separates ions of opposite charge by solvating each ion, pulling those ions apart as the charges develop. This effect is known as *solvation*. As water separates the

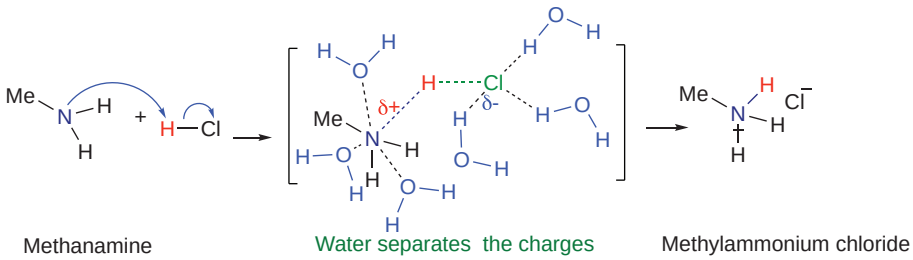


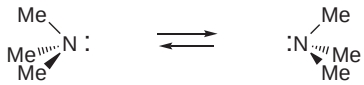
FIGURE 6.4 The reaction of methanamine with HCl in water.

[3] Stewart, R. *The Proton: Applications to Organic Chemistry*, Academic Press, Orlando, FL, 1985, p. 102.
[4] Van, L.H.; Bruggeman, J.J. PerkinElmer Life and Analytica, Patent WO 2006121331 A1, 2006.

developing charges, the reaction is driven to the right, increasing K_a for the reaction relative to a solvent that does not separate charge (e.g., diethyl ether). Therefore, the relative basicity of an amine is if greater in a solvent that solvates and separates ions.

6.15 Using only simple arguments, predict whether the conjugate acid of ethylamine ($EtNH_2$) is more or less stable than that of triethylamine (Et_3N). Draw both products.

Remember that the nitrogen must collide with the proton to react as a base, so the availability of the amine nitrogen for reaction with an acid is critical, as illustrated in Figure 6.3. Another important property of amines is *fluxional inversion* (Section 5.5.3), where an amine exists as an equilibrating mixture of two pyramidal structures. Trimethylamine, for example, flips back and forth, much like an umbrella inverting in a windstorm so the methyl groups are "moving" around the nitrogen and interfere with any reaction of the lone electron pair at any positive center. Fluxional inversion diminishes the basicity of an amine.



If an electron-withdrawing group is attached to nitrogen, the electron-withdrawing inductive effects make the molecule a weaker base because electron density is removed from the nitrogen. Chloramine (NH_2Cl), for example, has an electron withdrawing chlorine atom attached to nitrogen, and it is expected to be less basic.

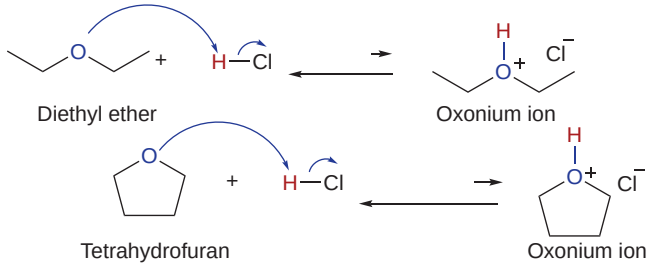
6.7.2 ALCOHOLS ARE BASES

In Section 6.4 alcohols were shown to react as acids, but it was noted that they are amphoteric. The reaction of an alcohol as a base with a strong acid generates an *oxonium ion*. Oxonium ions contain a proton on the oxygen, and they are rather strong acids (pK_a is about -2) and the K_a for this reaction generally lies to the left. However, the oxonium ion is present in the acid-base equilibrium, and it is important in several reactions to be discussed in Chapter 10. Therefore, oxonium ions are transient products and highly reactive species known as intermediates (Section 7.2).

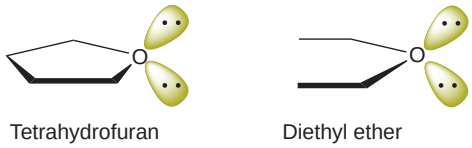
6.16 Draw the product formed when cyclopentanol reacts with HBr.

6.7.3 ETHERS ARE BASES

As introduced in Section 5.5.2, ethers are molecules that have two alkyl groups flanking a central oxygen. The hydrogen atom on the carbon attached to oxygen is a very weak acid ($pK_a > 30$), but the electron-rich oxygen atom of ethers will react as a base. Diethyl ether is a typical acyclic ether and the reaction with a strong acid (e.g., HCl) gives an oxonium ion as the conjugate acid product. Note the similarity of this reaction with that of water and HCl or alcohols with HCl. The conjugate base is formally the chloride ion. Oxonium salts derived from ethers are very strong acids ($pK_a \sim -3.5$) so the K_a for the reaction is small. When compared to amines, diethyl ether is a weaker base.

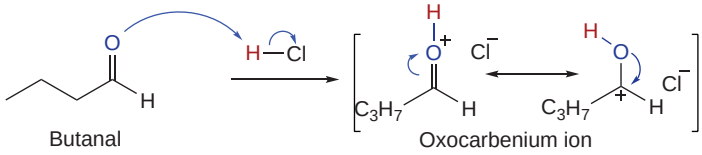


A cyclic ether (e.g., tetrahydrofuran; THF; Section 23.5) will react in a similar manner with HCl to yield an oxonium salt. The cyclic ether tetrahydrofuran (THF) is a stronger base than diethyl ether. The carbon groups attached to oxygen in THF are "tied back," whereas the carbon groups in diethyl ether have more freedom to move around. It is more conformationally mobile (Sections 8.1, 8.2, and 8.5). As a result, the electrons on oxygen in THF are "more available" for donation due to less steric hindrance, and THF is a stronger base than diethyl ether.



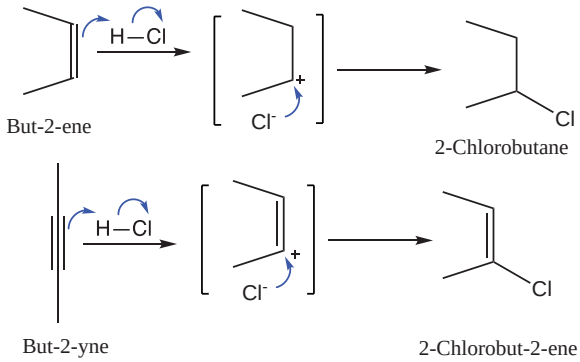
6.7.4 CARBONYL COMPOUNDS ARE BASES

The oxygen of carbonyl compounds (e.g., ketones and aldehydes, Section 5.6.2) has unshared electrons that react as a weak Brønsted-Lowry base. When an aldehyde or ketone reacts with a relatively strong Brønsted-Lowry acid such as HCl the conjugate acid that is formed is a "protonated carbonyl," an *oxocarbenium ion* (Sections 16.4 and 18.4). The oxygen atom in butanal reacts with HCl, for example, to form an oxocarbenium ion that is resonance stabilized with two resonance contributors as shown. The resonance contributor with a positive charge on carbon is considered to be an oxygen-stabilized carbocation (hence the term oxocarbenium ion) and it can react with nucleophiles. Ketones react similarly. Oxocarbenium ions will be generated in several chemical reactions with suitable nucleophiles in Chapters 16 and 18.



6.17 Draw the product of a reaction between cyclopentanone and HCl.

6.7.5 ALKENES AND ALKYNES ARE BASES



Alkenes react as a Brønsted-Lowry base in the presence of a strong mineral acid such as HCl to yield a transient product known as a *carbocation intermediate* (Section 7.2). This carbocation intermediate is highly reactive with the nucleophilic chloride counterion and generates an alkyl halide that is the isolated product of this reaction. An example is the reaction of but-2-ene with HCl to give a carbocation intermediate. Subsequent in situ reaction with the nucleophilic chloride counterion yields 2-chlorobutane as the isolated product, as will be

described in Section 10.2. Alkynes also have a π-bond and reaction with a strong mineral acid will give an intermediate known as a vinyl carbocation (C=C⁺), as described in Section 10.8. An example is the reaction of but-2-yne and HCl to give a vinyl carbocation intermediate, and subsequent reaction with the chloride ion gives 2-chlorobut-2-ene.

Lewis Acids and Lewis Bases

6.8 LEWIS ACIDS AND LEWIS BASES

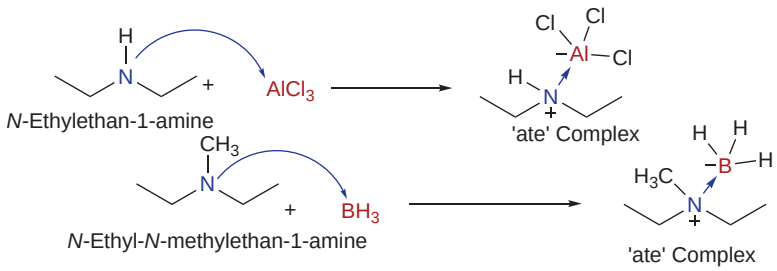
As introduced in Section 2.7, the formal definition of a Lewis base is an electron-pair donor, and a Lewis acid is an electron-pair acceptor. The reactions of Lewis acids and bases are common in organic chemistry and there are distinguishing characteristics of these reactions. A Bronsted-Lowry acid-base donates two electrons to a proton to give two products, *a conjugate acid and a conjugate base*. A Lewis base donates electrons to an electron deficient atom other than hydrogen or carbon. In Lewis acid-base reactions a dative bond is formed to give the Lewis acid-Lewis base complexes (an *"ate" complex*) so there is one product not two. The "ate" complex product can be described as a *zwitterion* (a *dipolar ion*), a molecule that contains both a positive and a negative charge

6.18 Draw the product expected to form when BH_3 reacts with ammonia; with diethyl ether.

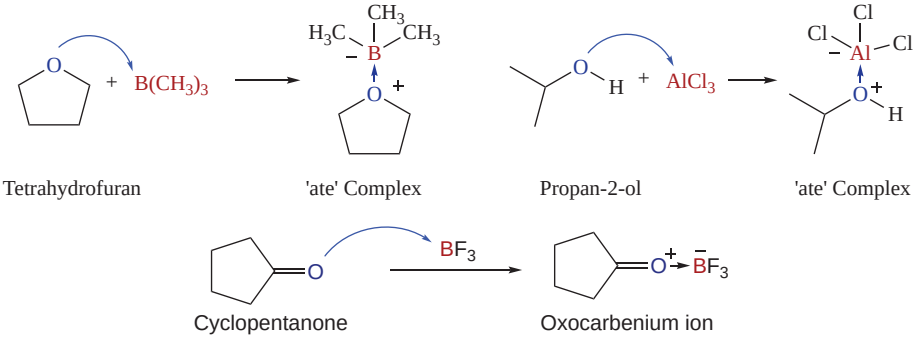
In general, the inductive effects that played a role in Brønsted-Lowry acids and bases will also influence the relative acidity or basicity of a Lewis acid or a Lewis base. The pertinent inductive effects are clear when comparing BF_3 and $B(CH_3)_3$, where fluorine in BF_3 is electron withdrawing but methyl in $B(CH_3)_3$ is electron releasing. This difference leads to the δ^+ boron atom being more electron deficient when a fluorine is attached than when carbon groups are attached, making BF_3 a stronger acid.

Formally, a Lewis base is any compound that has an atom capable of donating electrons to an electron-deficient center, other than a proton or carbon. In general, basicity increases going up the periodic table and to the left. If the trend increases basicity to the left, then an amine (R_3N) is a stronger Lewis base than an ether (ROR) or an alcohol (ROH). If the trend for basicity increases going up the periodic table, then an amine (R_3N) is a stronger Lewis base than a phosphine (R_3P) and an ether (ROR) is a stronger Lewis base than the sulfur analog of an ether (a sulfide, RSR). Based on these trends, the most common Lewis bases in organic chemistry are probably amines. *N*-Ethylethanamine readily reacts with the strong Lewis acid aluminum chloride ($AlCl_3$), for example, to form an "ate" complex as shown. Note the dative bond between nitrogen and aluminum, and the direction of the arrow *from* the electron-rich nitrogen atom *to* the electron-deficient aluminum atom. Similarly, the tertiary amine *N*-ethyl-*N*-methylethan-1-amine reacts with borane (BH_3) to form an "ate" complex. Borane will be discussed in Section 10.6. The usual inductive and steric effects noted in previous sections determine the relative strength of a base when comparing several amines.

6.19 Predict whether diethyl ether (EtOEt) or dimethyl sulfide (MeSMe) is the stronger Lewis base. Explain.
6.20 Draw the product when diethylamine reacts with triethylborane (BEt_3), using the dative bond formalism.



Ethers are weaker Lewis bases than amines. Ethers are somewhat stronger Lewis bases than alcohols because there are two electron releasing carbon groups attached to oxygen, making oxygen more electron rich and a better electron donor. The reaction of THF with trimethylborane [$B(CH_3)_3$; Section 10.5] gives the corresponding "ate" complex. Propan-2-ol reacts with aluminum chloride ($AlCl_3$) gives the expected "ate" complex. When an aldehyde or ketone reacts with a Lewis acid (e.g., boron trifluoride, BF_3). The reaction of cyclopentanone and BF_3, for example, leads to the "ate" complex shown.



6.9 NUCLEOPHILES

Nucleophiles and Organic Molecules

If a base donates electrons to an electron deficient hydrogen atom it is called a Brønsted-Lowry base. If a base donates electrons to an electron deficient atom other than hydrogen it is called a Lewis base. A species that donates electrons to an electron deficient carbon is a *nucleophile* (Section 2.8). In principle, any electron rich species can react as a nucleophile, and indeed a wide range of atoms and groups function as nucleophiles. Charged species (anions) can be nucleophiles, including halide ions (Cl^-, Br^-, I^-), alkoxides (RO^-), amide anions ($R_2N:^-$). There are "carbon nucleophiles," including alkyne anions ($RC{\equiv}C:^-$; the conjugate base of the acid-base reaction of an alkyne). In all cases, the nucleophile donates two electrons to a δ^+ carbon to form a new bond: C—X, C—OR, C—NR_2, C—C≡CR. Nucleophiles can also be neutral species (e.g., amines). Such nucleophiles will be discussed in Section 11.3 in their reactions with an electrophilic carbon.

Nucleophiles that have a localized negative charge on an atom (e.g., oxygen and nitrogen) are stronger than uncharged (neutral) nucleophiles having the same atom. The greater reactivity for a charged nucleophile is explained by the greater electron density on a charged anion than on an δ^- polarized atom. Specifically, an alkoxide (RO^-) is a stronger nucleophile than an alcohol (ROH) and an amide anion (R_2N^-) is a stronger nucleophile than an amine (R_2NH). The general trend is for nucleophilic strength to increase going down the periodic table and to the left. Inductive effects play a role and carbon groups are generally electron releasing when attached to nitrogen or oxygen. Therefore, $(CH_3)_2N^-$ is expected to be a stronger nucleophile when compared with NH_2^-. Electron withdrawing groups connected to a nucleophilic atom make that species less nucleophilic.

6.21 Briefly discuss whether CH_3O^- or HO^- is the stronger nucleophile; acetate vs ethoxide.

6.10 BIOLOGICAL RELEVANCE

Acid-base reactions are ubiquitous in biological transformations. One example is the hydrolysis of a cholesterol ester with an enzyme known as *cholesterol esterase* in Figure 6.5.[5] Esters

[5] Sutton, L.D.; Froelich, S.; Hendrickson, H.S.; Quinn, D.M. *Biochemistry* 1991, 30, 5888–5893.

are described in Section 18.5. At the active site, the enzyme contains a carboxylate anion residue, an imidazole residue from the amino acid histidine (Sections 23.1 and 24.3) and

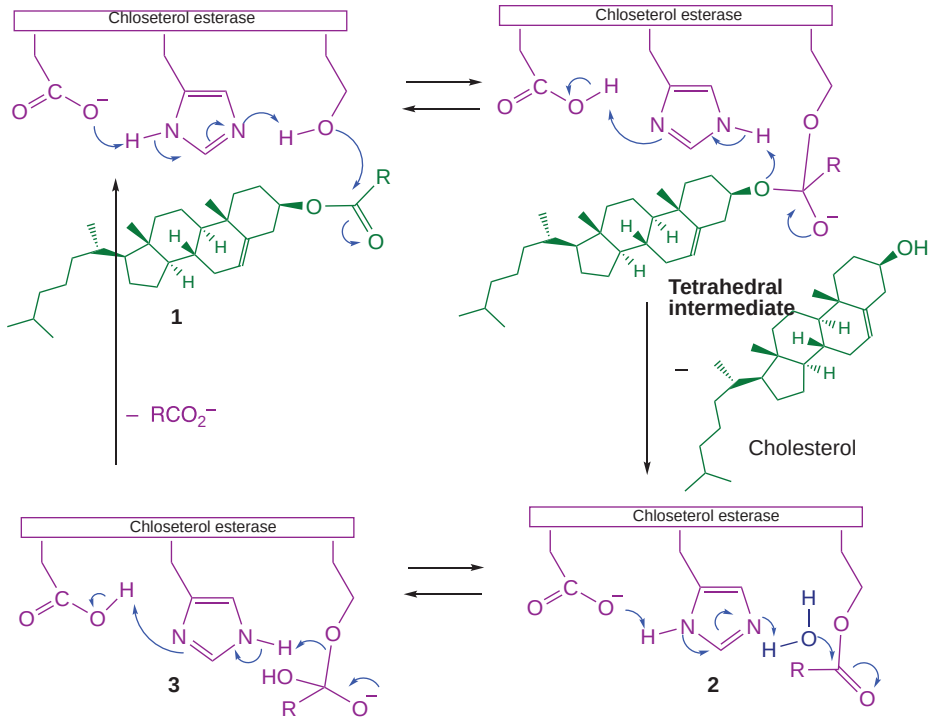


FIGURE 6.5 Hydrolysis of a cholesterol ester. (Reprinted with Permission from Sutton, L.D.; Froelich, S.; Henrickson, S.; Quinn, D.M. *Biochemistry*, 1991, 30, 5888. Copyright 1991 American Chemistry Society).

an alcohol unit. The reaction with **1**, an ester derived from cholesterol (Section 5.4), is a so-called *acyl substitution reaction* (Section 18.3) of an alcohol unit associated with the enzyme, as shown in Figure 6.5. The histidine residue (Section 24.3) is deprotonated by an internal acid-base reaction. This allows a second acid-base reaction to generate the alkoxide unit that reacts as a nucleophile with the carbonyl unit of the cholesteroyl ester to give the key *tetrahedral intermediate* (Section 18.3). This transformation converts the RO ester unit (RO_2CR') to the alcohol ROH and the alcohol unit of the enzyme is converted to an ester ($R"O_2R'$), a *transesterification* (Section 18.6). A subsequent acid-base reaction of **2** with water, which is in the cellular medium, generates **3**, which regenerates *cholesterol esterase* by loss of a carboxylate unit, RCO_2^-. While the focus of the reaction is conversion of a cholesterol ester to cholesterol (a hydrolysis reaction), the reaction is driven by acid-base reactions that occur on the amino acid residues of enzyme, *cholesterol esterase*.

CORRELATION OF HOMEWORK WITH CONCEPTS

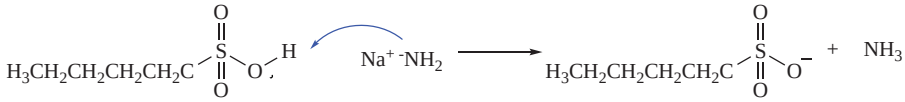
- Acids react with bases to generate conjugate acids and conjugate bases: 3, 24, 25, 36.
- The equilibrium constant for an acid-base reaction that involves organic acids is the same as any other acid-base reaction, K_a, where $K_a = \frac{[\text{products}]}{[\text{reactants}]}$, and $pK_a = -\log K_a$: 1, 22, 23.
- Acid strength is influenced by greater stability of the conjugate base, either by resonance stability or by charge dispersal due to size, which leads to a larger K_a : 2, 4, 5, 6, 9, 15, 27.
- Sulfonic acids are more acidic than carboxylic acids: 5

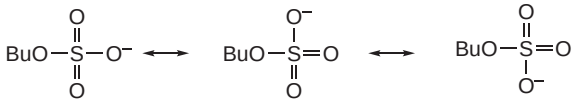
- The solvent plays a significant role in determining K_a for an acid. Polar ionizing solvents are more effective for promotion of ionization than nonpolar solvents: 8, 31.
- Inductive effects, charge density and steric hindrance influence the strength of bases: 6, 7, 9, 26, 30, 36, 37.
- Alcohols, amines ethers, aldehydes and ketones, and alkynes are Brønsted-Lowry acids: 10, 11, 12, 13, 16, 17, 33, 40.
- Compounds that behave as an acid in the presence of a strong base and a base in the presence of a strong acid are called amphoteric compounds: 28.
- Alcohols, amines, ethers, aldehydes and ketones are Brønsted-Lowry and Lewis bases: 15, 32, 37, 38.
- The basicity of an amine is measured using pK_{BH}: 14, 37, 38.
- Lewis acids are electron-pair acceptors and Lewis bases are electron-pair donors: 18, 19, 20, 32, 34, 39.
- Nucleophiles are molecules that donate electrons to carbon: 21, 35.
- Spectroscopy can be used to identify acid and base molecules: 41, 42, 43, 44.

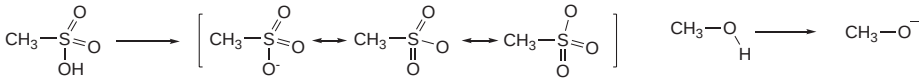
ANSWERS TO IN-CHAPTER QUESTIONS

6.1 Since $pK_a = -\log K_a$, then $pK_a = -\log 6.34\text{x}10^{-8} = -(-7.2) = 7.2$.
Since $K_a = 10^{-p}K_a$, then $K_a = 10^{-11.78} = 1.66\text{x}10^{-12}$.

6.2 

6.3 

6.4 

6.5 

The pK_a of methanesulfonic acid is known to be ~ -2, whereas that of methanol is just over 15. The carbanion formed from methanesulfonic acid is a resonance-stabilized anion, where the charge is delocalized over four atoms with three resonance contributors. When the proton is removed from oxygen in methanol, the charge is localized on oxygen. Since the methanesulfonate anion is more stable it is a weaker base in a reaction with the conjugate acid, which is consistent with a larger K_a. The charge is localized on oxygen in methoxide, it is more reactive and therefore a stronger base with the conjugate acid and the K_a is smaller.

6.6 2-Nitroethanoic acid is stronger than ethanoic acid. The presence of the electron withdrawing nitro group close to the carbonyl unit makes that molecule more acidic. Since the nitro group is close to the carboxyl unit, there is maximum inductive effect induced by the electron withdrawing group.

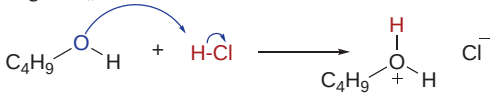
6.7 2-Methoxybutanoic acid is a stronger acid because the electron-withdrawing OMe unit is closer to the carboxyl unit. The through-space effect can occur via a five-membered cycle. In 4-methoxylbutanoic acid, the electron-withdrawing unit is too far away to provide a significant effect.

6.8 Water has both a polarized hydrogen and oxygen. The polarized hydrogen atom can hydrogen bond with oxygen atoms in the developing acetate anion. The oxygen of water can hydrogen bond with the proton of the acid that is being removed. Therefore, water helps to pull the atoms apart and stabilize the ions by solvation. Methanol has the carbon atom attached to the O, and while hydrogen bonding via

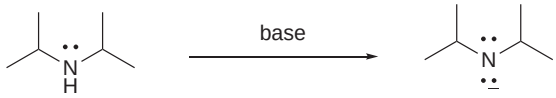
the hydrogen atom is possible, the carbon atom inhibits coordination of the oxygen, making it less efficient in terms of assisting ionization.

6.9 The OH bond in water is more polarized than the NH bond of ammonia since oxygen is more electronegative than nitrogen. This means that the H in water will have a greater δ^+ dipole than H in ammonia and is more reactive with a base. Reaction with water generates hydroxide (HO^-) and reaction with ammonia generates (H_2N^-). Hydroxide is less reactive (more stable) because oxygen is more electronegative, consistent with a larger K_a for water.

6.10



6.11



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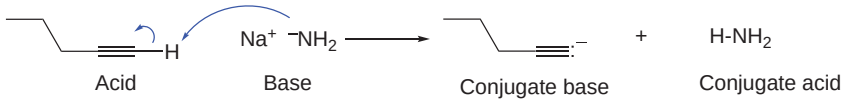
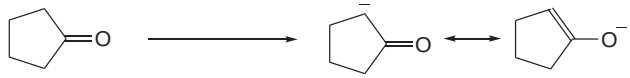


6.13

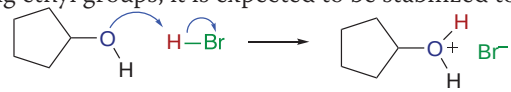


6.14 Since $pK_B = -\log K_B$, then $pK_B = -\log 3.92 \times 10^6 = -(6.59) = -6.59$.

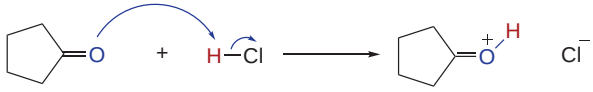
6.15

Using very simple inductive arguments, the conjugate acid from triethylamine has three electron-releasing ethyl groups that will diminish the net charge on nitrogen and stabilize it. Since the conjugate acid derived from diethylamine has only two electron-releasing ethyl groups, it is expected to be stabilized to a lesser degree.

6.16



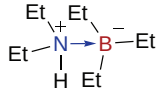
6.17



6.18

6.19 Diethyl ether is the stronger base. The sulfur atom is larger, making the net charge per unit centimeter for S less than for O. This finding means that less electron density is available for donation; a weaker base.

6.20



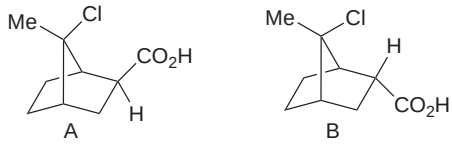
6.21 The answer really depends on what each nucleophile reacts with. However, since the electron releasing methyl group "pushes" electron density toward oxygen, more electron density on MeO^- will make it more reactive (it is more nucleophilic) than hydroxide (HO^-). Acetate is a resonance stabilized anion, so there is less electron density available for donation (it is a weaker nucleophile). In ethoxide, the electron density is effectively concentrated on oxygen and more available for donation so it is a stronger nucleophile.

HOMEWORK

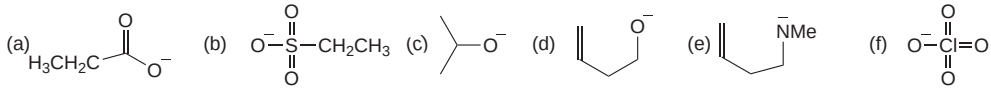
22. Calculate the pK_a given the following values for K_a :
    (a) 6.35×10^{-6} (b) 12.1×10^{7} (c) 18.5×10^{-12} (d) 9.2×10^{-3}
    (e) 10.33×10^{8} (f) 0.08×10^{-3}
23. Calculate the K_a given the following values for pK_a :

(a) 6.78 (b) -3.2 (c) 23.5 (d) 10.3 (e) 35.8 (f)v-11.1

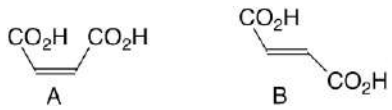
24. Draw complete reactions of each acid listed with (i) NaOH, and then (ii) $NaNH_2$, showing all starting materials and all products.
    (a) Propanoic acid (b) 2-Methylpropan-2-ol (c) $HC(CN)_3$ (d) Methanesulfonic acid
25. Draw the structure of the following acids:
    (a) 3,3-Diphenylbutanoic acid (b) 4-Chloro-2-methylpentanoic acid
    (c) 5,5-Diethyloctanesulfonic acid (d) Hex-(4*Z*)-enoic acid
26. Carboxylic acid **A** has a smaller pK_a than carboxylic acid **B**. Suggest a reason for this observation.



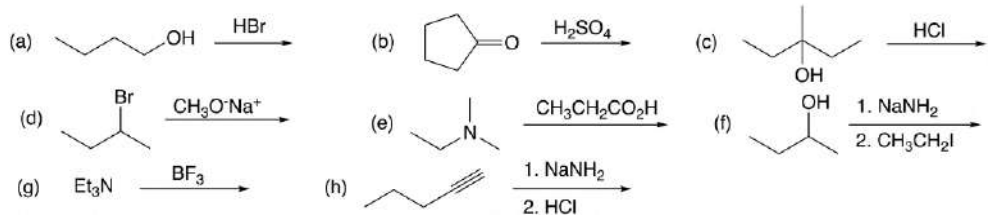
27. Draw all resonance structures for those anions that are resonance stabilized and indicate which are not resonance stabilized.



28. Alcohols are known to be amphoteric. Predict whether propan-1-ol will be an acid or a base or will be neutral in the presence of each of the following:
    (a) NaOH (b) HCl (c) Water (d) Ethanol (e) $NaNH_2$ (f) Butan-2-one (g) Methane (h) H_2SO_4
29. Maleic acid (**A**) is known to have a pK_a of ~ 1.8 whereas fumaric acid (**B**) has a pK_a of ~ 3. Explain.



30. Explain why 5-bromopentanoic acid has a pK_a close to that of pentanoic acid, whereas 2-bromopentanoic acid is significantly more acidic.
31. Discuss whether propanoic acid is more acidic in diethyl ether or in diethylamine.
32. Draw the product formed when triethylamine (Et_3N) reacts with:
    (a) HCl (b) BF_3 (c) Propanoic acid (d) $AlCl_3$ (e) Methanesulfonic acid (f) $FeCl_3$
33. Draw the conjugate acid formed when each of the following reacts with HCl:
    (a) Pentan-3-one (b) Dimethyl ether (c) Diethylamine (d) Water (e) Cyclopentanecarbaldehyde
    (f) CH_3-S-CH_3 (g) Propan-2-ol (h) Acetic acid.
34. Draw the product for each of the following reactions:
    (a) Butan-2-one and $AlCl_3$ (b) Diethyl ether and BF_3 (c) Triethylamine and Et_3B
    (d) Prop-2-enal (called acrolein) and BF_3 (e) Chloroethane and $FeBr_3$ (f) THF and ZnI_2
35. It is known that ammonia (NH_3) is a much weaker nucleophile in its reaction with acetone than is the amide anion ($^-NH_2$). Suggest reasons why this is so.
36. Draw the structure of hexanesulfonic acid, 3-methylbutanesulfonic acid, and 2-chlorobutanesulfonic acid. Of these three, indicate which may be the stronger acid.
37. Give the products formed in each of the following reactions:



38. Briefly explain why H_2NCH_3 is more basic than H_2NBr.
39. Which amine is likely to react faster with formic acid, $(CH_3CH_2)_3N$ or $(Me_3C)_3N$? Draw both reactions with the conjugate acid–base that is formed and explain your answer.
40. Which of the following should react faster with $AlCl_3$, diethyl ether or fluoromethane? Draw the products expected from both reactions and explain your answer.

Spectroscopic Problems (to be done only after Chapter 13 is read and understood)

41. Briefly describe how one can use infrared (IR) and ^1H NMR (proton nuclear magnetic resonance) to distinguish between propanoic acid and propan-1-ol.
42. The proton of the OH unit in propan-2-ol can resonate between 1–5 ppm in the ^1H NMR, in deuterochloroform, as the concentration changes. Why?
43. Briefly describe the differences in the IR and ^1H NMR that will allow one to distinguish between trimethylamine, *N*-methylaminoethane, and propan-1-amine.
44. Predict the ^1H NMR for formic acid versus formal (formaldehyde).

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-7.php

7

Chemical Reactions, Bond Energy, and Kinetics

A chemical reaction transforms one molecule into another molecule. Understanding key characteristics of chemical reactions helps to understand how reactions work, why they work, what energy characteristics drive a reaction, and if there is an intermediate. It must also be known if the reaction proceeds in one step or several steps to the final isolated product.

To begin this chapter, you should know the following points:

- The structure and nomenclature of functional groups (Sections 5.1, 5.3, 5.5, and 5.6).
- The chemical bond in general, and the polarized covalent bond in particular (Sections 3.3, 3.5, and 3.8).
- An understanding of the factors that influence making and breaking bonds (Section 3.7).
- The fundamentals of acid-base equilibria and pK_a (Sections 2.1–2.3 and 6.1–6.3).

7.1 A CHEMICAL REACTION

Formally, a chemical reaction is a process that converts the molecular or ionic structure of one substance to another substance. When chemical reactions occur, the atoms are rearranged. A reaction is accompanied by an energy change as new products are generated. The substance (or substances) initially involved in a chemical reaction is (are) called *reactants* and *reagents*. Chemical reactions usually yield one or more *products*, with a structure and properties different from the reactants. Reactions may go to completion or proceed in the forward or reverse direction until they reach equilibrium. Many reactions proceed in the forward direction to give an isolated product once the reaction begins and require no further input of energy to go forward. These reactions are said to be spontaneous. Some reactions require an input of energy to go forward even after the reaction has begun. These reactions are said to be non-spontaneous.

There are thought to be four fundamental types of reactions. (1) *Synthesis*. In a synthesis reaction, two or more simple substances combine to form a more complex substance. Chemical synthesis uses several different chemical reactions in a sequence. The product of one reaction is the starting material for the next reaction. This protocol continues until a desired product called a *target* is obtained. (2) *Decomposition*. A decomposition reaction is the breakdown of a more complex into its simpler parts. (3) *Single Replacement*. In a single replacement reaction, a single uncombined element replaces another in a compound; one structural unit trades places with another structural unit in a compound. (4) *Double Replacement*. In a double replacement reaction, the anions and cations of two compounds switch places and form two entirely different compounds.

Reactive Intermediates-A

7.2 REACTIVE INTERMEDIATES

Reactive Intermediates-B

Many reactions do not give an isolated product directly but generate an intermediate product that is highly reactive. The intermediate product reacts further to give the isolated product. Such transient products are known as *intermediates*. A generic reaction is shown that

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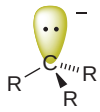
illustrates formation of an intermediate. Starting material **A** reacts with **B** to yield a product **C** but **C** is not isolated in this reaction.

Once formed, **C** quickly reacts with additional **B** in a second chemical reaction to yield an isolated product, **D**. A transient and relatively high-energy product such as [**C**] is a *reactive intermediate*. The brackets set it apart to indicate a transient species that is not isolated. A reactive intermediate reacts before it can be isolated so it is high in energy (unstable). In reality there are two reactions, not one, but if the focus is on starting materials and isolated product, then **A** + **B** → **D**. Formation of a reactive intermediate in a reaction must be determined experimentally since it is usually not intuitively obvious. In other words, the book and/or your instructor must provide the information that a reaction has a reactive intermediate. Three types of reactive intermediates will be discussed in this book: *a carbocation, a radical, or a carbanion.*

An important reactive intermediate in many organic reactions is a positively charged carbon atom, a *carbocation*. A *carbocation,* also called a *carbenium ion*, is an electron-deficient species that has a charge of +1 (Section 7.3). This charged intermediate has three covalent bonds, is high in energy, unstable and highly reactive. Formation of a carbocation usually accompanies a reaction in which a covalent bond to carbon is broken via heterolytic cleavage (Section 3.7). The structure of a generic carbocation is shown using structures **A** and **B**. The carbon of a carbocation has a positive charge, is sp^2 hybridized, and so it must have trigonal planar geometry (see **A).** The positive charge is *localized* on the sp^2-carbon, and that charge is associated with an empty p-orbital on carbon as shown in **B**. This empty orbital can accept electron density from a nucleophile to form a new bond, so it is an *electrophile*.

A B

7.1 Draw the structure of a carbocation where all the "R" groups in A are ethyl groups.



Carbanion

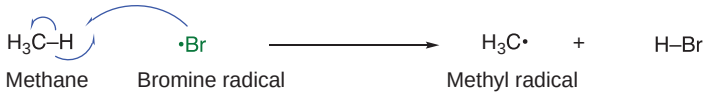
An anion is a species that has an excess of electrons and bears a charge of -1. When the negative charge resides on carbon, it is called a *carbanion*. In general, carbanions are formed by breaking a covalent bond in such a way that two electrons are transferred to the carbon involved in that bond during a heterolytic cleavage. A generic carbanion is shown with three covalent bonds between C and R, and a pair of electrons in a p-orbital. Indeed, a negative charge can be viewed as a filled p-orbital. Since electrons in covalent bonds are repelled by the lone electron pair, the three-dimensional structure shown for a carbanion resembles a "squashed tetrahedron."

A carbanion is a high energy intermediate, unstable, and very reactive. Since a carbanion has an excess of electrons, it will readily react with an electron-deficient carbon atom, so it is classified as a nucleophile. If a carbanion reacts with the acidic proton of a Brønsted-Lowry acid, however, it is classified as a base. Carbanions are not as prevalent as carbocations unless they are stabilized by an electron withdrawing unit such as a carbonyl.

D C

7.2 Draw the structure of a carbanion where two of the "R" groups in R_3C^- are methyl groups and the third is a phenyl, assuming a pyramidal structure.

When a p-orbital on any given atom has only has one unshared electron, it is called a *radical*. A carbon radical is represented as $R_3C\bullet$ (see **D** and **C**). With three covalent bonds and one extra electron, $R_3C\bullet$ is a high-energy species and a very reactive intermediate. Although one might expect a "squashed" tetrahedron (pyramidal) shape (**D**) for a carbon radical there is evidence that a planar structure (**C**) is probably the low-energy structure, at least for the methyl radical ($H_3C\bullet$). One way to form a carbon radical is by a chemical reaction between a neutral species (e.g., methane) and an existing radical (e.g., Br•; Sections 10.10 and 11.7). The bromine radical donates a single electron to one hydrogen atom of methane to form HBr and one electron is transferred to carbon from the C—H bond to form the methyl radical, $\bullet CH_3$. Note the single headed arrows, much like a fishhook.



7.3 Draw the structure of a planar radical where two of the "R" groups in C are hydrogen atoms and the third group is an ethyl.

7.3 FORMAL CHARGE

Formal Charge

The preceding discussion of reactive intermediates raises the issue of identifying a structure that has a charge. A chemical structure can be analyzed for a parameter called *formal charge*. Formal charge is calculated by examining the difference between the last number of the group number, which is the number of valence electrons, and eight, which is the maximum number of valence electrons for the second row (Section 3.1.2). The number of bonds that each atom can form to other atoms and remain neutral is called the *valence* for that atom. For example, carbon has a valence of four and nitrogen has a valence of three. If an atom forms more bonds or fewer than is required by the valence, it must take on a charge. To determine if the number of covalent bonds to a given atom will generate a charge, *formal charge (FC)* must be calculated using a specific formula.

FC = Ending Number of the Group Number - 0.5 (shared electrons) - (unshared electrons).

Note that counting one-half of the shared electrons is the same as counting the number of bonds. Examples are shown in Figure 7.1. Begin with C2 in ethoxide, the conjugate base of the alcohol, ethanol. Carbon is in group 14 and forms four covalent bonds with zero unshared electrons. The formal charge for C2 is calculated by $FC^{C2} = 4 - \frac{1}{2}(8) - 0 = 4 - 4 = 0$. Subsequent calculations show that none of the carbons in ethoxide have a charge.

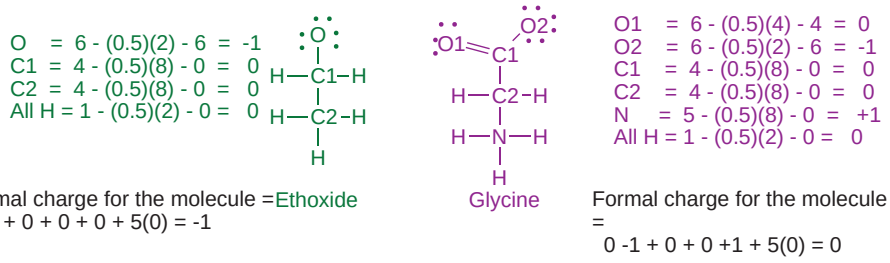


FIGURE 7.1 Calculation of formal charge for ethoxide and glycine.

The charge for the entire molecule is calculated by summing the charges for all the atoms. Adding the formal charge of -1 on oxygen with zero formal charge for all other atoms gives the formal charge for the ethoxide -1. Note that in ethoxide, the negative charge resides on the oxygen. Glycine (Section 24.3) in Figure 7.1 shows that O2 has a formal charge of -1, the nitrogen has a formal charge of +1 and all other atoms have a formal charge of zero. When these are added together, the formal charge for the molecule glycine is *zero*. Formal charge allows inspection of any structure to determine if it is a neutral or a charged molecule, and if there is charge on any atom in that molecule.

7.4 Determine the formal charge of bromine and carbon in CH_3Br (bromomethane, also called bromoform).

The Free Energy Equation

7.4 FREE ENERGY: ENTHALPY AND ENTROPY

Heating imparts the energy to molecules needed for chemical reactions. Energy can be transferred by collision with another atom or molecule. The energy released by such collisions is utilized in bond breaking and bond-making. Changes in energy are used to follow the progress of a chemical reaction to determine whether or not that reaction is spontaneous. The spontaneity of a chemical reaction is determined by the change in *standard free energy* ($\Delta G°$). The change in free energy is calculated from the change in enthalpy ($H°$) and the change in entropy ($S°$) using the *Gibbs Free Energy equation:* $\Delta G° = \Delta H° - T\Delta S°$. This calculation assumes that the reaction is done under standard conditions, in solution at a concentration of 1 M and at 298.15 K. Note that the term "T" is temperature, measured in Kelvin. The change in entropy term ($\Delta S°$) measures the "disorder" of a given system. If the number of particles for a reaction remains the same or decreases, the magnitude of the entropy term is quite small. If the number of particles increases during the course of a reaction, then entropy usually increases. For most reactions presented in this book the change in entropy is small.

The term $H°$ is measured in kcal (or kJ) mol^{-1}, so $\Delta H°$ will also have units of kcal (or kJ) mol^{-1}. The entropy term is measured in *calories* (cal) or joules (J) not in kcal or kJ. When the change in entropy is only a few calories or a few joules, the $T\Delta S°$ term is much smaller than the $\Delta H°$ term (often < 1%, *but it is not zero*). Therefore, ignoring it will introduce only a tiny error. For example, if $\Delta H°$ for a reaction is about 19.1 kcal, the $\Delta S°$ for that reaction is 0.01 kcal. Therefore, ignoring $\Delta S°$ will introduce a tiny error (0.05% in this case). Dropping the $T\Delta S°$ term out of the equation gives $\Delta G° \approx \Delta H°$, which is a good *first approximation*. Note, however, that ignoring entropy is an assumption. If the $\Delta H°$ term is > 2–4 kcal (8.4–16.7 kJ) mol^{-1}, the entropy term ($T\Delta S°$) should be included. There are reactions, especially cyclization reactions, where the change in entropy is large enough to influence the reaction.

7.5 If $\Delta H° = 21.5$ kcal (89.9 kJ) mol^{-1}, $\Delta G° = 22.4$ kcal (93.7 kJ) mol^{-1}, $T = 298$ K, what is the value of $\Delta S°$ in kcal (kJ) mol^{-1}? How serious is the error introduced into a $\Delta G°$ calculation if the $\Delta S°$ term is ignored?

When $\Delta G°$ for a reaction is calculated, it can have a positive or a negative value. If $\Delta G°$ has a negative value, energy is *released* as the reaction proceeds and the process is *exothermic* (exergonic). Such a reaction is said to be *spontaneous* because it produces enough energy during the course of the reaction to be self-sustaining, once it has started. If $\Delta G°$ has a positive value, the process is *endothermic (endergonic)* and energy must be continually added to the system for it to continue. An endothermic process is therefore *non-spontaneous* because less energy is produced during the reaction than is required to keep it going. The energy for a given reaction, say A + B → C + D, can be displayed as a reaction curve. Figure 7.2a shows the reaction curve for an exothermic reaction whereas 7.2.b shows the reaction curve for an endothermic reaction. It is noted that no reaction can *begin* until energy equal to the energy of activation is attained.

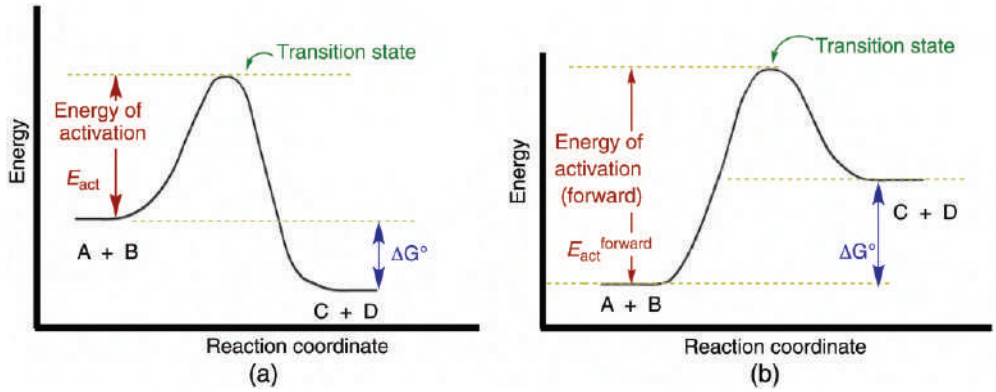


FIGURE 7.2 Exothermic and endothermic reaction curves, with the energy of activation, the transition state and the change in free energy for each reaction.

7.6 Determine if a reaction is spontaneous or not when $\Delta H°$ is known to be -30 kcal (125.5 kJ) mol^{-1}.

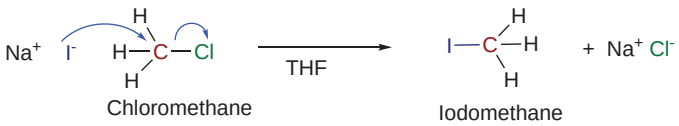
Energy Curves and Reactions

For any reaction to begin, *energy* must be applied to initiate the reaction. In most cases, heating increases the kinetic energy of both the starting materials and solvent molecules. Molecular collisions transfer energy from one molecule to another. The starting materials must absorb sufficient energy, called the *activation energy, E_{act}*, to initiate the bond-breaking-bond-making process. The E_{act} is attained at the maximum point on the reaction energy curve and correlates with the *transition state*. Once the transition state has been reached, the reaction proceeds to the final products. It is important to reiterate that until energy equal to E_{act} is applied, no chemical reaction takes place. A reaction will spontaneously proceed to products if $\Delta G°$ is negative (Figure 7.2a) but if $\Delta G°$ is positive (Figure 7.2b) energy must be continuously added to the reaction for it to continue.

7.5 BOND DISSOCIATION ENTHALPY AND REACTIONS

Bond Dissociation Energy and Bond Strength

As introduced in Section 3.7, the energy stored in a σ-covalent bond is called the *bond dissociation enthalpy*, $H°$, although it is usually called *bond dissociation energy*. To break bonds, energy is absorbed so bond-breaking is an endothermic process. When bonds form, energy is released so bond-making is an exothermic process. Bond dissociation energy should be correlated with a specific molecule rather than a generic value for a given bond. However, generic bond dissociation energy values may be used for a discussion of the principles. An example is the so-called *substitution reaction* (Sections 11.1–11.3). The iodide ion (from the *ionic* compound NaI) reacts with chloromethane to give the chloride ion and iodomethane as products. The solvent is the ether THF (tetrahydrofuran, Sections 5.5.2 and 6.7.3), shown under the reaction arrow.



It does not participate in the bond-making and bond-breaking process. The iodide ion reacts as a nucleophile with carbon of the C—Cl unit, which is broken. Chloromethane, the *starting material*, is always drawn on the left side of the equation. A new C—I bond is formed in iodomethane, the *product*, which is always drawn on the right side of the equation. The bond strength for the C—Cl bond in chloromethane is 84 kcal (351.5 kJ) mol^{-1} and the bond

strength of C—I in iodomethane is 56 kcal (234.3 kJ) mol^{-1}, as shown in Table 7.1.[1] The *change in* energy from reactant to product is the difference in the two values of $H°$ or $\Delta H°$ (change in energy), and $\Delta H°$ is $H°_{(\text{bonds broken})}$ - $H°_{(\text{bonds made})}$. For the reaction shown, $\Delta H°$ is

$$\Delta H = H_{(\text{bonds broken})} - H_{(\text{bonds made})} \text{ and } \Delta H = H_{(\text{Cl–C})} - H_{(\text{C–I})}$$

$$\Delta H = 84\,\text{kcal}(351.5\text{kJ})\text{mol}^{-1} - 56\,\text{kcal}(234.3\text{kJ})\text{mol}^{-1} = 28\text{kcal}(117.2)\text{mol}^{-1}$$

The free energy (ΔG°) is the important parameter. If the ΔS° is very small and assumed to be zero, it is clear the calculated value of ΔH° is close to the value of ΔG°, measured in kilocalories. The difference is usually only a few calories. The positive sign for ΔG° (from $\Delta H°$) for this substitution reaction means that this is an *endothermic reaction (endergonic)*.

TABLE 7.1 Selected Bond Dissociation Energy Values for Bonds In Specific Molecules

Bond	Bond Strength ($H°_{298}$) in kcal (kJ) mol^{-1}	Bond	Bond Strength ($H°_{298}$) in kcal (kJ) mol^{-1}
I—CH_3	56 (234.3)	H—$C(CH_3)_3$	92 (384.9)
Br—CH_3	70 (292.9)	H—$CH(CH_3)_2$	95 (397.5)
Cl—CH_3	84 (351.5)	H—CH_2CH_3	98 (410.0)
H_2N—CH_3	87 (364.0)	H—CH_3	104 (435.1)
H_3C—CH_3	88 (368.2)	F—CH_3	109 (456.1)
HO—CH_3	91 (380.7)		

7.7 Calculate $\Delta H°$ for a reaction if the energy required to make bonds is 100 kcal (418.4 kJ) mol^{-1} and that required to break bonds in the starting materials is 68 kcal mol^{-1}.

Transition States

7.6 TRANSITION STATES

Imagine the reaction of starting materials **A** and **B** give the final product **A**—**B**. This is a one-step reaction, meaning that **A** and **B** react to give **A**—**B** directly, with *no reactive intermediate*. The normal representation of this reaction is **A** + **B** → **A**—**B**. After the activation energy is applied there is enough energy to begin making and breaking bonds. The point at which the bond begins to form, represented by [**A**-----**B**], is the *transition state*, the logical mid-point of a reaction. In virtually all reactions, a transition state cannot be isolated or even detected. However, the transition-state region of a prototypical photodissociation reaction has been directly observed using femtosecond extreme ultraviolet transient absorption spectroscopy.[2]

$$\text{A} + \text{B} \rightarrow [\text{A---B}] \rightarrow \text{A—B}$$

Returning to the conversion of chloromethane to iodomethane in Section 7.5, no intermediate has been discovered in all of the experiments done for this type of reaction over many years. Therefore, when this reaction is said to have *no intermediate*, this statement is the result of experimental findings, and it is not intuitively obvious. If there is no intermediate, the course of that reaction can be understood only by describing the transition state. The transition state for the reaction of chloromethane and iodide is shown in Figure 7.3. The

[1] Haynes, W.M. *CRC Handbook of Chemistry*, 94th ed., CRC Press, Inc., Boca Raton, FL, 2013–2014, pp. 9–71 to 9–79.

[2] Attar, A.R.; Bhattacherjee, A.; Leon, S.R. *Journal of Physical Chemistry Letters*, 2015, 6, 5072–5077.

transition state must describe the Cl—C bond as it begins to break and the C—I bond as it begins to form. *Dashed lines* are used in the transition state, **1**, to represent bond breaking-bond formation. The transition state is shown in a bracket, to set it apart from the reaction.

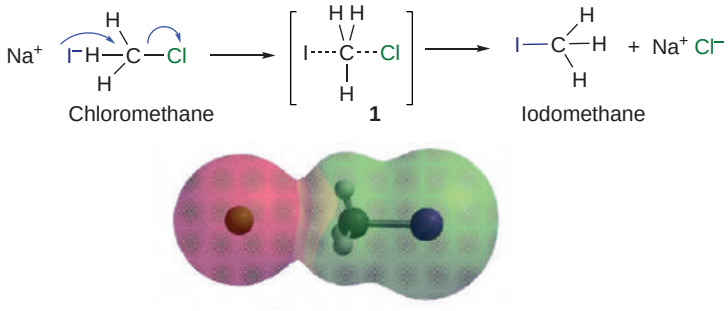


FIGURE 7.3 Pentacoordinate transition state for the reaction of sodium iodide and chloromethane.

Note that there are five atoms surrounding carbon in **1** so it is called a *pentacoordinate transition state*, but this does *not* mean there are five bonds. Transition state **1** is not a real molecule but represents bond breaking-bond making so there are never five formal bonds about that central carbon. Carbon can never have more than four covalent bonds. The reaction proceeds from the transition state to give iodomethane. Note that the transition state can be estimated by looking at the curved electron transfer arrows, which show that iodide donates an electron to carbon (I-----C) and the electron in the C—Cl bond are transferred to chlorine (C-----Cl). Replacing the curved arrows in the reaction shown with the dashed lines (-----) effectively generates the transition state, **1**. The molecular model of **1** in Figure 7.3 shows the I—C bond beginning to form and the C—Cl bond beginning to form. It also shows that the three hydrogen atoms attached to the central carbon are coplanar in the transition state.

7.8 If $\Delta H°$ for one reaction is -21 kcal (87.9 kJ) mol^{-1} and that for a second is -10 kcal (41.8 kJ) mol^{-1}, determine which reaction is likely to occur at a lower temperature if E_{act} for the first reaction is 35 kcal (146.4 kJ) mol^{-1} and E_{act} for the second reaction is 44 kcal (184.1 kJ) mol^{-1}.

7.7 COMPETING REACTIONS

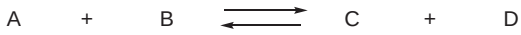
Imagine there are two competing reactions. A reactant **A** can go either to product **B** or to product **C** under the same conditions: C ⟵ A ⟶ B. Assume the E_{act} for the reaction that converts **A** to **C** is shown to be 5 kcal (20.9 kJ) mol^{-1} and the E_{act} for the conversion of **A** to **B** is 10 kcal (41.8 kJ) mol^{-1}. Note that E_{act} values are not intuitively obvious but are determined in the laboratory by experiments. If the actual applied energy is only 6 kcal (25.1 kJ) mol^{-1}, the product will be **C** and there will be no **B** because there is not enough energy for that reaction to begin. In other words, by controlling the amount of energy applied to the reaction it is possible to produce **C** as the exclusive product. If 15 kcal (62.8 kJ) mol^{-1} is applied there is enough energy for *both* reactions to occur, and *both* products **B** and **C** are produced. For competing reactions and indeed for any reaction, the importance of the energy of the system can be stated another way. The *Curtin-Hammett principle*[3] states that, for a reaction that has a pair of reactive intermediates each going irreversibly to a different product, the product ratio

[3] (a) Seeman, J.I. *Journal of Chemical Education* **1986**, *63*, 42–48; (b) Curtin, D.Y. *Record of Chemical Progress* 1954, 15, 111–128.

will depend the free energy of the transition state going to each product. This principle was proposed by David Y. Curtin (USA; 1920-–2011) and Louis P. Hammett (USA; 1894–1987).

7.8 REVERSIBLE CHEMICAL REACTIONS

A reversible chemical reaction, otherwise known as an equilibrium reaction, is one where the compounds defined as products react to regenerate the compounds normally defined as starting materials. These two reactions compete with each other. All of the Brønsted-Lowry acid-base reactions discussed in previous chapters are equilibrium reactions, defined by K_a. Other types of reversible reactions are common.



A generic example of a reversible reaction is **A** + **B** reacting to give **C** + **D**. The chemical reaction of **A** and **B** gives products **C** and **D**. The second chemical reaction is the "reverse" of the first one, where **C** and **D** react to give **A** and **B**. During this reaction, all four species **A**, **B**, **C** and **D** will be present, but the concentrations of each depends to the value of the *equilibrium constant,* (K). The products are defined as being on the right side of the reaction and reactants are defined as being on the left side of the equation. Indeed, the value of K is determined by the concentrations of reactants and products, $K = \frac{[\text{products}]}{[\text{reactants}]}$. For the generic reaction shown, $K = \frac{[C][D]}{[A][B]}$. If the value of K is small, the bottom term (reactants) is larger than the top term (products), which indicates that **A** does not react very well with **B** to give products. Therefore, the reverse reaction is more favorable, and the equilibrium is pushed to the left. If the value of K is large, the top term (products) has a greater concentration than the bottom term (reactants). Therefore, **A** reacted with **B** to give **C** + **D** as the products. If the value of K is about 1, the reaction has close to an equal mixture of products and reactants at equilibrium.

If a reaction is identified as reversible, the equilibrium constant (K) is related to the free energy ($\Delta G°$). This relationship is shown in eq. 7.1, where $R = 1.986$ cal deg^{-1} mol^{-1}, T = temperature in Kelvin, and $e = 2.718$ (base of natural logarithms). Conversion of the ln(K) to base 10 leads to 2.303 log(K). When the temperature of an experiment is reported in degrees Celsius, the temperature is converted to Kelvin by adding 273.15. With this equation, the values of K for two reactions can be compared and the values of $\Delta G°$ used to predict which one might be more favorable.

$$K = e^{-\frac{\Delta G°}{RT}} \text{ or } \Delta G° = -RT_{\text{Kelvin}}\left(\ln K\right) = -2.303R\left(T_{\text{Kelvin}}\right)\left(\log K\right) \quad (1)$$

7.9 Calculate the equilibrium constant, K, for a reaction where $\Delta H°$ is 68.2 kcal (285.3 kJ) mol^{-1} and the reaction temperature is 91°C.

Several points can be made that concern equilibrium reactions.

1. If the equilibrium constant for a reaction (K) is extremely large, the reaction is essentially irreversible.
2. One product may escape from the reaction medium (e.g., a low molecular weight gas) and the equilibrium will be shifted toward products.
3. If the two reactants are less stable (more reactive) than the products, the equilibrium constant is large (>> 1).
4. If the bonds being formed in the product are much stronger than those being broken in the reactant, the equilibrium usually shifts toward the products.
5. If the E_{act} for the reaction going to the right (forward) is much smaller than that going to the left (reverse), the reaction is effectively irreversible.

7.9 REACTION CURVES AND INTERMEDIATES

Three main categories of intermediates were introduced in Section 7.2, carbocations, carbanions, and radicals. When a reaction has an intermediate, formation of that intermediate constitutes one chemical step. Subsequent conversion of the intermediate to the isolated products will require additional chemical steps. When there are two or more chemical steps, each reaction generates a product and has an E_{act}. The E_{act} for each of these steps is reflected in a reaction curve, as shown in Figure 7.4.

For a generic reaction **A** + **B** ⟶ [**C**] ⟶ **D**, where [**C**] is a reactive intermediate, the energy curve in Figure 7.4 is a combination of two chemical reactions. The first is **A**+**B** ⟶ **C** and the second is **C** ⟶ **D**. The activation energy for the first reaction (marked E_{act}^{1}) must

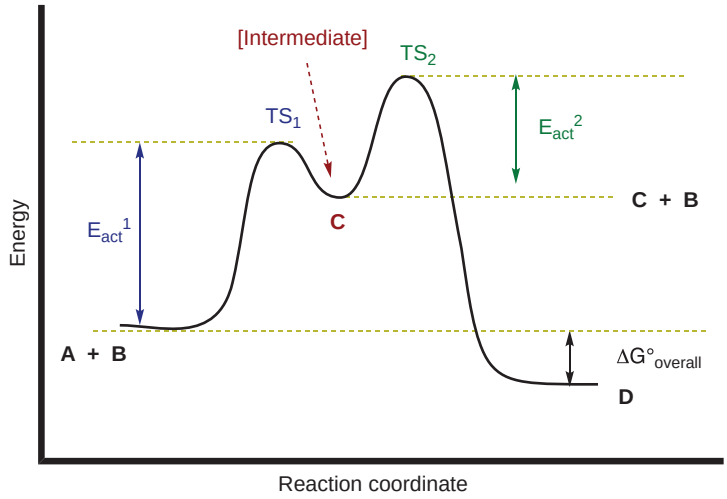


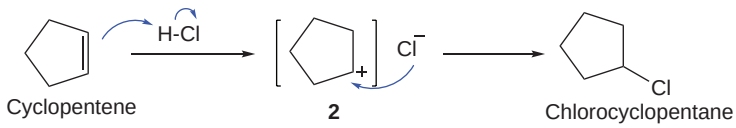
FIGURE 7.4 Energy curve for a reaction that has one intermediate.

be applied for conversion of the starting materials **A** and **B** to the point marked TS_1 (first transition state). Once TS_1 is attained the reaction proceeds to product **C**, which is an energy minimum. Reaction product **C** is an intermediate, not a transition state, so it can be detected. Intermediate **C** is highly reactive, and a new reaction requires a different energy, E_{act}^{2}, to reach a second transition state (marked TS_2). In this case E_{act}^{2} is $< E_{act}^{1}$, and once **C** begins to react, the energy curve shows that the reaction proceeds to product **D** in an exothermic reaction. Figure 7.4 therefore represents two reactions, each with an energy of activation and each with a separate transition state. If an external observer were to see this reaction, **A** and **B** would disappear to form an isolated product **D**. An intermediate such as ***C*** can usually be detected using experimental techniques and it is rarely if ever isolated.

7.10 MECHANISMS

What is a Mechanism?

Figure 7.4 shows the energy curve for a reaction that proceeds by initial formation of a reactive intermediate, followed by a second reaction that leads to the final, isolated product. Once an intermediate has been identified, it is possible to write a reaction sequence: starting material(s) to intermediate to product(s). This step-by-step description of a reaction is called the *mechanism*. Each step in a mechanism must be cited, including the structure of all reactive intermediates.



An example of a reaction that has an intermediate is the reaction of an alkene with a mineral acid to give a carbocation product. This reaction will be discussed in Section 10.2.1. Cyclopentene reacts with HCl to give chlorocyclopentane as the isolated product. Experimental evidence for this reaction shows that cyclopentene forms a product that can be detected but disappears over time to give the observed and isolated product, chlorocyclopentane. This unstable and transient product was identified as carbocation intermediate, **2**.

An example of an experiment used to detect the presence of an intermediate first determines the number of molar equivalents of the starting material, here cyclopentene. When mixed with HCl the reaction begins, and the disappearance of cyclopentene is monitored by examining the change in the molar equivalents of the starting material as a function of time. At some point in the reaction, chlorocyclopentane (the product) begins to form and the

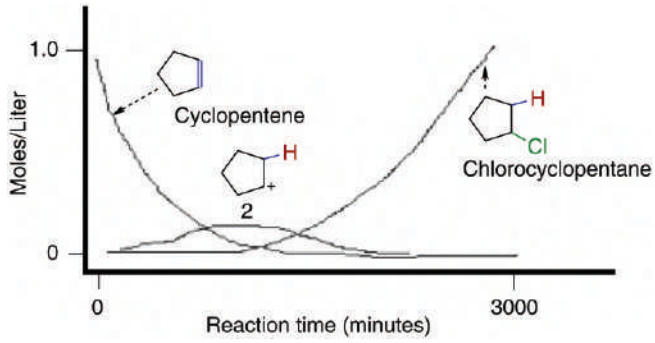


FIGURE 7.5 Disappearance of starting material cyclopentene and formation of chlorocyclopentane.

molar equivalents of product are monitored as a function of time. During the course of this reaction, a transient product may be detected that forms before and during the appearance of the chlorocyclopentane product, as illustrated by the formation of **2** in Figure 7.5, the transient "product," which appears during the course of the reaction and then disappears. Using other experimental techniques, not described here, this transient product was determined to be carbocation intermediate **2**. Identification of all intermediates in a reaction allows one to define the step-by-step process by which starting materials are converted to products. The step-by-step listing of intermediates is called the *mechanism* of that reaction. For all reactions in this book, the following protocol will be used to discuss a mechanism.

1. Examine the products and compare them with the starting material.
2. If no intermediates can be found experimentally, *you will be told that there are none when that reaction is first introduced*.
3. When experiments show that there is an intermediate, *you will be told when that reaction is first introduced*. Draw the intermediate, the starting materials and all products.
4. Make an educated guess on where the product came from based on structural changes, one chemical step at a time. Essentially, construct a step-by-step walk-through for that reaction.

As suggested in step 4, it is possible to ascertain a reasonable mechanism for most reactions by working "backwards." The process begins with a comparison of the product structure(s) with the structures of the starting material(s). In the reaction of cyclopentene and HCl, chlorocyclopentane is the product, and the Cl must come from HCl. This requires cleavage of the H—Cl bond. However, one must answer the question of which adds first to C=C, the H or the Cl. Since HCl is a Brønsted-Lowry acid, it is reasonable to assume that cyclopentene reacts as a Brønsted-Lowry base with H—Cl. In other words, the C=C unit reacts first with the H of HCl in an acid-base reaction. Indeed, all reactions of an alkene and a mineral acid will give a carbocation intermediate such as **2**. Once the reactive intermediate is formed, the chloride ion reacts as a nucleophile is a second chemical step to give the product, chlorocyclopentane.

The mechanism is therefore reaction of the alkene with HCl to give a carbocation followed by a second reaction with the chloride ion to give the product. This approach generates the step-by-step sequence shown above with the structures of the starting materials, the intermediate and the final product, which is the mechanism.

The mechanism of the reaction of cyclopentene and HCl involves two chemical reactions. These reactions are represented by the energy diagram in Figure 7.6, where the intermediate

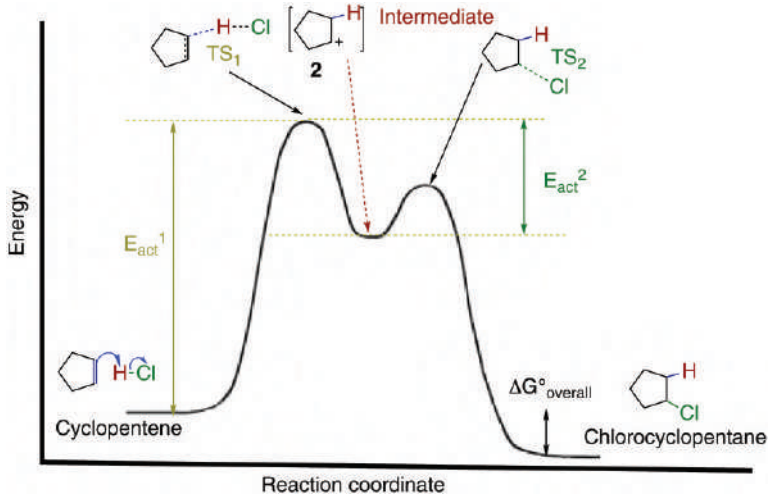


FIGURE 7.6 Energy diagram for the reaction of cyclopentene and HCl.

carbocation **2** is shown as a high-energy transient product of the first reaction. This intermediate is higher in energy than chlorocyclopentane, but lower in energy than either transition state. In transition state [TS_1], the π-bond is breaking and the new C—H bond is beginning to form. For transition state [TS_2], the chloride ion is beginning to attack the positive carbon, so the C—Cl bond is beginning to form. As drawn in Figure 7.6, this overall reaction is exothermic. The real point of this figure is to associate actual structures with key energy points or energy terms on the reaction curve. Note that $E_{act}{}^2$ is shown to be lower than $E_{act}{}^1$, indicating that intermediate **2** should easily proceed to product.

7.10 Write out the mechanism for the reaction of 2,3-dimethylbut-2-ene with HBr.

7.11 KINETICS

Kinetics and Half-Life

Once a chemical reaction has been identified, it is reasonable to question how fast it will go. How long does it take until the reaction is complete? Apart from the obvious concern about how long one will have to monitor the reaction, other information can be obtained from knowledge of how fast a reaction goes and how long it takes. In many cases, such knowledge can give insight into the mechanism of a reaction.

7.11.1 REACTION RATE AND FIRST-ORDER REACTIONS

The *rate of reaction* is a parameter that measures how quickly a reaction proceeds. In other words, how long does it take to consume a starting material and convert it to product. To answer this question for a chemical reaction, the change in molar concentration of either the starting materials (reactants) or the products can be monitored. A simple reaction in which **A** is transformed into **B** (**A** ⟶ **B**), with no intermediate, will be used to illustrate the concept. The starting material is consumed as a function of time to form product **B** so the number of

molar equivalents must *decrease*. In other words, **A** is consumed to form the product **B**. The rate is determined by first measuring the initial concentration (in mol L^{-1}) of a reactant (**A**), which is 1.0 M (time = 0 s). The concentration of **A** is measured at certain time intervals as it is consumed. Brackets are used to indicate molar concentration, so [**A**] is the molar concentration of reactant **A** for each time point in the reaction. The measurements are continued until **A** has disappeared. Since the concentration changes as a function of time, which also changes, and the data can be interpreted using a differential equation, *rate* = $\frac{-d[A]}{dt}$.

The rate is proportional to the concentration of **A** and also to time. The differential equation is shown in eq. 2, where $[\mathbf{A}]_o$ is the concentration of **A** at time = 0, and $[A]_t$ is the concentration of **A** at any specified time.

$$\text{Rate} = -\int_{[A]_0}^{[A]_t} \frac{d[A]}{A} = k\int_0^t dt \tag{2}$$

When this differential equation is integrated such that [**A**] is $[\mathbf{A}]_o$ at t=0 and it is $[\mathbf{A}]_t$ at t="end time," the expression obtained is shown in eq. 3.

$$\ln\frac{[A]_o}{[A]_t} = k(t_{\text{end time}} - t_o) \text{ and if } t_o = 0, \text{then } \ln\frac{[A]_o}{[A]_t} = kt \tag{3}$$

Since concentration is proportional to time (conc ∝ t), the rate of change in concentration is set equal to the rate of change of time using a proportionality constant, k. The proportionality constant (k) is defined as the *rate constant* and in this reaction, *conc = k t*. This expression is called the *rate equation* for the reaction. The small k represents the rate constant, whereas a capital K is used to indicate an equilibrium constant. The value of k is determined by first plotting the concentration of **A** against time, which results in a curve as [**A**] diminishes during the reaction. To obtain a straight-line plot and ln $\frac{[A]_o}{[A]_t}$ is plotted versus time and the slope *of* this line gives k, the rate constant. A typical value for the slope of such a plot is 2.8 x 10^{-3} mol L^{-1} min^{-1}. Note the units of the rate constant, which show a change in concentration per unit of time. The reaction and the rate constant just described is for a *first-order reaction*. How fast a first order reaction proceeds depends only on the concentration of reactant **A** in the rate determining (the slowest) step, and not on the interaction with another molecule. The definition of a first order reaction is: a reaction in which the concentration of **A** is the only concentration term in the equation. Based on eq. 2 and 3 above, the *rate equation of the first order reaction is rate = k [A].*

7.11 Examine the first order rate constant and determine whether the rate would be increased, decreased, or remain unchanged if [A] was increased by a factor of 100.

7.11.2 SECOND-ORDER REACTIONS

Another type of reaction is quite different from the one discussed above, and it is illustrated by the reaction **A** + **B** ⟶ **A—B**, where starting material **A** reacts with **B** to form a new product, **A—B**.[4] The rate constant is determined by monitoring the change in the concentration of the stating materials as a function of time. When [**A**] is plotted against time, the resulting curve does not give the rate constant since the rate of the reaction depends on the concentration of both **A** and **B**. Reactant **A** must react with **B** for the reaction to occur and the concentrations of both **A** and **B** must be plotted against time to obtain the correct result

[4] For a discussion of second-order kinetics, see Daniels, F.; Alberty, R.A. *Physical Chemistry*, 2nd ed., John Wiley and Sons, New York, 1961, p. 331.

for formation of the product. The differential equation derived from the resulting curve is shown in eq. 4.

$$\frac{1}{[A]_o - [B]_o} \ln \frac{[B]_o - [A]_t}{[A]_o - [B]_o} = kt \tag{4}$$

where the $[]_o$ terms denote the initial concentrations of **A** or **B** (at time = 0) and the $[]_t$ terms indicate the concentrations of **A** and **B** at a specified time. To obtain a straight-line plot, time is plotted against the integrated rate expression $\ln \frac{[A][B]_o}{[A]_o[B]}$ and a typical the slope is 5.93 x 10^{-4} $M^{-1}sec^{-1}$. This is the *second-order rate constant*, *rate = k [A] [B]*. This rate equation is shown in eq. 5.

$$-\frac{d[A]}{dt} = k[A][B] \text{ or rate} = k[A][B] \tag{5}$$

7.12. Examine the second order rate constant and determine whether the rate would be increased, decreased, or remain unchanged if [A] was increased by a factor of 100.

7.11.3 HALF-LIFE

The *half-life* of a reaction is the amount of time required for one-half of the starting material to react. This parameter is useful for determining how long it takes for a reaction to proceed to completion. Assume that it takes 100 min for 50% of a starting material to be converted to product, which is the half-life. If the initial concentration of a reactant X is 1.0 M, then the concentration of X after 100 min (one half-life) will be 0.5 M. After the second half-life (100 min), 50% of the remaining X will react, and the concentration of X is 0.25 M. Another 100 min is required to bring the concentration to 0.125 M, and after a total reaction time of 600 min (six half-lives) the concentration of X is 0.016 M. In other words, 0.984 mol of X have reacted so the reaction is 98.4% complete. A reaction is usually considered to be "complete" if at least 98–99% of the starting material has reacted, so a reaction must be allowed to proceed for six or more half-lives**.** This "rule of thumb" gives one an estimate of how long to allow a reaction must proceed before it can be stopped. A reaction with a half-life of 6 minutes should be complete in 36–48 minutes (6–8 half-lives) whereas a reaction with a half-life of 2 hours would take 12–16 hours (6–8 half-lives) for completion. This data would allow a scientist to plan the required work and the time frame required for their reaction.

7.13 Determine how many moles of A have reacted after five half-lives, if the initial concentration of A is 1.8 Molar.

The half-life is given the symbol $t_{1/2}$. Half-life = $t_{1/2} = \frac{ln2}{k} = \frac{0.693}{k}$ for a first-order reaction (Section 7.11.1). If the rate constant (k) for a first-order reaction is 12 M min^{-1} (moles per liter per minute), then the $t_{1/2}$ is $\frac{0.693}{12} = 0.06$ minutes. For this reaction, five half-lives will be 5 x 0.06 min = 0.3 min, so the reaction will be complete in < 1 min. This is a fast reaction. If the rate constant is very slow, say 1.4x10^{-5} M s^{-1}, then $t_{1/2} = \frac{0.693}{0.000014} = 49.5x10^3$ s five half-lives will be 5 x 49.5x10^3 s = 247,500 s. The reaction will be a little under 98% complete in ~ 68.8 h. or 2.86 days. Imagine another reaction that takes ~ 93 days for one half-life, then after four

half-lives, or 374.1 days (> 1 year), only 93% of the starting materials will have reacted, a slow reaction indeed.

For a second-order reaction, the half-life formula is different because the rate equation is different. For a second-order reaction (**A** + **B**) where the initial concentration of **A** is the same as **B** (i.e. $[\mathbf{A}]_o = [\mathbf{B}]_o$). The half-life for a second-order reaction is: *half-life (second-order)* $= t_{1/2} = \frac{1}{k[A]_o}$. The second-order half-life is used the same way as the first-order half-life.

The units for a second-order half-life (M^{-1} sec^{-1}) are different, but six half-lives or more are required for a reaction to be "complete." If k = 2 M^{-1} s^{-1} and [**A**] = 1, the $\boldsymbol{t_{1/2}} = 0.5$ s. For this reaction, five half-lives is 3.0 s. Similarly, if k = 3x10^{-3} M^{-1} s^{-1} and [**A**] = 1, then $\boldsymbol{t_{1/2}} = 333.3$ s and if $k = 3x10^5$ M^{-1} s^{-1} and [**A**] = 1, then $\boldsymbol{t_{1/2}} = 3.3x10^{-6}$ s.

7.11.4 NO REACTION

How long does it take for a reaction to be complete? This question is important since it defines the term *no reaction*. Imagine that mixing two reactants does not give a product. There is no reaction. **A** + **B** ⟶ No Reaction, or N.R. However, imagine that this reaction actually does give a product, but the rate of this reaction has a half-life of 285.39 years. Six half-lives are required to obtain a >98% yield, which is 1712.3 years. Obviously, this is an absurd scenario. However, this example does pose interesting, albeit silly questions. Are you willing to wait 10 years for a reaction to be complete? How about 1 year? Clearly, the answer is no! Allowing minutes, hours, or even several days for a reaction to be complete is probably reasonable, but waiting longer than a few weeks except under special circumstances is not. The point is, for all practical purposes reactions are defined as working or not working (reaction or no reaction) by the time required for their completion, which is measured by the half-life. Another point to consider is that a reaction may be very slow, but a catalyst may be found that will increase the rate of the reaction to the point that it is practical and useful. Half-life calculations are very useful for determining that a reaction is slow and requires a suitable catalyst.

There is a tendency to think when there are two competing reactions, one process will occur and the other is impossible. That is usually incorrect. More commonly, one process is simply slower than another and given enough time, a product may be observed from the slower reaction. It is very important to differentiate reaction rates that are so slow they are unlikely to compete with another reaction in a given time from those that will give product. When there are two competing reactions, the term no reaction should question if the reaction is actually impossible, or just too slow to be observed.

7.14 Is a reaction that produced a molecule with a half-life of 6.2x10^{15} s considered to be commercially viable? Why or why not?

7.12 BIOLOGICAL RELEVANCE

In biological chemical processes enzymes mediate reactions that are inherently slow and often act as a catalyst to provide an alternative mechanistic pathway. A catalyst participates in a reaction to either initiate the reaction or influence the rate of the reaction, but it is regenerated during the course of the reaction. Enzyme-catalyzed reactions are ubiquitous in biological systems. Figure 7.7 shows an energy profile of a catalyzed and an uncatalyzed reaction.[5] Complexation with the enzyme catalysts leads to a lower activation energy. Catalysis by an enzyme will mediate biological reactions that are similar to those discussed in this book. It is just organic chemistry![6] Many of the reaction are more complex, to be sure, but it is organic chemistry.

[5] Warshel, A.; Sharma, P.K.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M.H.M. *Chemical Reviews* 2006, 106, 3210.
[6] Smith, M.B. *Biochemistry. An Organic Chemistry Approach,* CRC Press, Boca Raton, FL, 2020.

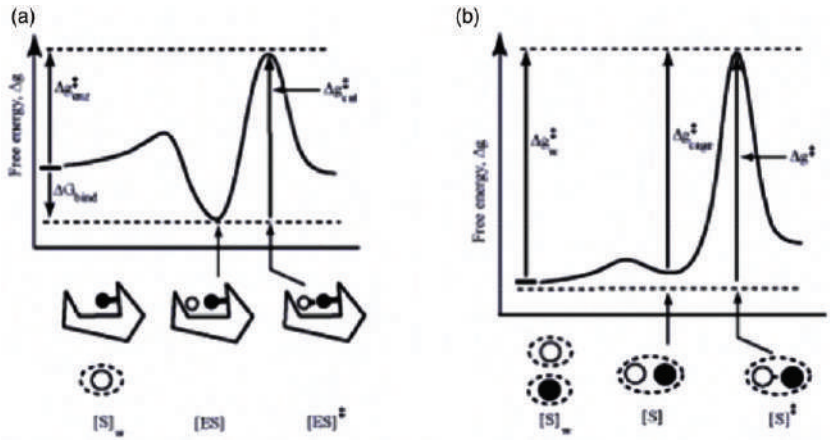


FIGURE 7.7 Energy curves for an enzymatically catalyzed reaction compared with an uncatalyzed reaction. (*a*) Free energy profile for an enzymatic reaction and that for the corresponding solution reaction. The figure describes the free energies associated with k_{cat}/KM and k_{cat}. (*b*) describes the energetics of a reference solution reaction that is not catalyzed. Reprinted with permission from Warshel, A.; Sharma, P.K.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M.H.M. *Chemical Reviews*, 2006, 106, 3210. Copyright 2006 American Chemical Society.

For enzymatic reactions, the rate of a reaction has been called the velocity of the reaction, and rate constants can be determined for each process. It has been observed that at low substrate concentration, the reaction velocity is proportional to the substrate concentration and the reaction is first order with respect to substrate.[7] Increasing the concentration of the substrate causes the reaction rate to diminish, and there is a point where it is no longer proportional to the substrate concentration. Indeed, the rate of the enzyme-catalyzed reaction becomes constant and independent of substrate concentration. The reaction is zero-order with respect to the substrate and the enzyme is said to be saturated with substrate (saturation). A *zero-order* reaction is independent of the concentration of the reactants, so a higher concentration of reactants will not increase the rate of reaction.

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_4}{\overset{k_3}{\rightleftharpoons}} E + P$$

This enzymatic reaction is described by a process in which the enzyme (*E*) reacts with substrate (*S*) to form a complex *ES*, which then breaks down to regenerate the enzyme and products (*P*).[6] Both reactions are reversible, with the rate constants that are indicated k_1-k_4. This reaction has been analyzed to give where the second equation has a constant K_M.

$$\frac{[S]\,([E]-[ES])}{[ES]} = \frac{k_2 + k_3}{k_1} = K_M \qquad \text{and,} \qquad [ES] = \frac{[E]\,[S]}{K_M + [S]}$$

This term replaces the rate constant term and is called the *Michaelis-Menten constant.* Further manipulation of the equation leads to the *Michaelis-Menten equation,* which defines the quantitative relationship between the enzyme reaction rate and the substrate concentration [*S*]. Noe that $V_{max} = k\,[E]$ and V_{max} is the maximum velocity for formation of the complex *ES*.

$$\text{Velocity} = v = \frac{V_{max}\,[S]}{K_M + [S]}$$

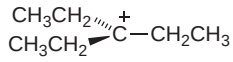
[7] Lehninger, A.L. *Biochemistry,* Worth Publishing Inc., New York, 1970, pp. 153–154.

CORRELATION OF HOMEWORK WITH CONCEPTS

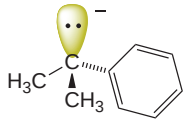
- Intermediates are transient products such as carbocations, carbanions or radicals: 1, 2, 3.
- Formal charge can be calculated for a molecule or an ion: 4, 23
- Enthalpy is the term used to measure bond dissociation energy, and $\Delta H°$ for a reaction is the difference in bond dissociation energy for bonds made - that for bonds broken: products - reactants. The free energy ($\Delta G°$) is calculated. The free energy of a reaction determines if the reaction is spontaneous (exothermic) or nonspontaneous (endothermic): $\Delta G° = \Delta H° - T\Delta S°$: 5, 6, 7, 8, 9, 15, 17, 20, 22.
- The energy of activation (E_{act}) is the energy required to initiate the bond making/bond breaking process of a chemical reaction. The transition state for a reaction is the highest energy portion of a reaction curve and corresponds to the point in a reaction where bonds in the starting materials are "partly broken" and bonds in the products are "partly made": 8, 16, 19.
- A mechanism is a step-by-step roadmap that shows the presence or absence of intermediates and the total number of steps required to convert the string materials to the products: 10.
- Reversible chemical reactions have an E_{act} (reverse) equal to or less than E_{act} (forward), for the reactions. The position of the equilibrium is measured by the equilibrium constant K, defined as $[\frac{\text{Products}}{\text{Reactants}}]$: 20.
- Rate of reaction describes how fast reactants are consumed and products are formed. The rate equation for a first-order reaction is rate = k [A], where k is the rate constant. The rate equation for a second-order reaction is rate = k [A] [B], where k is the rate constant: 11, 12.
- The half-life of a reaction is the time required for half of the starting materials to react: 1, 14, 18, 21.

ANSWERS TO IN-CHAPTER QUESTIONS

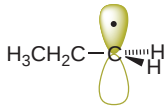
7.1



7.2



7.3



7.4 For bromomethane, CH_3Br, the formal charge for C is C = 4 - $\frac{1}{2}$(8) - 0 = 0; for Br, Br = 7 - $\frac{1}{2}$(2) - 6 = 0. Therefore, the formal charge for this molecule is 0.

7.5 $\Delta G° = \Delta H° - T\Delta S°$. Therefore, 22.4 = 21.5 - 298 ($\Delta S°$) = 22.4 - 21.5 = -298 $\Delta S°$ Therefore, $\Delta S° = \frac{0.9}{-298°}$ = -0.0030 kcal (0.013 kJ) mol^{-1} = -3 cal. Since the $\Delta G°$ term is 22.4 kcal (93.7 kJ) mol^{-1} and the $\Delta S°$ term is ~ 3 cal (13 J), leaving out the $T\Delta H°$ term will introduce only a small error into the calculation. Specially, 0.9 kcal (3.77 kJ) mol^{-1} out of 22.4 kcal (93.7 kJ) mol^{-1} = 4% error.

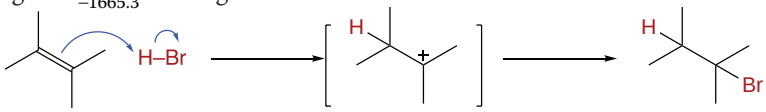
7.6 Assume that $\Delta H° = \Delta G°$, and since the $\Delta H°$ term is negative, this indicates an exothermic (spontaneous) reaction.

7.7 $\Delta H° = H°_{\text{bonds broken}} - H°_{\text{bonds made}} = 68 - 100 = -32$ kcal (-133.9 kJ) mol^{-1}.

7.8 The reaction with the lower E_{act} [35 kcal (136.4 kJ) mol^{-1}] will occur at a lower temperature. The value of $\Delta H°$ does not play a role in initiating the reaction, but initiation is determined by the E_{act}.

7.9 $\Delta G° = -RT\ (\ln K) = -2.303\ RT\ (\log K)$; convert centigrade to kelvin: K = °C + 273.15. Assume that $\Delta S°$ is zero, so $\Delta G° = \Delta H°$. Therefore, 68.2 = -2.303(1.986)(364.15) log K and $\log K = \frac{68.2}{-1665.3}$ and $\log K = -0.041$. Then $K = 10^{-\frac{\Delta G°}{RT}} = 10^{-(-0.041)} = 1.099$. $K = 1.099$.

7.10



7.11 Increasing or decreasing the concentration of **A** in a first-order reaction has no effect on the rate constant, therefore, it will remain unchanged.

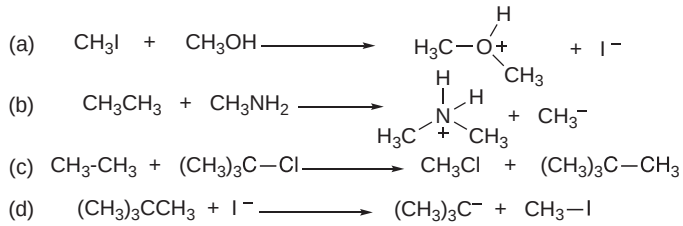
7.12 For a second-order reaction, the rate is dependent on both reaction partners, **A** and **B**. Increasing the concentration of one increases the overall rate, so increasing the concentration of **A** by 100 should increase the rate by a factor of 100.

7.13 For an initial concentration of 1.8 M, one-half will be consumed after one half-life: = 0.9 M. Therefore, we expect 0.9 mol have reacted after one half-life, 0.9+0.45=1.35 after two, 0.9+0.45+0.225=1.575 after three, 0.9+0.45+0.225+0.113=1.688 after four, and 0.9+0.45+0.225+0.113+0.0561.744 after five. After five half-lives, 1.744 mol of the initial 1.8 have reacted: this means that 96.9% of *A* has reacted.

7.14 No! If we convert this half-life to years, we find that it is $1.97x10^8$ years. Clearly, 0.2 billion years is a long time to wait for a commercial product.

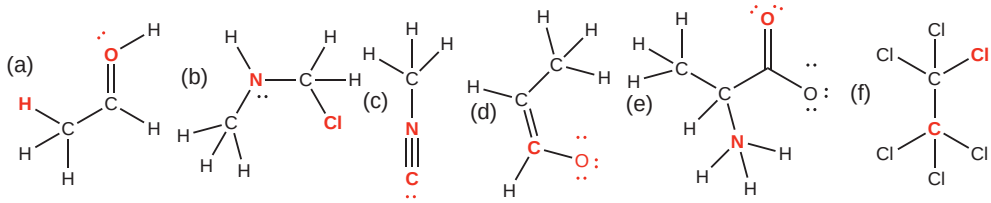
HOMEWORK

15. Use the energy values in Table 7.1 to determine the value of $\Delta H°$ for the following *hypothetical* reactions (virtually none of these transformations actually occur). Determine if each is endothermic or exothermic.



16. For a given reaction, explain the relationship between the energy of activation and the transition state.
17. When a reaction has a negative value for $\Delta H°$ it is said to be spontaneous. Does this mean that simply mixing the reactants together will automatically produce the product in a reaction that generates heat? Why or why not?
18. Calculate the half-lives given the following data.
    (a) A first order reaction where $k = 1.2x10^{-6}$ (b) A second order reaction where $k = 4.5$
    (c) A first order reaction where $k = 5.8x10^{3}$ (d) A second order reaction where $k = 9.25x10^{-4}$
19. Calculate $\Delta G°$ given the following equilibrium constants for reactions at 25 °C.
    (a) 2.5 (b) $1.55x10^{-6}$ (c) $8.77x10^{-9}$ (d) $4.4x10^{5}$
20. Calculate the equilibrium constants given $\Delta H°$ for reactions at 25 °C, assuming that $\Delta S°$ is < 1 cal in all cases.
    (a) -1.5 kcal (-6.3 kJ) mol^{-1} (b) 100.3 kcal (419.6 kJ) mol^{-1}
    (c) $-4.5x10^{4}$ cal mol^{-1} (d) 18.5 kcal (77.4 kJ) mol^{-1}
    (e) -33 kcal (-137.1 kJ) mol^{-1} (f) $-12.5x10^{6}$ kcal ($-5.2x10^{7}$ kJ) mol^{-1}.

21. The half-life for a certain reaction is 8 h. Estimate how many half-lives, and how many hours would be required for the reaction to go to at least 98% completion.
22. For reaction **A**, $\Delta G°$ is -200 kcal (837.4 kJ) mol^{-1} and for reaction **B**, $\Delta G°$ is -20 kcal (83.7 kJ) mol^{-1}. For reaction **A**, $\Delta G^{\ddagger}$ = +100 kcal (418.7 kJ) mol^{-1} and for reaction **B**, $\Delta G^{\ddagger}$ = +10 kcal (41.9 kJ) mol^{-1}. Both reactions are run at room temperature without any other source of heat or energy, except the energy at room temperature (25 kcal or 104.7 kJ) mol^{-1}. Briefly discuss which, if either, of these reactions will go to products.
23. Calculate the formal charge for all atoms marked in red and then calculate the formal charge for each molecule. Do **not** assume unshared electrons are present unless they are shown or indicated.



The video clips for this chapter are available at:
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The scientist photographs are also available at:
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8

Conformations

As molecules absorb energy from their surroundings, their incipient kinetic energy increases. One of the ways that molecules dissipate energy is by molecular vibrations that include the stretching and the bending of covalent bonds. In addition, there is internal rotation around single covalent σ-bonds. This rotation leads to different arrangements of atoms and groups in space.

To begin this chapter, you should know the following:

- σ-Bonds. (Sections 3.3 and 3.5).
- π-Bonds. (Sections 5.1–5.3).
- Cyclic compound and acyclic compounds. (Sections 4.3 and 4.4).
- The nature and nomenclature of functional groups. (Sections 5.1, 5.2, 5.3, 5.5, and 5.6).
- The VSEPR model for predicting the shape of simple molecules. (Section 3.6).
- The concept of equilibrium constants *K*, other than K_a. (Section 7.8).

8.1 ROTATION AROUND C—C BONDS

Rotamers

8.1.1 STAGGERED AND ECLIPSED ROTAMERS

The C—C single bonds found in an organic molecule can rotate. Rotation about the C—C bond in ethane, for example, leads to different relative spatial arrangements of atoms attached to each carbon. If each arrangement could be "frozen" at a particular rotation angle, a "snapshot" of each arrangement is obtained called a *rotamer.* It is important to point out that rotamers are never "frozen" and rotation occurs continuously at temperatures above absolute zero.

In principle, 360° rotation about a C—C bond will produce an infinite number of rotamers. However, only a few rotamers describe the energy required for rotation about a given bond. For ethane the two energetically important rotamers are shown in Figure 8.1. Figure 8.1a, shows that the H atoms on C1 marked are "in between" the H atoms on C2 so the bonds are *staggered*. This arrangement is identified as a *staggered rotamer*. In Figure 8.1b, the hydrogen atom on C1 overlaps (eclipses) the hydrogen atom on C2. The bonds also *eclipse* and this arrangement is identified as an *eclipsed rotamer*. The figures in Figure 8.1a are *sawhorse diagrams*, where C1 is to the front and C2 is to the rear. A ball-and-stick molecular model of sawhorse ethane is drawn using the same perspective to show the relationship of the atoms and bonds. The two rotamers in Figure 8.1b have been turned so the view is "head on," with C1 in the front and C2 in the rear. The "front" carbon (C2) is shown as a "dot" in the center of the circle and the carbon atom in the rear (C2) is represented as a "circle." Each carbon is tetrahedral, so another carbon and three hydrogen atoms are attached to it. This second representation is known as a *Newman projection* named after Melvin Spencer Newman (USA; 1908–1993). A ball-and-stick molecular model is drawn from the same perspective, again to show the relationship of the bonds and atoms. In the eclipsed rotamer (Figure 8.1a) the overlap of the atoms and the bonds that connect the hydrogen atoms to carbon leads

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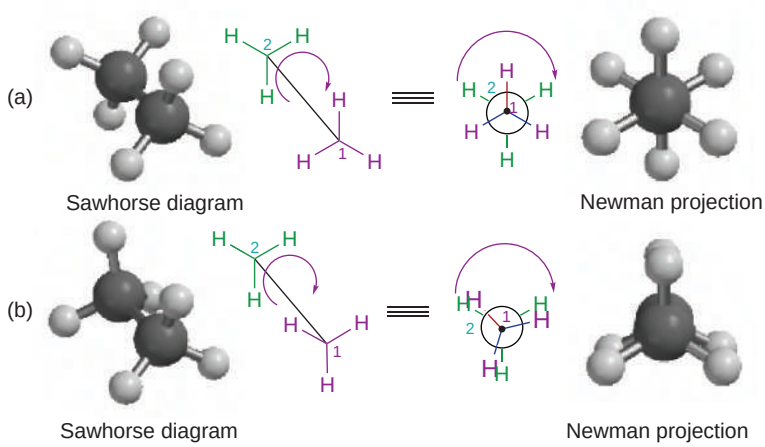


FIGURE 8.1 Sawhorse diagrams and Newman projections for rotamers of ethane.

to repulson of the electrons in the covalent bonds and also repulsion of atoms. This type of repulsion is called *steric hindrance*. Due to this hindrance *the eclipsed rotamer is higher in energy than the staggered rotamer.* The measured energy difference of 2.9 kcal mol^{-1} (13.95 kJ mol^{-1})[1] imposes an energy barrier to rotation about the C—C bond of ethane as discussed in Section 8.1.2.

Ethane

8.1 Draw the staggered rotamer of 1-deuterioethane (one hydrogen atom of ethane is replaced with a deuterium) using D for the deuterium atom.

8.1.2 TORSIONAL STRAIN: STERIC HINDRANCE AND ENERGY BARRIERS

Rotation about the C—C bond of ethane by 360° will generate all possible rotamers. It is known that ethane spends most of the time as a staggered rotamer and only a small percentage of the time as an eclipsed rotamer. Indeed, the eclipsed rotamers define the highest energy barrier to rotation and the staggered rotamers define the lowest energy barrier. As shown in Figure 8.2 an eclipsed rotamer is generated by rotation of 60°, 180° and 300° and a staggered rotamer is generated by rotation of 120°, 240° and 360°. In the eclipsed rotamer, there is steric hindrance due to the proximity of the atoms. The eclipsing bonds repel one another, and this interaction generates what is called *torsional energy*. However, the term *torsional strain* is often used to indicate both eclipsing bond repulsion energy and steric hindrance due to eclipsing atoms. In the staggered rotamer of ethane, the hydrogen atoms and the bonds are as far apart as possible, so torsional strain is greatly diminished. Rotation is facile in this low energy rotamer. The steric interaction for rotation in the eclipsed rotamer imposes *an energy barrier to rotation* of 2.9 kcal (13.95 kJ) mol^{-1}.[1] This energy barrier impedes rotation but does *not* stop it. There is continuous but *hindered rotation* about the C—C bond. As a consequence of this energy barrier, the staggered rotamers account for the highest percentage of all rotamers that are possible during the 360°rotation.

8.2 Draw all rotamers for 1,2-dichloroethane generated by rotation of 60° and focusing attention on the chlorine atoms.

It is possible to plot angular rotation of the C—C bond of ethane versus the relative energy of each rotamer generated by that rotation. The resulting energy curve is essentially a "map"

[1] (a) Aston, J.G.; Isserow, S.; Szasz, G.J.; Kennedy, R.M. *Journal of Chemical Physics* 1944, 12, 336–344; (b) Mason, E.A.; Kreevoy, M.M. *Journal of the American Chemical Society* 1955, 77, 5808–5814; (c) Mason, E.A.; Kreevoy, M.M. *Journal of the American Chemical Society* 1957, 79, 4851–4854; (d) see Weinhold, F. *Nature* 2001, 411, 539–541. Figure 1 therein.

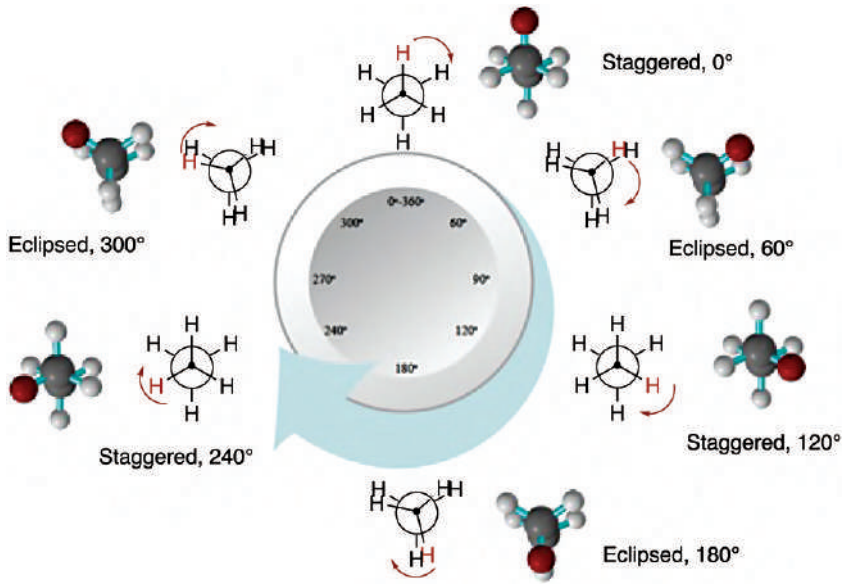


FIGURE 8.2 Rotation about the carbon–carbon bond in a "labeled" ethane using Newman projections.

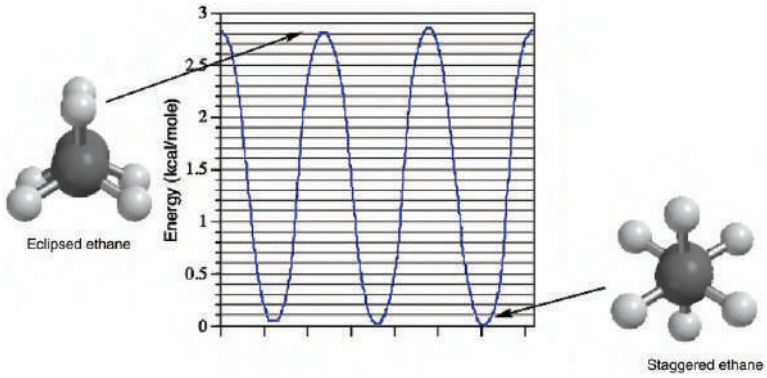


FIGURE 8.3 Rotation about the C—C bond of ethane and the energy barriers to rotation in ethane (plot of energy vs angular rotation).

that shows the magnitude of the energy barriers to rotation (see Figure 8.3).[1d] Complete rotation around the carbon-carbon bond in ethane generates three eclipsed-rotamers, as shown in Figure 8.3, each with an energy barrier of 2.9 kcal (13.95 kJ) mol^{-1} so rotation "slows down" when these eclipsed-rotamers are encountered but at normal temperatures there is plenty of energy for 360° rotation about carbon-carbon bonds.

8.3 Briefly discuss why eclipsed ethane is higher in energy than staggered ethane.

8.2 LONGER CHAIN ALKANES

Propane and Butane

Rotation about a C—C bond occurs in all organic molecules with sp^3-hybridized carbon atoms that are connected by a covalent σ-bond and rotation occurs about all single covalent bonds in that molecule. The collection of all rotamers for all bonds generates shapes for the molecule called *conformations*. For a molecule with several bonds, many conformations are possible, but some conformations are lower in energy than others and are therefore more

abundant. The presence of substituents on one or more of the carbons of a C—C bond will influence the conformational preference.

To examine rotation about C—C bonds, molecules with an alkane backbone can be categorized into three fundamental units that are "ethane" derivatives. As shown in Figure 8.4,

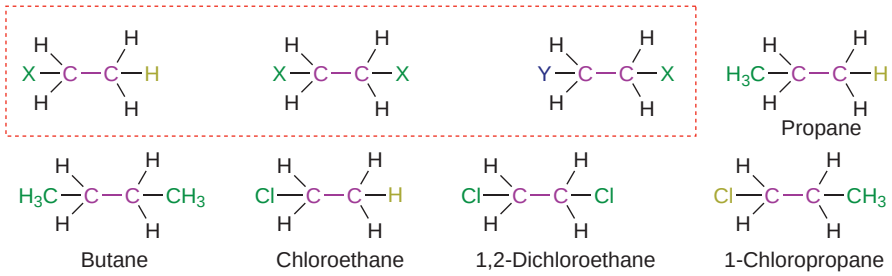
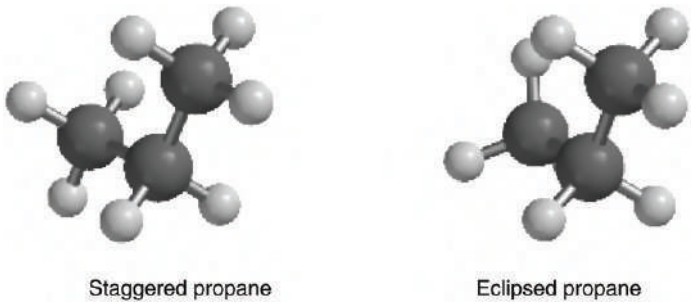


FIGURE 8.4 "Ethane" model for longer chain and substituted alkanes.

these units serve as models to help understand the rotamer population. One model is the unit X—**C—C**—H, where X represents one substituent. A second model is X—**C—C**—X for a bond with two identical substituents, and the third is X—**C—C**—Y for a bond with two different substituents. Propane is the three-carbon alkane, and it is represented as an X—C—C—H system, where X is methyl (CH_3, abbreviated Me). In an eclipsed rotamer there are H_3C–H interactions and H–H interactions for rotation about the Me—C—C—H bond. 1,2-Dichloroethane is a X—C—C—X system where X = Cl, so there are Cl–Cl and Cl–H interactions in the eclipsed rotamers. 1-Chloropropane is a X—C—C—Y system where X = Cl and Y = methyl, so there are Cl– CH_3, Cl—H and H_3C —H interactions. The steric interactions of the larger groups are more important since they present higher energy barriers to rotation.

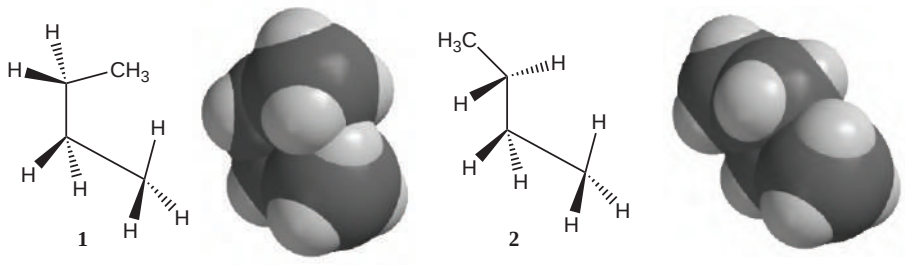
8.4. For X—CH_2CH_2—X where X = Me and X = CMe_3, briefly discuss which will have the higher energy barrier to rotation around the C—C bond.



Propane is symmetrical with a central CH_2 unit with a methyl group on either end. Rotation about either the C^1—C^2 or the C^2—C^3 bond will therefore generate identical rotamers. It is a X—**C—C**—H system. A staggered rotamer of propane has the methyl group on the C^1 opposite a hydrogen on C^2. The higher energy eclipsed rotamer has a methyl that eclipses a hydrogen atom. This methyl-hydrogen interaction is measured to be ~ 3.5 kcal (14.6 kJ) mol^{-1}. This interaction is higher than the hydrogen-hydrogen interaction in ethane of ~ 2.9 kcal (12.1 kJ) mol^{-1}. Therefore, the staggered rotamer is the most abundant.

Butane is the linear four-carbon alkane, and several rotamers as well as the space-filling model of each is shown in Figure 8.5. There are three C—C bonds in butane: C^1—C^2, C^2—C^3, and C^3—C^4. Examination of the identical C^1—C^2 and C^2—C^4 bonds shows that both are X—**C—C**—H systems (Me—**C—C**—H) whereas the C^2—C^3 bond is a X—**C—C**—X system (Me—**C—C**—Me). If rotation about C^1—C^2 or C^3—C^2 is examined, C^1 and C^4 have

three attached hydrogen atoms but C^2 or C^3 in these bonds have an attached ethyl group and two hydrogen atoms. For the C^2 and C^3 bond, each carbon has an attached methyl group. Although an ethyl group is larger than a methyl group, the steric demands of an ethyl group are not significantly greater than those of a methyl group. Rotation about the C^1—C^2 bond or the C^2—C^3 bonds can bring the methyl group very close to the eclipsing hydrogen atom (**1**). However, rotation about the C^1—C^2 bond or the C^2—C^3 bonds swings the methyl group away from the eclipsing hydrogen atom and diminishes the steric effect (**2**) to give a much lower energy rotamer. There is a significant steric effect when the two methyl group eclipse during rotation about the C^2–C^3 bond.



The Me–Me interaction in the syn rotamer is about 5.9 kcal (24.7 kJ) mol^{-1},[2] and it is the maximum interaction for rotation of all the bonds in butane. In other words, the higher energy rotamers in butane are associated with rotation about C^2—C^3.

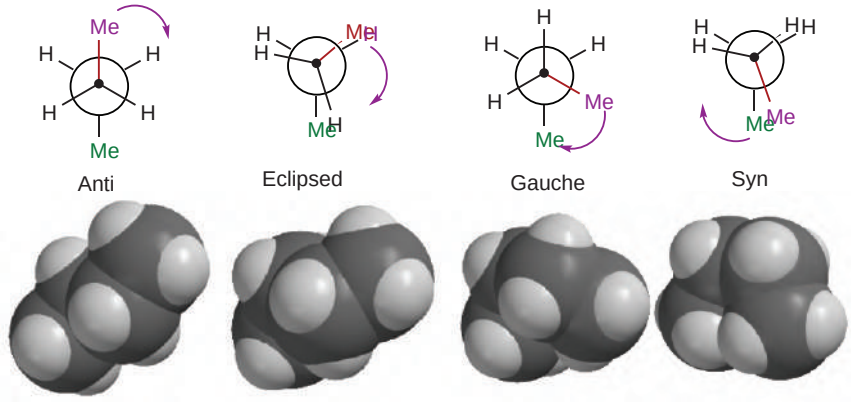


FIGURE 8.5 Important rotamers for the C^2—C^3 bond in butane.

Imagine that rotation about C^2—C^3 begins with the *staggered rotamer* or *anti-rotamer* of butane where the two methyl groups are ~180° apart. This *anti rotamer* is the lowest in energy for the C^2—C^3 bond. Rotation through 360° at 60° intervals gives several rotamers that are taken to be important, and they relate to the energetics of bond rotation. Rotation through 60° leads to an *eclipsed rotamer* where the two methyl groups do not eclipse each other, but one methyl eclipses a hydrogen and the other methyl eclipses a different hydrogen. Rotation by another 60° leads to a *staggered rotamer*, but the spatial proximity of the methyl groups leads to a steric interaction, despite the fact there are no eclipsing bonds or atoms. This rotamer is labeled as a *gauche-rotamer*. The next 60° rotation generates an *eclipsed rotamer* that is different from the first eclipsed rotamer since the two methyl groups completely eclipse each other, which is clearly the *highest energy rotamer*, the *syn-rotamer*. As rotation is continued, a second *gauche rotamer* is generated, and then a second *eclipsed rotamer*. The plot of rotamer energy vs. rotation angle for butane is shown in Figure 8.6.[3] The Me–Me interaction in the *syn*-rotamer gives the highest barrier to rotation, 5.86 kcal (24.5

[2] Kagan, H. *Organic Stereochemistry*, Halsted Press, New York, 1979, p. 50.
[3] Jorgensen, W.L. *Journal of the American Chemical Society* 1981, 103, 677–679, Figure 1a therein.

kJ) mol^{-1}, and the *anti*-rotamer is the lowest energy rotamer. There are smaller energy barriers for *eclipsed*-rotamers, and "valleys" for *gauche*-rotamers that are higher in energy than the *anti*-rotamer.

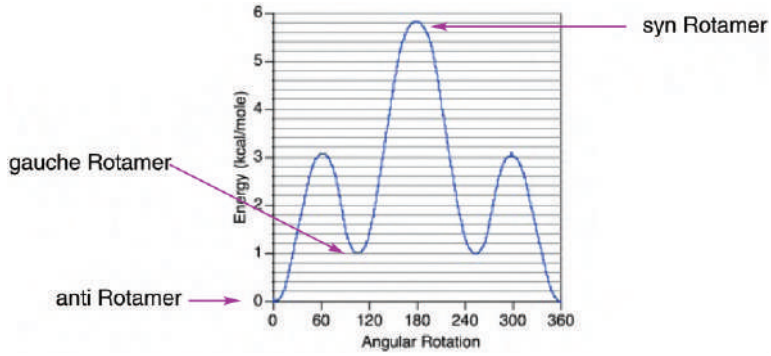


FIGURE 8.6 Angular rotation-energy map for butane. Reprinted with permission Jorgensen, W.L. *Journal of the American Chemical Society*, 1981, 103, 677–679, Figure 1a therein. Copyright 1981 American Chemical Society.

The "ethane model" used for propane and butane can be extended to other alkanes. In virtually all alkanes, the anti-rotamer for a given C—C unit is assumed to be the lowest energy rotamer for every bond in the alkane. Taking decane as an example, every C—C bond is assumed to exist as the anti-rotamer in the most abundant conformation. This assumption leads to a so-called "zigzag" structure, which is taken to be the low energy *conformation* of long chain alkanes.

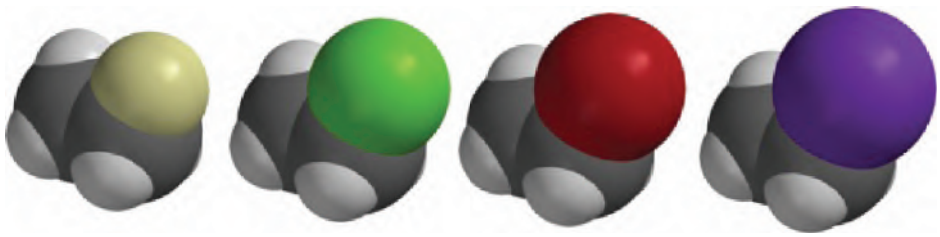
8.5 Draw both gauche rotamers for 1,2-dichloroethane in Newman projection.

8.3 INFLUENCE OF HETEROATOMS ON THE ROTAMER POPULATION

If heteroatoms or functional groups containing heteroatoms are introduced into a carbon chain, the size of the atoms or groups and the influence of the lone electron pairs associated with any heteroatoms will influence the rotamer populations of individual bonds and therefore the overall conformation of molecule.

8.3.1 HALOGEN SUBSTITUENTS

Halogens (F, Cl, Br, I) have the same valence as hydrogen. The tetrahedral geometry around each sp^3 carbon is retained when a halogen atom replaces a hydrogen atom in a carbon. Halogens are larger than hydrogen atoms, however, so the bond angles around the tetrahedral carbon bearing the halogen will be different. Haloethanes are X—C—C—H systems, where X = halogen. Space-filling models of the eclipsed rotamers of the four haloethanes are shown.

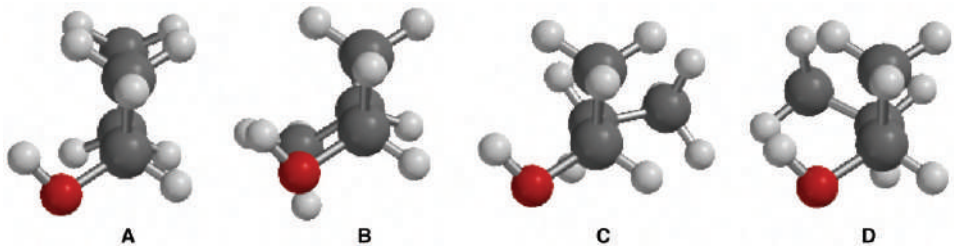


Fluoroethane Chloroethane Bromoethane Iodoethane

The increase in steric hindrance is apparent and it influences the rotamer populations in organic compounds bearing halogen atoms. The covalent radius of fluorine is 0.64 Å (64 pm), that of chlorine is 0.99 Å (99 pm), that of bromine is 1.14 Å (114 pm), and that of iodine is 1.33 Å (133 pm) and the difference in size is reflected in the models.[4] Interestingly, the fluorine atom shows a steric interaction similar to that of hydrogen, although the covalent radius of hydrogen is only 0.37 Å (37 pm).[4] As the size of the halogen increases there is greater destabilization of the eclipsed rotamer and a lower percentage of that rotamer. Halogens also have three lone pairs of electrons that contribute to the steric effects of the substituent. Halopropanes such as 1-chloropropane are X—C—C—Y systems, where X = halogen and Y = methyl. 1,2-Dihaloethanes are an example of a X—C—C—X system if both halogens are the same and a X—C—C—Y system if the halogens are different.

8.6 Briefly discuss the energy diagram for rotation about the C—C bond of 1,1,1,2-tetrachloroethane. Should it look more like that of ethane or more like that of propane?

8.3.2 OH OR NH GROUPS IN ALCOHOLS OR AMINES



The rotamer population for a molecule that has one hydroxyl group (OH), as in butan-2-ol, is more complex. There is a rotamer with eclipsing methyl-methyl groups (**A**) and another rotamer with eclipsing methyl-hydroxyl groups (**B**). In addition, there are important staggered rotamers, one with a methyl-methyl *gauche* interaction (**C**), and one with a methyl-methyl-hydroxyl interaction (**D**). These interactions and others will produce a complex energy-rotamer diagram. The O—H unit also contains a polarized hydrogen atoms that is capable of hydrogen bonding with a polar solvent or another molecule. The presence of hydrogen bonding in a rotamer may bias the rotamer population to favor that rotamer.

When two OH units are introduced into the same molecule, such as in ethane-1,2-diol (ethylene glycol; a common ingredient in automobile anti-freeze), hydrogen bonding will influence the rotamer populations. Ethane-1,2-diol has two OH units on adjacent carbon atoms, so it is a *vicinal* diol and it fits the X—C—C—X model. Ball and stick models are shown in Figure 8.7 for three rotamers of ethane-1,2-diol, the *syn*-rotamer, the anti-rotamer, and a *gauche*-rotamer. The anti-rotamer should be the lowest energy rotamer. In a nonpolar solvent, however, the *syn*-rotamer is capable of intramolecular hydrogen bonding (O----H—O) that partially stabilizes the *syn*-rotamer, offsetting some of the steric interaction. The steric interaction in the eclipsing rotamer is not entirely offset by the hydrogen bond and partial rotation gives the lower energy *gauche*-rotamer, which retains the hydrogen bond. Therefore, the gauche rotamer accounts for the highest percentage of rotamers found for ethylene glycol in the absence of a hydrogen-bonding solvent. If ethylene glycol is dissolved in water, *intermolecular* hydrogen bonds are possible between the OH unit of the alcohol and the OH unit of water. Therefore, the *anti*-rotamer will be the lowest energy rotamer since extensive intermolecular hydrogen-bonding effectively makes the OH groups "larger" than normal. The structure marked "hydrogen bonding" for ethane-1,2-diol in Figure 8.7 illustrates this point, showing each OH unit hydrogen bonded to water molecules.

[4] Dean, J.A. *Handbook of Organic Chemistry,* McGraw-Hill, New York, 1987, Table 3–10, pp. 3–122 to 3–126.

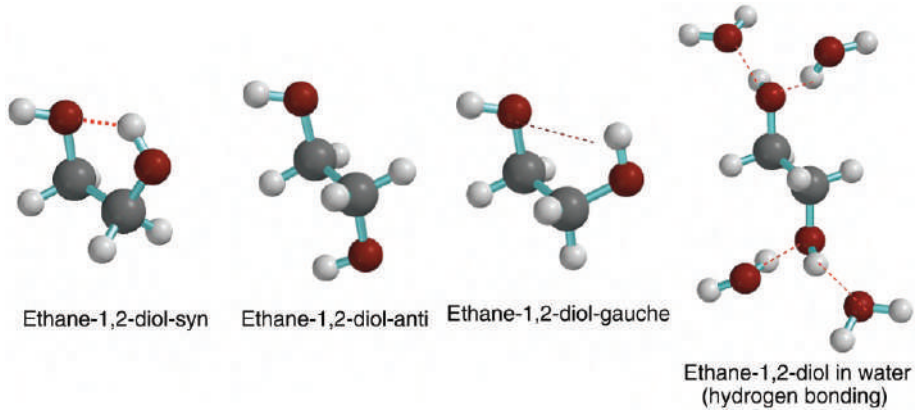


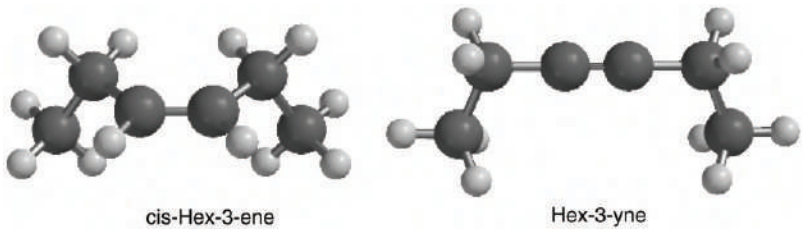
FIGURE 8.7 Rotamers and hydrogen bonding in ethane-1,2-diol.

Amines are also capable of hydrogen bonding, so introduction of an NHR or NH_2 unit (from a secondary or primary amine) will have a similar hydrogen-bonding effect as described for the diol, but to a lesser degree. When a single amine unit is present, there can be no intramolecular hydrogen-bonding, only intermolecular hydrogen-bonding in a polar solvent. When two NH units are present, as in 1,2-diaminoethane ($NH_2CH_2CH_2NH_2$; ethylenediamine, a *vicinal* diamine), intramolecular hydrogen bonding is possible just as in 1,2-diols in a nonpolar solvent. The effect on the rotamer population is similar.

π-Bonds and Rotamers

8.4 INTRODUCING Π-BONDS

In alkanes, the carbon structure contains nothing but sp^3 carbon atoms, which all have a tetrahedral shape. The presence of trigonal planar sp^2 carbon atoms in an alkene unit will lead to flattening about each carbon, since all four atoms connected to those carbons lie in the same plane. If the C=C unit is incorporated into a chain of sp^3 carbons, as in cis-hex-3-ene, the C=C unit "flattens" a portion of the carbon chain as shown with the ball-and- stick model. The term cis refers to the attachment of the ethyl groups on the C=C unit and is explained in Section 9.7. *Rotation about the C=C unit is not possible* and the resulting rigidity in each structure is the result of the planar alkene unit.

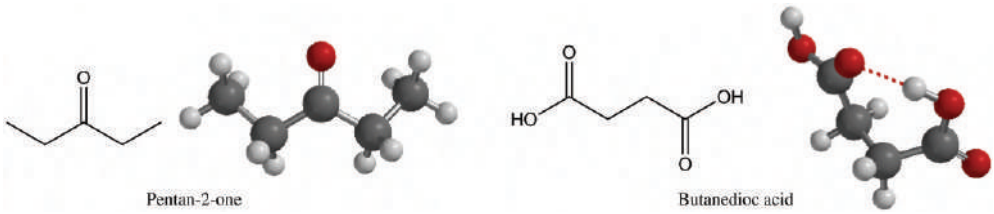


The four carbon atoms of the alkyne unit (C—C≡C—C) give linear array that flattens the molecule in the region of the triple bond to an even greater extent than seen with alkenes. The flattening effect is quite clear in the ball-and-stick model of hex-3-yne.

8.7 Is there a steric interaction between the methyl groups of but-2-yne.

A carbonyl group (C=O) has a sp^2-hybridized carbon and a trigonal planar geometry for the groups attached to the carbonyl carbon. If the carbonyl is part of a ketone, as in pentan-3-one, there is localized flattening due to the sp^2 hybridization and a bond angle is ~ 120°. Carboxylic acids contain the carboxyl group (COOH), which also contains a carbonyl carbon. It is a X—**C—C**—H system. When a molecule contains two carboxyl units (e.g., butane-1,4-dioic acid) it can be correlated with a X—**C—C**—X system. Intramolecular

hydrogen-bonding in a nonpolar solvent can play a role, just as it does with diols. Internal hydrogen-bonding is shown that will stabilize a *gauche*-rotamer.

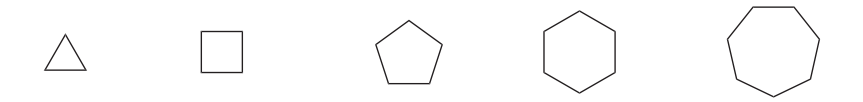


8.8 Speculate as to whether the gauche rotamer of 2-hydroxybutanoic acid will be stabilized by hydrogen-bonding.

8.5 CYCLIC ALKANES

8.5.1 STRAIN AND STERIC HINDRANCE IN CYCLIC ALKANES

The preceding sections discussed the conformation of acyclic molecules, where 360° rotation around carbon-carbon bonds is possible. Molecules that have a ring of carbon atoms, *cyclic compounds*, exhibit different behavior, however. In a cyclic compound, the carbon-carbon bonds cannot rotate around 360° without breaking those bonds. However, it is possible to "partially rotate" the bond, depending on the flexibility of the ring. Such partial rotation is called *pseudorotation*. In order to examine the effect of pseudorotation in cyclic alkanes, a discussion begins with the planar, two-dimensional geometric figures that are the simplest drawings of cyclic alkanes.



In cyclic alkanes of three to seven-membered rings, a planar geometry requires significant distortion of the C–C–C bond angles. The bond angle for a tetrahedral carbon is 109°28' in methane, which is taken as a typical value for sp^3 hybridized carbon atoms. Distortion of bond angles in a molecule from the "ideal" 109°29' requires energy. Johann Friedrich Wilhelm Adolf von Baeyer (Germany; 1935–1917) proposed this idea, which is now called *Baeyer strain*. Baeyer strain therefore increases the energy in a conformation by distortion of the bond angles away from the tetrahedral ideal. Bayer strain destabilizes the planar form of cyclic molecules.

In planar cyclic alkanes there is another form of strain because all the C—H bond eclipse, which leads to a steric interaction and an increase in the strain energy. The strain energy from eclipsing interactions of proximal atoms in cyclic molecules is called *Pitzer strain*, although it may also be called *torsional strain*. Pitzer strain is named after Kenneth S. Pitzer (USA; 1914–1997). All the C—H bonds on both sides of the ring eclipse in planar cycloalkanes so there is great Pitzer strain. Because of the Baeyer strain and the Pitzer strain the planar structure of a ring is probably the highest energy and least likely to form of all the possible conformations. Lower energy conformations are available because of pseudorotation, however.

8.5.2 CONFORMATIONS OF C3–C5 CYCLOALKANES

Pseudorotation of C3-C5 Cycloalkanes

The C—C bonds in cyclic alkanes try to rotate but cannot rotate through 360° because of the ring. The bonds twist in a motion called *pseudorotation*, if possible. Pseudorotation dissipates

energy and minimizes steric strain and torsion strain and leads to the lowest energy conformation. Cyclopropane is a three-membered ring and trying to "twist" this three-membered ring about any given C—C bond by pseudorotation is very difficult because of the small ring. Since virtually no pseudorotation is possible. Cyclopropane is indeed planar as shown in the ball-and-stick model in Figure 8.8. In planar cyclopropane, there is considerable Bayer strain because the bond angles are distorted from 109°29' to 60°. All of the C—H bond eclipse so there is steric interaction and significant Pitzer strain.

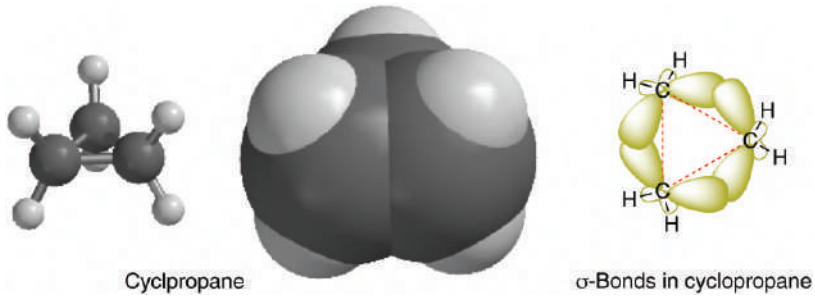


FIGURE 8.8 Bond distortion in the strained cyclopropane ring.

The C—C—C bond angles for cyclopropane are 60° and the shortest distance between carbon nuclei is represented by a "dashed" line in Figure 8.8. The three-membered ring forces the bonds in cyclopropane close together, however, which leads to significant distortion of those bonds. The electron density of the σ-bonds does not follow the red dashed line in Figure 8.8, but is pushed out of linearity. To describe these distorted covalent bonds, cyclopropane is said to have "banana-bonds," and they look a little bit like π-bonds. *They are not π-bonds!* There is less electron density between the carbon nuclei than in a normal σ-bond due to the distortion, however.

The bonds are weaker than a normal alkane carbon-carbon bond and they are easier to break. Although cyclopropane is a stable molecule it can react with several reagents. This reactivity stands in contrast to the poor reactivity of other alkanes.

In planar cyclobutane the bond angles are about 90° in planar cyclobutane, so there is less Baeyer strain than in cyclopropane. There is significant torsion strain since all the atoms eclipse. The ring is larger and some pseudorotation of the C—C bonds is possible due to greater flexibility of the ring. Pseudorotation leads to a low energy conformation that is "puckered" and called the *butterfly conformation*. Note the use of bold bonds to indicate bonds that are projected out of the plane of the page. In the ball-and-stick model and in the space-filling model in Figure 8.9, fewer atoms eclipse so there is diminished Pitzer strain in

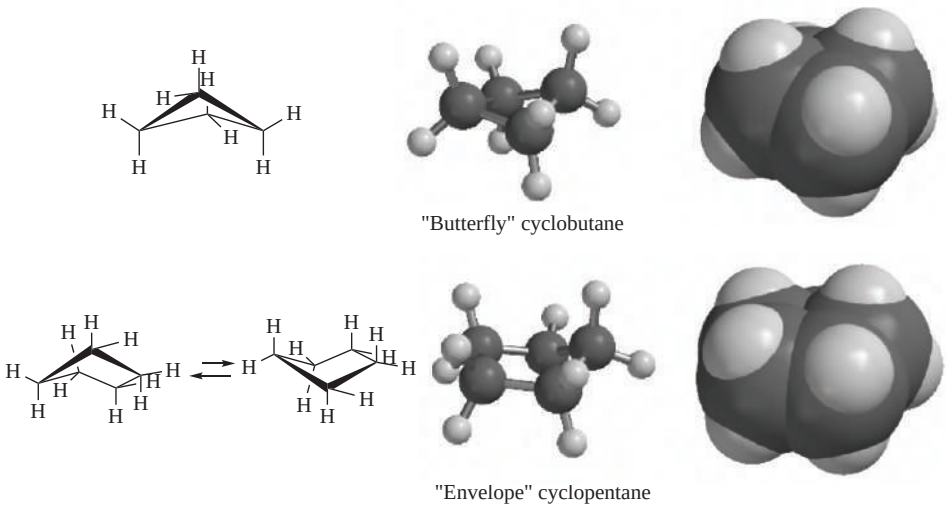


FIGURE 8.9 Low energy conformations of cyclobutane and cyclopentane.

the butterfly conformation relative to the planar form. The butterfly conformation is the low energy conformation of cyclobutane.

Cyclopentane is a larger ring that has even more flexibility and therefore more pseudorotation is possible. Planar cyclopentane is very high in energy and pseudorotation leads to a low energy conformation called the *envelope conformation*, shown in Figure 8.9. Two envelope conformations are shown to emphasize the greater pseudorotation possible in the five-membered ring. Interestingly, the bond angles for planar cyclopentane are 108°, very close to the ideal tetrahedral angle of 109°28'. Pseudorotation diminishes the *torsion strain* of the planar conformation since the eclipsing hydrogen atoms are moved further apart, but the bond angles change to 105° so there is a small increase in Baeyer strain. The observation that cyclopentane exists primarily in the envelope conformation is an indication that *relief of torsion strain is more important than the increase in Baeyer strain for cyclopentane.*

8.9 Briefly explain why changing the bond angles to 105° increases Baeyer strain in the envelope conformation.

8.5.3 CONFORMATIONALLY MOBILE CYCLOHEXANE

Conformations of Cyclohexane

Planar cyclohexane has significant torsion strain as shown by the ball-and-stick model in Figure 8.10 and there is Baeyer strain since the bond angles would be 120° Due to the size of the ring there is great flexibility and pseudorotation leads to several important conformations. Of all the conformations that are possible, experimental data for cyclohexane indicates that one is lowest in energy. This conformation looks a little like an easy-chair, so it is called a *chair conformation*. Planar cyclohexane is shown as a line drawing and a Newman projection using ball-and-stick models in Figure 8.10. In chair cyclohexane the H—C—H bond angles of chair cyclohexane are about 109.5°, indicative of little or no torsion or Baeyer strain. A line drawing and two ball-and-stick models are shown. One is a Newman projection and the other offers the same view as the line drawing.

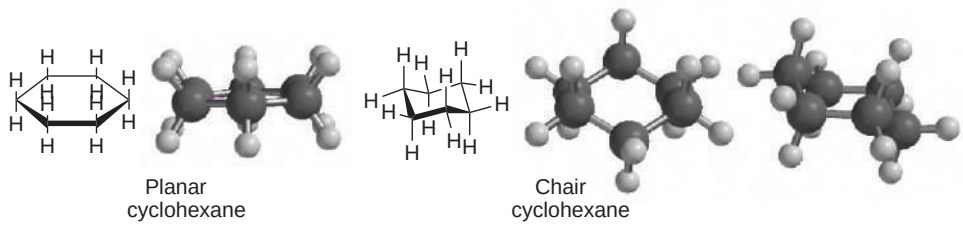


FIGURE 8.10 Planar and chair cyclohexane.

Figure 8.11 shows a chair conformation of cyclohexane inserted into a "planet. A ball-and-stick chair cyclohexane is also shown from the same perspective as the chair in the "planet." In the planetary view, the bonds in the vertical plane are aligned in the direction of the axis and are called *axial bonds*. Indeed, six of the twelve bonds that connect hydrogen atoms are in the vertical plane, three up and three down toward the axes. The other six bonds and the attached hydrogen atoms are in the horizontal plane, around the equator. These are called *equatorial bonds*. The hydrogen atoms attached to the axial or equatorial bonds are referred to as *axial* or *equatorial hydrogen atoms*.

The chair conformation is the lowest energy conformation of cyclohexane, but in fact there are *two equilibrating chair conformations.* Twisting the bonds (pseudorotation) in the chair on the left in Figure 8.12 will interconvert it to the chair on the right. The two chair conformations are in equilibrium and because they are of the same energy, the equilibrium

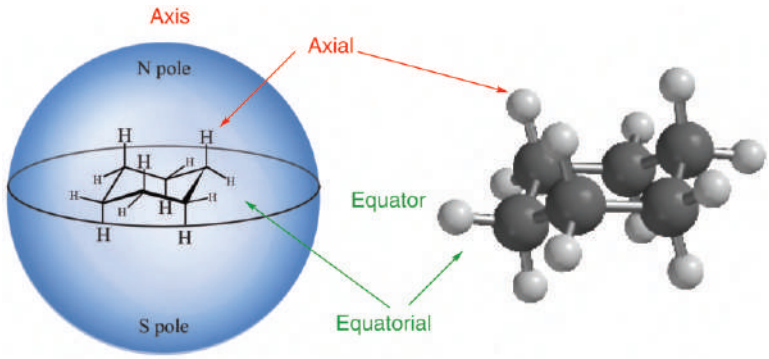


FIGURE 8.11 Axial and equatorial hydrogen atoms in chair cyclohexane.

constant is unity ($K_{eq} = 1$). In other words, there is a 50:50 mixture of the two chair conformations. Note that all the axial hydrogen atoms in one chair become equatorial hydrogen atoms in the other chair, and vice-versa. Examination of the planar cyclohexane in Figure 8.12

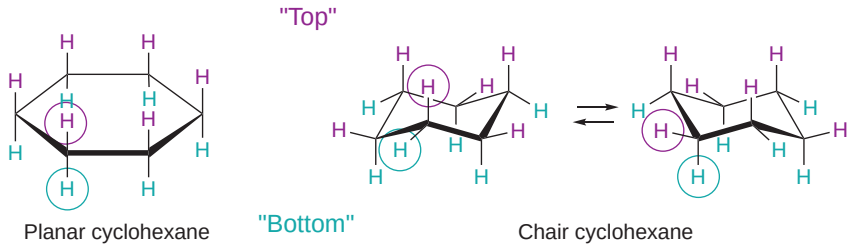


FIGURE 8.12 Interconversion of axial-equatorial hydrogen atoms in chair cyclohexane.

reveals that the ring has two sides, "top" and "bottom." Six hydrogen atoms are on the "top" of the molecule and six more are on the "bottom" of the molecule. In a chair, three of the "top" hydrogen atoms are axial and three are equatorial. The six hydrogen atoms on the "top" in the chair show an alternating pattern, axial-equatorial-axial-equatorial-axial-equat orial (three axial and three equatorial). Likewise, the "bottom" of the chair conformation has six hydrogen atoms with three axial hydrogen atoms and three equatorial hydrogen atoms. Further, a carbon atom in the ring with an axial hydrogen atom on the top has a equatorial hydrogen atom on the bottom. A carbon atom with an equatorial hydrogen atom on the top has an axial hydrogen atom on the bottom. Pseudorotation converts all axial hydrogen atoms in one chair to equatorial hydrogen atoms in the other and all equatorial hydrogen atoms in one are axial in the other. To repeat, the pseudorotation that converts one chair to another also converts all axial bonds in one chair to equatorial in the other and all equatorial bonds to axial. This interconversion is sometimes called a "ring flip," but *there is no flip*. One chair is converted into the other by pseudorotation (twisting).

8.10 Draw both chair conformations of chlorocyclohexane, one with an axial chlorine and one with an equatorial chlorine.

The two chair conformations of cyclohexane are the lowest energy. Planar cyclohexane is the highest in energy, so high in energy that it cannot be attained. As pseudorotation converts one chair to the other, several new conformations are generated that are relevant to a discussion of cyclohexane. A plot of each conformation with its incipient energy generates an energy curve for cyclohexane, and this plot is shown in Figure 8.13.[5] Beginning

[5] Leventis, N.; Hanna, S.B.; Sotiriou-Leventis, C. *Journal of Chemical Education* 1997, 74, 813–814. Figure 3 therein.

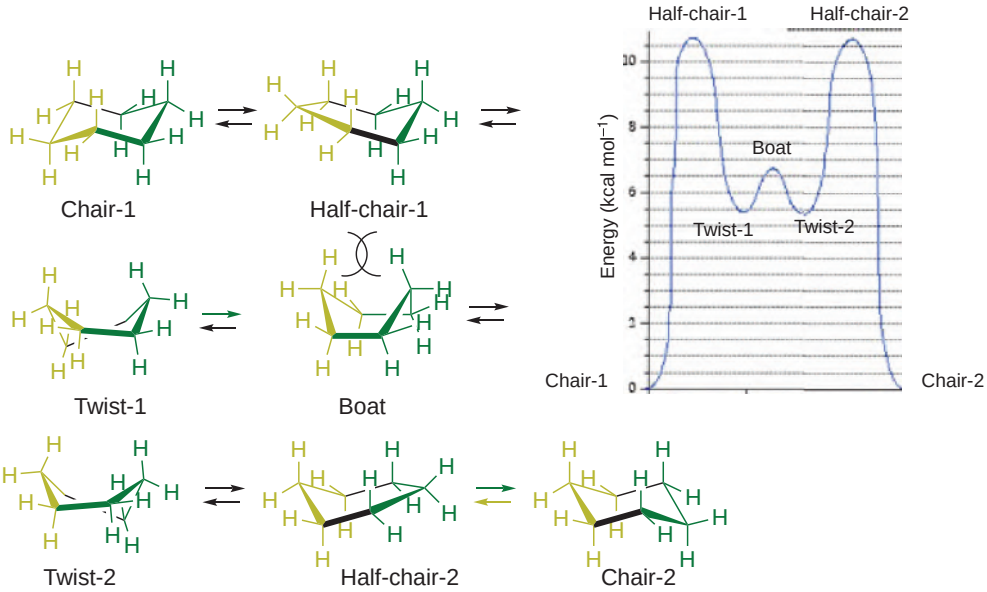


FIGURE 8.13 Important conformations in the chair-to-chair cyclohexane pseudorotation. The energy curve shows the relative energy of each important conformation. Reprinted with permission from Leventis, N.; Hanna, S.B.; Sotiriou-Leventis, C. *Journal of Chemical Education*, 1997, 74, 813–814. Figure 3 therein. Copyright 1997 American Chemical Society.

with the chair cyclohexane marked chair-1, twisting the left side of the ring upwards will flatten that region of the molecule to give what is known as a "*half-chair*" conformation, marked half-chair-1. The five co-planar carbon atoms increase both torsion strain and Baeyer strain and makes the *half-chair conformation* high in energy. If the twisting motion is continued, a twist is put into the molecule to give what is called a "*twist*" *conformation* (also known as a "*twist-boat*" conformation), marked twist-1. This *twist* is higher in energy than the chair, but lower in energy than the *half-chair*. If the twisting motion is continued, the "*boat*" conformation results, so named because it looks a little like the paper boats a child might make. Once the left side of the *chair* has twisted up to form the *boat*, the carbons on the right side of the molecule begin to twist "down," as shown for the conversion of the *boat* to a new *twist*, marked twist-2. Twist-2 should be of the same energy as twist-1. Further twisting gives another *half-chair* marked half-chair-2, which is analogous to half-chair-1. Completing the twisting motion generates the second *chair conformation*, marked chair-2.

As chair-1 is converted to chair-2, two large energy barriers are imposed by the half-chair conformations, and a small barrier for the boat conformation, as shown by the energy curve in Figure 8.13. The energy of a half-chair is measured to be ~ 10.8 kcal (45.2 kJ) mol^{-1} relative to the energy of the chair conformations. That of the boat is ~ 6.7 kcal (28.0 kJ) mol^{-1}. The twist is lower in energy [~ 5.4 kcal (2.6 kJ) mol^{-1}]. The lower energy chair conformations constitute the vast majority of conformations available to cyclohexane.

The *boat conformation* is interesting. Torsion strain in the four coplanar carbon atoms makes the boat conformation higher in energy than the chair conformations. The two ends of the "boat" (C1 and C4) are sometimes labeled the *bow* and the *stern*. It is apparent that two of the hydrogen atoms attached to these carbons are relatively close to each other in this conformation. These *"bowsprit" hydrogen atoms are not connected but they* compete for the same space over the cavity of the cyclohexane ring. This interaction is seen more clearly by comparing views of space-filling models of chair and boat cyclohexane in Figure 8.14. Sighting directly down the cavity of the ring shows that the bowsprit hydrogen atoms are "inside" the ring cavity of the *boat*. This brings them close together in space in what is called a *transannular interaction, which* raises energy of the boat conformation.

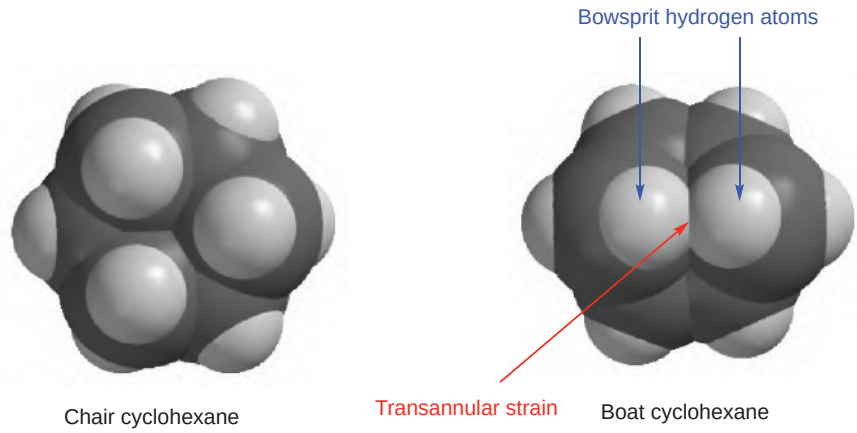


FIGURE 8.14 Transannular interactions in boat cyclohexane.

A[1,3] Strain

8.6 SUBSTITUTED CYCLOHEXANES. A[1,3]-STRAIN

When substituents are attached to a ring carbon of cyclohexane, one of the two chair conformations is lower in energy than the other. A substituent in one chair will be equatorial but it will be axial in the other. In chair cyclohexane the axial hydrogen atoms are not on adjacent carbons but on every other atom. The steric interaction between them is minimal. If one of the axial hydrogen atoms is replaced with the larger chlorine atom, however, the steric interaction of axial Cl with the two axial H atoms is much greater. In Figure 8.15 the two chair conformations of chlorocyclohexane are shown, along with space-filling models of each conformation.

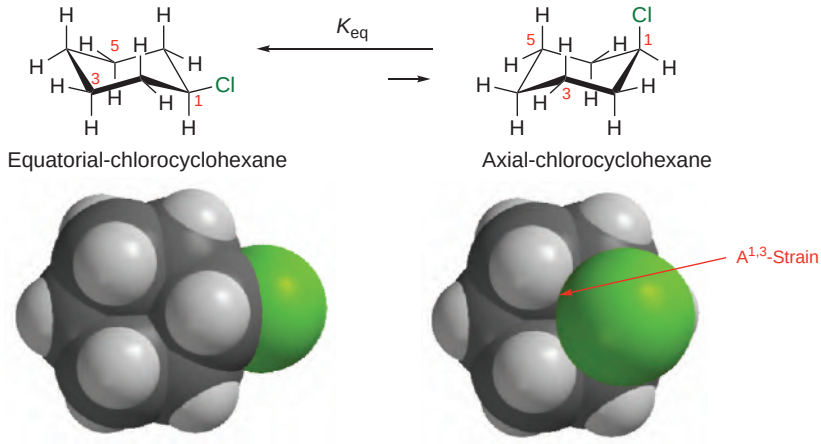


FIGURE 8.15 A[1,3]-strain in chlorocyclohexane.

The axial hydrogen atoms on C3 and C5 as well as the chorine on C1 have a "1,3" relationship. In the chair conformation that has an axial chlorine atom there is a steric interaction of the axial chlorine with the two axial hydrogen atoms across the ring, as shown in Figure 8.15. This *transannular steric interaction* of the substituent with the two axial hydrogen atoms is known as a *1,3-diaxial interaction*, but more commonly it is called *A-strain or A[1,3]-strain.* Cyclohexane is taken as the standard for comparison with substituted cyclohexane derivatives since there is *no A[1,3]-interaction* of the three axial hydrogen atoms in the chair conformation. There is *no A[1,3]-interaction* of the three axial hydrogen atoms in the chair conformation when the chlorine is equatorial. The conformation with the axial chlorine atom is therefore *higher* in energy than the conformation with the chlorine atom in the equatorial position. The strain in axial chlorocyclohexane will influence the equilibrium of

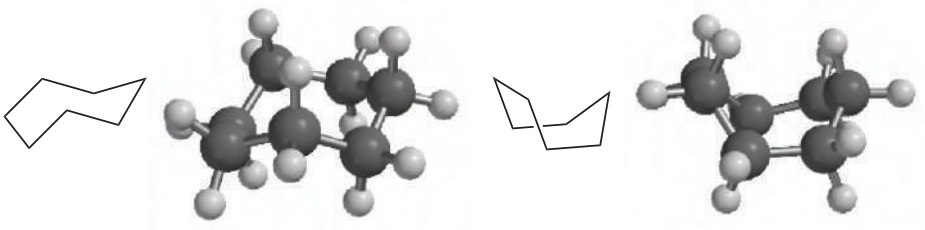
the chair-chair interconversion because conversion of the chair conformation with an axial chlorine to the chair with an equatorial chlorine by pseudorotation relieves the $A^{1,3}$-strain. Since the chair-to-chair equilibrium favors the lower energy conformation there is a smaller concentration of the higher energy axial chlorine conformation and a higher concentration of the lower energy equatorial chlorine conformation. The "bigger" the substituent on cyclohexane the greater the A-strain and the more the chair-chair equilibrium favors the chair conformation with an equatorial substituent.

8.11 Calculate K_{eq} if the molar concentration of axial-methylcyclohexane is 0.95 and the molar concentration of equatorial methylcyclohexane were 0.15; if the molar concentration of axial-methylcyclohexane were 0.22 and the molar concentration of equatorial methylcyclohexane were 0.77.

8.7 LARGE RINGS

Larger Ring Cyclic Compounds

As the size of the ring in cyclic alkanes increases, there is more conformational flexibility, and more conformations are possible. This section will focus on a few of those larger ring compounds. Cycloheptane has a larger ring cavity that leads to greater flexibility via pseudorotation and several important conformations.

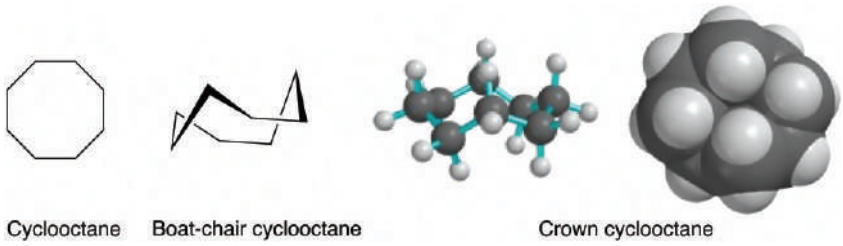


Chair cycloheptane Boat cycloheptane

One of the chair-like conformations is shown. The larger size of the ring allows the pseudo-axial hydrogen atoms to be further apart so there is less $A^{1,3}$-strain than in cyclohexane. Closer examination reveals that two of the carbons of cycloheptane are nearly coplanar. This flattening of the ring increases the torsion strain due to eclipsing bonds and atoms, which raises the energy slightly. A "boat-like" conformation is shown with some transannular strain. The strain energies for chair-cycloheptane and boat-cycloheptane are close, and one does not greatly predominate over the other. There are several other conformations for cycloheptane, but they will not be discussed.

8.12 Speculate as to whether "boat" cycloheptane is higher or lower in energy than boat cyclohexane.

For cycloalkanes that contain eight carbons or more, the larger size of the cavity allows a greater number of conformations via pseudorotation. An example is cyclooctane, which is known to have 10 important conformations, including the "boat-chair" conformation. Cyclooctane can also assume the so-called *crown conformation*. The "crown" shape is apparent in the ball-and-stick model of cyclooctane. If viewed from a "top" perspective that allows one to sight down the cavity of the ring, the space-filling model shows that those "inside-the-ring" hydrogen atoms are relatively close together, which imposes significant *transannular strain*. In 8-13 membered rings the hydrogen atoms in the ring cavity are close enough that this steric interaction destabilizes the ring by making it higher in energy.

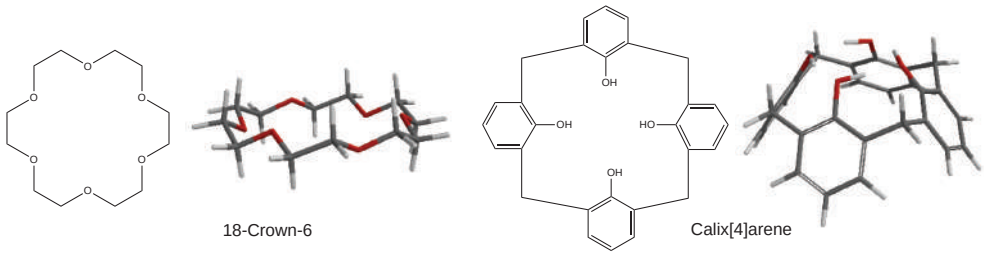


Macrocycles

In smaller rings, the hydrogen atoms cannot interact inside the ring cavity via pseudo-rotation. Therefore, transannular strain does not exist in rings of 5-7 carbon atoms. An important consequence of this transannular strain is that any reaction that attempts to join together the two ends of an 8-13 carbon chain will assume transition state that mimics the conformation of that ring at the instant the new bond is being formed and the ring is made. In principle, transannular strain should not inhibit formation of large rings (>14) since the cavity is large.

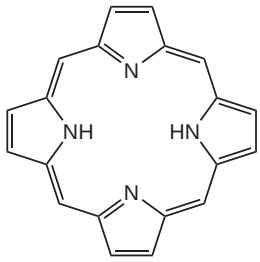
8.13 Look at cyclooctadecane, and speculate on the possibility of transannular strain.

Macrocycles are cyclic molecules and ions that contain a twelve-membered ring or greater. Examples of important macrocycles include crown ethers, calixarenes, porphyrins and cyclodextrins. Crown ethers are cyclic molecules with a ring that contains many ether units. The term "crown" arises from the conformation of these compounds, which resemble a crown. The first number in a crown ether's name refers to the total number of atoms in the ring, and the second number refers to the number of oxygen atoms in the ring. An example is 18-crown-6 with an 18-membered ring containing six oxygen atoms. The IUPAC name of 1,4,7,10,13,16-hexaoxacyclooctadecane. The molecular model shows the crown-type structure. 18-Crown-6 binds to a variety of small cations and can be used in the laboratory as a phase transfer catalyst. A *phase-transfer catalyst* is a molecule that facilitates the migration of a reactant from one phase into another phase where reaction occurs. Salts that are normally insoluble in organic solvents are made soluble by complexing to a crown ether.

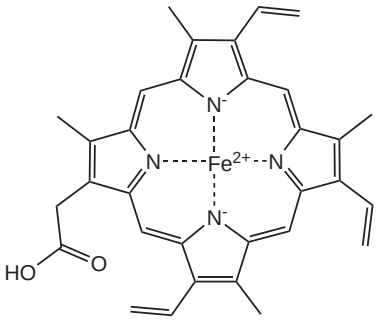


A calixarene is a macrocyclic compound derived from the reactions of a phenol (Section 19.2.2) and an aldehyde. Calixarenes have hydrophobic cavities that can hold smaller molecules or ions and belong to the class of cavitand, which is a container shaped molecule with a cavity that allows it to be a host-guest molecule. Host-guest chemistry describes complexes that are composed of two or more molecules or ions are held together in unique structural relationships by forces other than full covalent bonds. Calixarene nomenclature counts the number of repeating units in a ring, as in calix[4]arene. Water soluble calixarenes are useful in drug delivery and sodium ionophore calixarenes are potentially useful in chemical sensors.

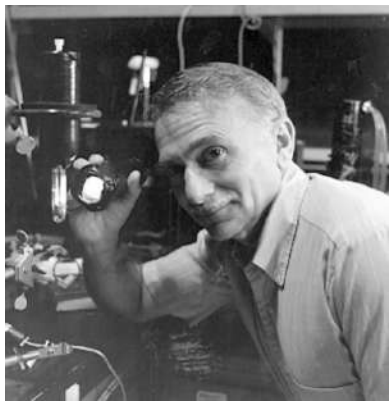
Porphyrins are heterocyclic macrocycles that consist of four pyrrole units (Section 23.1) connected by methine (=CH—) bridges as in the parent, porphine. Metal complexes derived from porphyrins, such as heme, which is the pigment in red blood cells and a cofactor of the protein hemoglobin. Heme is a coordination complex of iron, which is a tetradentate ligand with the nitrogen atoms of a porphyrin, A ligand is a molecule that binds to another (usually larger) molecule. Porphyrins are essential to much of life, helping form both the red hemoglobin in blood and the green chlorophyll in plants.



Porphine



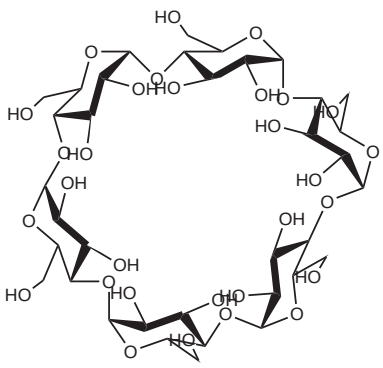
Heme



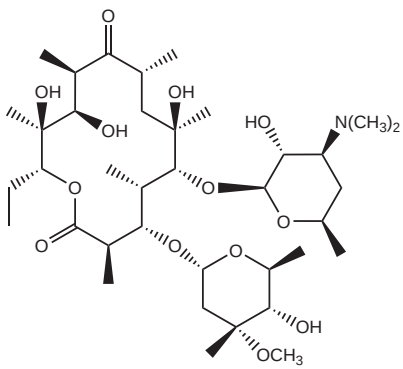
Martin Paul Gouterman

Martin Paul Gouterman (USA; 1931–2020) was a Professor of Chemistry at the University of Washington who is best known for seminal work on the optical spectra of porphyrins, for which he developed a simple model generally referred to as *Gouterman's four-orbital model. This model* predicts the intensity differences between the absorption bands of porphyrins. He described how the chemical structures of porphyrins determine whether the spectral shape was "normal," *hyper-* and *hypso-*.

Cyclodextrins are a family of cyclic oligosaccharides (Section 25.2) composed of glucose units that are joined by α-1,4-glycosidic bonds (Sections 25.2,4). They are ingredients in many approved medicines since they form complexes with hydrophobic compounds. They have been used for delivery of a variety of drugs since the cyclodextrin imparts solubility and stability to these drugs. Cyclodextrins are used in food, pharmaceutical, drug delivery, and in chemical industries. Categories of cyclodextrins include alpha-cyclodextrins with six glucose subunits which is shown, beta-cyclodextrins with seven glucose subunits and gamma-cyclodextrins with eight glucose subunits.



alpha-Cyclodextrin



Erythromycin

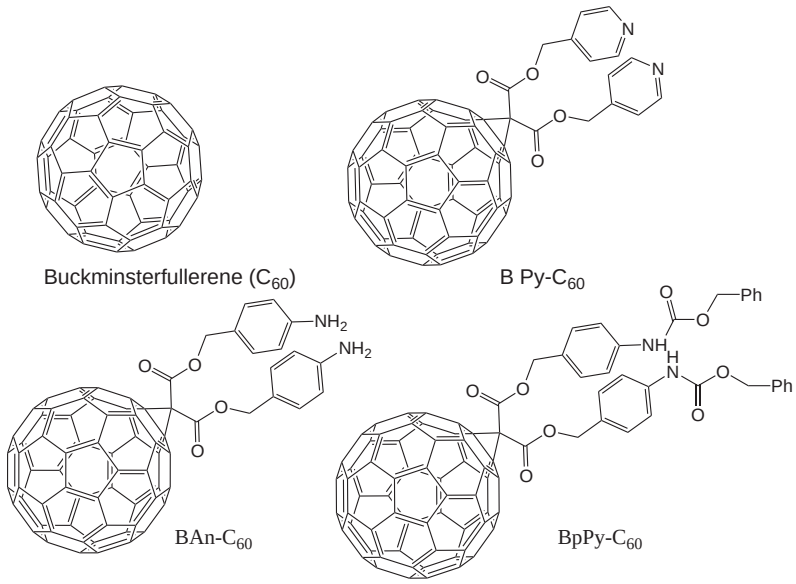
There are many macrocyclic drugs and most have heterocyclic atoms or functional groups as part of the ring. Many macrocyclic drugs are derived from natural sources, including *erythromycin*. Erythromycin is an antibiotic that is used to treat a wide variety of bacterial infections by stopping the growth of bacteria.

A *fullerene* is a macrocyclic compound with carbon atoms connected by single and double bonds to form fused five, six, and seven-membered rings that assume the shape of a sphere, an ellipsoid, or a tube. Fullerenes with a closed mesh topology have the empirical formula C_n, where "*n*" is the number of carbon atoms. The first characterized fullerene was named buckminsterfullerene (C_{60}), sometimes called a "buckyball." Fullerenes have been detected in nature and in outer space. Fullerenes are used in molecular electronics, with interesting properties as rectifiers. In biomedicine, gadolinium atoms have been enclosed inside the sphere and due to their magnetic properties, they increase proton relaxivity in magnetic resonance studies using MRI (Section 13.7).

Luis A. Echegoyen

Luis A. Echegoyen (USA) is a professor at the University of Texas, El Paso. His research focuses on new materials, complexes of fullerenes, recognition complexes, and self-assembly. He has an active research program in fullerene electrochemistry, monolayer films, supramolecular chemistry, endohedral fullerene chemistry and electrochemistry. Professor Echegoyen also studies carbon nano onions, and the synthesis, derivatization and fractionation of fullerenes. Some of Professor Echegoyen's recent work involves the role of fullerenes in solar cells.[6] Fullerene C_{60}, C_{70}, and their derivatives have been used in Perovskite solar cells to enhance device efficiency by improving the open circuit voltage, fill factor and by reducing photocurrent hysteresis. The active Perovskite layer in solar cells is typically composed of methylammonium lead iodide ($[CH_3NH]PbI_3$). Derivatives of buckminsterfullerene (C_{60}) were studied, including BPy-C60, BAn-C_{60} and BpAn-C_{60}.[6] These derivatives have a nitrogen atom with a different basicity, allowing compounds to be tested as conventional electron transporting materials in a single layer. This allows a study of how this affects the interfacial interactions with the perovskite layer. The new fullerenes perform better as electron extracting layers than as electron transporting materials.[6]

[6] Fernandez-Delgado, O.; Chandrasekhar, P.S.; Cano, N.; Simon, Z.C.; Puente-Santiago, S.R.; Liu, F.; Castro, E.; Echegoyen, L. *Journal of Materials Chemistry C* 2021, 10759–10767.



Carbon nanotubes are cylindrical fullerenes that are usually only a few nanometers wide, as illustrated in Figure 8.16a. They have high tensile strength, high electrical conductivity, high ductility, high heat conductivity and they are relatively inert to chemical reactions. Graphene is composed of isolated atomic layers of graphite and consist of a single layer of atoms arranged in a two-dimensional honeycomb lattice, shown in Figure 8.16b. Graphene is a semimetal with unusual electronic properties. Graphene conducts heat and electricity very efficiently along its plane and strongly absorbs light of all visible wavelengths, which accounts for the black color of graphite. However, a single graphene sheet is nearly transparent because it is very thin.

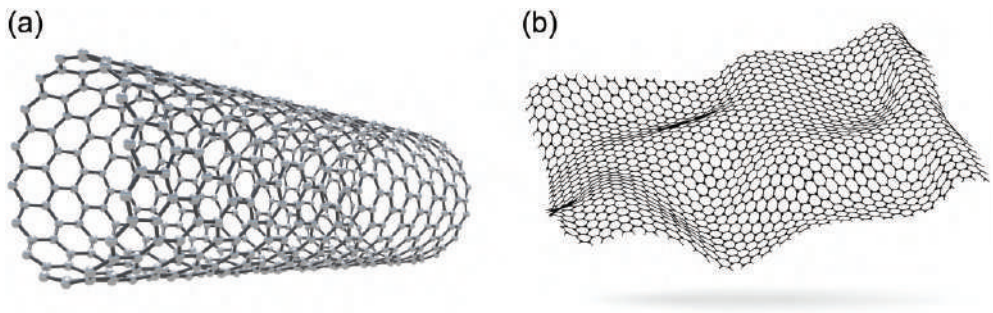


FIGURE 8.16 (a) Carbon nanotubes molecule structure, atoms in wrapped hexagonal lattice isolated on white background, 3d illustration. Shutterstock, Royalty-free stock illustration ID: 780740074. (b) Graphene, a molecular network of hexagons connected together. Chemical network. Carbon, nanomaterials, nanotechnology. Vector 3d illustration. Shutterstock, Royalty-free stock vector ID: 1559827085.

8.8 CYCLIC ALKENES

Cyclohexene

There are interesting conformational differences between cyclic alkenes and cyclic alkanes. The C=C unit of an alkene has two sp^2 hybridized carbon atoms, and each atom has a trigonal

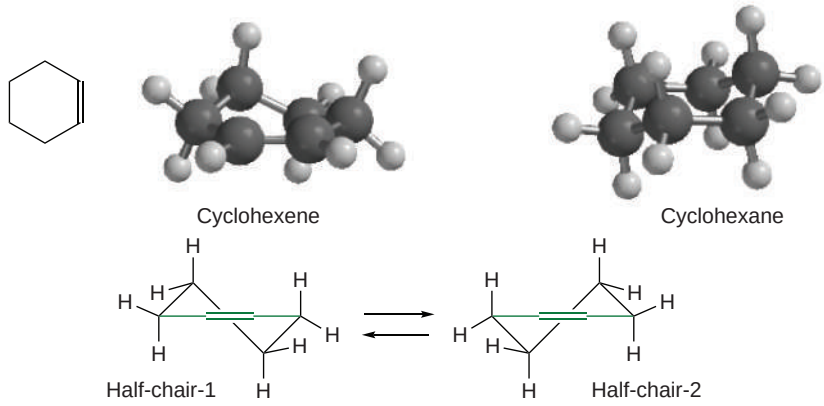
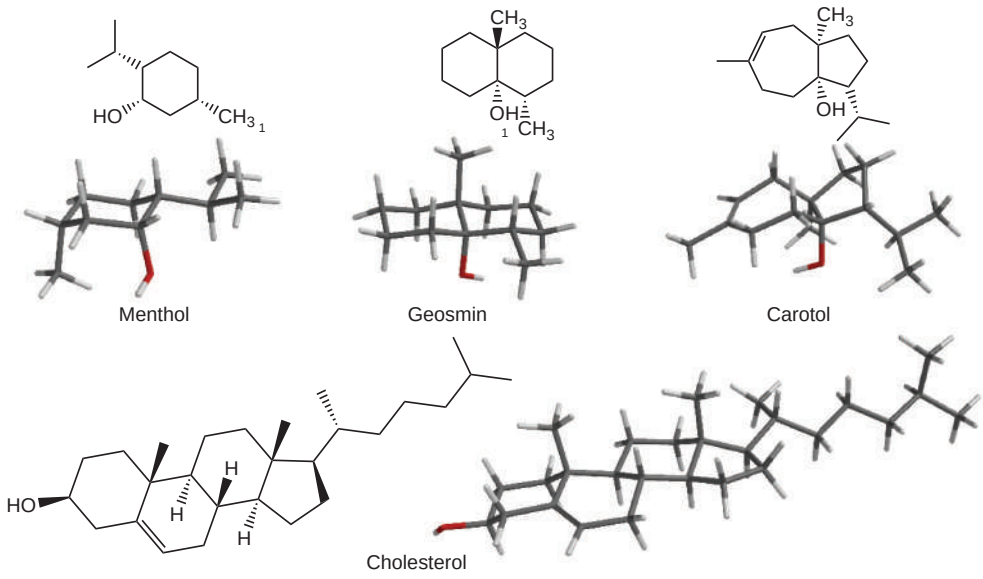


FIGURE 8.17 Half-chair conformations of cyclohexene.

planar geometry. The C=C unit and the atoms attached to that unit are all coplanar so the C—C=C—C unit is flat. The ball-and-stick molecular model of cyclohexene clearly shows flattening in the region of the C=C unit when compared with cyclohexane (Section 8.4). Four carbons of cyclohexene are coplanar with one of the other ring carbons "up" and one "down" relative to the C=C. The low energy conformation of cyclohexene is a *half-chair conformation*, which is a consequence of the ring flattening. The two equilibrating *half-chair* conformations are shown in Figure 8.17. Pseudorotation is responsible for shifting one half-chair to the other where the two carbon atoms projected to the "back" will flip. The hydrogen atoms are labeled as *pseudo-axial* and *pseudo-equatorial* since their position is different from those atoms in cyclohexane.

8.9 BIOLOGICAL RELEVANCE

Many of the biologically important molecules have multiple rings. The fundamental shapes of individual small rings are retained in many, if not most cases. The conformation of these compounds can be predicted by an understanding the fundamental shapes of five, six, and seven membered ring hydrocarbons. Terpenes were introduced in Section 5.4 and an example is menthol, which is obtained from the oils of corn mint or peppermint. Methanol clearly shows a chair conformation for the six-membered ring in the molecular model. Menthol has local anesthetic and counterirritant effects and is commonly used to alleviate throat irritation. Geosmin is a sesquiterpene with a distinct earthy or musty odor. It is also responsible for the earthy taste of beetroots and contributes to the strong scent that occurs in the air when soil is disturbed. It has a structure that is formed by two fused six-membered rings, and each assumes a chair conformation. Carotol is one of the primary components found in carrot seed oil and exhibits a half-chair type conformation for the cycloheptene ring and an envelope for the five-membered ring. Steroids were introduced in Section 5.4 and the conformation of the four rings is illustrated by cholesterol. It is biosynthesized by animal cells, and it is a structural component of animal cell membranes. As shown, each of the six-membered rings exists in a chair conformation similar to that found in cyclohexane or cyclohexene. The five-membered ring exists as an envelope. The lesson from these four examples is that the most fundamental principles presented in this chapter for conformation of rings applies to more complex molecules, certainly as a first estimate of the conformation.

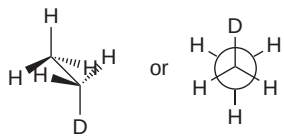


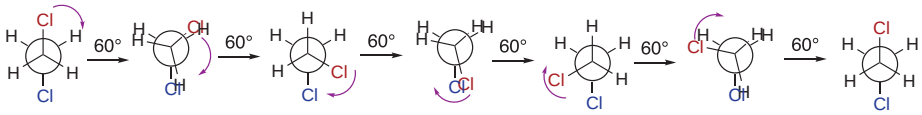
CORRELATION OF CONCEPTS WITH HOMEWORK

- A rotamer is one position of bonds, atoms, and groups in a molecule, generated by rotation around a single bond in acyclic molecules. A conformation for a molecule represents one position of bonds, atoms, and groups in the molecule: 1, 2, 3, 5, 6, 8, 15, 19, 20, 22, 24, 27.
- When rotation around a bond brings two atoms or groups on adjacent atoms, as well as the electrons in those bonds close together in space, competition for that space and electronic repulsion of the bonds leads to repulsion called steric strain. This result increases the energy of that rotamer: 2, 3, 4, 6, 7, 8, 15, 21.
- Introduction of a π -bond leads to flattening of the conformation in the region of the π-bond. There is no rotation about multiple bonds: 7.
- Planar cycloalkanes are high in energy due to torsion strain and Baeyer strain. Cyclic alkanes undergo pseudorotation to give low energy conformations because rotation by 360° is not possible: 9, 23.
- In cyclohexane, the chair conformation is lower in energy when substituents are in the equatorial position because steric interactions of axial substituents at C1, C3, and C5 in substituted cyclohexanes leads to A-strain and the conformation with the most A-strain is higher in energy: 10, 11, 12, 14, 6, 17, 18, 25.
- Medium sized rings (8-13) are less stable (higher in energy) because of transannular interactions within the cavity of the ring. Large rings (>14 carbons) are lower in energy than medium-sized rings because the cavity of the ring is so large that transannular strain is diminished: 13, 26.

ANSWERS ON IN-CHAPTER QUESTIONS

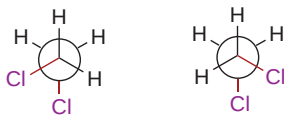
8.1



8.2 

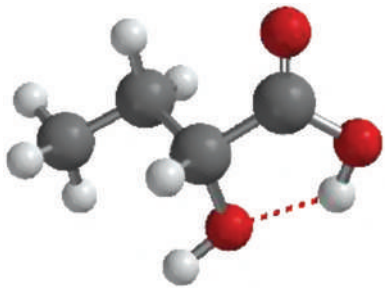
8.3 The eclipsed rotamer has all the hydrogen atoms eclipsing so they are close together and the electrons in those bonds repel. Therefore, there is electronic repulsion and steric repulsion. When looking at the staggered rotamer, the atoms are further apart, there is little repulsion.

8.4 The CMe_3 group (*tert*-butyl) is much larger than methyl, so the energy barrier to rotation around the indicated bond will be much greater, making rotation more difficult. The steric interaction of two *tert*-butyl groups will be much greater than that of two methyl groups, so the energy barrier is greater.

8.5 

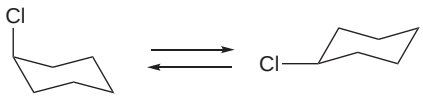
8.6 There are Cl—Cl interactions and Cl—H interactions, but they are degenerate. Therefore, one conformation will have a Cl—Cl eclipsing interaction and the other will have the two chlorine atoms staggered. The energy diagram will look more like ethane, except for the magnitude of the energy barriers.

8.7 No! The two methyl groups are 180° apart since they are connected to different carbons of the linear C≡C unit. Therefore, there is zero interaction between them.

8.8 

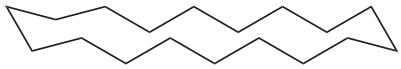
As shown in the accompanying figure, rotation about the carbon attached to the C=O unit, and the carbonyl carbon leads to a conformation where the OH unit can easily form an intramolecular hydrogen bond that helps to stabilize that rotamer of 2-hydroxybutanoic acid.

8.9 As the bond angles in the envelope form of cyclopentane distort from planar cyclopentane, the hydrogen atoms are further apart, which decreases torsion strain. Forming the envelope conformation, however, requires changing the bond angles to something other than the 108° found in planar cyclopentane. This increases Bayer strain, but the energy savings in torsion strain more than compensates.

8.10 

8.11 Since $K_{eq} = [ax]/[eq]$, and $[eq] = 0.15$ and $[ax] = 0.95$, $K_{eq} = [0.95]/[0.15] = K_{eq} = 6.33$. In the second part, $[eq] = 0.77$ and $[ax] = 0.22$, $K_{eq} = [0.22]/[0.77] = K_{eq} = 0.286$.

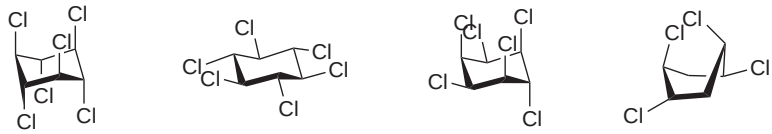
8.12 Two carbons in "boat" cycloheptane are essentially coplanar and eclipsing. The cross-ring interaction with the CH_2 group is minimal because of the "flattening." For that reason and since the two atoms are closer together in the smaller ring, the flagpole interaction in boat cyclohexane is probably greater. Therefore, "boat" cycloheptane is expected to be lower in energy than boat cyclohexane.

8.13 

As drawn, it appears that the molecule might have transannular strain. However, the ring is so large that the hydrogen atoms rarely come into close contact, so there is minimal transannular strain.

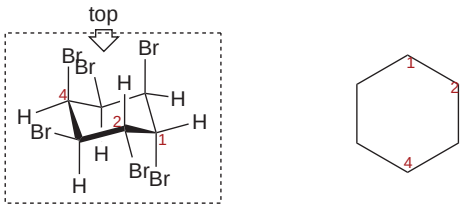
HOMEWORK

14. Which of the following conformations has the *least* transannular steric interactions, assuming each molecule is "locked" in the conformation shown.

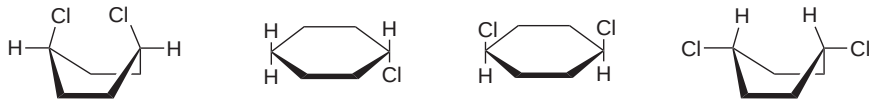


15. Briefly explain why ethylene diamine ($H_2N—CH_2CH_2—NH_2$) may exist primarily as the *anti*-rotamer rather than the *gauche*-rotamer in methanol. *Draw both conformations as part of your answer.*
16. Look at the molecule drawn in the box, as a chair. Note the numbering scheme for the carbons.

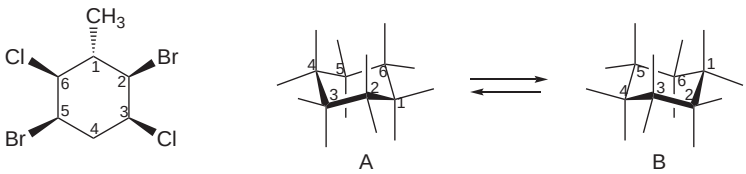
    Draw in the bonds on the flat ring, using wedges and dashed lines, to indicate the proper arrangement of atoms for this molecule. For the flat ring, the "top" is the one facing you, as you look at the sheet of paper. The "top" for the chair form is as indicated.



17. Assuming that each of the following is frozen, which of the following is the *lowest* energy conformation?



18. On the diagrams provide, fill in the appropriate atoms on the proper carbon and in the proper axial or equatorial position. These are two chair conformations for the same molecule, not isomers. Note the numbering scheme and assign the proper atoms to the properly numbered carbons in each chair. Which is lower in energy, A or B?



19. Draw the *syn*- and *anti*-rotamer for each of the following in Newman projection.
    (a) butane along the C2—C3 bond (b) 1,2-difluoroethane
    (c) 2,2,3,3-tetramethylbutane along the C2—C3 bond (d) 1,2-dimethoxyethane
    (e) pentane along the C1—C2 bond (f) 1-chloropropane along the C2—C3 bond
20. Draw the *syn*- and *anti*-rotamer for each of the following in a sawhorse projection.
    (a) butane along the C2—C3 bond (b) 1,2-difluoroethane
    (c) 2,2,3,3-tetramethylbutane along the C2—C3 bond (d) 1,2-dimethoxyethane
    (e) pentane along the C1—C2 bond (f) 1-chloropropane along the C2—C3 bond

21. The *gauche*-rotamer of 1,2-dichloroethane [1.2 kcal (5.0 kJ) mol^{-1}] is slightly higher in energy than the *gauche*-rotamer of butane [1.0 kcal (4.18 kJ) mol^{-1}]. Offer an explanation.
22. Although it was stated that ethane-1,2-diol exists primarily as a *gauche*-rotamer, neat (no solvent) diol has a significant concentration of the *anti*-rotamer. In the gas phase, ethane-1,2-diol exists almost exclusively as the *gauche*-rotamer. Explain.
23. Generating a C=C unit such as that found in ***A*** is very difficult because the structure is very unstable whereas forming the C=C unit in ***B*** is rather easy. This observation is often called Bredt's rule. Explain the observation!

24. Describe the structure of the prevalent conformation of 3-hydroxybutanoic acid in hexane solvent and give reasons for your choice.
25. It is known that 1,2-di-*tert*-butylcyclohexane exists in a boat conformation to a large extent. Draw a chair conformation for this molecule and suggest a reason why this should be so.
26. It is known that oxidation of cyclooctanol (Section 15.2) to cyclooctanone (draw both structures) is relatively difficult, whereas the conversion of the alcohol to the ketone is relatively easy. Explain why.
27. Briefly explain why 1,4-cyclohexanedicarboxylic acid with both COOH units on the same side of the molecule has a relatively high percentage of a boat conformation.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-9.php

9

Stereoisomers

Chirality, Enantiomers, and Diastereomers

This chapter will focus on a class of isomers that differ only in the spatial arrangement of attached atoms and groups about an atom. When two different molecules have the same atoms, groups, and the same empirical formula, they are isomers. When they have the same points of attachment (the same connectivity), but differ in the spatial arrangement of those groups, they are different molecules known as *stereoisomers*.

To begin this chapter, you should know the following points:

- Name organic molecules, based on the nomenclature rules (Sections 4.4,5 and 5.1–5.6).
- The VSEPR model for drawing structures (Section 3.6).
- σ-bonds. (Sections 3.3 and 3.8).
- π-Bonds. (Sections 5.1–5.3).
- Constitutional isomers (Sections 4.2 and 4.4).
- Rotation about covalent single bonds (Section 8.1).
- Conformations of acyclic molecules (Sections 8.1–8.3).
- Conformations of cyclic molecules (Sections 8.5–8.7).
- Physical properties associated with organic compounds (Section 5.8).

Defining a Stereogenic Center

9.1 STEREOGENIC CARBONS AND STEREOISOMERS

A mirror image is defined as an image or object that is identical except that the structure is reversed. A "W" and its mirror image are shown and it is easy to see that one "W" can be placed on the mirror image "W" so they are completely *superimposable*. In other words, the two images represent one "W," not two.

Since the "W" is symmetrical there is a plane of symmetry as shown. When a sp^3-hybridized carbon has four identical atoms or groups attached the mirror image of that molecule is superimposable. Such a molecule has symmetry and if it is superimposable, it is the same molecule. An example is methane. There is a plane of symmetry that bisects the central carbon and two of the hydrogen atoms, illustrated by the pane through the tetrahedron superimposed on methane in Figure 9.1. The atoms on either side of the plane are identical (both H). Methane and its mirror image will superimpose so there is one molecule, not two. Similarly,

DOI: 10.1201/9781003174929-9

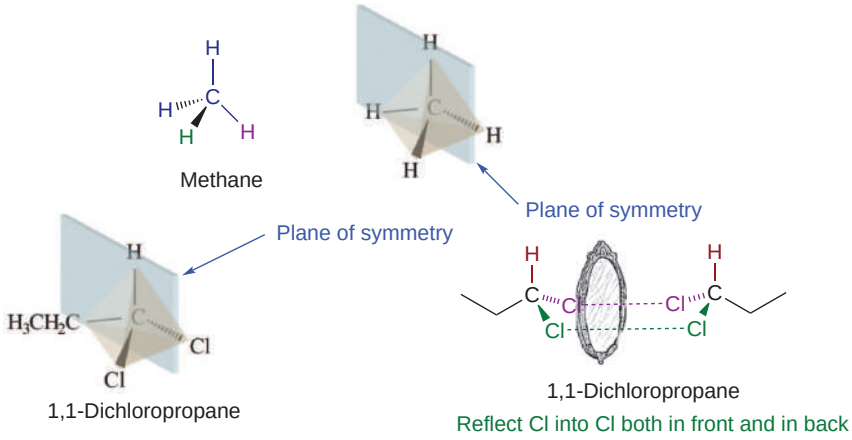


FIGURE 9.1 Planes of symmetry in methane and 1,1-dichloropropane.

1,1-dichloropropane has two chlorine atoms attached to the same carbon and there is a plane of symmetry that bisects the H—C—C unit. One chlorine reflects into the other chlorine. Since there is a plane of symmetry, the mirror image of 1,1-dichloropropane is completely superimposable on the original. There is one molecule not two, and 1,1-dichloropropane.

Enantiomers and Non-Superimposability

9.1 Indicate the stereogenic carbon atom(s), if any, in 3-chloro-4,5-dimethylnonane, 3,3-diethylpentane, and 3-methyl-5,6-diphenylhexan-1-ol.

When a sp^3-hybridized carbon has four different atoms or groups attached, arranged in a tetrahedral array around that central carbon, their relative positions are fixed. The only way to change the relative and specific positions of those four atoms or groups is to make or break bonds. A molecule that bears a carbon with four different atoms or groups has no symmetry in the molecule, so it is *asymmetric*. Interestingly, the mirror image of that molecule is a different molecule since it cannot be superimposed on the original. The carbon bearing four different atoms or groups is said to be *a chiral carbon or* a *stereogenic carbon.* A molecule with at least one *stereogenic carbon* is said to be a *chiral molecule.*

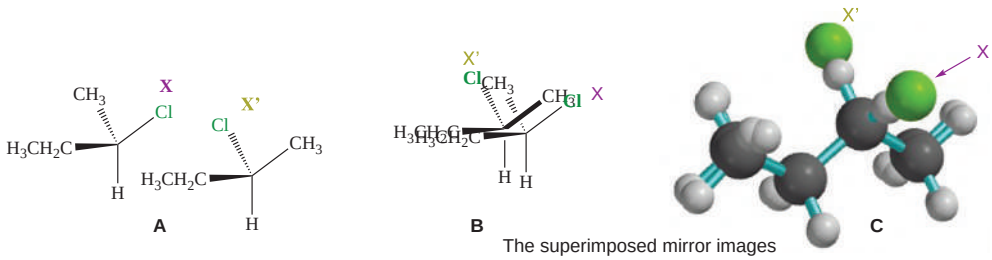


FIGURE 9.2 2-Chlorobutane and its nonsuperimposable mirror image.

2-Chlorobutane is an example of an asymmetric molecule, where C2 has four different attached atoms or groups, Cl, H, methyl, and ethyl. The structures of 2-chlorobutane (X) and its mirror image (X') are shown in Figure 9.2, **A**, but they are not superimposable. There is an attempt to superimpose the line drawing structures in **B.** In **C**, there is an attempt to superimpose the ball-and-stick model of 2-chlorobutane (X) and the mirror image (X') from the same perspective. It is not possible to make all of the atoms and groups match up and the two molecules are clearly not superimposable. Therefore, C2 is stereogenic and these two structures are different molecules. 2-Chlorobutane and its mirror image are *stereoisomers* with the same empirical formula, the same atoms, and the same attachment of atoms. They differ in the spatial arrangement of the atoms, and they cannot be interconverted except by breaking bonds. Mirror image stereoisomers that do not superimpose are called *enantiomers.*

A molecule that has a stereogenic carbon and generates at least one pair of enantiomers is said to be *chiral molecule*.

9.2 Draw each molecule and its mirror image and determine if they are enantiomers or not: 2-bromo-2-chloropentane, 2,2-dimethylhexane, and 4-(1-methylethyl) octane.

Nobel laureate Emil Fischer (Germany; 1825–1919) developed a method for drawing stereoisomers. One enantiomer of 2-chlorobutane in Figure 9.3 shows the stereochemistry of the stereogenic carbon using line notation. The four groups or atoms attached to the stereogenic carbon are ethyl, methyl, chlorine, and hydrogen. The stereogenic carbon is viewed from a different perspective of the tetrahedron, from one *edge* of a tetrahedron. The methyl and the hydrogen atom on the horizontal plane are projected out from the front of the page (solid wedges). The chlorine atom and the ethyl group on the vertical plane are projected behind the page (dashed lines). If the wedges and dashes are replaced with lines, a *Fischer*

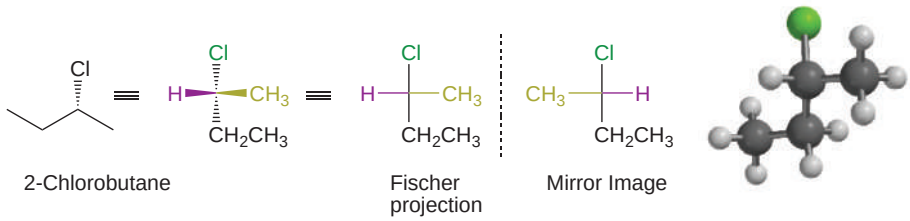


FIGURE 9.3 Fischer projection of 2-chlorobutane.

projection is obtained where two groups are attached to the vertical line and two are attached to the horizontal line. Drawing a molecule this way constitutes the *definition* of a *Fischer projection*. Groups on the horizontal line are projected in front of the page and those on the vertical line is projected behind the page. A ball-and-stick model of the Fischer projection is shown to give a three-dimensional view. The mirror image of this molecule in Fischer projection is easily drawn by switching the position of the H and the CH_3 on the *horizontal line*. It should be emphasized that the use of Fischer projections is not encouraged since there a better ways to show the spatial oriental of atoms in a molecule. However, they are widely used in biochemistry and biology and so they are introduced here.

Fischer Projections

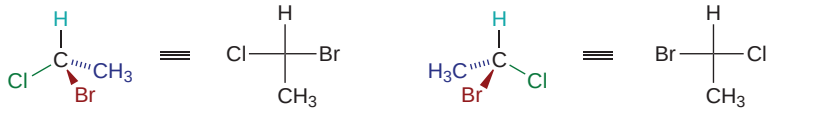
9.3 Draw the structure of 3-bromohexane and its enantiomer in Fischer projection.

9.2 ABSOLUTE CONFIGURATION [(R) AND (S) NOMENCLATURE]

Cahn-Ingold-Prelog Selection Rules

Enantiomers are different molecules, and each requires a unique name. A set of standardized rules of nomenclature have been developed that distinguish two enantiomers based on the relative position of atoms or groups. The rules define the *absolute configuration* of each enantiomer, which becomes part of the name. Three chemists, Robert Sidney Cahn (England; 1899–1981), Sir Christopher Kelk Ingold (England; 1893–1970), and Vladimir Prelog (Croatia-Czech Republic-Switzerland; 1906–1998), developed the rules. They are called the *Cahn-Ingold-Prelog selection rules (the CIP rules)*. These rules for determining stereochemistry have been formalized and expanded by IUPAC.

Both enantiomers of 1-bromo-1-chloroethane are shown, drawn in line notation and in Fischer projection. All atoms attached to a stereogenic carbon atom are assigned a priority of importance for each attached atom. The spatial arrangement of these atoms about the central carbon will determine the absolute configuration of each molecule.



First, assign a priority based on the atomic mass of each *atom*. 1-Bromo-1-chloroethane, for example, has a H, Cl, Br, and a CH_3 group attached to the stereogenic carbon. The mass of the group ($-CH_3$) is *not* used but rather the *mass of the carbon atom attached to the stereogenic atom*. The atomic masses of Br, Cl, H, and C are compared, and the order of descending atomic mass is *Br > Cl > C > H*. The priority letters ***a***, ***b***, **c**, and ***d*** are assigned for each atom in a tetrahedral representation of 1-bromo-1-chloroethane. The *"a"* has the highest priority and *"d"* the lowest priority: *Br = a, Cl = b, C = c, and H = d* (see **A** in Figure 9.4).

Before the absolute configuration can be assigned, the model must be viewed with *the lowest priority group (d) projected to the rear* (180° from the viewer). The a-b-c atoms form the base of the tetrahedron projected to the front, as illustrated in Figure 9.4. Starting with **A**, the tetrahedron is tipped back and slightly to the right so the *d* group is moved to the rear as the *a* group and the *c* group tip up. The *b* group remains more or less in the same position

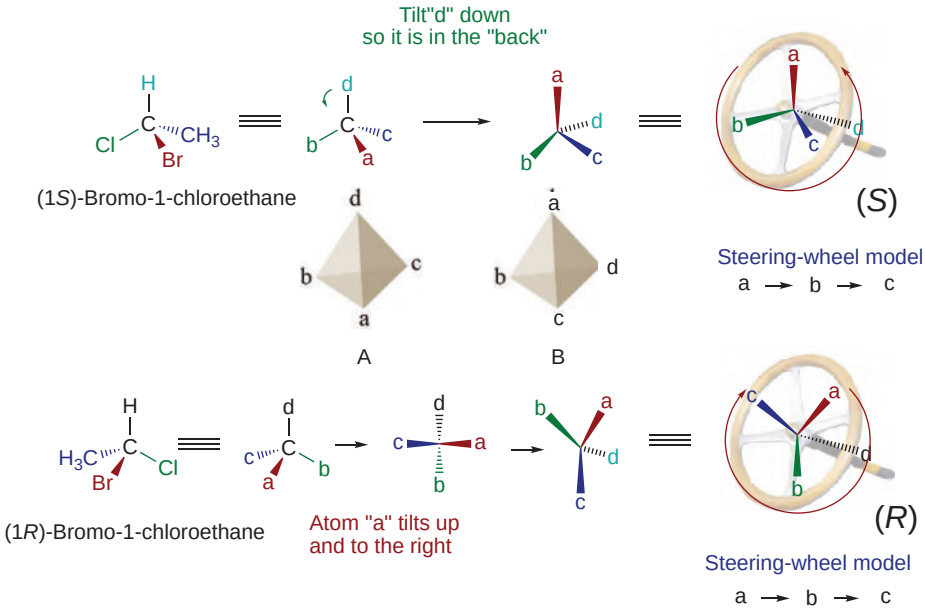


FIGURE 9.4 Assignment of absolute configuration for 1-brnomo-1-chloroethane using the steering wheel model.

to give **B**. Atoms a-b-c form the base of the tetrahedron, and this view can be imagined as the steering wheel of an old-time car. Indeed, this representation is called the *steering-wheel model* (see Figure 9.4). An imaginary arrow can be drawn to generate the arc of a circle from the highest priority atom (*a*) toward the next highest priority atom (*b*) and finally toward (*c*). If this imaginary arrow proceeds in a *clockwise direction*, the term (*R)* for rectus (*Latin* for right) is used. If this imaginary arrow proceeds in a *counterclockwise direction*, the term (*S)* for sinister (*Latin* for left) is used. In this example, the imaginary arrow from *a* → *b* → *c* proceeds in *a counterclockwise direction, so* it is labeled the (*S*)-configuration. The name is (1*S*)-bromo-1-chloroethane. Using the same protocol and priority scheme for the enantiomer leads to an arrangement in which the arrow from *a* → *b* → *c* proceeds in a *clockwise direction* and the name is (1*R*)-bromo-1-chloroethane. To summarize, the absolute configuration for an enantiomer is determined by assigning priorities a-d for atoms connected to a stereogenic center. Attach these atoms to a tetrahedron with the stereogenic carbon in the center. Rotate the molecule so the (d) group is projected to the rear. Trace a circle from a → b → c. If the

direction a → b → c is clockwise, the absolute configuration is (*R*) but if the direction is counterclockwise, the absolute configuration is (*S*).

Other methods for determining the absolute configuration have been reported.[1] One method uses the relationship of the spatial arrangement of the priority atom with the right and left hand. The thumb is pointed in the direction of the lowest priority group as the (d) group. If tracking a → b → c requires the left hand, the absolute configuration is (*S*) but if it requires the right hand, it is (*R*).[2]

If a molecule has a stereogenic carbon with two different groups but the atoms attached to the stereogenic carbon are the same, then another rule is required. An example is 2-chlorobutane and both enantiomers are shown in Figure 9.5. Ethyl, methyl, hydrogen, and Cl are attached to the stereogenic carbon. The atoms attached to the stereogenic carbon are C, C, H, and Cl. Chlorine has the higher atomic mass, so it is assigned "a" and hydrogen has the lowest atomic mass, so it is assigned "d". However, two of the atoms attached to the central carbon are carbon. Remember that the ethyl group is not compared with the methyl group, but rather the carbon atom of each group that is attached to the stereogenic carbon. The carbon of the ethyl group is compared with the carbon atom of the methyl group. The atomic mass rule does not work since both atoms are the same and another rule is required to find a point of difference in these two groups. Before solving this problem, a shorthand method to represent the three hydrogen atoms on the methyl carbon is shown. The three hydrogen

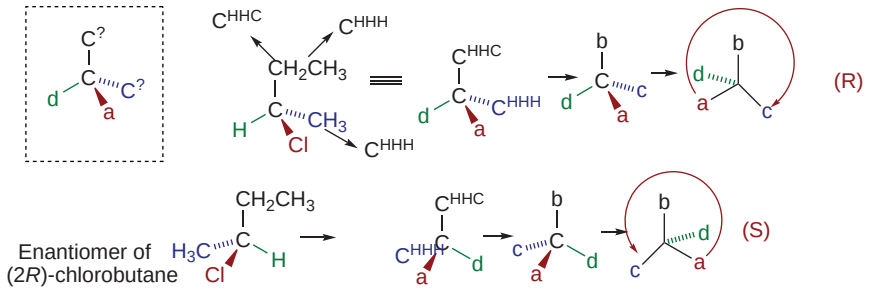


FIGURE 9.5 Determining absolute configuration for (2*R*)- and for (2*S*)-chlorobutane.

atoms attached to the methyl carbon can be represented by a superscript method, C^{HHH}. The two hydrogen atoms and the methyl group attached to the carbon of the ethyl group can be represented by C^{CHH}.

Using the *superscript protocol*, C^{HHH} and C^{CHH} are clearly different, and they constitute a *point of difference*. At this point of difference, the highest priority atom is determined by comparison of the atomic mass of the atoms *attached* to each carbon. Carbon has a greater mass than hydrogen, so C^{CHH} has a higher priority than C^{HHH}. The C^{CHH} is "b" and C^{HHH} is "c" so this enantiomer is (2*R*)-chlorobutane. Using the same protocol leads to the opposite absolute configuration for the mirror image and the name of the enantiomer is (2*S*)-chlorobutane.

9.4 Draw the structure of (3*R*)-methylhexane in Fischer projection; of (4*S*)-ethyloctane; of (5*R*)-chloro-(2*R*)-bromoheptane.

Chiral Molecules with Substitution

There are several rules to assign the (*R*) or (*S*) configuration.

1. Assign a priority to the four atoms directly connected to the stereogenic atom based on the atomic mass of each atom attached to the chiral atom. The higher the atomic mass, the higher the priority. If isotopes are involved, the higher mass isotope takes the higher priority ($^3H > ^2H > ^1H$, e.g.).

[1] (a) Juszczak, L.J. *Journal of Chemical Education* 2021, 98, 3384–3389; (b) Idoux, J.P. *Journal of Chemical Education* 1982, 59, 553.

[2] See www.youtube.com/watch?v=rC295Q07BrM.

2. If any atoms directly attached to the stereogenic atom are the same (same atomic mass), proceed down each chain (away from the stereogenic atom) until a point of difference is found. At that point use the atomic mass rule to determine the priority. If the end of a chain is reached and there is no point of difference, those groups are the same and the atom of interest is not stereogenic.
3. If the first point of difference is reached and priority cannot be determined by differences in atomic mass, count the number of the highest priority atoms at that point. The atom with the largest number of priority atoms takes the highest priority.
4. If the atom being considered is part of a π-bond, each bond is counted as being attached to a substituent (two atoms for a double bond, and three atoms for a triple bond).

A few examples that use all of the CIP rules will address structural differences found in most molecules encountered in this book. In 6-chloro-1-fluorohexan-3-ol, the tetrahedral representation in Figure 9.6 shows that the stereogenic center (C) is attached to H, O, C, and C. The O is the highest priority atom (a) and hydrogen is the lowest priority (d), but C and C remain unassigned. The carbon of the fluoroethyl fragment has a substitution pattern C^{CHH} but the carbon of the chloropropyl fragment also has a C^{CHH} substitution pattern. That position is no point of difference because the highest priority attached atoms are identical (C and C). The search is continued further down the two chains in question. Moving along the chains away from the stereogenic carbon leads to the first point of difference, C^{FHH} and C^{HHC}. The F is higher in priority relative to C by atomic mass, so C^{FHH} is (b) and C^{HHC} is (c). This alcohol has an (*S*) absolute configuration and the name is 6-chloro-1-fluoro-(3*S*)-hexanol. Note that the chlorine atom in 6-chloro-1-fluorohexan-3-ol is not used for priority assignment because the point of difference is encountered before the chlorine atom is encountered in that chain. Remember that the atoms are compared, not the group.

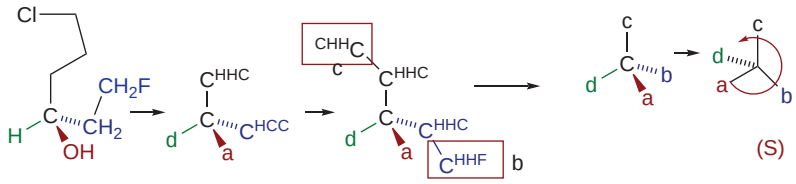


FIGURE 9.6 Absolute configuration of (6*S*)-chloro-1-fluorohexan-3-ol.

The absolute configuration of 2,2,6-trimethylheptan-4-ol is determined in Figure 9.7. The priority comparison is C, C, H, and O for the four groups. Once again, O is the highest priority (a) and hydrogen is the lowest priority (d). Looking at the carbon atoms attached to the stereogenic center, there is C^{CHH} for 2-methylpropyl and C^{CHH} for 2,2-dimethylpropyl. Moving down the chain to the next carbon finds a point of difference, C^{CCH} vs C^{CCC}.

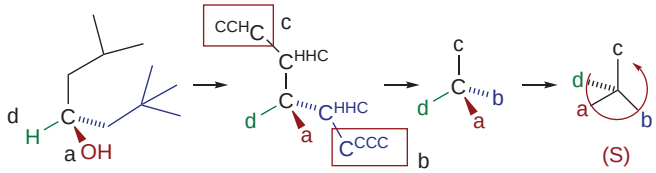


FIGURE 9.7 Absolute configuration of 2,2,6-trimethylhetpan-4(*S*)-ol.

While it is a point of difference, carbon is the priority atom in both cases so it cannot be used to determine priority using atomic mass. Further examination of both chains reveals there are no atoms in the two chains of higher priority. In such as case, the *number* of priority atoms is determined. The 2,2-dimethylpropyl chain has three carbons (C^{CCC}) so it is (*b*) whereas the 2-methylpropyl chain has two carbons (C^{CCH}) so it (*c*). The assignment is (*S*) and the name is 2,2,6-trimethyl-(4*S*)-heptanol. When, and only when, the first point of difference

cannot be resolved because the priority atoms are the same, count the number of priority atoms.

It is possible to draw a molecule with a specific absolute configuration using this approach. If the structure of 3(*R*)-bromo-5-methylpentane is required, for example, simply draw one structure with a wedge or a solid line at the stereogenic center as shown in Figure 9.8. There

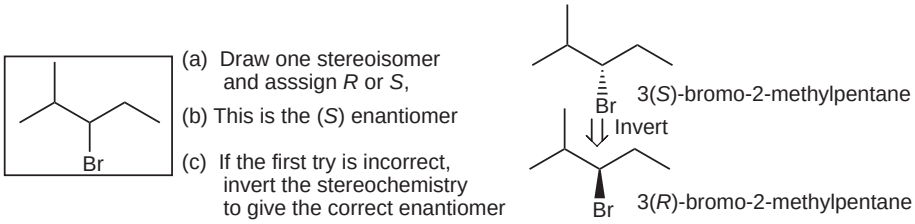


FIGURE 9.8 Drawing a stereoisomer with a specific absolute configuration.

is a 50:50 chance of getting it correct. Use the CIP rules to determine the absolute configuration of the molecule that is drawn. In the example shown, the first try gave 3(*S*)-bromo-5-methylpentane. If incorrect, simply change the wedge to a dashed line, or in this case the dashed lined to a wedge to obtain the correct 3(*R*)-bromo-5-methylpentane.

9.5 Draw the structure of (3,3,5*S*)-trichlorononane.
9.6 Draw the structure of (3*R*)-bromo-2-methylhexane.

In the preceding examples no substituent or group contained a π-bond such as that found in 2,4-dimethylpent-1-en-3-ol. An analysis of this structural variation is shown in Figure 9.9. The atoms attached to the stereogenic carbon in this alcohol are H, O, C, and C, with O assigned (*a*) and H assigned (*d*). Comparing the 1-methylethyl group and the 1-methylethenyl groups poses a problem in that one of the attached carbon atoms is part of a C=C unit. In

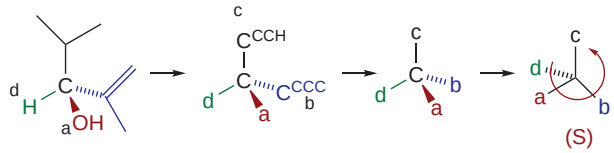


FIGURE 9.9 Absolute configuration of 2,4-dimethylpent-1-en-3-ol.

such a case, assume that the σ-bond and the π-bond of the C=C carbon unit are attached to separate carbon groups. In effect a carbon substituent is assigned for each bond. Using this rule, $-C(CH_3)=CH_2$ is C^{CCC}, because there are three attached carbon atoms, one for each bond of the double bond plus the carbon of the methyl group. The 1-methylethyl group is C^{CCH}. Therefore, at this point of difference C^{CCH} is compared with C^{CCC} so C^{CCC} is (b) and C^{CCH} is (c). The alkene unit is the higher priority, and the name is (3*S*)-2,4-dimethylpent-1-en-3-ol.

9.7 Draw the structure of 5-methylhex-1-yn-4-en-(3*S*)-ol.

9.3 SPECIFIC ROTATION: A PHYSICAL PROPERTY

Specific Rotation

The two enantiomers (2*S*)-chlorobutane and (2*R*)-chlorobutane are different molecules with different names. It is one thing to draw pictures, but it is quite another to experimentally distinguish the two enantiomers based on a difference in a physical property. Two enantiomers differ in their spatial arrangement of atoms, but they have identical physical properties such as boiling point, melting point, solubility in various solvents, refractive index, flash point,

adsorptivity, and so on. These physical properties cannot be used to distinguish one enantiomer from the other. However, there is one physical property in which enantiomers differ. They differ in their interaction with plane polarized light.

Chiral molecules in solution rotate plane polarized light. A *polarimeter* measures the angle and the direction of rotation. A diagram of a basic polarimeter is shown in Figure 9.10.[3]

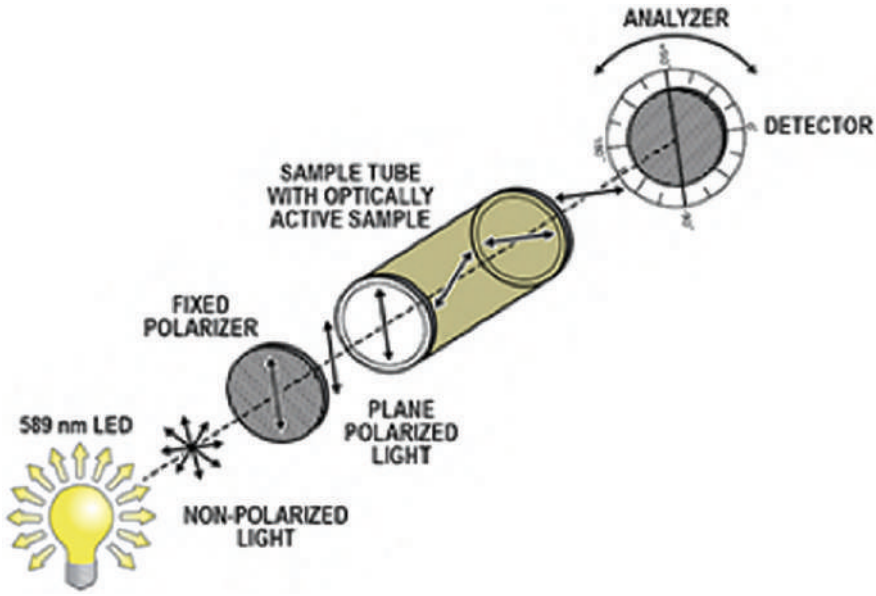


FIGURE 9.10 Diagram of a polarimeter. (c) Vernier Software & Technology. Used with permission.

Nowadays, fully automatic polarimeters are available with a digital readout of this angle. All instruments have a light source and a polarizing filter. Modern polarimeters use a Faraday modulator that creates an alternating current magnetic field and oscillates the plane of polarization to enhance the detection accuracy. A long-life yellow LED (A light-emitting diode is a semiconductor light source that emits light when current flows through it) is commonly used in place of the traditional sodium arc lamp as a light source.

When light is passed through a polarizing filter all the light that leaves the filter is in one plane. It is known as *plane polarized light*. Light is an electromagnetic wave and when plane polarized light passes through a chiral molecule, the plane of polarized light is rotated. Enantiomers will interact with the electromagnetic wave differently. The plane of the light is rotated clockwise in one case and counterclockwise in the other. The plane of light is monitored before and after it interacts with the chiral molecule, and the angle of rotation in degrees is determined for each enantiomer. The degree of rotation is called the *observed rotation,* α.

A ***solution*** of the enantiomer is placed in a sample tube where the polarizing light can pass directly ***through*** the solution containing the enantiomer. Sometimes the neat liquid is used, where *neat* indicates there is ***no solvent.*** In other words, pure sample is placed in the polarimeter cell to measure α. If the enantiomer is a solid, it must be dissolved in a solvent before it can be analyzed. Even if it is a liquid, the sample is often dissolved in a solvent and the solution added to a sample tube. *The solvent cannot have a stereogenic center* because the optical rotation of the solvent is so strong that the optical rotation of the sample cannot be detected.

The concentration of the enantiomer in the solvent is reported in grams per milliliter (g mL^{-1}). The magnitude of this angle, the *observed rotation* α, is measured as well as the direction of the rotation, clockwise (+) or counterclockwise (-). Typical numbers read from the polarimeter are (+)-23° or (-)-56°. *One pure enantiomer will have a (+) rotation and its pure mirror image will have a (-) rotation of exactly the same magnitude.* A molecule that rotates plane polarized light in

[3] www.vernier.com/experiment/chem-o-6_understanding-polarimetry/.

this manner is said to be *optically active*. The observed rotation will change with the solvent used, with the concentration of the enantiomer, with the length of the container used to hold the solution, and even with temperature. With these variables, a measurement with one instrument may record a *different* observed rotation than a measurement of the same compound using a different instrument and different conditions. A standardized method is required that normalizes the differences in measurement conditions. This standardized method converts the observed rotation to *specific rotation*, which is given the symbol $[\alpha]_D^{20}$, and it is considered to be a *physical property of optically active (chiral) molecules*.

$$[\alpha]_D^{20} = \frac{\alpha}{l \cdot c}$$

The "D" in the formula refers to the D-line of sodium when a sodium light source is used. It is the yellow line that appears in the visible spectrum at wavelength 589 nm. If a different wavelength of light is used from a different light source, the wavelength of light is recorded in place of "D". The 20 on the bracket is the temperature at which the measurement was made in degrees Celsius. In this calculation, α is the observed rotation and *"l"* is the length of the sample holder (the cell that holds the sample solution) measured in decimeters (dm). Most polarimeters have sample tubes that are 0.5, 1.0, 5.0, or 10.0 dm in length. The *"c"* term is concentration measured in g mL^{-1} (grams of enantiomer per mL of solvent). The solvent is usually specified for the measurement. The specific rotation for a compound with an observed rotation of +102° at a concentration of 2.1 g mL^{-1} in ethanol, in a 5.0 dm cell is:

$[\alpha]_D^{20} = \frac{+102}{5.02.1} = \frac{+102}{10.5} = +9.71$ so the specific rotation is $[\alpha]_D^{20}$, +9.71 (*c* 2.1, ethanol).

9.8 Determine the specific rotation of an enantiomer when α = -58.1°, c = 0.52, and *l* = 5 dm.

(*R*)-Butan-2-ol (*S*)-Butan-2-ol

The two enantiomers of butan-2-ol are shown with the correct absolute configuration for (*R*) and (*S*), but the specific rotation for each enantiomer is an experimental parameter. It is known that one enantiomer will have a specific rotation with a clockwise rotation (+) and the other enantiomer will have a specific rotation with counterclockwise rotation. Butan-2-ol has two enantiomers, one with a $[\alpha]_D^{20}$ of +13° (neat) and can be named (+)-butan-2-ol. The other enantiomer must be (-)-butan-2-ol with $[\alpha]_D^{20}$, -13° (neat). When there is a sample of a pure compound uncontaminated by its enantiomer, this compound is said to be *enantiopure*. *There is no correlation between specific rotation and the absolute configuration of a molecule (R or S).* Simply put, an enantiomer with a (+)-specific rotation could have either an (*R*) or an (*S*) absolute configuration. A sample of enantiopure (2*R*)-butanol or (2*S*)-butanol is placed in a polarimeter, the observed rotation is measured, and the specific rotation is calculated. There is no other way to know the specific rotation unless it has reported in the chemical literature. Once the experiment is done (2*S*)-butanol has a $[\alpha]_D^{20}$ of +13° (neat). Therefore (2*S*)-butanol correlates with (+) (2*S*)-butanol and (2*R*)-butanol correlates with (-)-(2*R*)-butanol.

9.9 If a sample of 3-phenylpentan-1-ol is labeled as having a specific rotation of 26.8°, but the sign is missing, is there a way to tell if it is + or - without putting the sample into a polarimeter?

A chiral compound that is not enantiopure is a mixture of both enantiomers. The specific rotation of a mixture can be calculated if the percentage of each enantiomer in a mixture is known. For example, a mixture of 72% of (+)-butan-2*S*-ol and 28% of (-)-butan-2*R*-ol is

prepared. The values of specific rotation in the mixture are additive, so the value of the specific rotation of this mixture can be predicted.

$$[\alpha]_D^{20}(\text{mixture}) = 0.72(+13°) + 0.28(-13°) = (+9.36°) + (-3.64°) = +2.62.$$

Since the specific rotation values are additive in a mixture, a 50:50 mixture of enantiomers is a special case in that the specific rotation is zero. Indeed, a 50:50 mixture of (+)- and (-)-butan-2-ol is labeled (±)-butan-2-ol, and it has a specific rotation of zero: $[\alpha]_D^{20}(\text{mixture}) = 0.5(+13°) + 0.5(-13°) = +6.5° + -6.5° = 0$. The butan-2-ol is said to be *racemic* or it is a *racemic mixture*.

When butan-2-ol is prepared by a chemical reaction and purified, it is not known if it is enantiopure or if it is a mixture of enantiomers. The prepared butan-2-ol in this example has a specific rotation -10.5°, so it is clear that it is a mixture of (+) and (-) enantiomers favoring (-)-butan-2-ol. If the butan-2-ol is a mixture of enantiomers, the relative percentage of each much be determined. This determination requires the availability of an enantiopure sample of the compound. If there is no report of butan-2-ol in the chemical literature, an enantiopure compound must be made or isolated in an unambiguous manner and the specific rotation determined. In this case, it is known that (-)-butan-2-ol has $[\alpha]_D^{20}$ of -13° and that (+)-butan-2-ol has $[\alpha]_D^{20}$ of +13°. The specific rotation of the mixture is known and since the *specific rotation of each enantiomer is additive* it is possible to calculate the percentage of each enantiomer. Assume that this mixture is 100% of the (+) and the (-) enantiomers. Therefore,

$$[\alpha]_D^{20}(\text{mixture}) = x(+13°) + y(-13°) = 10.5.$$

The term x is the % of (+)-butan-2-ol, and y is the % of (-)-butan-2-ol. Specific rotation is additive so, $x+y = 1$:

$$= x(+13°) + y(-13°) = -10.5 \qquad = (1-y)(+13°) - 13°y = -10.5°$$

$$= +13° - 13°y + 13°y = -10.5° \qquad = 26°y = -10.5° - 13°$$

$$= -26°y = -23.5° = y = \frac{+23.5°}{-26°} = 0.904$$

This calculation means that if the mixture obtained from a reaction has a specific rotation of -10.5°, it contains 90.4% of (-)-butan-2-ol and 9.6% of (+)-butan-2-ol.

%ee of A	% Enantiomer A	% Enantiomer B
0	50	50
10	55	45
20	60	40
30	65	35
40	70	30
50	75	25
60	80	20
70	85	15
80	90	10
90	95	5
100	100	0

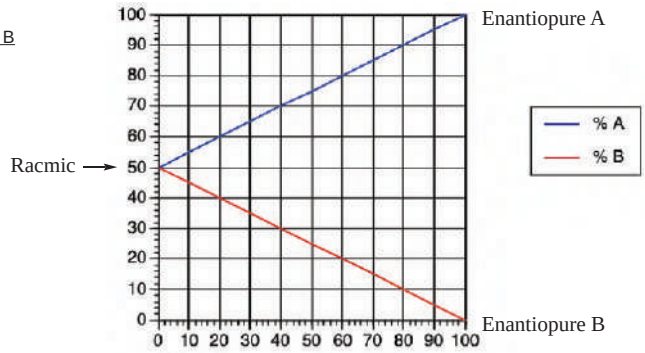


FIGURE 9.11 The % composition of enantiomers as a function of % ee.

In the 90.4:9.6 mixture of enantiomers of butan-2-ol from the previous calculation, the molecule is not enantiopure. It is not a racemic mixture since it not a 50:50 mixture. This type of enantiomeric mixture is referred to as *nonracemic*. In this context, *percent enantiomeric excess (%ee)* must be introduced. If there is a 50:50 mixture, no single enantiomer is in excess of the other, so there is zero (0) enantiomeric excess. If there is only one enantiomer it is enantiopure, so there is a 100% excess of that enantiomer over the other one. The scale for % ee therefore ranges from 0

% ee (50:50 mixture) to 100% ee (100% of one enantiomer), and the simple scale in Figure 9.11 can be constructed. This linear plot is used to determine % ee for a given mixture. If the mixture has a purity of 90% ee, there is 95% of **A** and 5% of **B**. A mixture of 98% ee **A** is ~ 99% of **A** and 1% of **B**. The use of % ee is widespread for reporting the enantiomeric purity of nonracemic mixtures. If a ratio of enantiomers is reported, it is called the *enantiomeric ratio (% er). In this example cited a 90.4:9.6 mixture corresponds to about an 82 %ee for the major enantiomer.*

9.10 Calculate the % of each enantiomer of an unknown (X) if the specific rotation of (+)-X is +109.3° and the specific rotation of the mixture is +27.7°.
9.11 Estimate the %ee of a molecule that has 93% of one enantiomer and 7% of the other. Of a molecule that has 99.4% of one enantiomer and 0.6% of the other. Of a molecule that has 55% of one enantiomer and 45% of the other.

9.4 CIRCULAR DICHROISM

Circular Dichroism

Electromagnetic radiation travels as a transverse wave that consists of electric and magnetic fields that oscillate perpendicular to one another. A transverse wave oscillates perpendicular to the direction of the wave's advance. An electric field of linearly polarized light oscillates in only one plane, but circularly polarized light can occur when the electric field vector (direction) rotates about the direction of the transverse wave. A circularly polarized-vector will trace out a circle over one period of the wave frequency. As circularly polarized light passes through an optically active medium, it is absorbed and the extent to which right and left polarizations are absorbed is known as *circular dichroism*.

Circular dichroism (CD) is an absorption spectroscopy method based on the differential absorption of left and right circularly polarized light. Optically active chiral molecules preferentially absorb one direction of the circularly polarized light, so CD is quite useful for structure evaluation of chiral molecules. The CD of optically active molecules show absorption bands that are representative of their chirality. This technique is especially useful for biomolecules. The secondary structure of proteins (Section 24.6), for example, can be probed using ultraviolet circular dichroism (UV CD). In addition, UV/Vis CD (ultraviolet-visible circular dichroism) can be used to examine charge transfer transitions. Vibration circular dichroism uses infrared light (Section 13.3) to examine the structures of proteins and DNA and small organic molecules. The far-UV CD spectrum of proteins can be used to estimate the fraction of a molecule that is in the alpha-helix conformation, the beta-sheet conformation or other conformations (Section 24.6). The near-UV CD spectrum (>250 nm) of proteins provides information on the tertiary structure (Section 24.6).

Koji Nakanishi (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Koji Nakanishi (Japan-USA; 1925–2019) was an organic chemist at Columbia University whose work involved the isolation, structural evaluation, and studies of bioactive compounds, including proteins. He did a great deal of work with infrared spectroscopy and helped develop various spectroscopic methods, including circular dichroic spectroscopy. He determined the structures of over 200 biologically active animal and plant natural products. His work led to clarification of the porphyrin/porphyrin interactions (Section 8.7). He also performed stereochemical studies that included *ab initio* calculation of CD and ORD (optical rotatory dispersion) of natural products.[4]

Diastereomers and the 2^n Rule

9.5 DIASTEREOMERS

New stereoisomers are possible when there is more than one stereogenic center. Two stereoisomers that are not superimposable and not mirror images are defined as *diastereomers*. To name diastereomers, every stereogenic center is assigned the appropriate (*R)* or (*S)* absolute configuration. An example of a molecule that has diastereomers is 2,3-dichloropentane. It is possible to draw two stereoisomers, (2*S*,3*R*)-dichloropentane and (2*R*,3*S*)-dichloropentane. These stereoisomers are nonsuperimposable mirror images as shown in Figure 9.12, so they are enantiomers. It is also possible to draw a different stereoisomer, (2*R*,3*R*)-dichloropentane, which has an enantiomer (2*S*,3*S*)-dichloropentane. Therefore, there are four stereoisomers for 2,3-dichloropentane. The (2*S*,3*R*) and (2*R*,3*R*) or (2*S*,3*S*) stereoisomers are not mirror images of one another and not superimposable. They are diastereomers. Likewise, the (2*R*,3*S*) and the (2*R*,3*R*) or (2*S*,3*S*) stereoisomers are not enantiomers and are not mirror images so they are diastereomers.

The diastereomer definition appears to be strange because if an apple is compared with an orange, they are nonsuperimposable, non-mirror images. However, the definition of diastereomer applies *only* to two stereoisomers that are not the same molecule and are not mirror

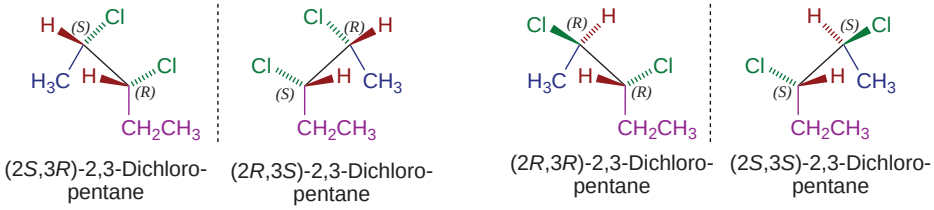


FIGURE 9.12 Four stereoisomers of 2,3-dichloropentane.

images of each other. There is a useful protocol that will allow one to draw all four stereoisomers, as illustrated with the drawings in Figure 9.12. Draw one stereoisomer, say (2*S*,3*R*)-2,3-dichloropentane. If *both* stereocenters are inverted [(2*S)* to (2*R)* and (3*R)* to (3*S*)], the enantiomer (2*R*,3*S*)-2,3-dichloropentane is generated. Choose one enantiomer and invert *one* stereocenter but *not both* to give a diastereomer. Swapping (2*S)* to (2*R)* in (2*S*,3*R*)-2,3-dichloropentane gives the (2*R*,3*R)* diastereomer and swapping (3*R)* to (3*S)* give the (2*S*,3*S)* diastereomer.

9.12 Using the protocol just described, draw all four stereoisomers for 3,4-dimethylheptane in Fischer projection and label enantiomers and diastereomers.

A molecule with two stereogenic centers will have two diastereomers and each will have a mirror image. This means there is a maximum total of four stereoisomers (2^2) for a molecule with two stereogenic centers. This observation can be extended to all molecules that have more than one stereogenic center. For a given number of stereogenic centers (say *n*)

[4] (a) Nakanishi, K.; Berova, N.; Woody, R.W. *Circular Dichroism: Principles and Applications* VCH Publishers, 1994; (b) Nakanishi, K.; Kuroyanagi, M.; Nambu, H.; Oltz, E.M.; Takeda, R.; Verdine, G.L.; Arie Zask, A. *Pure and Applied Chemistry* 1984, 56, 1031–1048.

there are a maximum of 2^n stereoisomers. A molecule with 4 stereogenic centers will have a maximum of 2^4 or 16 stereoisomers. If a molecule has 9 stereogenic centers, the maximum number of stereoisomers will be 2^9 or 512 stereoisomers. If 512 stereoisomers does not seem like a large enough number, a molecule with 28 stereogenic centers will have $2^{28} = 2.684 \times 10^8$ stereoisomers (> 268 million stereoisomers) for one constitutional isomer of a single empirical formula.

The 2^n rule is used to calculate the *maximum* number of stereoisomers for a molecule with more than one stereogenic center. While there are never > 2^n stereoisomers, it is possible to have *fewer* stereoisomers if a molecule with two or more stereogenic centers has symmetry. Symmetry occurs when there are identical groups so that one part of the molecule is identical to another. One such case is 2,3-dibromobutane. It is clear that (2*R*,3*R*)-dibromobutane and the mirror image (2*S*,3*S*)-dibromobutane are enantiomers, as shown in Figure 9.13. Similar drawings are provided for the (2*R*,3*S*)-diastereomer and its mirror image (2*S*,3*R*)-dibromobutane, but something is different. The (2*R*,3*S*)- structure is *superimposable* on the (2*S*,3*R*)- structure, which means that these two structures constitute one molecule, not two. Note the structures are seen to be superimposable only when they are in an eclipsed rotamer.

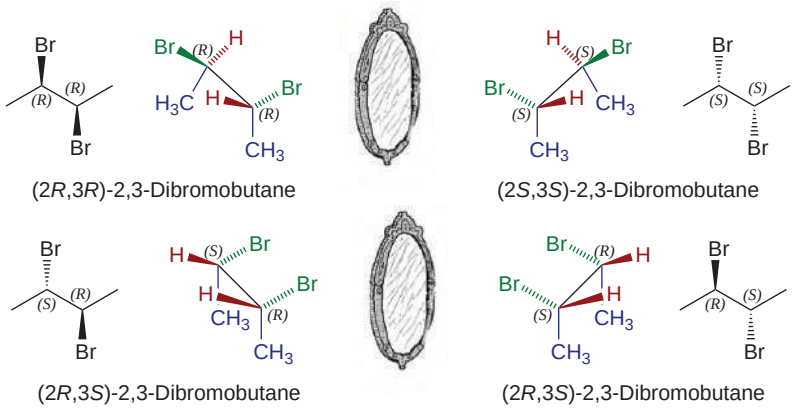


FIGURE 9.13 Stereoisomers of 2,3-dibromobutane.

Meso Compounds

If an eclipsed rotamer of (2*R*,3*S*)-dibromobutane is examined in Figure 9.14*a*, C2 is attached to Br, H, and Me and C3 is also attached to Br, H, and Me. In other words, each stereogenic carbon atom has the same attached atoms and groups. If the eclipsed conformation of this stereoisomer is turned as in Figure 9.14*b*, it is easy to see that the "top" and "bottom" are identical. The top atoms or groups reflect perfectly into those at the bottom so there is a plane of symmetry in the molecule as shown. (2*R*,3*S*)-Dibromobutane is called a *meso compound*. The meso compound is diastereomer of the enantiomeric pair, (2*R*,3*R*)-dibromobutane and (2*S*,3*S*)-dibromobutane. A meso compound is optically inactive stereoisomer due to symmetry that makes the mirror image superimposable. The 2^n rule predicts a maximum of four stereoisomers for 2,3-dibromobutane. However, *there are only three stereoi*somers. A diastereomer should always be examined for symmetry and the presence of a meso compound.

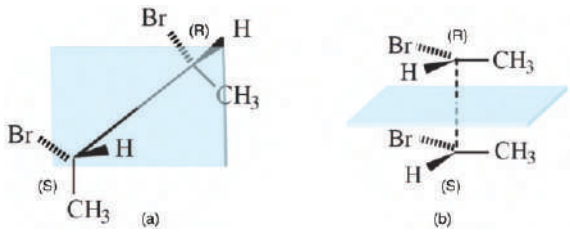
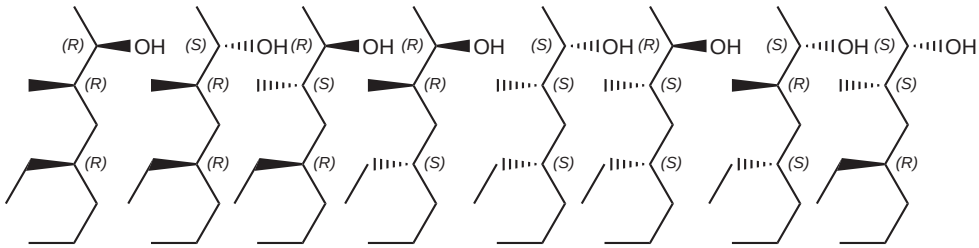


FIGURE 9.14 Plane of symmetry in (2*R*,3*S*)-dibromobutane from two perspectives, (*a*) and (*b*).

9.13 Decide if hexane-3,4-diol has a meso compound. Draw it as well as the structure of *meso*-butane-2,3-diol.
9.14 Draw the meso compounds of 3,4,5-trichloroheptane.

Going from one to two stereogenic centers in a molecule led to more complexity with respect to the number of stereoisomers. Molecules with three or more stereogenic centers are even more complex. An example is 5-ethyl-3-methyl-octan-2-ol. There are three stereogenic carbons, so a maximum of $2^3 = 8$ stereoisomers is expected. These stereoisomers include all diastereomers and all pairs of enantiomers. All eight stereoisomers of 5-ethyl-3-methyl-octan-2-ol are shown. If there are four diastereomers and each diastereomer has an enantiomer there are $2^4 = 16$ stereoisomers. The principles used to distinguish diastereomers and enantiomers are the same, but more patience is required to find all the stereoisomers. As the number of stereogenic centers increases, great care must be exercised in drawing various structures and testing them for the presence of meso compounds.

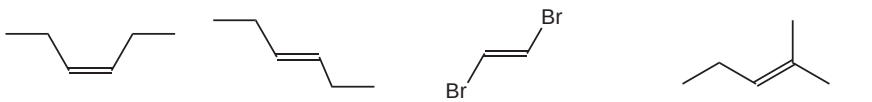


cis-trans and *E-Z* Nomenclature

9.6 ALKENES

The C=C unit of an alkene has two sp^2-hybridized carbon atoms, it is planar, and *a sp^2-hybridized carbon cannot be a stereogenic center*. Rotation about the C=C unit is not possible because of the C=C unit so there are no rotamers associated with the C=C unit. The attached atoms or groups are effectively fixed in space. Using hex-3-ene as an example there are two different hex-3-ene derivatives, one with two ethyl groups on the same side of the C=C unit and the other with the two ethyl groups on opposite sides. Since there is no rotation about a C=C unit they are isomers with the same empirical formula and same connectivity, but they differ in the spatial arrangement of atoms and groups. They are stereoisomers and diastereomers. There are two nomenclature systems used to differentiate such alkenes, the cis/trans system and the E/Z system.

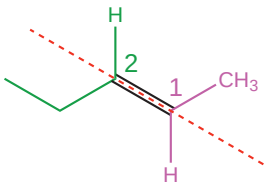
The cis/trans nomenclature system is an older system for classifying alkenes. If two *like (identical) groups* are on the same side of an alkene, the molecule is a *cis-alkene*. If two like groups are on opposite sides of an alkene, the molecule is a *trans-alkene*. *The key word* in these definitions is "like". The cis-trans nomenclature applies *only* when identical groups are on each carbon of the C=C unit, (e.g., XYC=CXZ), where there is an X group on both sp^2 carbon atoms. Examples are *cis*-hex-3-ene with two ethyl groups on the same side of the molecule and *trans*-hex-3-ene with two ethyl groups on opposite side of the molecule. Another example is *trans*-1,2-dibromoethane, with two bromine atoms on opposite sides of the molecule. When the same group is on a single carbon, as in $X_2C{=}CYZ$, there is only one possible structure. In other words, when two identical groups are on the same carbon of the C=C unit, there is no possibility for *cis-trans* isomers. An example is 2-methylpent-2-ene where one carbon of the C=C unit has two identical groups, both methyl.



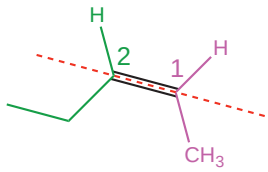
cis-Hex-3-ene *trans*-Hex-3-ene *trans*-1,2-Dibromoethene 2-Methylpent-2-ene

9.16 Draw the structures of *cis*-hept-3-ene and *trans*-hept-3-ene.

If the groups to be compared on each carbon of the C=C unit are not the same, the cis/trans nomenclature does not apply. In pent-2-ene a methyl group and an ethyl group are attached to the C=C unit and two stereoisomers are possible, as shown. An alternative nomenclature method called the (*E-Z) nomenclature system* has been developed that determines the relative priority of groups attached to the C=C unit. The term (*E)* comes from the German word *entgegen*, which means "against" or "toward" or "contrary to," but it is used here to indicate opposite or apart. The term (*Z)* comes from the German word *zusammen*, which means "together." What constitutes "apart" and what constitutes "together" is determined by the priority rules introduced in Section 9.2, the Cahn-Ingold-Prelog (CIP) priority rules. To determine the stereochemistry of the two stereoisomers of pent-2-ene, compare sidedness of the priority groups or atoms on one side (EtCH=) with those on the other side of the C=C unit (=CHMe). This system compares the higher priority group on each carbon (C1 vs C2) of the C=C unit, relative to a plane that bisects both carbon atoms of the C=C unit.



Pent-2*E*-ene

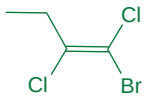


Pent-2*Z*-ene

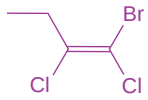
This plane is shown as a red dashed line and the goal is to find the highest priority atom on C1 and then C2. For one stereoisomer of pent-2-ene, carbon C1 of the C=C unit has an attached carbon and a hydrogen atom. Comparing C with H, the C of methyl is clearly the higher priority. For carbon C2 of the C=C unit, a H is attached as well as a C of the ethyl group and again C is the higher priority. In one stereoisomer, the priority groups (ethyl and methyl) are on opposite sides, so the name is (*E*)-pent-2-ene. When the two priority groups are on the same side the stereoisomer is (*Z*)-pent-2-ene.

9.17 Draw the structures of hex-(2*E*)-ene, 3,5-dimethyloct-(3*Z*)-ene, and 1-chloro-(1*Z*)-heptene.

It is important to emphasize that although (*Z*) and cis are both derived from groups being on the same side of the double bond and (*E*) and trans are both derived from groups being on the same side of the double bond, they arise from completely different definitions. 1-Bromo-1,2-dichlorobut-1-ene illustrates the point about cis–trans vs (*E*/*Z*). There are two identical atoms, the chlorine atoms on either carbon of the C=C unit, so the cis or trans nomenclature is appropriate. In one isomer, the two chlorine atoms are on opposite sides of the molecule, so it can be named *trans*-1-bromo-1,2-dichlorobut-1-ene, whereas the chlorine atoms are on the same side in the other isomer, so it can be named *cis*-1-bromo-1,2-dichlorobut-1-ene. Using (*E*/*Z*) nomenclature, the bromine and the chlorine are the two priority groups and in trans-alkene the priority groups are on the same side, so it is 1-bromo-1,2-dichloro-(1*Z)*-butene. In the cis-alkene, the two priority groups are on opposite sides so the name is 1-bromo-1,2-dichloro-(1*E)*-butene. Clearly, the *trans* alkene is the (*Z)* alkene and the *cis* alkene is the (*E)* alkene. Choose one name or the other, but *do not mix them*. The formal IUPAC name should use the (*E*/*Z*) nomenclature. *Never* mix (*E*/*Z*) and cis-trans nomenclature. *Never* assume that (*Z*) is *cis* or that (*E*) is *trans*.



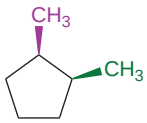
1-Bromo-1,2-dichlorobut-(1*Z*)-ene
or
trans-1-Bromo-1,2-dichlorobut-1-ene



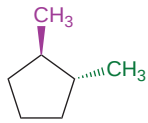
1-Bromo-1,2-dichlorobut-(1*E*)-ene
or
cis-1-Bromo-1,2-dichlorobut-1-ene

9.7 CIS AND TRANS SUBSTITUENTS ATTACHED TO RINGS

A carbon ring is flexible, but 360° rotation is not possible, so substituents on that ring are fixed (locked) onto one side of the ring or another. Therefore, two substituents can be on the same side of a ring, as in racemic (1*R*,2*S*)-1,2-dimethylcyclopentane and (1*S*,2*R*)-1,2-dimethylcyclopentane, or on opposite sides of that ring, as in racemic (1*R*,2*R*)-1,2-dimethylcyclopentane or (1*S*,2*S*)-1,2-dimethylcyclopentane.



cis-1,2-Dimethylcyclopentane



trans-1,2-Dimethylcyclopentane

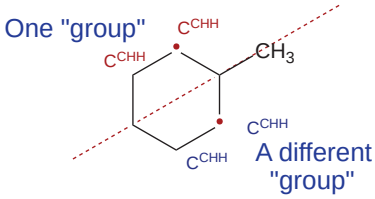
The cis-trans nomenclature introduced in Section 9.6 for alkenes can be used for substituents that are attached to rings. However, *the (E/Z) nomenclature cannot be used for cyclic compounds.* The solid wedges show the group projected out of the paper and the dashed lines show groups projected behind the paper. If two like groups are on the same side of a ring, it is a cis-cycloalkane and if the like groups are on opposite sides of the ring, it is a trans-cyclic alkane. Both structures have two methyl groups, so the names are *cis*-1,2-dimethylcyclopentane and *trans*-1,2-dimethylcyclopentane.

9.18 Draw the structure of *cis*-3-bromo-1-methylcyclopentane.

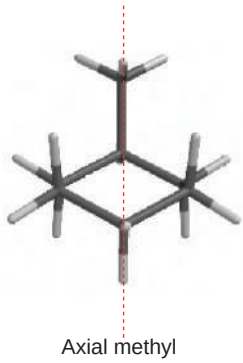
Stereoisomers in Cyclic Molecules

9.8 STEREOGENIC CENTERS IN CYCLIC MOLECULES

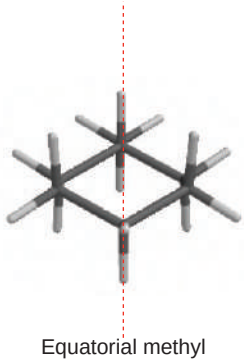
Stereogenic carbons are found in cyclic molecules but monosubstituted cycloalkanes are not chiral. An example is methylcyclohexane. The methyl-bearing carbon atom of methylcyclohexane is connected to a methylene unit (–CH_2–) of either side. Each of these ring carbons



Methylcyclohexane



Axial methyl



Equatorial methyl

FIGURE 9.15 Symmetry in methylcyclohexane.

are marked with a red dot in Figure 9.15. Both sides of the ring are treated as a separate group and evaluated to determine if there is a point of difference. The "top-left" red carbon atom is C^{CHH} and the "bottom-right" red carbon is also C^{CHH}, so there is no point of difference. Going to the next carbon atom on each side, the assignments remain C^{CHH} and C^{CHH}. Attempts to go to the next atom in either chain leads to the same carbon. Therefore, comparing each "side" or "group" of the ring does not lead to a point of difference and each is identical. Methylcyclohexane is not chiral. There is a plane of symmetry along a line between C1 and C4, as shown for the two molecular models when the methyl group is axial and when it is equatorial.

In cyclic molecules with more than one stereogenic center it is possible to generate diastereomers. The identification of the stereogenic center and the number of stereoisomers is complicated because several conformations may be available via pseudorotation. Cyclopropane, cyclobutane and cyclopentane derivatives have fewer conformations and analysis is usually straightforward. In 1,2-dimethylcyclopentane, for example, there are two stereogenic carbons. The four poten-

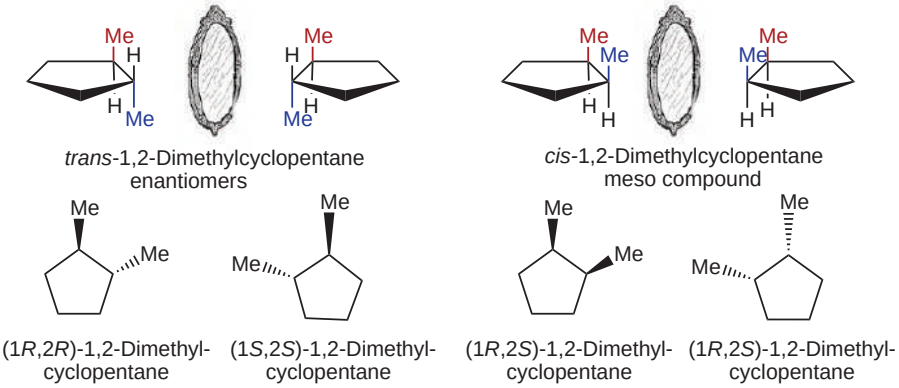


FIGURE 9.16 Stereoisomers in 1,2-dimethylcyclopentane.

tial stereoisomers are (1*R*,2*S*)-dimethylcyclopentane, (1*S*,2*R*)-dimethylcyclopentane, (1*R*,2*R*)-dimethylcyclopentane, and (1*S*,2*S*)-dimethylcyclopentane, as shown in Figure 9.16. When the methyl groups are on the same side, as in the cis diastereomer (1*R*,2*S*)-dimethylcyclopentane (Section 9.8), that stereoisomer and its mirror image (1*S*,2*R*)-dimethylcyclopentane are superimposable so it is a meso compound. When the two methyl groups are on opposite sides, as in the trans diastereomer (1*R*,2*R*)-dimethylcyclopentane and (1*S*,2*S*)-dimethylcyclopentane, the two mirror images are *not* superimposable so they are enantiomers. Therefore, 1,2-dimethylcyclopentane has only three stereoisomers because of the presence of symmetry in one stereoisomer.

Inspection of disubstituted cyclohexane derivatives for the number of diastereomers and the presence or absence of meso compounds is complicated by the greater pseudorotation of the ring. Both lower energy chair conformations must be examined. An example is 1,2-dimethylcyclohexane with the cis- and trans- diastereomers shown in Figure 9.17. When both methyl groups are cis, as in **A**, (1*R*,2*S*)-1,2-dimethylcyclohexane, examining the planar structure for the molecule appears to show a plane of symmetry. A realistic analysis must

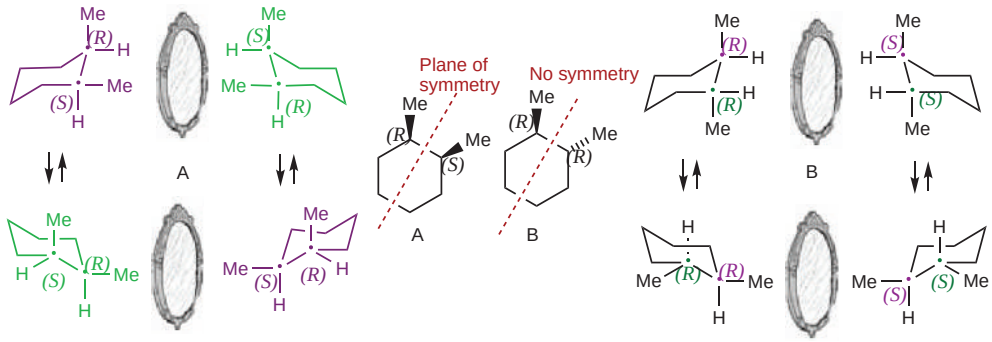


FIGURE 9.17 Stereoisomers in 1,2-dimethylcyclohexane.

examine the chair conformations, and each of the equilibrating chairs has a mirror image. Close inspection of **A** shows that the two chairs are superimposable by simply rotating one of them. Similarly, the other chairs are superimposable by simple rotation of one of them. Therefore, the plane of symmetry is confirmed and **A** is a meso compound. Note that this symmetry is confirmed only when both of the equilibrating chairs of **A** and those of its mirror image are examined. When the methyl groups are trans as in **B**, (1*R*,2*R*-1,2-dimethylcycohxane), an inspection shows that when the two methyl groups are axial, and

they do not superimpose in any of the chairs. Similar analysis of the chairs with both methyl groups equatorial also show that the mirror image is not superimposable. Therefore, **B** is a mixture of enantiomers and 1,2-dimethylcyclohexane has three stereoisomers, two enantiomers (**B**) and one meso compound (**A**).

9.19 Is *trans*-1,4-dimethylcyclohexane a meso compound?

Bicyclic Compounds

9.9 BICYCLIC MOLECULES

Many organic molecules have two rings joined together and the term bicyclic is used in the name. Some examples are shown in Figure 9.18 where the rings share a common "edge" or a common "face. For molecules where two or more rings are joined or fused together, imagine

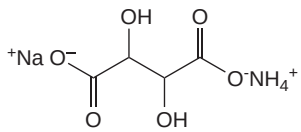
FIGURE 9.18 Nomenclature for bicyclic compounds.

a "pinwheel" with three arms (**A**, violet, green, yellow arms in Figure 9.18). The total number of atoms in all rings define the base name (e.g., hexane or heptane). The bicyclic compounds are color-coded for comparison with the "pinwheel" in order to correlate those chains with each "arm." Each "arm" represents a chain or "bridge" of atoms (2, 3, 4, 5, etc.) that is connected to bridgehead atoms (those holding the rings together), which are the bold dots in **A**. The number of atoms in each "bridge" of the molecule is included in brackets. For the structure on the left, only two of the three arms are present. The bridgehead carbons are not counted in determining the number of atoms in each arm. There are three atoms in one arm and two atoms in the second arm, and there is no third loop (zero atoms in the third arm). All of the atoms in each arm are carbon atoms and there are a total of seven carbons in the molecule, so it is a heptane. Since there are two rings, it is a bicycloheptane. The atoms in each arm are placed in a bracket, and this molecule has three carbons, two carbons and zero carbons so it is [3.2.0], ranking the numbers from the longest arm to the smallest. The name is bicyclo[3.2.0] heptane. There are a total of six carbons in both rings of the second compound, so it is a hexane. The term bicyclo is used to indicate the presence of two rings fused together (bicyclohexane). In this example, all three arms have carbon atoms; two carbon atoms, one carbon, and one carbon, so it is [2.1.1]. The name is bicyclo[2.1.1]hexane.

9.20 Draw the structure of bicyclo[3.3.2]decane; of bicyclo[5.3.0]decane; of bicyclo[1.1.1]pentane.

Optical Resolution

9.10 OPTICAL RESOLUTION



Sodium ammonium tartrate

Two different molecules are usually separated by exploiting a difference in physical properties such as boiling point, melting point, solubility, adsorptivity, and so on. Enantiomers

have identical physical properties, and for the most part so physical property differences cannot be used to separate enantiomers. Occasionally, however, the crystal structure of one solid enantiomer is noticeably different from the other so they can be separated. Louis Pasteur (France; 1822–1895) purified the sodium ammonium tartrate salt of tartaric acid by crystallization. The crystalline enantiomers formed with a right- or a left-hand morphology.[5] It is possible to grow the tartrate crystals to a large size, so this morphology was apparent. Using a microscope, the differences in crystal morphology were clearly seen and Pasteur could physically pick out the different crystals with tweezers. Separation of enantiomers is called *optical resolution*. Using this separation method is rare.

The vast majority of *optical resolution* procedures require that a chemical reaction be done first to convert *both* enantiomers in a mixture to the corresponding diastereomer. Diastereomers are different compounds, so they are separable based on different physical properties. After separation, a second chemical reaction is required to convert the separated

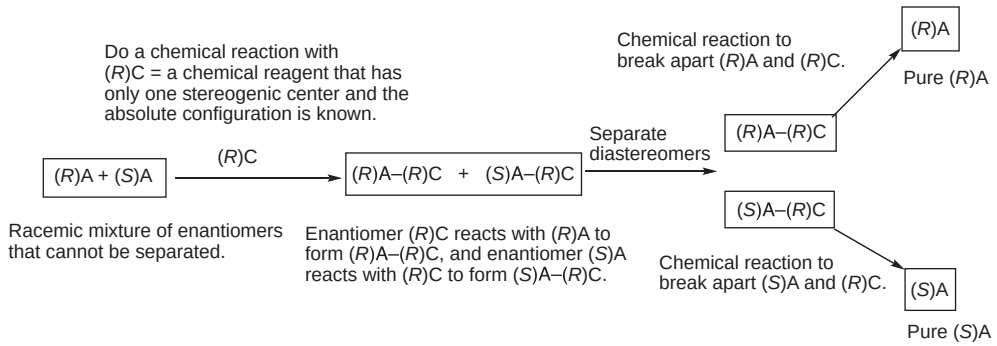


FIGURE 9.19 An outline of optical resolution.

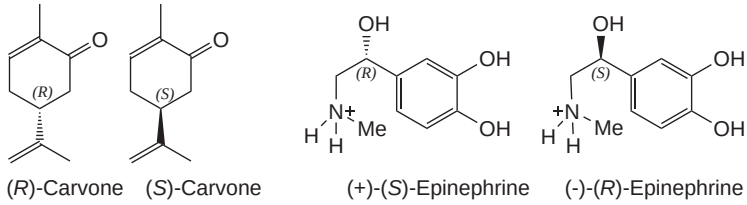
diastereomer back to the pure enantiomer. An example of this technique *begins with a chiral* mixture (*R*)A+(*S*)A), which reacts with a chiral molecule with a well-defined stereogenic center (*R*)C. When (*R*)C reacts with (*R*)A, the product (*R)*A–(*R*)C, whereas when (*S*)A reacts, the product is (*S*)A–(*R*)C. These two compounds are diastereomers, with different physical properties. In principle they can be separated. After separation, another chemical reaction converts (*R*)A–(*R*)C to pure (*R*)A and pure (*R*)C. Similarly, (*S*)A–(*R*)C is converted to (*S*)A and (*R*)C. This method is only useful if (*R*)C can be separated from (*R*)A and from (*S*)A, and hopefully recovered, purified, and used again. This method *resolves* the individual enantiomers into enantiopure compounds as outline*d in* Figure 9.19*. This procedure is a common method of optical resolution.*

9.11 BIOLOGICAL RELEVANCE

Stereochemistry plays an important role in many aspects of the things that surround us, including biology, medicine. Many things in everyday life involve chemicals that have different smells, and this property often depends on the stereochemistry of the chemicals responsible for the odor. Molecules with different stereogenic centers can impact olfactory receptors differently. A classic example is the difference in smell of spearmint leaves and caraway seeds. Spearmint leaves contain (*R*)-carvone and caraway seeds contain (*S*)-carvone (Section 5.4), and the different enantiomers smell differently to most people. Chirality also plays a major role in the influence of many chemicals on receptor sites in the body. One enantiomer may have a greater biological response than its enantiomer. A simple example is the hormone and neurotransmitter epinephrine. It is known that (+)-(*S*)-epinephrine is less active than (-)-(*R*)-epinephrine. The chirality of

[5] Pérez-García, L.; Amabilino, D.B. *Chemical Society Reviews* 2007, 36, 941–967.

(-)-epinephrine (also known as adrenaline) allows it to interact with the receptor site far better than the enantiomer.



The stereochemistry of alkenes is also important in many biological processes. Retinol (Vitamin A_1) and dehydroretinol (vitamin A_2) are found in animal products (e.g., eggs, dairy products and animal liver and kidneys, as well as fish liver oils). These retinoids are known to act as signaling molecules that regulate aspects of cell differentiation, embryonic development, growth, and vision.[6] In mammals, retinol is obtained by cleavage of the tetraterpenoid

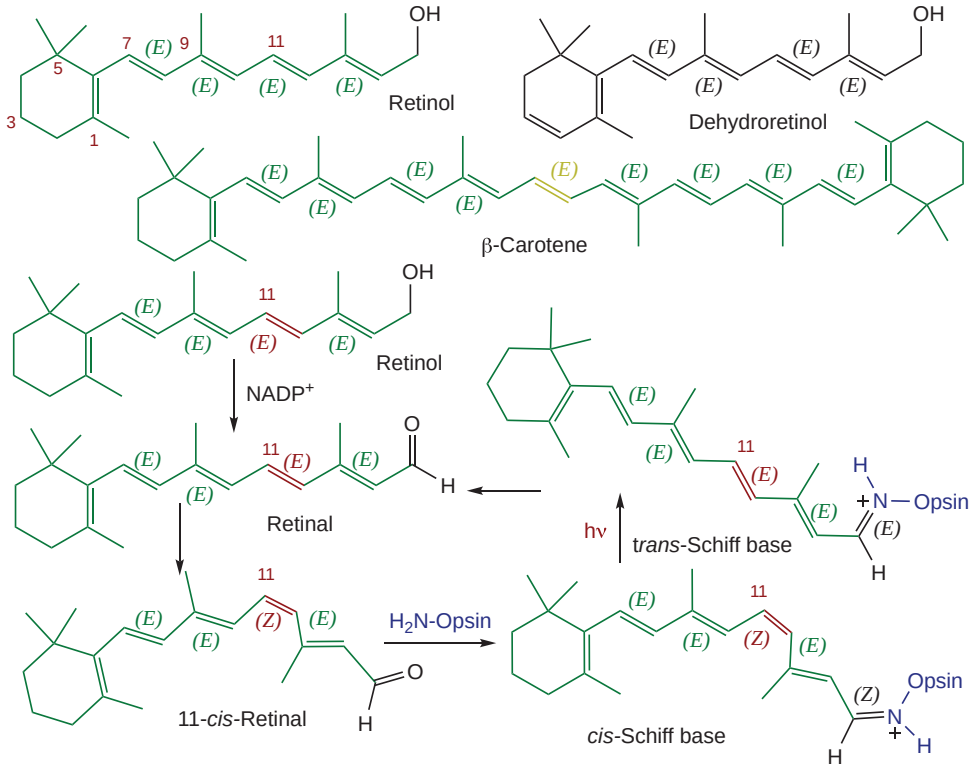


FIGURE 9.20 *cis-trans*-Isomerization in retinal. [Dewick, P.M. *Medicinal Natural Products, 2nd ed*, Wiley, West Sussex, UK, 2002, pp. 230–231 and Figure 5.73. With permission from John Wiley & Sons.]

β-carotene at the highlighted bond in Figure 9.20, usually in the intestine, to give the aldehyde retinal, which is enzymatically reduced to retinol.

The biological process known as vision involves conversion of retinol to retinal via an oxidation reaction (Chapter 15) that uses the cofactor $NADP^+$ (nicotinamide adenine dinucleotide phosphate; also see Section 17.7).[6] Note the (*E*)-geometry of the C_{11}–C_{12} double bond in retinol (the numbering is based on numbering that begins in the cyclohexene unit, as shown). The key process is the change of an (*E*)-alkene to a (*Z*)-alkene using an enzyme. Coordination to an enzyme and the interaction with light to change the alkene stereochemistry back to (*E*)-. Enzymatic conversion of the C_{11}-(*E*)-double bond to the C_{11}-(*Z*)-double

[6] Dewick, P.M. *Medicinal Natural Products*, 2nd ed., Wiley, West Sussex, UK, 2002, pp. 230–231 and Figure 5.73.

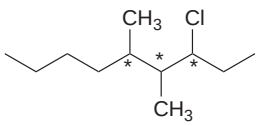
bond (11-*cis*-retinal), allows reaction with an amine unit on a protein called opsin to form an imine (a *cis*-Schiff base; Section 16.6.1 is a discussion of imines). Retinal is the visual pigment, and exposure to light ($h\nu$) converts the C_{11}-(*Z*)-double bond back to the C_{11}-(*E*)-double bond (a trans-Schiff base), and this triggers a nerve impulse to the brain.[3] Conversion of the trans-Schiff base back to retinal allows the process to cycle again.

CORRELATION OF HOMEWORK WITH CONCEPTS

- Two or more molecules with the same empirical formula, same points of attachment for the atoms or groups, but different spatial arrangement are called stereoisomers. A stereogenic carbon has four different atoms or groups attached, and a nonsuperimposable mirror image known as an enantiomer: 1, 2, 3, 24, 25, 35, 38, 39.
- The absolute configuration (*R*) or (*S*) of an enantiomer is determined by applying the Cahn-Ingold-Prelog selection rules and the "steering wheel" model: 4, 5, 6, 7, 20, 26, 29.
- A polarimeter measures the rotation angle of plane polarized light for an enantiomer, the observed rotation (α). Specific rotation ([α]) is calculated and is the physical property: 8, 9, 21, 23, 27, 28, 40.
- The percentage of enantiomeric excess (%ee) is a measure of the excess of one enantiomer over another, where 0 %ee indicates a racemic mixture and 100% ee indicates an enantiopure stereoisomer: 10, 11, 22.
- When a molecule has two or more stereogenic (chiral) centers, diastereomers are possible and there are a maximum of 2^n stereoisomers. Diastereomer is the term for two or more stereoisomers that are not superimposable and not mirror images: 12, 13, 14, 24, 25, 27, 28, 32, 34, 38, 39.
- A diastereomer with symmetry such that its mirror image is superimposable is called a meso compound: 13, 14, 33, 35, 37.
- If there is no symmetry, cyclic molecules can have enantiomers and diastereomers: 15.
- The C=C unit of an alkene does not have a stereogenic center, but alkenes can exist as stereoisomers and are named using the (*E*/*Z*) or cis–trans nomenclature: 16, 17, 30, 31, 35.
- The terms cis and trans are used to indicate the relative stereochemistry of disubstituted cyclic compounds: 18.
- Bicyclic compounds are named using a "pinwheel" model and the number of atoms in each chain are indicated in brackets, with numbers, such as [*x.y.z*]: 19, 36.

ANSWERS TO IN-CHAPTER QUESTIONS

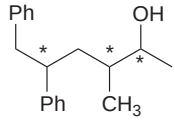
9.1



3-Chloro-4,5-dimethylnonane

No stereogenic carbon

3,3-Diethylpentane



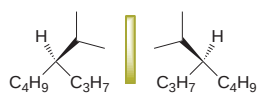
3-Methyl-5,6-diphenylhexan-1-ol

* = stereogenic carbon

9.2

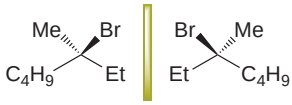
Non-superimposable = enantiomers

Superimposable = one molecule with no stereogenic carbon

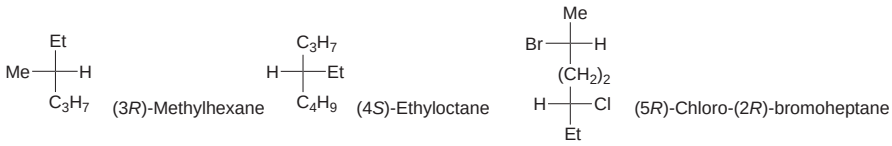


Non-superimposable = enantiomers

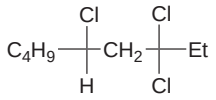
9.3



9.4

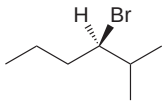


9.5



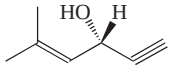
(3,3,5*S*)-Trichlorononane

9.6



(3*R*)-Bromo-2-methylhexane

9.7



5-Methylhex-1-yn-4-en-(3*S*)-ol

9.8

$$[\alpha] = \frac{\alpha}{1 \bullet d} = \frac{-58.1}{5 \bullet 0.52} = \frac{-58.1}{2.6} = -22.4$$

9.9 No! Specific rotation is a physical property, and the direction of rotation (sign) is part of that property. It must be measured in a polarimeter.

9.10 $[\alpha]^{20}_{D}$ (mixture) $= x$ (+109.3°) $+ y$ (-109.3°) $= 27.7$ and specific rotation is additive, $x+y = 1$. Therefore,

$$= x(+109.3°) + y(-109.3°) = 27.7° \qquad = (1-y)(+109.3°) - 109.3°y = 27.7°$$

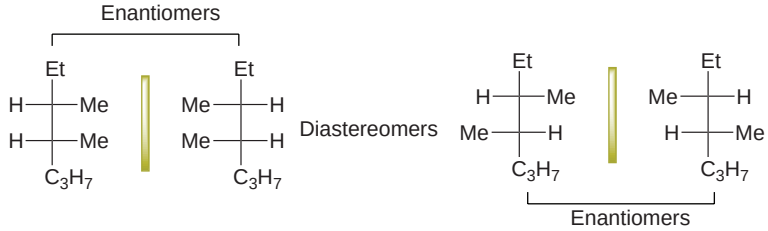
$$= +109.3° - 109.3°y - 109.3°y = 27.7° \qquad = -218.6°y = 27.7° - 109.3°$$

$$= -218.6y = -81.6° = y = \frac{-81.6°}{-218.6°} = 0.37.3 = 37.3\% \text{ of } (-)\text{X}$$

Therefore, 37.3% of (-)X and 62,7% of (+)X

9.11 For a 93% :7% mixture, 88%ee; for a 99.4%:0.6% mixture, 99%ee; for a 55% :45% mixture, 11%ee.

9.12

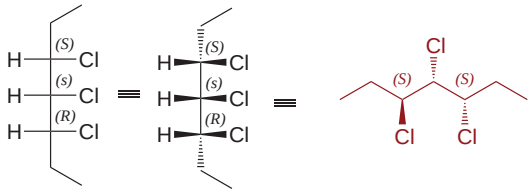


9.13

This diastereomer of hexane-3,4-diol has a superimposable mirror image. Therefore, it is a meso compound.

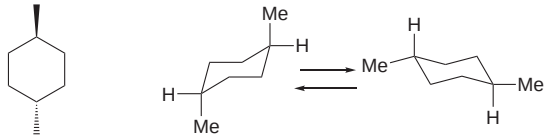
This compound is meso-butane-2,3-diol

9.14



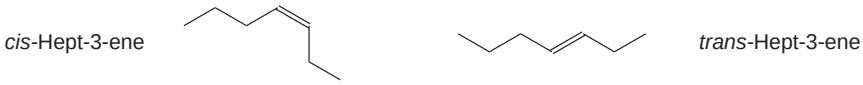
C4 is achiral because this is a meso compound; ignore the designation in the Fischer projection

9.15



Plane of symmetry in both chairs so this is a meso compound

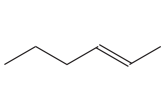
9.16



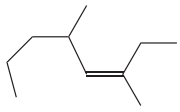
cis-Hept-3-ene

trans-Hept-3-ene

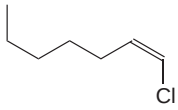
9.17



Hex-(2*E*)-ene

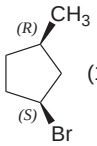


3,5-Dimethyloct-(3*Z*)-ene



1-Chlorohept-(1*Z*)-ene

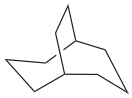
9.18



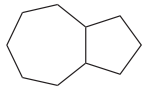
(1S,3*R*)-1-Bromo-3-methylcyclopentane

9.19 No. There are no stereogenic centers since trans-1,4-dimethylyclohexane has a plane of symmetry.

9.20



Bicyclo[3.3.2]decane



Bicyclo[5.3.0]decane

Bicyclo[1.1.1]pentane

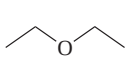
HOMEWORK

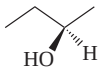
21. Each of the four groups shown are connected to one stereogenic carbon atom. Indicate the highest priority group using the Cahn–Ingold–Prelog selection rules.

(a) —CH_2CH_2Br —$CH_2CHBrCH_3$ —$CH_2CH_2CH_2CH_2OH$ —CH_2F

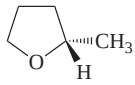
(b) —CH_2CH_2OH —$CH_2CHBrCH_3$ —$CH_2CH_2CH_2CH_2I$ —CH_2CH_3

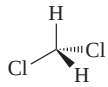
22. There are two enantiomers, **A** and **A'**. Enantiomer of **A** has a specific rotation of +70°. A mixture of **A** and **A'** has a measured specific rotation of -35°. Calculate the % of both **A** and **A'**.
23. If the specific rotation of a pure enantiomer is +100°, and the specific rotation of a mixture of both enantiomers is -20°, the ratio of the two enantiomers in the mixture is:
50:50 20:80 30:70 40:60 10:90
24. Which of the following solvents cannot be used for determining [α] of a compound in a polarimeter?



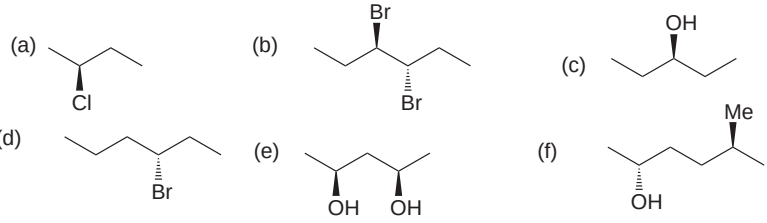


H_2O

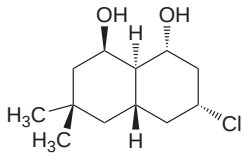




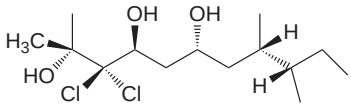
25. Determine which of the following has a superimposable mirror image and which has an enantiomer:



26. What is the maximum number of stereoisomers that are possible for the compound shown? Indicate each stereogenic center with a *.

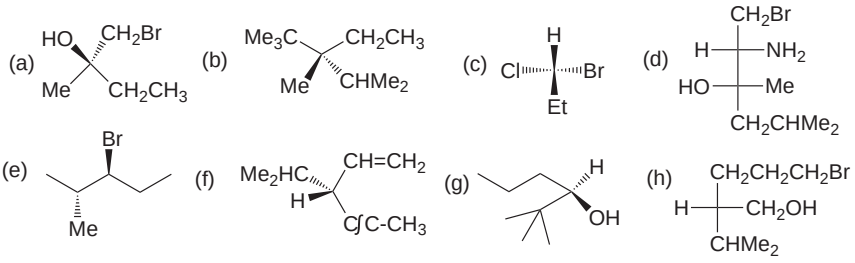
(a) 

2 2^2 2^3 2^4 2^5 2^6

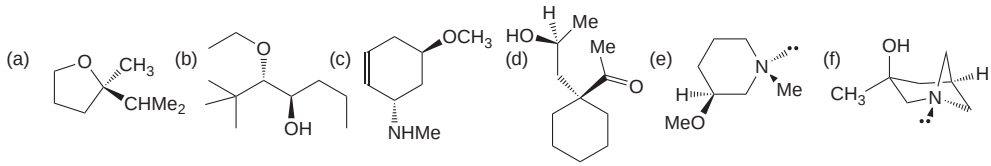
(b) 

2^3 2^4 2^5 2^6 2^7 2^8

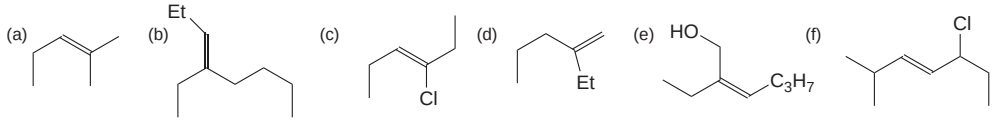
27. Determine the absolute configuration of each stereogenic carbon in the following molecules.



28. Determine the specific rotation for each of the following:
    (a) $\alpha = +18°$, $c = 1.1$ g mL^{-1} in a 25-cm tube (b) $\alpha = -176°$, $c = 0.3$ g mL^{-1} in a 50-cm tube
    (c) $\alpha = -1.4°$, $c = 5.4$ g mL^{-1} in a 25-cm tube (d) $\alpha = +94°$, $c = 2.3$ g mL^{-1} in a 30-cm tube
29. Calculate the percentage of each enantiomer and the %ee for the mixture given the following information:
    (a) $[\alpha]_D^{20} = +18.6°$ for the (*S*)-enantiomer and $[\alpha]_D^{20} = -2.5°$ for the mixture.
    (b) $[\alpha]_D^{20} = -166°$ for the (*R*)-enantiomer and $[\alpha]_D^{20} = -154°$ for the mixture.
30. Determine the absolute configuration of each stereogenic carbon in the following molecules:



31. Determine if each of the following alkenes has an (*E*), a (*Z*) double bond, or if it has no stereoisomers.



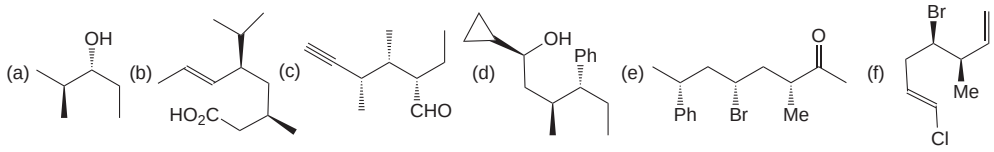
32. Draw the structure for each of the following:
    (a) 3,3-Diphenyl-(4*E*)-nonen-1-ol (b) 2,3,4,5-Tetrachlorohex-(2*Z*)-ene
    (c) 3-Bromo-6-fluorodeca-(3*Z*,6*E*)-dien-2-one (d) 3-Ethylhept-(2*E*)-ene
33. Draw all stereoisomers for the following molecules in Fischer projection, labeling diastereomers, meso compounds, and enantiomers where appropriate.
    (a) 3,4-Dichloroheptane (b) 2-Bromo-3-methylhexane
    (c) 4-Phenylheptan-3-ol (d) 3,4-Dibromohexane

(e) Hexane-2,5-diol (f) Heptane-3,4,5-triol
(g) 2-Bromo-5-methylhexane (h) 2,3,4,5-Tetramethylhexane

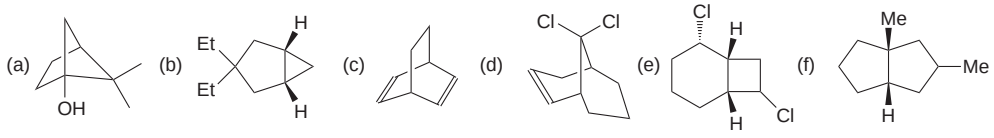
34. Draw the meso compound(s) for each of the following:
(a) butane-2,3-diol (b) 1,2-dibromocyclopentane
(c) nonane-3,4,5-triol (d) nonane-2,5,8-triol

35. Draw both chair conformations and the mirror image of each chair conformation for the following, and determine if the molecule has enantiomers–diastereomers.
(a) *cis*-2-Chlorocyclohexanol (b) *trans*-1,4-Dimethylcyclohexane
(c) *cis*-Cyclohexane-2,3-diol (d) *cis*-1-Bromo-2-chlorocyclohexane

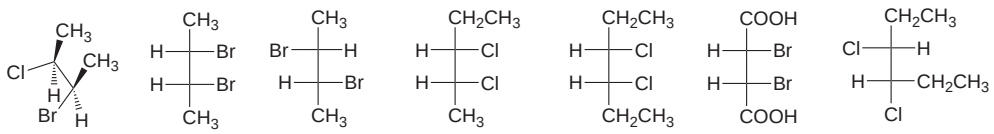
36. Give an unambiguous IUPAC name to each of the following:



37. Name each of the following:

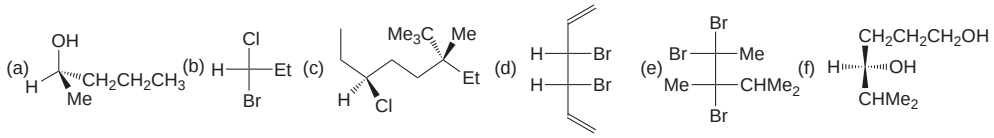


38. Which of the following are meso compounds?



39. Draw all *different* stereoisomers of 3,4-dichlorohexane and give each one the correct unique name.

40. Determine the absolute configuration (*R)* or (*S*) for all stereogenic centers in the following molecules:



41. Convert each of the following ratios to %ee for the (*R*) enantiomer.
(a) 82:18 *(R):(S)* (b) 55:45 *(R):(S)* (c) 99:1 *(R):(S)* (d) 75:25 *(R):(S)*

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-10.php

10

Acid-Base Reactions of π-Bonds

Addition Reactions

The fundamental principles of acid-base reactions were presented in Chapters 2 and 6. Alkenes (see Section 5.1) and alkynes (Section 5.3) react as bases with various reagents in what are known as addition reactions.

To begin this chapter, you should know the following points:

- Functional Groups (Sections 4.3, 5.1, 5.2, 5.5, and 5.6).
- σ-Bonds (Sections 3.3–3.6).
- π-Bonds (Sections 5.1 and 5.2).
- Brønsted-Lowry acids and bases (Sections 2.1–2.4, 6.1–6.3, 6.6, and 6.7).
- Lewis acids and bases (Sections 2.7 and 6.8).
- Nucleophiles (Section 6.9).
- Resonance (Sections 2.6, 5.6.3, 5.9, and 6.3.1).
- Reactive intermediates (Section 7.2).
- Mechanisms (Section 7.10).
- Conformations of acyclic molecules (Sections 8.1–8.4).
- Conformations of cyclic molecules (Sections 8.5–8.7).
- Stereogenic centers, chirality, and absolute configuration (Sections 9.1–9.3).
- Diastereomers (Section 9.5).

10.1 CARBOCATION STABILITY

Carbocation Stability

Carbocations were introduced as reactive intermediates in Section 7.2.1. They are unstable and reactive transient products. Several important features of carbocations will be reviewed. Carbocations may be formed with one, two, or three carbon groups attached, as shown in Figure 10.1. A *tertiary carbocation* [R_3C^+] has three carbon groups, a *secondary carbocation* has two carbon groups, [R_2HC^+], a *primary carbocation* has one carbon group, [RH_2C^+], and a *methyl carbocation* has no attached carbon groups, [H_3C^+]. Carbocations have a sp^2 hybridized carbon with three σ-covalent bonds, a trigonal planar geometry, and a formal charge of +1 (Section 7.3). The positive charge is essentially an empty p-orbital and the induced dipole on an adjacent carbon atom is δ^- (see **1**). This dipole will shift electron density *from* the δ^- carbon *to* C^+. In other words, carbon substituents (alkyl groups) attached to C^+ are *electron releasing* relative to the electron deficient carbon. The more alkyl groups to the sp^2 carbon, the more electron density is shifted toward the positive center. The inductive effect of these groups diminishes the net positive charge on that carbon. Greater stability and less reactivity is associated with a diminished positive charge, so a tertiary carbocation with three carbon substituents is more stable than a secondary carbocation with only two carbon substituents or a primary carbocation with only one substituent. A secondary carbocation is more stable than a primary carbocation by ~ 12–15 kcal (50.2–62.8 kJ) mol^{-1}. Similarly, a tertiary carbocation is more stable than a secondary carbocation by the same amount. The general order of stability is

More stable $3° > 2° > 1° > CH_3$ **Less stable**

In a chemical reaction, the activation energy (E_{act}) for a reaction that generates a tertiary carbocation is lower that the E_{act} for a reaction that generates a secondary or a primary carbocation.

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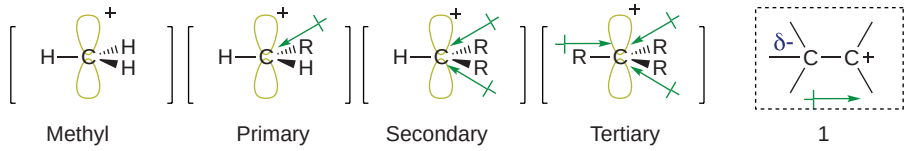


FIGURE 10.1 Structural differences of carbocations.

In other words, a reaction that generates a tertiary carbocation in a chemical reaction is more facile than one that generates a less stable secondary carbocation. A methyl carbocation is extremely unstable and very difficult to form, and it has a very high energy transition state.

Alkenes are Brønsted-Lowry Bases

10.2 ALKENES REACT WITH BRØNSTED-LOWRY ACIDS

As briefly introduced in Sections 5.7 and 6.7.5, the π-bond of an alkene reacts as a Brønsted-Lowry base with a strong acid. Indeed, alkenes react with HCl, HBr or HI to yield a carbocation intermediate (Section 7.2) with a halide counterion. This carbocation intermediate reacts with the nucleophilic halide counterion to form a new σ-bond in an alkyl halide product. An example is the reaction of cyclopentene with HCl to give a carbocation intermediate. Subsequent reaction with the chloride counterion gives chlorocyclopentane. Writing the starting materials, the reagents, all intermediates, and all products is taken as the *mechanism* of this reaction (Section 7.10). One way to look at this process is to say that the elements H and Cl *added* to the π-bond, so it can be classified as an *addition reaction*.

Since HCl is clearly recognized as an acid and it reacts with cyclopentene, the alkene must react as a base. It is reasonable to question the base strength of an alkene. The relative reactivity of cyclopentene with several acids is shown in Figure 10.2, and the pK_a of those acids

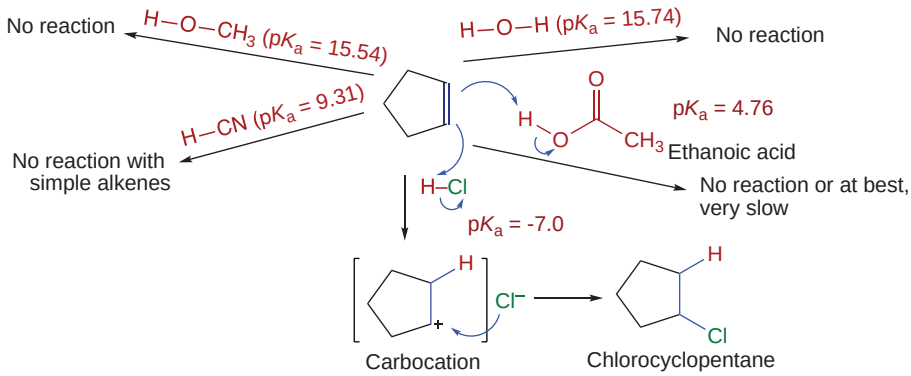


FIGURE 10.2 The Reactivity of cyclopentene with Brønsted-Lowry acids.

is given. Experiments show that cyclopentene does not react with water (pK_a, 15.7) under neutral conditions, so water is not a strong enough acid. Similarly, methanol (pK_a, 15.54) does not react with cyclopentene under neutral conditions nor does HCN (pK_a, 9.31). Ethanoic acid (acetic acid, pK_a = 4.76) is a significantly stronger acid, but simple alkenes do not react at ambient temperatures. Alkenes are weak bases and they only with a strong acid such as HCl, which has a pK_a of -7 and generally only with strong acids with pK_a values of 1 or less.

10.1 When cyclohexene is mixed with HBr, draw the reactive intermediate and the final product.

Regioselectivity

Cyclopentene is a symmetrical alkene in that both carbon groups of the C=C unit are the same. When an unsymmetrical alkene such as 2-methylbut-2-ene reacts with HCl there are two possible carbocation intermediates, **2** and **3**, which give two different isomeric alkyl chloride products. These two products are generated by two competing mechanisms, as

shown in Figure 10.3. One mechanism leads to 2-chloro-3-methylbutane via **2** and the other leads to 2-chloro-2-methylbutane via **3**. The major isolated product of this reaction is the tertiary halide via **3**. The tertiary carbocation **3** is more stable that the secondary carbocation **2**.

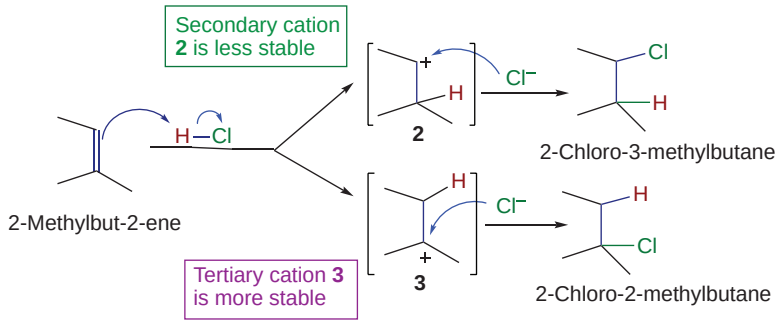


FIGURE 10.3 Competing pathways in the reaction of 2-methylbut-2-ene with HCl.

Therefore, **3** should form faster since it has a lower E_{act}. Indeed, reactions of an alkene with an acid give the more stable carbocation intermediate, which leads to the more highly substituted halide as the major product. There are two isomeric products, one major and one minor. Such isomers are called *regioisomers*. A regioisomer is a product formed by a reaction when there are two or more sites for positioning a group or substituent are possible. Since the addition of HX to an alkene generates one regioisomer in preference to the other, but both are formed, the reaction is said to be highly *regioselective*.

The reaction of alkenes with mineral acids was discovered in the latter part of the 19th century. Scientists working during that time did not understand how reactions worked at the molecular level, so they did not understand mechanisms. At that time, reactions had to be described in terms of the products that were formed. In 1869, Vladimir Vassilyevich Markovnikov (Russia; 1838–1904) observed that many different alkenes reacted with HCl or HBr. The reactions always gave products in which the halogen atom was on the most substituted carbon and the hydrogen atom was on the less substituted carbon. This observation is now known as *Markovnikov's rule*. Acids (HX) react with acids via *Markovnikov addition*, or in a Markovnikov manner.

10.2 Draw the structure of the Markovnikov product formed when 3-ethyl-(2*Z*)-hexene reacts with HCl.

Other Acids React with Alkenes

A different example is the reaction of hex-(2*E*)-ene with HCl, which gives two secondary carbocation intermediates so there will be two regioisomer products, 2-bromohexane and 3-bromohexane. The two secondary carbocations are expected to have similar E_{act} so the two products are expected to be formed in roughly equal amounts. A laboratory experiment, however, showed that the reaction of hex-2-ene and aqueous HBr gave isolated yields of 55% of 2-bromohexane and 27% of 3-bromohexane.[1] This result shows that other factors may influence the actual percentage of a reaction and it is not predicted by simple assumptions. For all cases encountered in this book, however, unless actual experimental details are presented *assume* that both products are formed in roughly equal amounts.

10.3 Are regioisomers possible when hex-3-ene reacts with HBr?

Hydrofluoric acid (HF) can react with alkenes, but much slower than the reaction of HCl, HBr or HI Indeed, hydrogen iodide reacts rapidly with alkenes, as will HBr and HCl. Note that HF is highly corrosive and a powerful contact poison. It is reactive with glass, so it is stored in plastic containers. Apart from HCl, HBr, and HI, there are other strong mineral acids, including nitric acid (HNO_3; $pK_a = -1.3$), sulfuric acid (H_2SO_4; $pK_a = -5.2$), and perchloric acid ($HClO_4$; $pK_a = -4.8$). The reactions of these three mineral acids with pent-1-ene

[1] Landini, D.; Rolla, F. *Journal of Organic Chemistry* 1980, 45, 3527–3529.

are shown in Figure 10.4, where the initial product will be a secondary carbocation. The carbocation should react with the counterion in each case to give the corresponding product. However, each of these anions is resonance stabilized so they are unreactive. They are

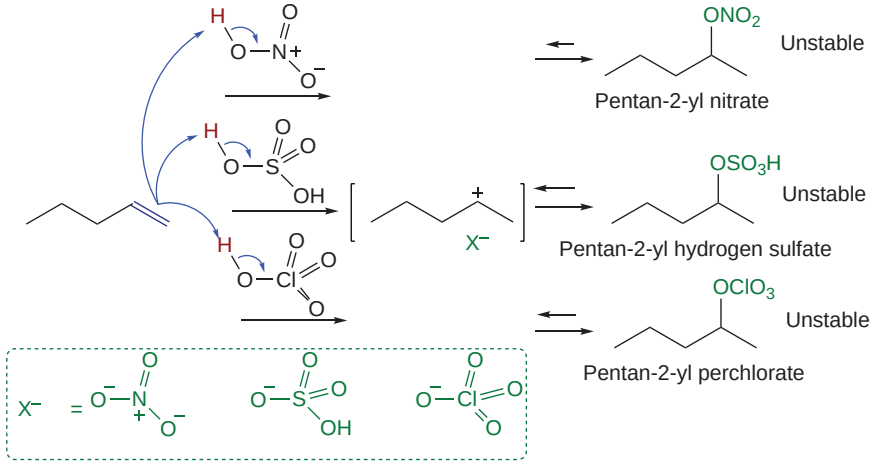


FIGURE 10.4 Reactions of pent-1-ene with mineral acids.

therefore weak nucleophiles. When nitric acid reacts with pent-1-ene the nucleophile is the nitrate anion (NO_3^-). If it reacts as a nucleophile the product should be pentan-2-yl nitrate. Likewise, when pent-1-ene reacts with sulfuric acid the nucleophile is the hydrogen sulfate anion (HSO_3^-) and the product should be pentan-2-yl hydrogen sulfate. The reaction with perchloric acid gives perchlorate (ClO_4^-) as the nucleophile so the product should be pentan-2-yl perchlorate. Even if these products form, pentan-2-yl nitrate, pentan-2-yl hydrogen sulfate and pentan-2-yl perchlorate are unstable in an acidic medium. Indeed, alkyl nitrates ($RONO_2$), alkyl sulfates ($ROSO_3H$), and alkyl perchlorates ($ROClO_3$) decompose to regenerate the secondary carbocation in an equilibrium reaction. In other words, the carbocation intermediate is present at equilibrium but there is no significant concentration of a nitrate, hydrogen sulfate, or perchlorate product.

10.4 Write all resonance contributors for NO_3^-, HSO_3^-, and ClO_4^-.

Carbocation Rearrangements

10.3 CARBOCATION REARRANGEMENTS

When 3-methylpent-1-ene reacts with HBr, the secondary carbocation **4** is the initially formed carbocation, which is expected to give 2-bromo-3-methylpentane as the product. However, the major product isolated from this reaction is 3-bromo-3-methylpentane. The initial reaction of the alkene must generate the more stable secondary carbocation **4** rather than the less stable primary carbocation. However, if the final product is 3-bromo-3-methylpentane the carbocation precursor must be tertiary carbocation **5**. Therefore, **4** must be transformed into **5** before the reaction with the bromide ion. This conversion requires that a hydrogen atom at C2 in **4** migrate to the adjacent carbon atom (C3) in **5**. This *rearrangement* gives a more stable tertiary carbocation. This rearrangement is formally a 1,2-shift of the hydrogen atom, *a so-called 1,2-hydride shift*. The *1,2- number simply means that the hydrogen* atom migrates from one carbon to an *adjacent* carbon. The rearrangement of a less stable secondary carbocation to a more stable tertiary carbocation is an *exothermic* process by 12–15 kcal (50–63 kJ) mol^{-1}. This rearrangement and both carbocation intermediates are part of the mechanism for the transformation of 3-methylpent-1-ene to 3-bromo-3-methylpentane shown in Figure 10.5. The initial reaction of 3-methylpent-1-ene to HBr yields **4**, which rearranges to carbocation **5** and the nucleophilic bromide counterion reacts with **5**

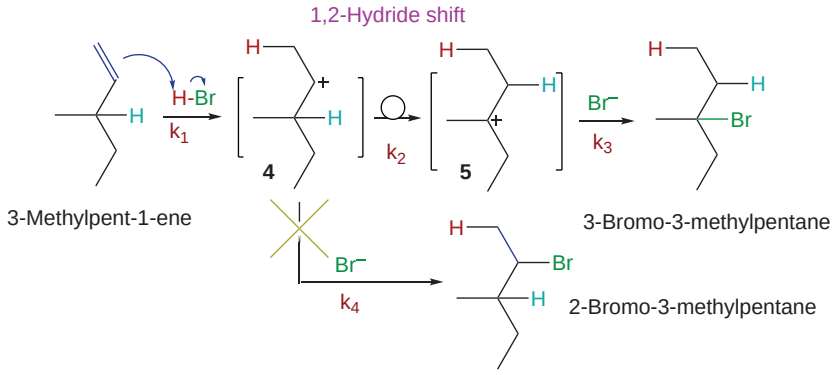


FIGURE 10.5 Rearrangement mechanism for the reaction of 3-methylpent-1-ene with HBr.

to yield 3-bromo-3-methylpentane. The "curly arrow" is used to indicate the rearrangement. In carbocation rearrangements, the migration must occur on adjacent atoms, so 1,3- or 1,4-migrations will NOT be observed.

This mechanism can be described in terms of the rate of each reaction (Section 7.11). The rate of formation of carbocation **4** is k_1 and the rate of rearrangement to **5** is k_2. The rate of the reaction to convert **5** to 3-bromo-3-methylpentane is k_3. Note that the putative reaction that converts **4** to 2-bromo-3-bromopentane is k_4. 2-Bromo-3-methylpentane is not formed so this particular reaction is *not* observed. If 3-bromo-3-methylpentane is the major product, the rearrangement of **4** to **5** must be faster than the reaction of bromide ion with **4** to give 2-bromo-3-methylpentane, so k_2 is faster than k_4. If a carbocation is generated next to a carbon atom that is potentially a more stable cation, *assume* that the rearrangement occurs faster than any other process. This assumption is not always true, but it is true most of the time and it is a good working assumption.

The rearrangement is monitored by the observation that a hydrogen atom migrates as **4** rearranges to **5**. In reality it is the electrons in the bond connecting the migrating hydrogen atom to the carbon that move. While the C^+ carbon in **4** is sp^2 hybridized in the carbocation, it is attached to a sp^3 hybridized carbon so that C—C bond can rotate (Section 8.1). Rotation leads to a rotamer in which the p-orbital of the positively charged carbon atom is parallel to

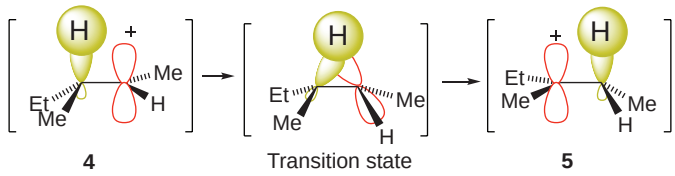


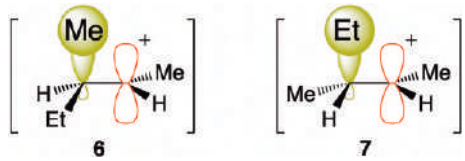
FIGURE 10.6 Mechanism of a 1,2-hydride shift.

the adjacent sp^3 hybrid orbitals of the C—H bond (**4** in Figure 10.6). The bonding electrons in the adjacent and parallel sp^3 orbital will begin to migrate toward the electron-deficient carbon. As the bonding electrons migrate, the hydrogen atom is carried along to give **5**, a more stable tertiary carbocation. The midpoint of this 1,2-hydride shift is the *transition state* (Section 7.6), which shows the hydrogen atom as it migrates and the two pertinent carbon atoms beginning to rehybridize.

10.5 Draw the mechanism and final product formed when 3-phenylpent-1-ene reacts with HCl.

The rearrangement of **4** to **5** leads to the observed product, but it is also possible to draw a rotamer for the intermediate carbocation that has a methyl group parallel to the p-orbital (**6**). In principle, migration of the electrons in the carbon-methyl bond should allow a *1,2-methyl*

shift. A similar argument can be made for the rotamer in which an ethyl group is in position to move (see **7**), giving a *1,2-ethyl shift*.



When there is the possibility of a hydrogen shift, a methyl shift or an ethyl shift, the smaller atom or group migrates. Migration of the smaller hydrogen atom requires less energy, so the rate of the 1,2-hydride shift is faster. Moving the smaller atom or group is usually a good *assumption* for most systems. However, in the presence of substituent groups that can stabilize the positive charge by delocalization in the transition state, (e.g., a phenyl group) this assumption may fail (Figure 10.7).

10.6 Draw the final product of the reaction of 3-ethyl-3-methylpent-1-ene and HCl and show the complete mechanism.

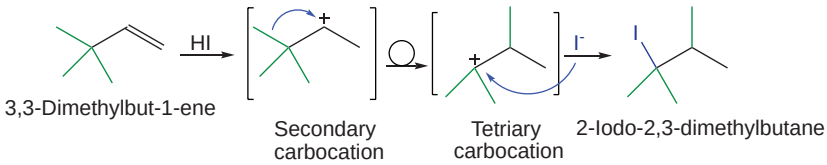


FIGURE 10.7 A 1,2-methyl shift for the reaction of 3,3-dimethylbut-1-ene and HI.

If there are no hydrogen atoms on carbon atoms adjacent to C⁺, then alkyl groups can migrate. When 3,3-dimethylbut-1-ene is treated with HI, for example, the reaction initially gives the more stable secondary carbocation. Migration of hydrogen from one carbon adjacent to C⁺ would give a less stable primary carbocation. Migration of a methyl group from the other adjacent carbon will generate a more stable tertiary carbocation. Therefore a *1,2-methyl shift* gives the more stable tertiary carbocation, which reacts with nucleophilic iodide to give 2-iodo-2,3-dimethylbutane.

Pinacol Rearrangement

Other rearrangement reactions involving a carbocation intermediate are known.[2] An important rearrangement occurs when 1.2-diols are treated with acids. The acid-catalyzed rearrangement of diols gives aldehydes or ketones in a reaction called the *pinacol rearrangement*.[3] The prototype reaction of pinacol (2,3-dimethylbutane-2,3-diol) to pinacolone (3,3-dimethylbutan-2-one) gives the reaction its name. Initial acid-base reaction of one of the OH units with an acid catalyst gives the oxonium ion **8** (Section 16.6), which loses water to give the carbocation **9**. A simple 1,2-methyl shift gives cation **10**, which is known as an *oxocarbenium ion* (Sections 16.2, 16.5–16.7). Loss of a proton from **10** gives the ketone product. The 1,2-methyl shift occurs from the tertiary position to the oxygen-bearing carbon because the oxocarbenium ion is even more stable than tertiary alkyl cations (Figure 10.8).

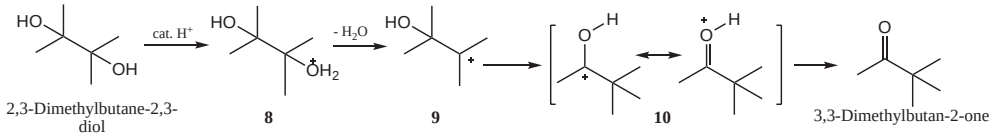


FIGURE 10.8 The mechanism of the pinacol rearrangement

[2] Smith, M.B. *March's Advanced Organic Chemistry*, 8th ed., John Wiley & Sons, Inc. Hoboken, MJ, 2020, pp. 1335–1438.

[3] Bartók, M.; Molnár, A. in Patai, S. *The Chemistry of Functional Groups, Supplement E*, Wiley, NY, **1980**, pp. 722–732.

10.4 HYDRATION REACTIONS OF ALKENES

Hydration Reactions

Although strong acids such as HCl or HBr react with alkenes, weak acids such as water and alcohols do *not* react directly with alkenes. Carbocations, however, are highly reactive intermediates, and once generated they easily react with weak nucleophiles such as water or alcohols. As shown in Figure 10.4, sulfuric, nitric, and perchloric acid react with an alkene to generate a carbocation but with a counterion that is a weak nucleophile. An alkene reacts with one of these acids will generate a carbocation in an equilibrium reaction, and that carbocation can react with even a weak nucleophile that is added to the reaction medium.

An example is the reaction of 2-methylbut-2-ene and water in the presence of a catalytic amount of sulfuric acid. This reaction gives 2-methylbutan-2-ol in 74% yield.[4] Water does not react directly with the alkene, but the requisite carbocation is formed in an equilibrium acid-base reaction with sulfuric acid. Once the carbocation is formed, water quickly reacts to give an oxonium ion (C—OH_2^+). Loss of a proton from the acidic oxonium ion in an acid-base reaction gives the alcohol product. The sequence just described constitutes the mechanism of the reaction, and it is shown in Figure 10.9. Since the elements of H and OH have been added to the C=C unit, which are the elements of water, this reaction is known as *hydration*. It is important to observe that H^+ is *regenerated* from the oxonium ion in the last step of the mechanism that converts 2-methylbut-2-ene to 2-methylbutan-2-ol, so this reaction is *catalytic in acid*.

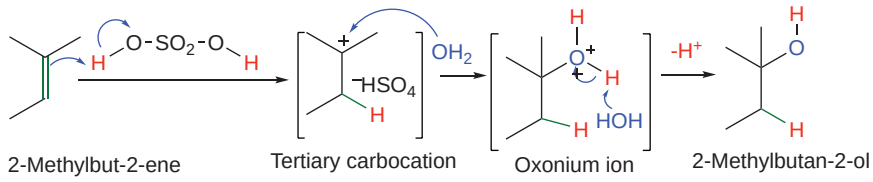


FIGURE 10.9 Hydration reaction of 2-methylbut-2-ene.

10.7 Draw the mechanism for the reaction of cyclohexene with water, using an acid catalyst H^+.

If an alkene reacts with an acid catalyst in an aqueous medium the product is an alcohol, but in an alcohol medium the product is an ether. The reaction of cyclohexene and methanol in the presence of an acid catalyst initially gives the expected carbocation, as shown in Figure 10.10. Note the use of H^+ in the mechanism as a generic acid. Excess methanol is present, and the oxygen atom of methanol is the nucleophile. The product of this reaction is an oxonium ion (**11**). If the proton of the acidic oxonium ion is lost via an acid-base reaction, as shown, the product is an ether, methoxycyclohexane (also known as cyclohexyl methyl ether; Section 5.5.2).

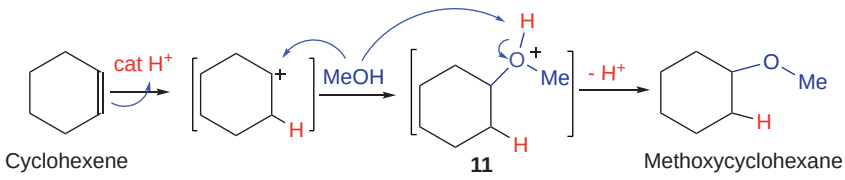


FIGURE 10.10 Acid catalyzed reaction of cyclohexene with methanol.

[4] Adams, R.; Kamm, O.; Marvel, C.S. *Journal of the American Chemical Society* 1918, 40, 1950–1955.

10.8 Draw the product formed when 2-phenylbut-1-ene is treated with a catalytic amount of sulfuric acid in an aqueous solution.
10.9 Draw the product formed when 3,3-dimethyl-hex-1-ene is treated with a catalytic amount of sulfuric acid in methanol.

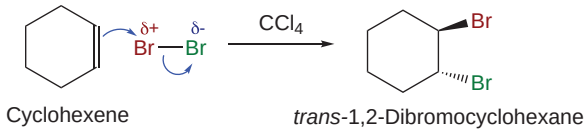
10.5 ALKENES REACT WITH DIHALOGENS

Dihalogenation

10.5.1 DIHALOGENATION

In the preceding sections, the C=C unit of an alkene reacted as a Brønsted-Lowry base with a Brønsted-Lowry acid. Alkenes also react with dihalogens in Lewis base-like reactions. The π-bond donates two electrons to an electrophilic halogen atom of the dihalogens, which mimics a Lewis acid-base reaction. The final product is not an "ate" complex as with traditional Lewis bases, however, so this is not a formal Lewis acid-base reaction. The Lewis base analogy is useful because it places the focus on an alkene as a two-electron donor. When cyclohexene is mixed with elemental bromine, for example, the product is *trans*-1,2-dibromocyclohexane, isolated in 57% yield.[5] Note the presence of carbon tetrachloride on the reaction arrow as a solvent but it does not participate in the reaction. This reaction is an example of *dihalogenation of alkenes*.

In the reaction of bromine and cyclohexene, the C=C unit of cyclohexene donated two electrons to one bromine of the Br_2. Why does an alkene react with diatomic bromine? Diatomic halogens are highly polarizable.



When one of the two halogen atoms is in close proximity to the electron rich π-bond, that halogen atom becomes δ^+ while the other becomes δ^-, as shown in Figure 10.11. An induced dipole is generated that allows the electron rich π-bond of an alkene to react with the proximal electron deficient bromine. This reaction does not generate a carbocation intermediate, but *there is a cation intermediate.*

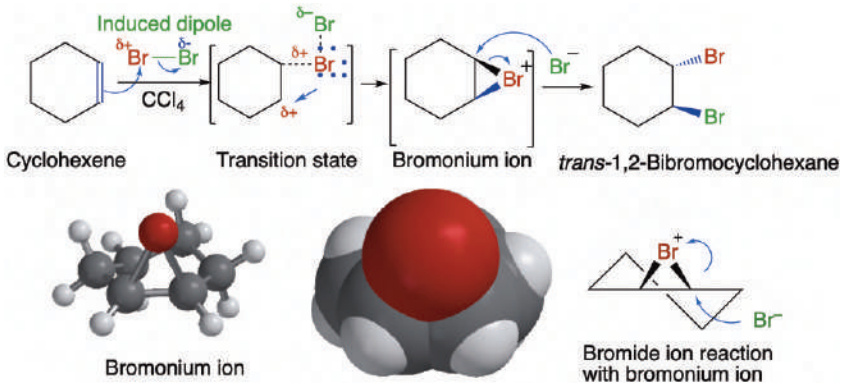


FIGURE 10.11 Mechanism of the reaction of cyclohexene with bromine.

In the transition state for the reaction of the C=C unit of an alkene reacts with Br—Br, one carbon of the alkene π-bond develops positive character as the π-electrons are transferred to bromine. The bromine participates in the reaction by donating electrons back to the carbon

[5] Barluenga, J.; Yus, M.; Concellón, J.M.; Bernad, P. *Journal of Organic Chemistry* 1981, 46, 2721–2726.

atom as positive charge develops. This so-called *back-donation* is indicated by the arrow. Back donation generates a positively charged three-membered ring cation called a *bromonium ion*. This reaction occurs with all the halogens when they react with alkenes. Bromine yields a bromonium ion, chlorine yields a chloronium ion, iodine yields an iodonium ion, and generically a halogen yields a *halonium ion.*

In this reaction, only the trans-dibromide is formed so there cannot be a carbocation intermediate. This observation is taken as confirmation that the intermediate is a bromonium ion, not a carbocation. If a carbocation were formed in this reaction, subsequent reaction with the nucleophilic bromide ion must occur from both sides of the planar carbocation. Both electrophilic carbon atoms of the cyclohexane bromonium ion can react with the nucleophilic bromide ion (Br^-). Approach of the nucleophilic bromide anion must be from the sterically less hindered side opposite the first bromine atom (as shown). The ball-and-stick model and the space-filling model of the bromonium ion in Figure 10.11 gives a clearer picture of the steric hindrance imposed by the large bromine atom. This reaction leads to cleavage of the three-membered ring to form the *trans* dibromide. This anti approach of the nucleophile to a halonium ion occurs with all dihalogenation reactions. Since none of the diastereomer (the cis-dibromide) is formed in this reaction this reaction is *diastereospecific*. Of the two possible diastereomers, one and only one is formed. Dihalogenation reactions with alkenes to give a trans-dihalide are reported only for chlorine, bromine, or iodine and not fluorine.

Elemental fluorine was thought to be too reactive and too dangerous for reaction with alkenes.[6] To avoid problems associated with this reaction, fluorine is typically mixed with an inert gas (e.g., nitrogen or argon).[7,6] Diluted in this manner, fluorine does react with alkenes, but the yields are often poor, and in some cases, solvents such as methanol participate in the reaction.[8] 1-Phenylprop-1-ene ($PhCH{=}CHCH_3$), for example, reacted with fluorine in methanol to yield 51% of the corresponding difluoride, along with 49% of 2-fluoro-1-methoxy-1-phenylpropane.[8] Because of the problems associated with reactions with fluorine only dihalogens reactions with chlorine, bromine or iodine will be presented in this book.

10.10 Draw the intermediate and final product formed when 2-methylbut-1-ene reacts with I_2.

10.5.2 DIASTEREOSELECTIVITY IN THE DIHALOGENATION REACTION OF ALKENES

Dihalogenation
Diastereoselectivity

As noted, the reaction of alkenes and halogens is *diastereospecific*, which means that two or more products are possible but only one is formed. Indeed, dihalogenation gives 100% of the *trans*-diastereomer with cyclic alkenes and 0% of the cis-diastereomer. In Figure 10.12, the bromine atom has reacted from the "top" of the cyclohexene ring in **12**, but from the bottom of the cyclohexene ring to form bromonium ion **13**. The large bromine atom in the

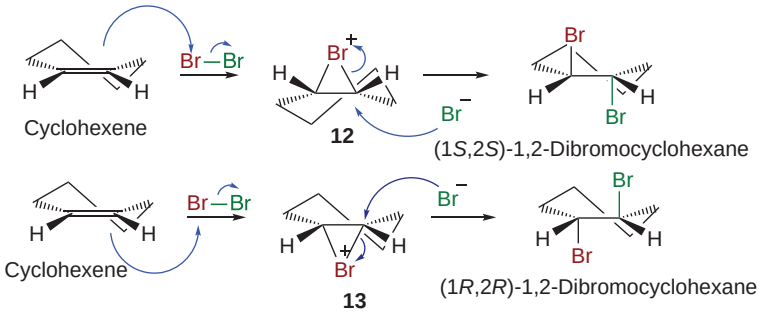


FIGURE 10.12 Diastereoselectivity and sidedness in bromonium ion formation.

[6] (a) Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chemical Reviews* 1986, 86, 997–1018; (b) Grakauskas, V. *Intra-Science Chemistry Reports* 1971, *5*, 85.
[7] Humiston, B. *Journal of Physical Chemistry* 1919, 23, 572–577.
[8] Merritt, R.F. *Journal of the American Chemical Society* 1967, 89, 609–612.

bromonium ion will effectively block that face of intermediate **12** or **13** (Figure 10.12). The nucleophilic bromide ion will react with **12** to give (*1S,2S*)-1,2-dibromocyclohexane, but bromonium ion **13** yields (*1R,2R*)-1,2-dibromocyclohexane. Clearly, attack from the top face leads to one enantiomer and attack from the bottom face leads to the other enantiomer. Attack from either face occurs with equal facility so the dibromide product is *racemic* but only one diastereomer is formed so the reaction is diastereospecific.

The reaction of an acyclic alkene with a halogen is also diastereospecific but the product is an acyclic dihalide. In order to demonstrate the diastereospecificity of both stereoisomers, *cis*-but-2-ene and *trans*-but-2-ene must be examined. When *cis*-but-2-ene reacts with bromine, the product is a racemic mixture of (2*S*,3*R*)-dibromobutane and the enantiomer (2*R*,3*S*)-dibromobutane, as shown in Figure 10.13. When *trans*-but-2-ene reacts with bromine, however, the product is (2*S*,3*S*)-dibromobutane and the enantiomer (2*R*,3*R*)-dibromobutane. One racemic diastereomer is formed from the cis-alkene and the other racemic diastereomer is formed from the trans-alkene. Each product can be identified by the absolute configuration.

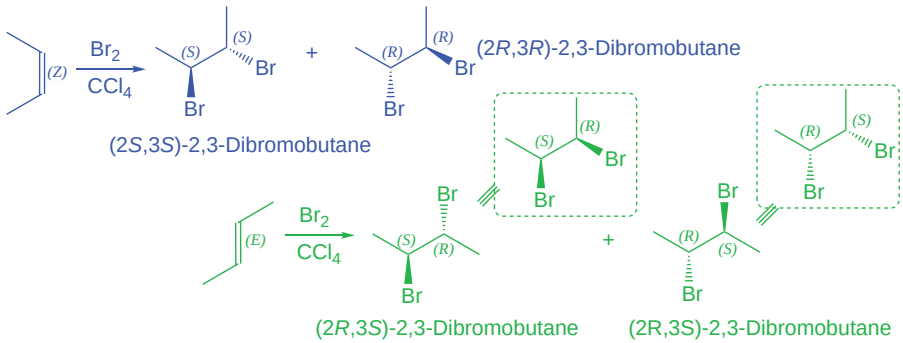
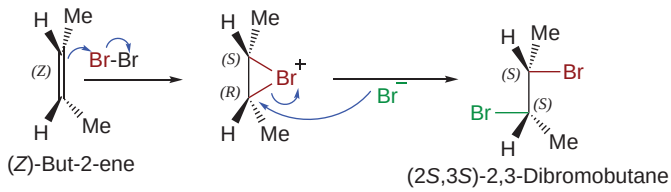


FIGURE 10.13 The reaction of *cis*-but-2-ene and *trans*-but-2-ene with bromine.

The diastereoselectivity of this reaction can be traced to the fact that, the two methyl groups (Me) in *cis*-but-2-ene are "locked" on one side of the C=C unit since there is no rotation around those carbon atoms. There is no rotation in the transition state or in the three-membered ring structure of the bromonium ion so the methyl groups are also "locked" in position.



Therefore, the stereochemistry of all groups in the alkene is retained in the bromonium ion. The bromide ion reacts with the bromonium ion via backside (anti) attack at carbon at the face opposite the bromine atom. This attack fixes the stereochemistry of the two bromine atoms as anti and the final product has a trans-relationship for the bromines. The bromonium ion is arbitrarily drawn with the bromine on the "right," although there is nothing to distinguish one side from another and both sides react equally, so the final product is racemic.

10.11 Determine which of the stereoisomers of hex-3-ene (cis- or trans-) reacts with bromine to generate a meso compound.

Alkenes with Hypohalous Acids

10.5.3 REACTION WITH AQUEOUS SOLUTIONS OF HALOGENS (HYPOHALOUS ACIDS)

In Sections 10.4.1,2 diatomic bromine, chlorine, or iodine were shown to react with an alkene to yield a dihalide in a nonaqueous solvent (e.g., CCl_4). Other solvents can be used in this

reaction including an aqueous solution saturated with chlorine gas. When chlorine gas is dissolved in water *hypochlorous acid* (HOCl) is generated in situ. Likewise, bromine dissolved in water generates *hypobromous acid* (HOBr). These hypohalous acids react with an alkene to form a halohydrin, which is an alcohol with a halogen substituent. The polarization of HOCl is $HO^{\delta-}—Cl^{\delta+}$ so *chlorine is the electrophilic atom*. The π-bond of an alkene reacts with the positive chlorine atom with cleavage of the Cl—OH bond to give hydroxide as the counterion, which is the nucleophile in this reaction. However, the hydroxyl unit does not react at the less substituted carbon. For example, pent-1-ene reacts with HOCl in aqueous

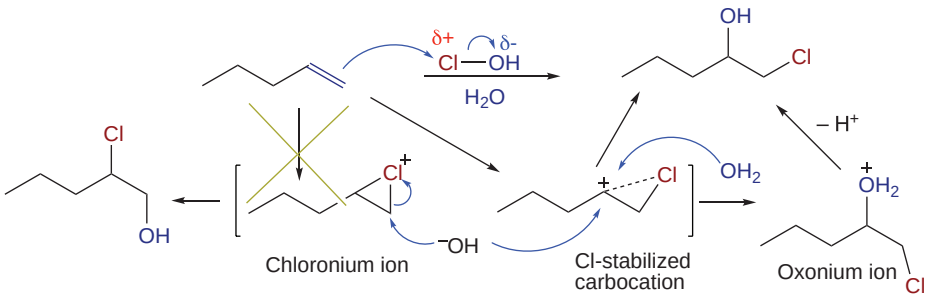


FIGURE 10.14 Reaction of pent-1-ene and hypochlorous acid.

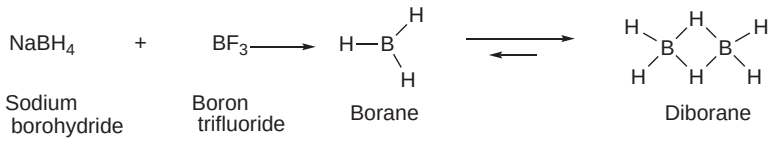
media, as shown in Figure 10.14, to give 1-chloropentan-2-ol in 43% isolated yield.[9] Water facilitates both ionization and solvation of ions, so a secondary carbocation is formed and not a chloronium ion. The isolated product is 1-chloropentan-2-ol, rather than 2-chloropentan-1-ol, which would be formed by attack at the less substituted carbon atom of a chloronium ion. The carbocation shown in Figure 10.14 is stabilized by *back-donation* of the chlorine. This carbocation may react directly with hydroxide to yield the observed product, but it can also react with water to give an oxonium ion. Reactions of chlorine or bromine with alkenes in aqueous media generally give the more stable carbocation, and attack by the nucleophile gives to the major product.

10.12 Write out the mechanism that describes the proposed reaction of water and chlorine with pent-1-ene.

10.6 ALKENES REACT WITH BORANE

Hydroboration

Borane is a Group 13 compound that reacts as a Lewis acid in the presence of a suitable electron-donating species. Borane can be prepared by the reaction of sodium borohydride ($NaBH_4$; Section 17.2) with boron trifluoride (BF_3) to give borane, which is a dimeric species called diborane (B_2H_6) with *hydrido bridges* (bridging hydrogen atoms). There is an equilibrium between diborane and the monomeric borane (BH_3), but the two structures are used interchangeably. Borane reacts with alkenes to yield a new product known as an *alkylborane* ($C{=}C + BH_3 \rightarrow H—C—C—BH_2$). When borane reacts with hex-1-ene an alkylborane product is formed but there is no intermediate. The reaction of borane with an alkene is said to be a *concerted reaction*. The term *concerted* means that breaking the π-bond and the B—H bond to make C—H and C—B bonds occurs more or less simultaneously.



[9] Glavis, F.J.; Ryden, L.L.; Marvel, C.S. *Journal of the American Chemical Society* 1937, 59, 707–711.

Hex-1-ene reacts with borane to form two alkylborane products, hexan-1-ylborane and hexan-2-ylborane as shown in Figure 10.15. There is no intermediate, so the transition states for each alkylborane product must be examined to explain the preference for hexan-1-ylborane over hexan-2-ylborane. The conversion of an alkene to an alkylborane is known to proceed via a *four-center transition state*. Transition states **14** and **15** are shown for each of the

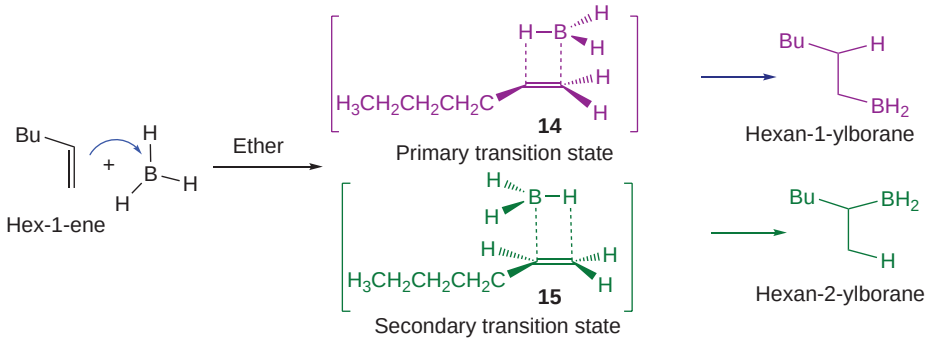


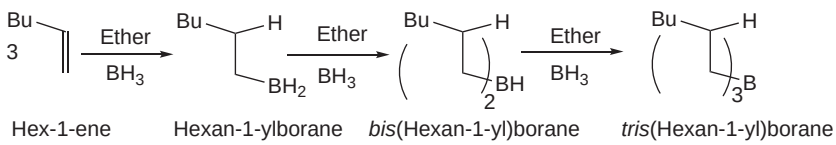
FIGURE 10.15 Formation of hexanylboranes from hex-1-ene.

two alkylborane products. Transition state **14** leads to the major product with boron attached to the primary carbon. Transition state **15** leads to the minor product with boron attached to the more substituted secondary carbon. Since hexan-1-ylborane is the major product, transition state **14** must be lower in energy and formed faster than transition state **15**.

10.13 Draw the transition state(s) for the reaction of cyclobutene with borane; of 2-methylpent-2-ene with borane.

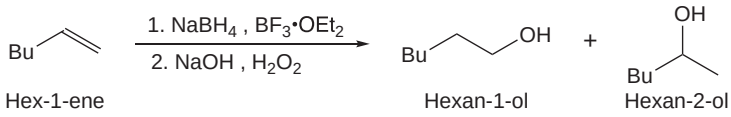
A comparison of **14** and **15** shows that there is steric hindrance between the butyl group of the alkene and the BH_2 unit of borane in **15**. The butyl group has minimal interaction in transition state **14** where the steric hindrance is minimized. Transition state **14** is lower in energy, forms faster and leads to the major product. The greater the steric bulk of substituents on the alkene C=C unit, the greater the steric hindrance in the transition state. There is therefore a greater preference for attaching boron to the *less substituted carbon*, which can be called an *anti-Markovnikov orientation* (Section 10.2). Indeed, alkenes react with borane to give the anti-Markovnikov product as the major product. Note that both products have a single alkyl group attached to the boron, and they are known as monoalkylboranes (RBH_2). Boranes with two alkyl groups attached to boron are dialkylboranes (R_2BH) and those with three alkyl groups are trialkylboranes (R_3B).

In hydroboration reactions, one molar equivalent of borane with three B—H units can react with three molar equivalents of an alkene to form a trialkylborane. For terminal alkenes, the reaction tends to favor formation of dialkyl- or trialkylboranes. With hindered alkenes, it is possible to stop this reaction at the dialkylborane or even the monoalkylborane stage. For convenience, assume that the reaction of borane (BH_3) and any alkene yields the trialkylborane since subsequent reaction with $NaOH/H_2O_2$ will give the alcohol regardless of the number of carbon groups on boron.



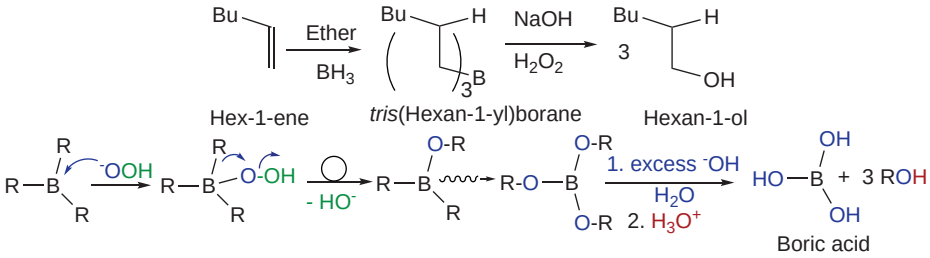
In the reaction of hex-1-ene, there is an important component that is not at all obvious. If borane is simply mixed with hex-1-ene with a non-ether solvent, no reaction occurs unless the mixture is heated to ~ 180–200 °C. In ether solvents, however, the reaction occurs rapidly at ambient temperatures. *Ethers catalyze the reaction of borane with an alkene*, but

an ether structure does not appear in the product. This catalytic activity is probably due to the fact that the oxygen atom of an ether reacts with diborane to form a highly reactive complex that reacts with the alkene. All reactions of alkenes with borane in this book will use an ether solvent.



Organoboranes are formed from the reaction of alkenes and BH_3 and they can be converted to alcohols in a second chemical step. Nobel laureate Herbert C. Brown (USA; 1912–2004) and co-workers discovered that reaction of an organoborane with a mixture of hydrogen peroxide (H_2O_2) and aqueous sodium hydroxide (NaOH) gives an alcohol and boric acid [$B(OH)_3$]. When borane reacted with hex-1-ene to give 1-hexanylborane, subsequent reaction with NaOH followed by H_2O_2 in a second chemical reaction gave hexan-1-ol in 81% yield.[10] This two-step transformation of an alkene to an alcohol is known as *hydroboration*.

Comparing the borane and alcohol products shows that the OH has "replaced" the boron. The mechanism for transformation of the organoborane to the alcohol is shown in Figure 10.16. The sequence begins with the reaction of HOOH with NaOH to yield sodium hydroperoxide ($Na^{+-}OOH$). The hydroperoxide anion reacts with the borane as a Lewis base with the boron to form an "ate" complex. This "ate" complex is not isolated because the carbon



Oxidation of Boranes to Alcohols

FIGURE 10.16 Mechanism of oxidation of an alkylborane to an alcohol.

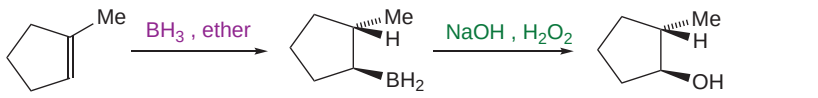
group undergoes a rapid *boron-to-oxygen shift* (a *rearrangement*), with loss of hydroxide (HO^-) to yield an alkylborate [$RO\text{-}Br_2$]. The B→O rearrangement occurs with retention of configuration when there is stereochemistry in the substrates. If HOO^- attacks boron twice more, there are two additional B→O alkyl shifts that transfer the remaining alkyl groups from boron to oxygen (Figure 10.16). The final product is the tris(borate), $(RO)_3B$. Hydroxide attacks boron in the tris(borate) three times in three successive steps to liberate boric acid and three equivalents of the alcohol (ROH, in this case hexan-1-ol) from the alkoxide. Note that the terminology "tris-" is used to show that there are three identical units attached to the boron.

10.14 Draw the major product formed when 3-ethylpent-2-ene is treated with (1) BH_3 (2) NaOH, H_2O_2.

The reaction of an alkene with borane proceeds by *cis addition of the H and the B*, which has stereochemical implications for reactions with substituted alkenes. In the reaction of methylcyclopentene with borane, followed by reaction with NaOH, H_2O_2 the product is *trans*-2-methycyclopentanol. The reaction of borane with the C=C is a *cis-addition.* The H and the boron add to the same side of the molecule due to the four-center transition state. Note the trans stereochemistry of the methyl group and the hydroxyl unit. The reaction

[10] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.44, pp. 543–544.

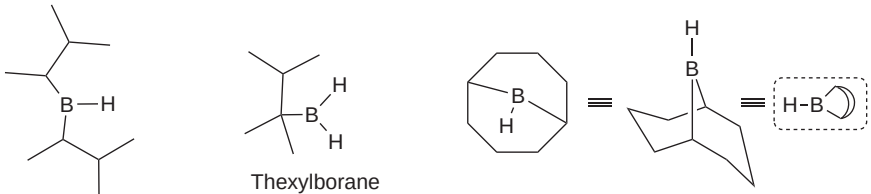
pushes the methyl group away so the B and H in the borane are on the opposite side of the ring relative to the methyl group. Oxidation transforms the borane to the alcohol with *retention* of stereochemistry, so the hydroxyl and the methyl have a trans relationship.



trans-2-Methylcyclopentanol

10.15 Show the monoalkylborane product formed when 3-methylhex-1-ene reacts with borane in an ether solvent.

When an alkene is highly substituted, hydroboration can generate monoalkylboranes or dialkylboranes. When 2-methylbut-2-ene reacts with borane, the product is the dialkylborane bis(3-methylbutan-2-yl)borane, but its common name is *disiamylborane* (from the common name di-*sec*-isoamylborane). Similar reaction of borane with 2,3-dimethylbut-2-ene leads to a monoalkylborane, (2,3-dimethylbutan-2-yl)borane. The common name of this product is *thexylborane* (from *tert*-hexylborane). Finally, reaction of borane with cycloocta-1,5-diene yields a product where one of the B—H units reacts with one of the C=C units.



Disiamylborane
bis(3-Methylbutan-2-yl)borane

Thexylborane
(2,3-Dimethylbutan-2-yl)borane

9-BBN
9-Borabicyclo[3.3.1]nonane

A second B—H unit in the initially formed alkylborane reacts with the second C=C unit across the ring to give a bicyclic dialkylborane, *9-borabicyclo[3.3.1]nonane,* which is often abbreviated *9-BBN*. It is often abbreviated as the cartoon structure in the box. Nomenclature rules for bicyclic systems such as this are described in Section 9.9. There are a total of nine atoms (nonane) but C9 has been replaced with boron (9-bora). These three substituted alkylboranes are commonly used in hydroboration reactions with other alkenes.

These three specialized alkylboranes are sterically bulky relative to BH_3. Attachment of boron to the more substituted carbon of a C=C unit by reaction of each alkylborane with an alkene leads to a four-center transition state that is higher in energy due to increased steric hindrance. Therefore, there is a very high preference for attachment of boron to the less substituted carbon. In other words, hydroboration is more regioselective than similar reactions with BH_3. An example is the reaction of methylcyclopentene with 9-BBN in Figure 10.17, which leads to two regioisomers via transition states **16** and **17**. There is a large steric interaction of the 9-BBN group with the methyl group of the alkene in transition state **17** that makes it very high in energy. Transition state **16** is much less sterically hindered and it is lower in energy. Therefore, transition state **16** forms faster and leads to (1*S*,5*S*)-9-(2-methylcyclopentyl)-9-borabicyclo[3.3.1]nonane as the major product with <0.1% of the regioisomer, 9-(1-methylcyclopentyl)-9-borabicyclo[3.3.1]nonane. The same reaction with BH_3 yields ~ 85–90% of (1*S*,5*S*)-9-(2-methylcyclopentyl)-9-borabicyclo[3.3.1]nonane and about 10% of 9-(1-methylcyclopentyl)-9-borabicyclo[3.3.1]nonane.

10.16 Draw the major product formed when 9-BBN reacts with 2,3-dimethyl-hex-3-ene.

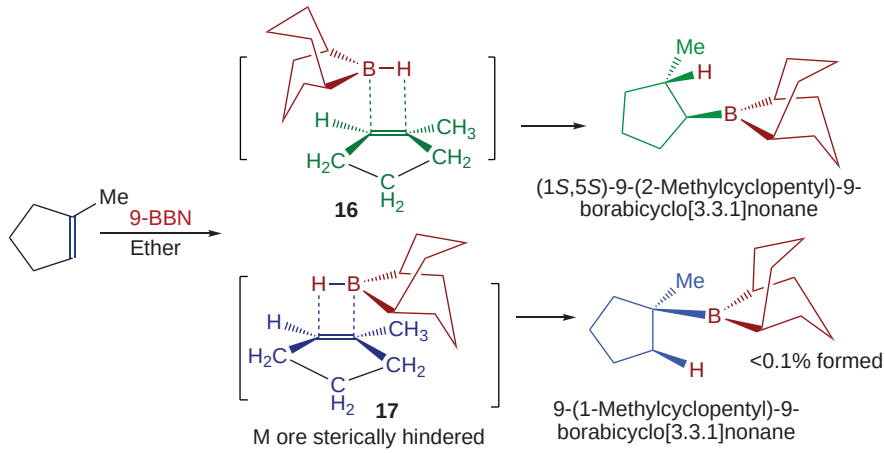


FIGURE 10.17 Regioselectivity in the reaction of methylcyclopent-1-ene with 9-BBN.

10.7 ALKENES REACT WITH MERCURY(II) COMPOUNDS

Oxymercuration-Demercuration

Mercuric salts (HgX_2) are Lewis acids that react with alkenes with formation of a carbocation intermediate. However, the product has a C—Hg bond. When 3-methylhex-1-ene reacts with mercuric acetate [$Hg(OAc)_2$ in THF-H_2O solvent, the isolated product is a mercuric compound identified as acetyl(2-hydroxy-3-methylhexyl)(oxo)mercurate(III). The structure of mercuric acetate is shown in Figure 10.18 (see Section 18.7). The mercury is removed in a second chemical step by reaction with sodium borohydride ($NaBH_4$; Section 17.2) to give 3-methylhexan-2-ol in 68% yield.[11] The mechanism begins with the reaction of mercuric acetate with the alkene to give the more stable secondary carbocation **18**. Mercury is a transition metal with d-orbitals that can coordinate to the carbocation in a way that

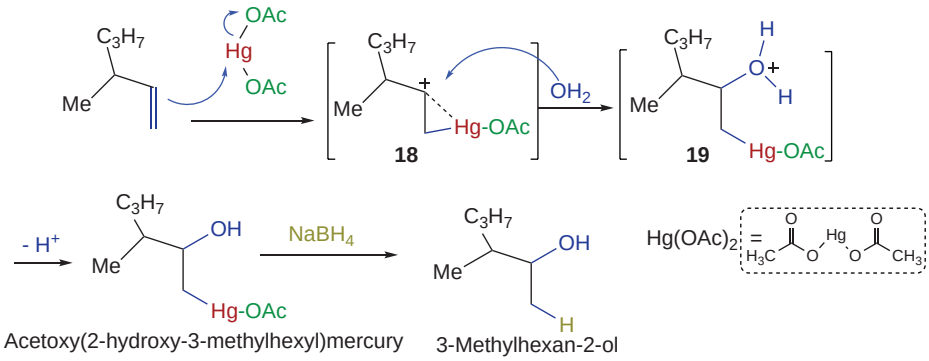


FIGURE 10.18 Oxymercuration–demercuration of 3-methylhex-1-ene.

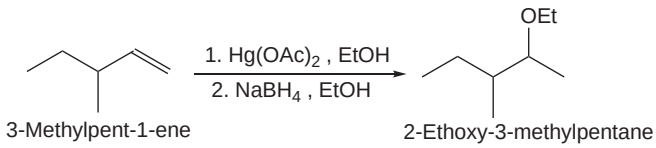
stabilizes the positive center. The "dashed line" (----) in Figure 10.18 indicates the significant coordination between the carbon and mercury known as *back-donation*. Because of the back-donation there is *no rearrangement* although **18** is a secondary carbocation that is proximal to a potential tertiary center. The water in the solvent reacts with **18** to form oxonium salt **19**. Loss of a proton in a simple acid-base reaction gives the mercury-alcohol product. The overall process converted an alkene to an alcohol, so it is a *hydrolysis* of the alkene. Subsequent reduction with $NaBH_4$ (Sections 17.2,3) converts the C—Hg bond to a C—H bond. This reductive cleavage of the carbon-metal bond and conversion to a C—H bond is known as *hydrogenolysis*. The overall transformation is a hydration process that adds water to the more substituted carbon of the alkene (a *Markovnikov addition*) followed by removal

[11] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.46, p. 546.

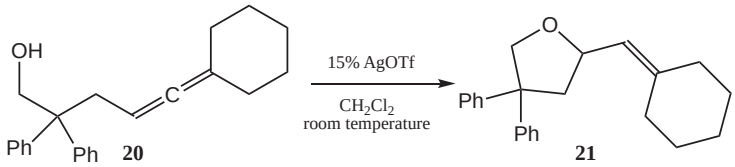
of mercury. This sequence is called *oxymercuration-demercuration,* or simply *oxymercuration*. The reaction of an alkene with mercuric acetate is attractive because *it generates a carbocation that does not rearrange*. However, a second reaction with sodium borohydride ($NaBH_4$) is required to remove the mercury and generate the alcohol.

3-Methylhex-1-ene is a terminal alkene, and formation of the more stable secondary cation leads to a single major product. However, oxymercuration of an internal alkene such as pent-2*E*-ene that generates two carbocations of equal stability leads to a mixture of products, pentan-2-ol and pentan-3-ol. Although rearrangement did not occur, two regioisomers are formed because both carbocation intermediates are secondary. Subsequent reaction with water followed by reduction with sodium borohydride gives the two alcohols.

An *alkoxymercuration* variation for this reaction is known. It simply involves using an alcohol as the solvent rather than water. The mechanism is identical to that shown in Figure 10.18 except that ROH replaces water. For example, the reaction of 3-methylpent-1-ene with mercuric acetate and ethanol, followed by reaction with sodium borohydride, gives 2-ethoxy-3-methylpentane. The alcohols used most often as solvents in this reaction are usually the lower molecular weight methanol, ethanol and propan-2-ol, with lower boiling points.



Brønsted acids are often used as catalysts for organic reactions and sulfuric acid, or sulfonic acids are commonly used. In the hydroxyalkylation and alkoxyalkylation reactions just introduced, coinage metal catalysts that include $Cu(OTf)_2$ and AgOTf have been used as catalysts, where OTf is triflate, $-SO_3CF_3$.



King Kuok (Mimi) Hii (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Used with a protic solvent or reactant such as water or alcohols, these catalysts generate the strong Brønsted acid triflic acid (CF_3SO_3H, TfOH), which catalyzes the reaction.[12] Hydroxyalkylation reactions are possible with allene derivatives (Section 5.3) and $AgNO_3$

[12] (a) Arbour, J.L.; Rzepa, H.S.; White, A.J.P.; Hii, K.K. *Chemical Communications* 2009, 7125–7127; (b) Also see Arbour, J.L.; Rzepa, H.S.; Contreras-García, J.; Adrio, L.A.; Barreiro, E.M.; Hii, K.K. *Chemistry, A European Journal* 2012, 18, 11317–11324.

has been shown to be very effective. The regiodivergent cyclisation of γ-allenols using silver nitrate was reported by Professor King Kuok (Mimi) Hii of Imperial College (London). The hydroxyalkylation reaction of allene **20** with silver triflate gave tetrahydrofuran derivative **21**.[12] Professor Hii's work has focused on the development of catalysis for organic reactions.

10.17 Draw both carbocation intermediates derived from oxymercuration of 4,4-dimethylhept-(2*E*)-ene in water.
10.18 Suggest a mechanism for the formation of the mercuric-alcohol precursor to 2-ethoxy-3-methylpentane via alkoxymercuration.

10.8 ALKYNES REACT AS BASES

Preceding sections focused on the acid-base reactions of alkenes. It is reasonable to assume that there are similarities in the chemical reactivity of alkenes and alkynes. It is known that one π-bond of a carbon-carbon triple bond is about 8.8 kcal (36.8 kJ) mol^{-1} weaker than the π-bond in an alkene. The alkyne π-bond is therefore less able to donate electrons to an acid (i.e., *it is a weaker base*). Nonetheless, alkynes react as a base with the reagents previously discussed but only one of the π-bonds reacts and the product retains one C=C unit.

10.8.1 REACTION WITH BRØNSTED-LOWRY ACIDS

Alkynes with HX

When 3,3-dimethylbut-1-yne reacts with HCl, only one π-bond reacts. The intermediate has a positive charge on a sp^2-hybridized carbon, a *vinyl carbocation*, as shown in Figure 10.19. Two possible vinyl carbocations can form from this alkyne, the more stable secondary vinyl

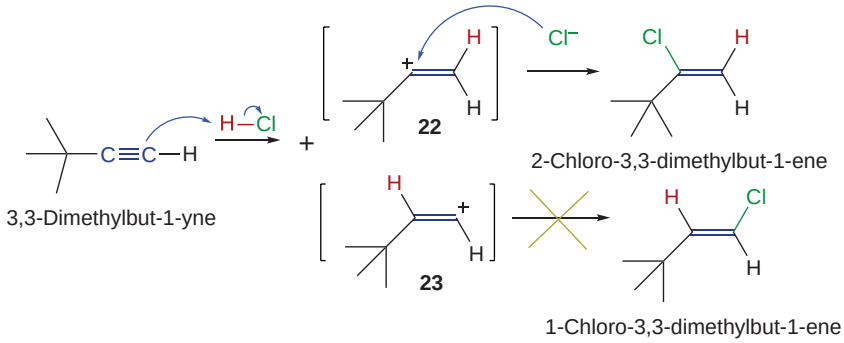


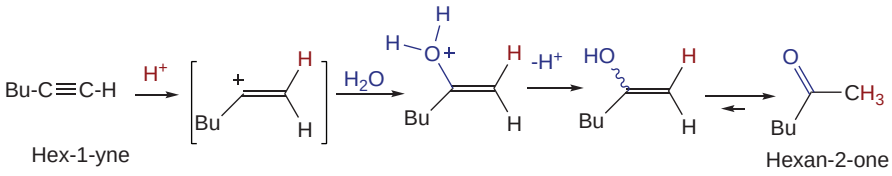
FIGURE 10.19 The reaction of 3,3-dimethylbut-1-yne with HCl.

carbocation **22** that forms preferentially to the primary vinyl carbocation **23**. In general, the relative order of stability for vinyl carbocations is $R_2C{=}C(R)^+ > RHC{=}C(R)^+ > RHC{=}C(H)^+$. Reaction with the nucleophilic chloride counterion to give the major product, 2-chloro-3,3-dimethylbut-1-ene but 1-chloro3,3-dimethylbut-1-ene is not formed. There are methyl groups on the carbon atom attached to the vinyl carbocation, but a *1,2-methyl shift did not occur*. Indeed, rearrangement does *not* occur in vinyl carbocations. The reaction of the unsymmetrical alkyne hex-2-yne with HCl generates two carbocations, and both are secondary vinyl carbocations. The stability of these two intermediates should be the same, so it is anticipated that both will be formed in roughly equal amounts. Subsequent reaction with chloride ion gives two products, 3-chlorohex-2-ene and 2-chlorohex-2-ene, in roughly a 50:50 ratio. The vinyl carbocations are a mixture of (*E*)- and (*Z*)-isomers, so the alkene products are a mixture of (*E*)- and (*Z*)-isomers.

10.19 Draw both carbocation intermediates formed when HCl reacts with 3,3-dimethylpent-1-yne, and draw the final major product.

10.8.2 HYDRATION OF ALKYNES

Since alkynes are weaker bases than alkenes, it is not surprising that alkynes do not react directly with weak acids such as water or alcohols. As with the alkenes, alkynes do react with water if a strong acid catalyst is added to generate the reactive vinyl carbocation intermediate *in situ*. An example is the reaction of hex-1-yne with a catalytic amount of sulfuric acid in an aqueous solvent. The initial reaction of the vinyl carbocation with water in the aqueous solvent leads to an oxonium ion. Loss of a proton in an acid-base reaction generates hex-1-en-2-ol where the OH unit is attached to a sp^2 hybridized carbon of a C=C unit rather than a sp^3 hybridized carbon. A compound in which an OH unit is attached to the C=C unit is known as an *enol*. Although it is not obvious based on anything previously discussed, *enols are known to be unstable*. An internal acid-base proton transfer converts enols to a carbonyl derivative, an aldehyde, or a ketone. This process is called *keto-enol tautomerization* and *tautomerization favors the keto form* hexan-2-one. Enols are discussed in more detail in Section 20.1. Note that tautomers are a distinct chemical species that can be identified by their different spectroscopic data.

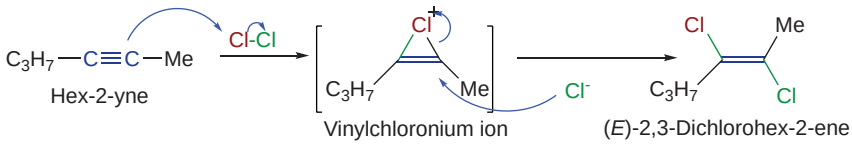


10.20 Draw both enol products expected when 5-methylhex-2-yne is treated with an acid catalyst in aq THF. Draw the carbonyl products expected from each enol.

Dihalogenation of Alkynes

10.8.3 DIHALOGENATION OF ALKYNES

Just as an alkene reacts with diatomic bromine, chlorine, or iodine, so an alkyne will react. Alkynes react with diatomic chlorine, bromine, or iodine to yield a dihalogenated alkene. Only one of the two π-bonds reacts. As example of the *dihalogenation of alkynes* is the reaction of hex-2-yne with chlorine (Cl_2), and the isolated product is a trans-vinyl dichloride, 2,3-dichlorohex-(2*E*)-ene. Formation of this product is explained by an intermediate "vinylchloronium ion," analogous to the halonium ions formed from alkenes in Section 10.5. The chloronium ion reacts with the nucleophilic chloride ion (Cl^-) via anti- attack on the face opposite the first chlorine atom. The final product is the *trans* alkene shown. In all dihalogenation reactions of alkynes, a vinyl halonium ion is the intermediate and the final product is a trans-vinyl dihalide.



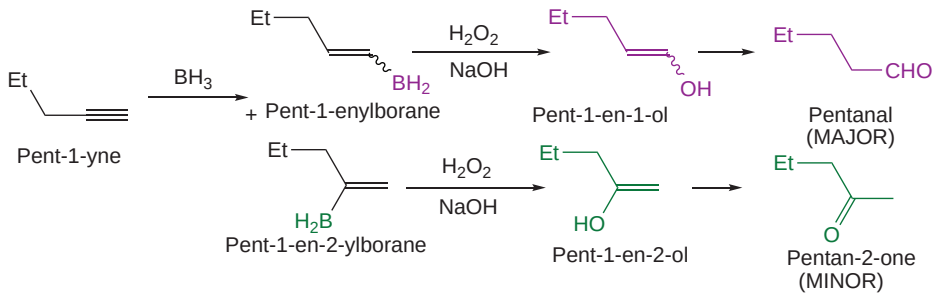
The trans-dihalide product is susceptible to further reaction with bromine, chlorine, or iodine to give tetrahalo derivatives. When pent-1-yne reacts with one molar equivalent of diatomic bromine, for example, 1,2-dibromopent-(1*E*)-ene is the product. In the presence of an excess of bromine, however, 1,2-dibromopent-(1*E*)-ene reacts with a second molar equivalent of bromine to give 1,1,2,2-tetrabromopentane. It is also possible to react pent-1-yne with one equivalent of chlorine to give 1,2-dichloropent-1*E*-ene and then add on equivalent of bromine to give 1,2-dibromo-1,2-dichoropentane. A number of highly halogenated alkanes may be prepared in this manner.

10.21 Draw the intermediate and final product(s) formed when 1-cyclohexylbut-1-yne reacts with iodine.
10.22 Draw the product(s) formed when 1-phenylbut-1-yne reacts with one molar equivalent of iodine and then with one molar equivalent of bromine.

10.8.4 HYDROBORATION OF ALKYNES

Hydration and Hydroboration of Alkynes

In Section 10.6, the π-bond of an alkene was shown to react with the H—B unit of borane via a four-center transition state to give an alkylborane. In this reaction the boron attaches to the less substituted carbon atom of the C=C unit. Alkynes are expected to react similarly, but only one π-bond of the alkyne reacts, so the product is a *vinylborane* ($R_2B—C=C$) rather than an alkylborane ($R_2B—CHR_2$).



The reaction of borane with a terminal alkyne will give the product with boron on the less substituted carbon, which is a primary vinylborane, $RCH=CHBH_2$. A small amount of the secondary vinyl borane is also formed, $BH_2(R)CH=CH_2$). An example is the reaction of pent-1-yne with BH_3, where the major product is pent-1-enylborane and the minor product is pent-1-en-2-ylborane. Subsequent reaction with NaOH and H_2O_2 replaces each BH_2 unit with an OH as expected, so pent-1-en-1-ol is the major product and the minor product is pent-1-en-2-ol. Both enols are unstable and tautomerize to the corresponding carbonyl derivative, pentanal and pentan-2-one respectively. Pentanal is the major product. In general, hydroboration of a terminal alkyne leads to an aldehyde as the major product, whereas hydroboration of an internal alkyne gives a mixture of two isomeric ketones.

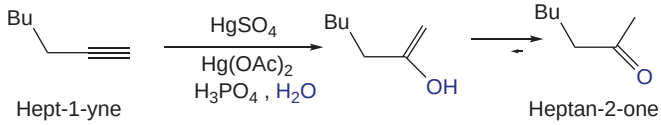
10.23 Draw both vinylborane products formed when pent-2-yne reacts with borane, and both ketones formed when the vinylboranes are oxidized.

10.8.5 OXYMERCURATION OF ALKYNES

Oxymercuration occurs with an alkyne just as with an alkene, but differences in the reactivity of alkenes and alkynes lead to a modification in the procedure. Specifically, the reaction of an alkyne and a mercuric compound leads to a vinyl mercury compound. This intermediate decomposes and mercury is lost without treatment with sodium borohydride, so different reagents are used for oxymercuration. For example, a mixture of both mercuric sulfate ($HgSO_4$) and mercuric acetate [$Hg(OAc)_2$] reacted with hept-1-yne in an aqueous acid solution. The initially formed vinylmercury compound decomposed to a secondary vinyl carbocation. Reaction with water and loss of a proton gave the enol in situ without the need to add $NaBH_4$ in a second step. Tautomerization gave heptan-2-one in 80% yield.[13] In the oxymercuration of alkynes, the reaction of a terminal alkyne yields a ketone. Oxymercuration of an

[13] Thomas, R.J.; Campbell, K.N.; Hennon, G.F. *Journal of the American Chemical Society* 1938, 60, 718–720.

internal alkyne such as pent-2-yne gives two different ketone products, pentan-2-one and pentan-3-one.

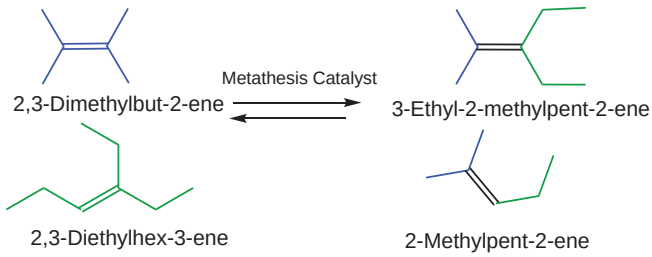


10.24 Draw the enol and ketone product formed when cyclopentylethyne is treated with mercuric sulfate and mercuric acetate in water containing phosphoric acid.

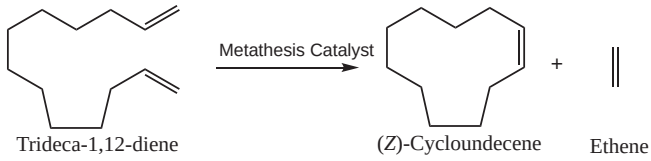
Metathesis

10.9 METATHESIS

In the presence of certain transition metal catalysts, two alkenes such as 2,3-dimethylbut-2-ene and 2,3-diethylhex-3-ene react to form 3-ethyl-2-methylpent-2-ene and 2-methylpent-2-ene in an equilibrium reaction, as shown. This reaction is known as *metathesis* or *alkene metathesis* (an older term is *olefin metathesis*).[14] The mechanism of this reaction is probably a chain mechanism that involves initial formation of a metal-carbene complex for each of the alkenes.[15] A transition metal carbene complex is an organometallic compound (Chapter 14) with a carbene coordinated to the metal.



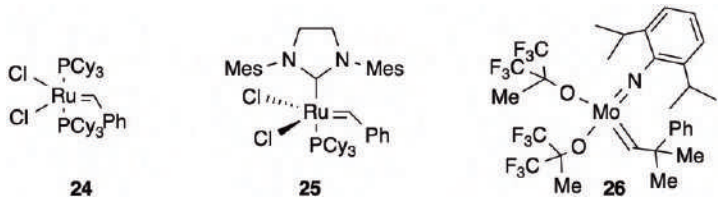
A carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons (R_2C:). The metal-carbene of each alkene reacts with each alkene to form a four four-membered ring complex that contains a metal. Each complex decomposes to regenerate 2,3-dimethylbut-2-ene and 3-ethyl-2-methylpent-2-ene but 3-ethyl-2-methylpent-2-ene and 2-methylpent-2-ene as well as the metal catalyst are also generated.



The intermolecular metathesis reaction is not very useful since all four possible alkenes are present in an equilibrium that favors the more stable alkenes. However, the intramolecular reaction of a diene with two terminal C=C units is very useful because the volatile ethylene is one of the metathesis products and escapes from the reaction to shift the equilibrium. Trideca-1,2-diene reacts with a metathesis catalyst, for example, to give cycloundecane and ethylene. This cyclization reaction is known as *ring-closing metathesis (RCM).*

[14] (a) Ivin, K.J. *Olefin Metathesis*, Academic Press, New York, 1983; (b) Grubbs, R.H. *Tetrahedron* 2004, 60, 7117–7140; (c) Smith, M.B. *March's Advanced Organic Chemistry*, 8th ed. John Wiley & Sons, New Jersey, 2020, pp. 1424–1431.

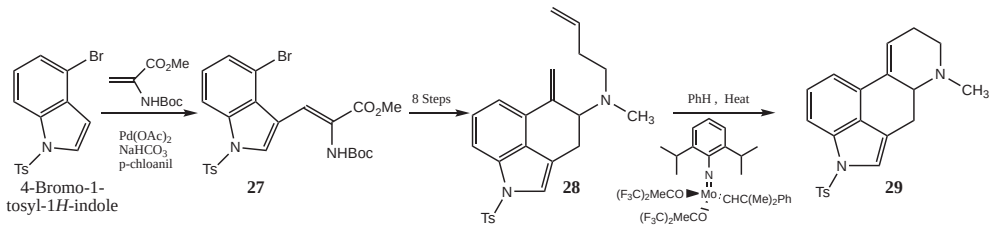
[15] Lindner, E. *Advances in Heterocyclic Chemistry* 1986, 39, 237–279.



The modern utility of RCM reactions also relies of the development of reliable transition metal catalysts. Perhaps the three most useful are the ruthenium carbene complexes called the *Grubbs I catalyst* (**24**),[16] and the *Grubbs II catalyst* (**25**),[17] named for Nobel Laureate Robert H. Grubbs, USA (1942-2021). Another important catalyst is the molybdenum carbene complex called the *Schrock catalyst* (**26**), named for Nobel Laureate Richard R. Schrock, USA.[18] Note that Mes is mesitoate, 2,4,6-trimethylbenzoate, and Cy is cyclohexyl.

Katherine Lee (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Katherine Lee (USA) a member of the Inflammation and Immunology Research Unit at Pfizer, Inc., where she is the Head of Scientific Planning and Operations. Katherine is an expert in medicinal chemistry, with research interests including fragment-based drug design, structure-based drug design, and optimization of ADME and safety properties. Katherine is a co-inventor of several clinical compounds, including a first-in-class IRAK4 inhibitor in Phase 2 and two $cPLA_2$a inhibitors that achieved Phase 2 Proof of Concept. In collaboration with Professor Stephen Martin (University of Texas, Austin) she developed a novel synthesis of Ergot alkaloids that used a Heck reaction (Section 19.6) and a ring closing metathesis reaction to give the tetracyclic ergoline ring system. An initial reaction of 4-bromo-1-tosyl-1*H*-indole with methyl 2-((*tert*-butoxycarbonyl)amino)acrylate in the presence of palladium acetate, sodium bicarbonate and chloranil (tetrachloro-1,4-benzoquinone) gives **27**. In eight chemical steps, **27** is converted to tricyclic indole **28**. An intramolecular metathesis reaction occurs when **28** is heated with the Shrock catalyst (**26)** in benzene at reflux, to give **29**. Treatment with Mg in methanol gives the ergoline by converted the N–Ts unit to a N—H unit. Note that Ts is tosyl, $-SO_2C_6H_4(4\text{-}CH_3)$.



[16] Schwab, P.; Grubbs, R.H.; Ziller, J.W. *Journal of the American Chemical Society* 1996, 118, 100–110.
[17] Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. *Organic Letters* 1999, 1, 953–956.
[18] Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *Journal of the American Chemical Society* 1991, 113, 6899–6907.

10.10 NON-IONIC REACTIONS. RADICAL REACTIONS

A radical is a reactive intermediate with a single, unshared electron (Section 7.2). A carbon radical can be viewed as a trivalent species containing a single electron in a p orbital. It is generally conceded that carbon radicals without significant steric encumbrance are planar, as represented by the carbon radical shown in Figure 10.20. In terms of its reactivity, a radical may be considered electron rich or electron poor. In most of its reactions, the electron-deficient characterization is useful since radicals such as this are not nucleophilic.

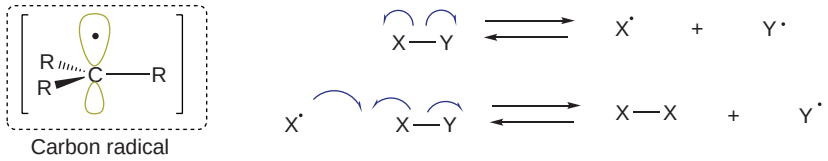


FIGURE 10.20 Carbon radicals and homoallylic cleavage reactions.

Radicals can be formed in several ways. Many reactions that generate radicals involve dissociative *homolytic cleavage* as a key step, as represented in Figure 10.20. In homolytic cleavage, one electron is transferred to each adjacent atom from the two-electron bond. The dissociation of X—Y gives two radical products, X● and Y●. Another important route to radical intermediates shown in Figure 10.20 involves the reaction of a radical (X•) and a neutral molecule (X—Y to give a new radical (Y•) and a new neutral molecule (X—X).

There are several reagents that generate radicals when heated or exposed to light (the symbol for a photon of light is $h\nu$). The dissociation of several compounds is shown in Figure 10.21. When heated, many peroxides undergo homolytic cleavage to generate radicals. Alkylhydroperoxides, ROOH, give RO● + ●OH and dialkylperoxides, ROOR), give two molar equivalents of RO●. *tert*-Butylhydroperoxide, for example, gives the *tert*-butoxy radical and the hydroxyl radical. Dibenzoyl peroxide (or just benzoyl peroxide), gives two molar equivalents of the acyl radical ($PhCO_2$●) when heated. Once formed, the acyl radical usually decomposes to generate two equivalents of the phenyl radical and carbon dioxide. Acyl compounds will be discussed in Chapter 18 in the context of carboxylic acid derivatives. The third reagent is an *azo compound* called *azobisisobutyronitrile* (AIBN). When heated, AIBN decomposes to produce two molar equivalents of the radical shown, along with nitrogen gas, which escapes from the reaction.

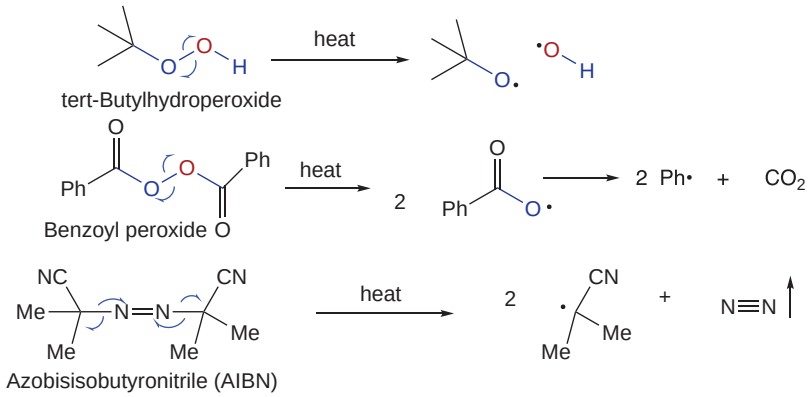


FIGURE 10.21 Radical initiators.

Alkenes React with HBr and Radicals

The acid-base reaction of an alkene with HBr gives the more substituted (and more stable) carbocation intermediate, as shown in Section 10.2. The major product has the halogen attached to the more substituted carbon. In experiments designed to further examine this reaction, HBr was added to undec-10-enoic acid in a hydrocarbon solvent, but benzoyl peroxide was added to the reaction. The isolated product was 11-bromoundecanoic acid, obtained in

70% yield.[19] In this product, the bromine is attached to the *less substituted carbon,* so it is categorized as an *anti-Markovnikov addition*. Since the reaction does not follow Markovnikov addition, the reaction does not proceed by formation of a carbocation. The normal mechanism for the reaction of HBr is changed by the addition of the peroxide. The complete mechanism of peroxide-mediated bromination is shown in Figure 10.22, beginning with the decomposition of benzyl peroxide to yield the acyl radical, which decomposes to the phenyl radical and CO_2.

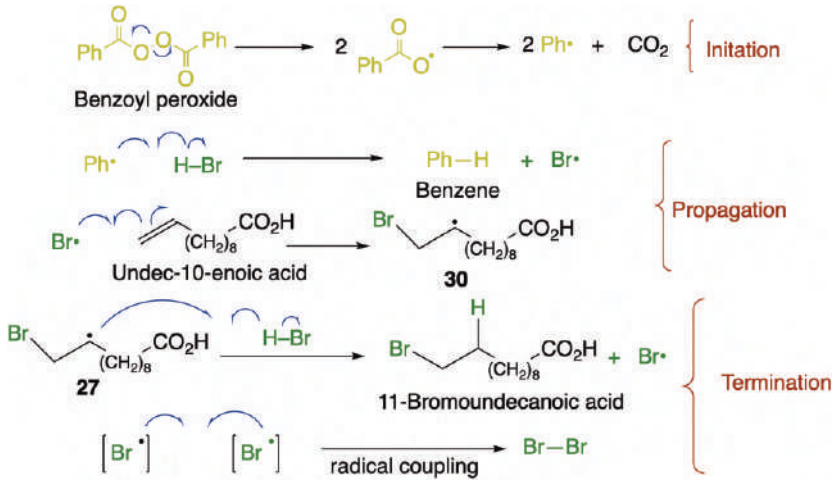


FIGURE 10.22 Mechanism of radical bromination of alkenes.

Reaction with HBr forms benzene and the bromine radical, Br•. The alkene unit in undec-10-enoic acid reacts with Br• to give the more stable secondary carbon radical (**30**) rather than a less stable primary radical. Radical **30** reacts with the hydrogen atom from another molecule of HBr to yield 11-bromoundecanoic acid and another equivalent of the bromine radical. This reaction works well with HBr, but not with HCl or HI because only the bromine radical reacts in such a selective manner (Section 11.8). Note that there is no rearrangement in this radical reaction. This mechanistic sequence is described as a *chain radical reaction*. Initial cleavage of the peroxide first generates the radical. No product can be formed until a radical is formed to begin the process, so this is called the chain *initiation step*. The next two steps in the sequence produce a reactive radical that goes on to react with either HBr or alkene and is called a chain *propagation step* since formation of the product is propagated. When no radicals are produced in a reaction, the reaction sequence stops. Therefore, the steps where two radicals react to produce a neutral molecule (Br_2) is called a chain *termination step*.

10.25 Draw the final product of the following reaction sequence cyclopentylethene + benzoyl peroxide in the presence of HBr.

10.11 POLYMERIZATION

Alkene Polymerization

Polymerization

A macromolecule is a very large molecule that may be composed of thousands of covalently bonded atoms. Polymer chemistry focuses on the preparation and properties of macromolecules and polymers. Polymers can be subdivided into biopolymers such as proteins (Section 24.6), polysaccharides, or DNA and RNA (Section 25.6). Synthetic polymers such as plastics and synthetic fibers are derived from small organic molecules generically known as monomers. Polymers are high molecular weight substances, usually long chain organic molecules that are assembled from many smaller repeating units called *monomers*. A monomer is defined as the single molecule precursor to a polymer. Some alkenes are monomers

[19] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.65, p. 576.

for example. Apart from long chains, polymers exist with *branching* or *cross-linking* between the chains. A *low polymer* will have a molecular weight below ~ 10,000–20,000, whereas a *high polymer* will have a molecular weight between 20,000 and several million. A chemical reaction that forms polymers from monomers is called *polymerization*. Ionic polymerization is a chain-growth polymerization in which active centers are ions or ion pairs. Radical polymerization builds a polymer by the successive addition of radical building blocks.

There are several classifications of polymers. *Homopolymers* consist of chains with identical bonding linkages to each monomer unit, which usually means that the polymer is made from identical monomer molecules. (-[A-A-A-A-A-A]-). Copolymers consist of chains with two or more linkages usually implying two or more different types of monomer units (-[A-B-A-B-A-B]-). *Copolymers* can be prepared by polymerizing one alkene in the presence of another. Copolymers can be random where there is no definite sequence of monomer units. They can also be regular copolymers where there is a regular alternating sequence of each monomeric unit. *Block copolymers* can be formed. In these polymers there is a sequence (or block) of one monomeric unit followed by a sequence (block) of the second monomeric unit, and these "blocks" repeat. A *graft copolymer* links together two different polymers. A *thermoplastic* is a polymer that softens when it is heated, but it usually describes a polymer that passes through a specified sequence of property changes as it is heated. An *elastomer* is a polymer that exhibits a physical state between its glass transition temperature and its liquefication temperature. Finally, there are *polymer blends*, obtained when two polymers are mixed together by mechanical means.

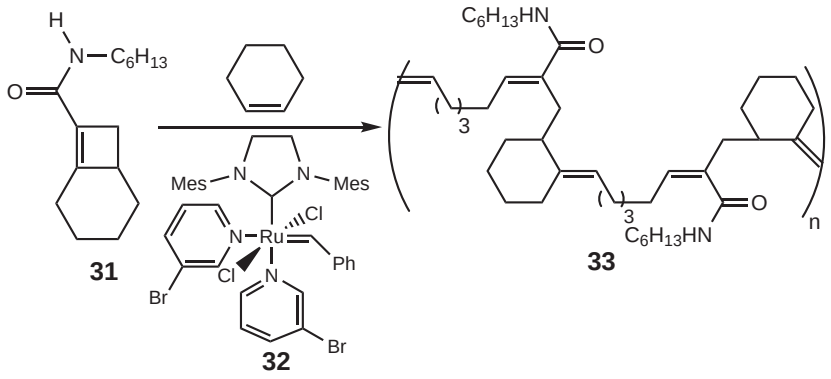
Radical polymerization of an alkene is a common method for the preparation of polymers. When the C=C unit of an alkene reacts with a radical X• to form a radical intermediate (X—C—C•), this radical can react with another molecule of the alkene to form another radical (X—C—C—C—C•). In this chain propagation reaction, another reaction with more alkene leads to X—C—C—C—C—C—C•. If this process continues, the final product is a *polymer*, $-(C—C)_n-$, where n is a large number (e.g., 500 or 2000) that represents the number of times that unit is repeated. In other words, there are 500 repeating C—C units or 2000 repeating C—C units. Ring opening polymerization can occur without the loss of any small molecules. Ring-opening metathesis polymerization (ROMP) is a type of alkene metathesis chain-growth polymerization. Relief of ring strain in an alkene monomer drives the reaction. The ROMP process is useful because a regular polymer with a regular amount of double bonds is formed. Propagation occurs via a metallacyclobutane intermediate as described in Section 10.9.

Nicole S. Sampson (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

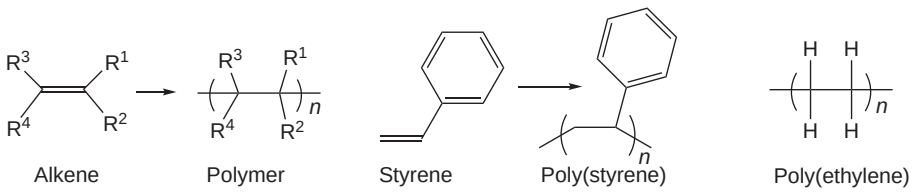
Professor Nicole S. Sampson (USA), at Stony Brook University does research into precision polymer synthesis for studying fertilization and cholera intoxication, and the study of lipid-protein interactions. Her work includes tuberculosis drug discovery and diagnosis through mycobacterial steroid metabolism. Recent work includes ruthenium-catalyzed ring opening metathesis polymerization, the design of new ROMP monomers, and the preparation of perfectly alternating copolymers.[20] The preparation of an AB copolymer requires two

[20] (a) Li, G. and Sampson, N.S. *Macromolecules* 2018 51, 3932–3940; (b) Zhang, J.; Li, G.; Sampson, N.S. *ACS Macro Letters* 2018, 7, 1068–1072.

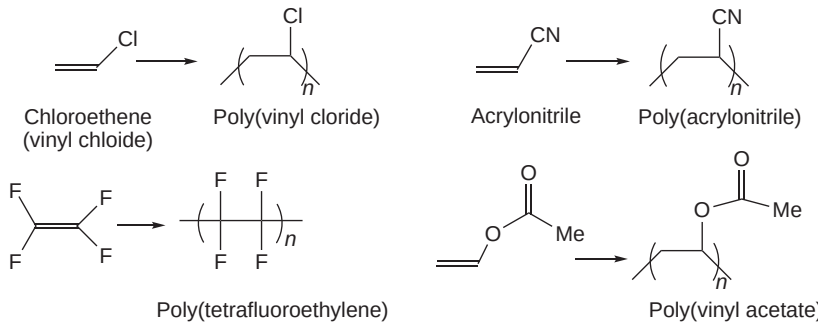
monomers, neither of which can homopolymerize but will undergo cross-polymerization. An alternating ring-opening metathesis polymerization (AROMP) reaction between bicyclo[4.2.0]oct-1(8)-ene-8-carboxamide **31** and cyclohexene using ruthenium catalyst **32** gave the alternating copolymer **33**. Alternating copolymers were prepared with different spacings between heteroatom functionalities on the side chains with tunable glass transition behavior and hydrophobicity.[20]



Many polymers are important in everyday life. When styrene (phenylethene) is heated in a special receptacle at 125 °C for several days the product is poly(styrene), an example of a linear polymer. The *n* in poly(styrene) indicates the number of times the styrene monomer unit is repeated, which varies with the way the polymer is formed. Poly(styrene) is widely used to manufacture plastic dinnerware. It is used to make polystyrene foam, marketed under the name of Styrofoam by Dow Chemical Co. Poly(ethylene) is prepared in several forms, including ultra-high molecular weight poly(ethylene) (UHMWPE), high-density polyethylene (HDPE), and medium-density poly(ethylene) (MDPE).

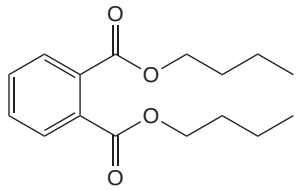


Ultra-high molecular weight poly(ethylene) is used to manufacture machine joints and gears and is used as a component of artificial hip and knee replacements. High-density polyethylene is used in milk jugs, detergent bottles, "plastic" toys, and water pipes while MDPE is used in gas pipes and packaging film. Low density poly(ethylene) products are typically prepared from a copolymer of ethylene that reacts with simple alkenes (e.g., but-1-ene or hex-1-ene). It is used in products such as Saran wrap, and bubble wrap. Poly(acrylonitrile) is often prepared as a copolymer that finds uses in membranes, filters, textile fibers, and as a chemical precursor to carbon fibers.



There are many other noteworthy polymers, including poly(vinyl chloride or PVC), poly(acrylonitrile) (trade names are Orlon® or Creslan®), poly(tetrafluoroethylene) or PTFE (Dupont's trade name for this material is Teflon®), and poly(vinyl acetate). Poly(vinyl chloride) is used in plumbing applications and in electrical cable insulation. Teflon is used as a non-stick coating for pots and pans, and as containers for corrosive chemicals. Teflon is used in bearings and gears and for the preparation of stopcocks in chemistry. Poly(vinyl acetate) is a component of wood glue and commercial glues, and is a component of adhesives for envelopes and wallpaper.

Polymers are often rigid and difficult to use. Compounds known as plasticizers can be added during the polymerization process. When dibutyl phthalate (see Section 16.8 for esters) is added to PVC, for example, a flexible polymer is produced. This material is known as Tygon® and is commonly seen in the laboratory as the clear "plastic" tubing. When Tygon® is used to transfer organic solvents from one place to another, the plasticizer may be leached out of the tubing and will subsequently be observed as a "product."



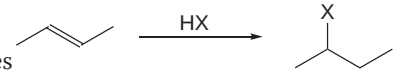
Dibutyl phthalate

10.12 ORGANIZATION OF REACTION TYPES

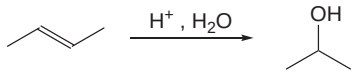
The reaction of alkenes and alkynes can be organized as follows:

What reactions are possible for alkenes?

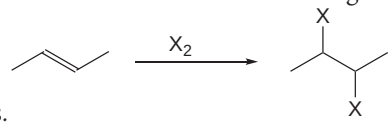
1. Alkenes react with Brønsted-Lowry acids, H—X, to yield alkyl halides



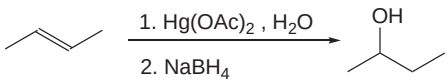
2. Alkenes react with weak acids (e.g., water and alcohols) using a catalytic amount of a strong acid to yield alcohols or ethers, respectively.



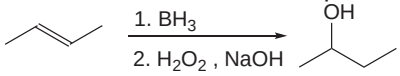
3. Alkenes react with dihalogens (X_2), to yield alkyl dihalides.



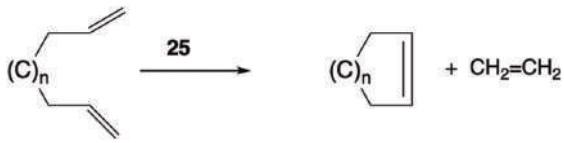
4. Alkenes react with mercuric compounds and water to yield an alcohol after reduction with $NaBH_4$.



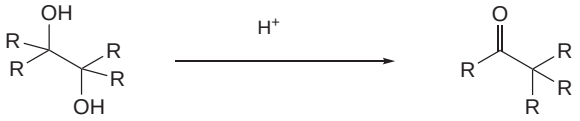
5. Alkenes react with boranes to yield alcohols, after treatment with NaOH/H_2O_2.



6. Terminal dienes react in the presence of a metathesis catalyst such as **24**, **25** or **26** to form cyclic alkenes: ring closing metathesis.

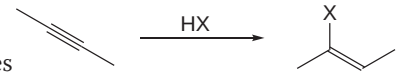


7. 1,2-Diols rearrange to ketone in the presence of an acid catalyst.

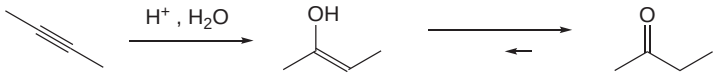


What reactions are possible for alkynes?

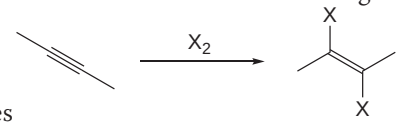
1. Alkynes react with Brønsted–Lowry acids, H—X, to yield vinyl halides



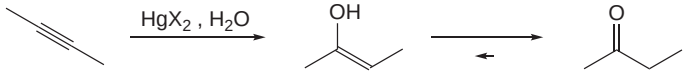
2. Alkynes react with weak acids (e.g., water and alcohols) using a catalytic amount of a strong acid to yield ketones or vinyl ethers, respectively.



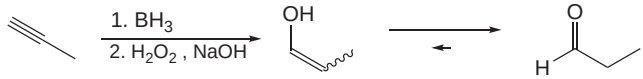
3. Alkynes react with dihalogens (X_2), to yield vinyl dihalides



4. Alkynes react with mercuric compounds and water to yield ketones or aldehydes.

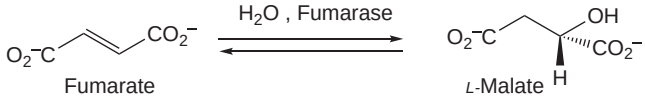


5. Alkynes react with boranes to yield aldehydes or ketones, after treatment with $NaOH/H_2O_2$.



10.13 BIOLOGICAL RELEVANCE

The hydration reaction of alkenes is known in biological systems. The Krebs cycle, also known as the citric acid cycle, is important for the metabolism of most aerobic cells. One step in this cycle converts fumarate to malate. This hydration reaction is catalyzed by the enzyme *fumarase hydrase*, or just *fumarase*.[21] This enzymatic conversion is a trans-addition of water, giving L-malate.[22]



[21] Lehninger, A.L. *Biochemistry*, Worth Publishers, Inc., New York, 1970, Chapter 16.
[22] Alberty, R.A. in Boyer, P.D.; Lardy, H.; Myrback, K. (Eds.), *The Enzymes*, 2nd ed., Academic Press, New York, 1961, p. 531 ff.

Halogenation is known in biological systems. In a biosynthetic process that produces C15 acetogenins derived from *Laurencia spp.*, a vanadium-dependent *bromoperoxidase* (V-BPO) enzyme is used for a bromoetherification reaction. Laurediol reacts with a V-BPO isolated from *L. nipponica* (Ln-VBPO) with bromide ion and hydrogen peroxide to give the metabolites, deacyllaurenicn and laurencin. The reaction proceeds via a bromonium ion, as shown in Figure 10.23 that reacts with an alcohol unit to give the ether. The C15 acetogenins are non-terpenoid cyclic ether metabolites.[23] Note that *Laurencia* is a genus of red algae that grows in temperate and tropical shore areas.

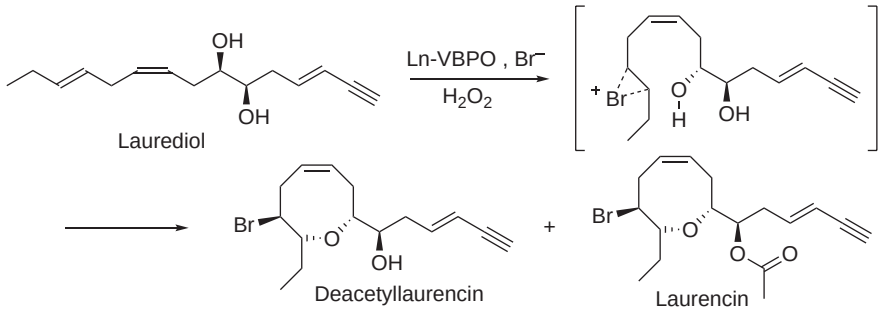
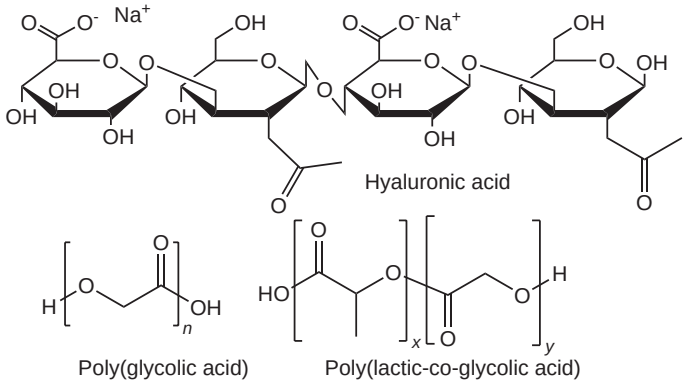


FIGURE 10.23 Biosynthesis of deacetyllutencin and Laurencin from laurediol by reaction with a vanadium-dependent bromoperoxidase (Ln-VBPO) derived from *L. nipponica*. Fukuzawa, A; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A.; Aye, M. *Chemistry Letters*, 1994, 23, 2307–2310. With Permission from the Chemical Society of Japan.

Biodegradable polymers reduce the harmful effects of the plastic waste that plagues the oceans and the land. Non-biodegradable plastic can take hundreds or even thousands of years to degrade. They often break down to small particles absorbed into human food stuffs or consumed by wildlife with devastating effects. Biodegradable polymers break down by a bacterial decomposition process to give benign products such as carbon dioxide or nitrogen, water, or inorganic salts. Such polymers are commonly composed of ester, amide, or ether functionality. Protein-based polymers, including collagen, albumin, gelatin, polysaccharides such as agarose, and *hyaluronic acid* are important for tissue engineering, drug delivery and nanomedicine. When used for drug delivery, the drug is carried to a specific site in the body, released as the polymer degrades. Degradation gives non-toxic material eliminated via metabolic pathways. Early biodegradable sutures were biopolyesters made from *poly(glycolic acid),* absorbed by the body and degraded over time. The hydrolytic instability of these sutures led to the development of copolymers such as *poly(lactic-co-glycolic acid*).



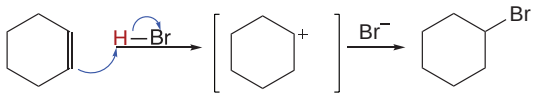
[23] (a) Fukuzawa, A; Takasugi, Y.; Nakamura, M.; Tamura, M.; Murai, A.; Aye, M. *Chemistry Letters* 1994, 23, 2307–2310; (b) Agarwal, V.; Miles, Z.D.; Winter, J.M.; Eustáquio, A.; El Gamal, A.A.; Moore, B.S. *Chemical Reviews* 2017, 117, 5619–5674.

CORRELATION OF HOMEWORK WITH CONCEPTS

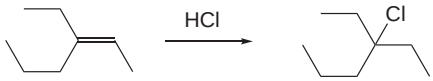
- Alkenes react as Brønsted-Lowry bases in the presence of strong mineral acids, HX. The reaction of alkenes and mineral acids (HX) generate the more stable carbocation, leading to substitution of X at the more substituted carbon. This is given the name Markovnikov addition: 1, 2, 3, 4, 26, 27, 28, 29, 32, 40. 42.
- If rearrangement can occur to yield a more stable carbocation, that carbocation is assumed to rearrange: 5, 6, 27, 30, 32, 42, 433, 46.
- Weak acids add to an alkene or an alkyne in the presence of a strong acid catalyst: 7, 8, 9, 19, 32, 35, 40, 42.
- Chlorine, bromine, and iodine react with alkenes or alkynes to yield a three-membered ring halonium ion, which reacts with the halide nucleophile to yield trans-dichlorides, dibromides, or diiodides. Alkynes react to yield vinylhalonium ions that lead to vinyl dihalides: 10, 11, 21, 22, 31, 32, 35, 37, 40.
- HOCl or HOBr react with alkenes to yield halohydrins: 12, 32, 35, 40.
- Mercuric acetate and water react with alkenes via a mercury-stabilized carbocation to yield a hydroxy alkyl-mercury compound. Reduction of the C—Hg bond with $NaBH_4$ leads to the Markovnikov alcohol. The reaction in an alcohol solvent leads to an ether product: 17, 18, 33, 34, 36.
- Alkynes react with an acid catalyst and water or with mercuric salts and water to yield an enol, which tautomerizes to a ketone: 20, 24, 33, 34, 40.
- Hydroboration of alkenes via a four-centered transition state gives an alkylborane. Reaction with $NaOH/H_2O_2$ gives an alcohol: 13, 14, 15, 16, 33, 35, 39.
- Hydroboration of alkynes leads to an enol after treatment with $NaOH/H_2O_2$, and tautomerization yields an aldehyde from terminal alkynes, or a ketone from internal alkynes: 23, 33, 40.
- Ring closing metathesis occurs with two alkenes or intramolecularly with terminal dienes in the presence of transition metal carbene catalysts: 44, 45
- In the presence of peroxides, alkenes react with HBr to yield the alkyl bromide having Br on the less substituted carbon. This is called anti-Markovnikov addition: 24, 33, 41.
- Spectroscopy is used to determine the structure of a particular molecule: 47, 48, 49, 50, 51, 52.

ANSWERS TO IN-CHAPTER PROBLEMS

10.1



10.2



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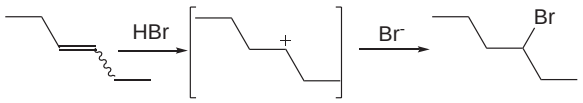
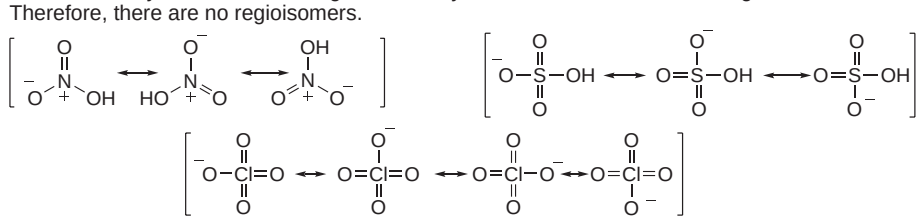


Hex-3-ene is symmetrical so a single secondary carbocation is formed, leading to one bromide. Therefore, there are no regioisomers.

10.4



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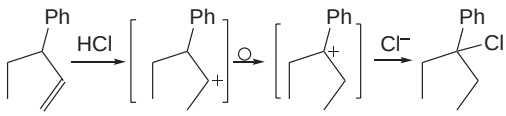

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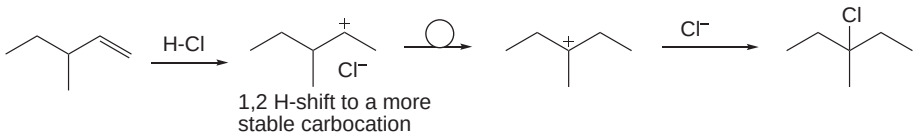
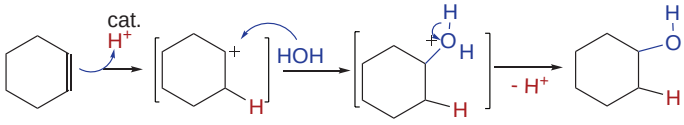


1,2 H-shift to a more stable carbocation

10.7



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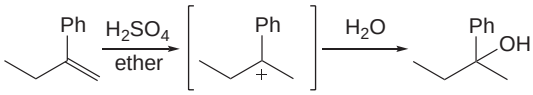

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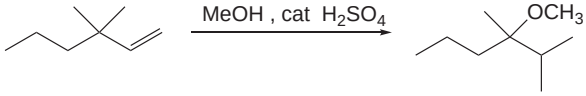
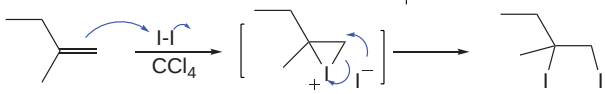


Via 1,2-methyl shift from a secondary carbocation to a tertiary carbocation

10.10



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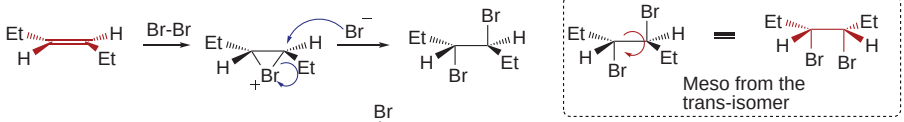
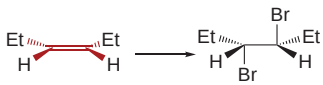
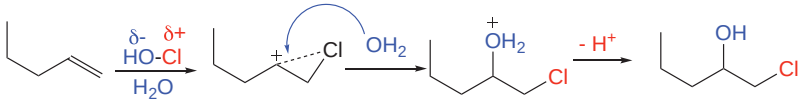




A cis-alkene leads to a mixture of enantiomers

10.12



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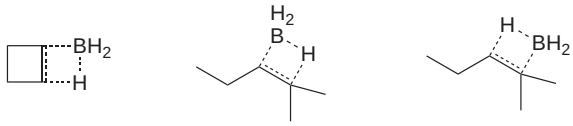

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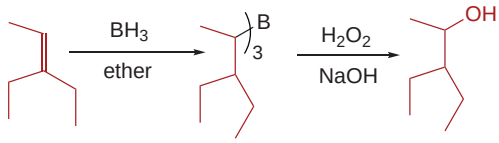

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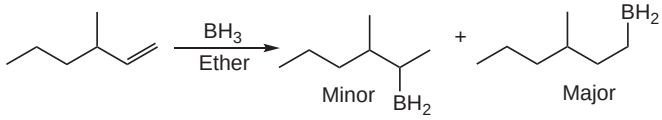

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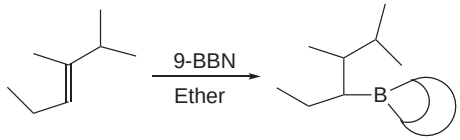

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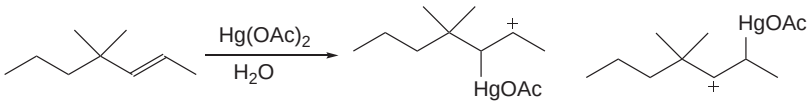
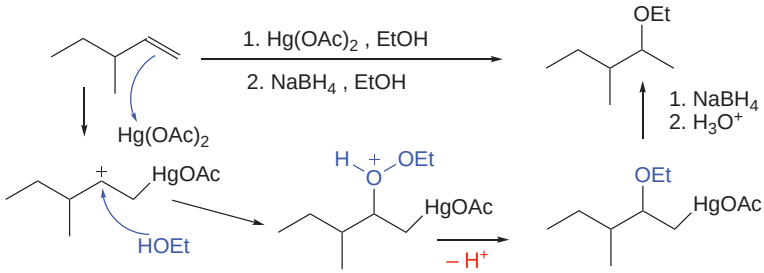


10.18



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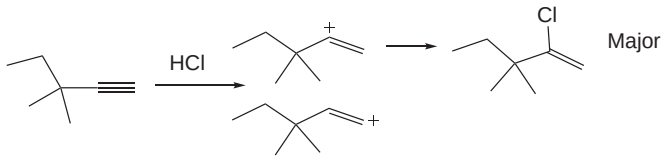

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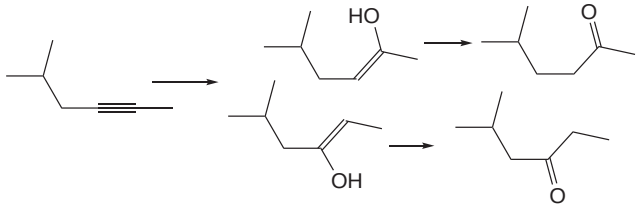

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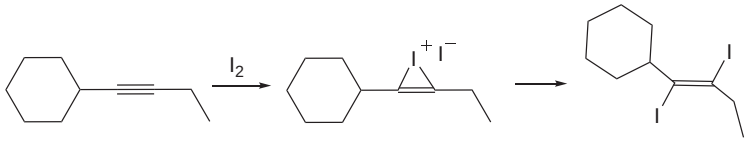

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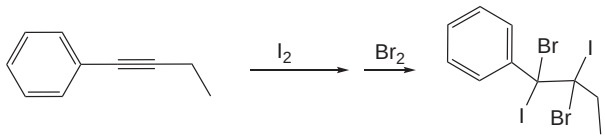

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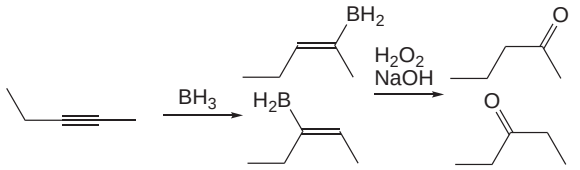

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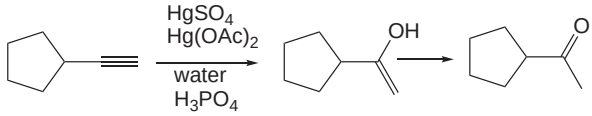

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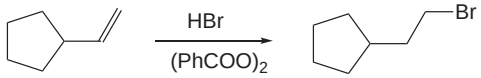
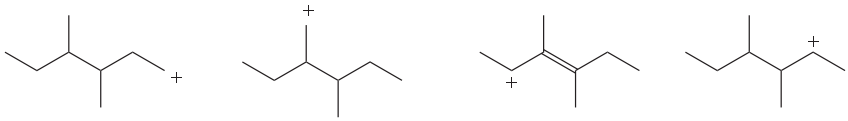


HOMEWORK

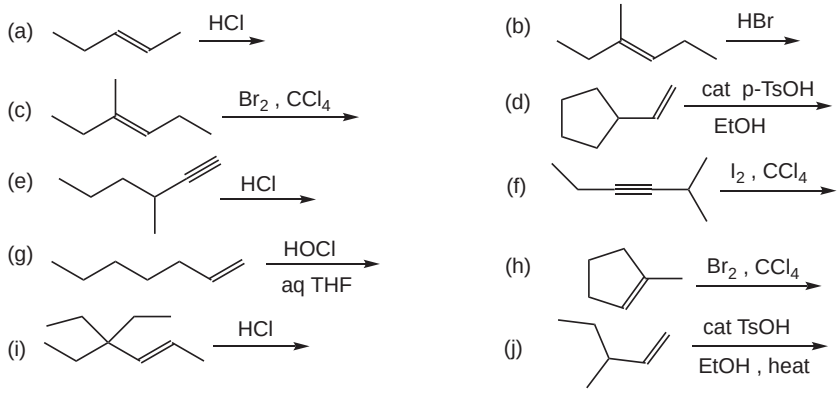
26. Which of the following molecules react with HBr to yield a vinyl bromide?

27. Briefly discuss why 2,3-dimethylbut-2-ene might react faster with HCl than with but-2-ene. Draw the mechanism for both reactions as part of your answer.
28. A carbocation is formed both when 2-methylprop-2-ene is reacted with a catalytic amount of acid, and a carbocation is also formed when acetone is treated with a catalytic amount of acid. Draw both carbocations cations and comment on their relative stability.
29. Which of the following is the more stable carbocation? *Assume* there is *no* rearrangement and explain.

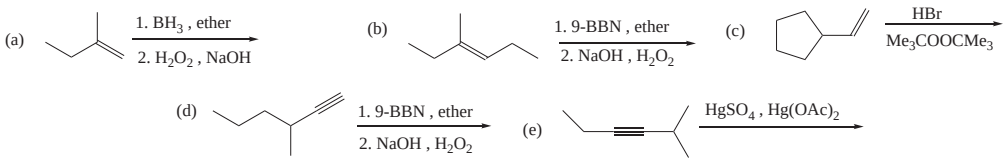


30. Draw the product expected when 1-(2-phenylcyclobutyl)-1-cyclohexene is treated with HBr and give a mechanism to support your answer.

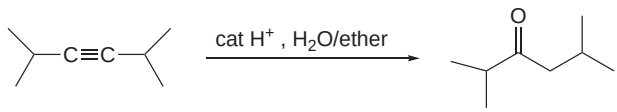
31. Bromine is a diatomic molecule that reacts with cyclopentene to form 1,2-dibromocyclopentane. Nitrogen is also diatomic but does not give a similar reaction. Why not?
32. Give the major product of the following reactions.



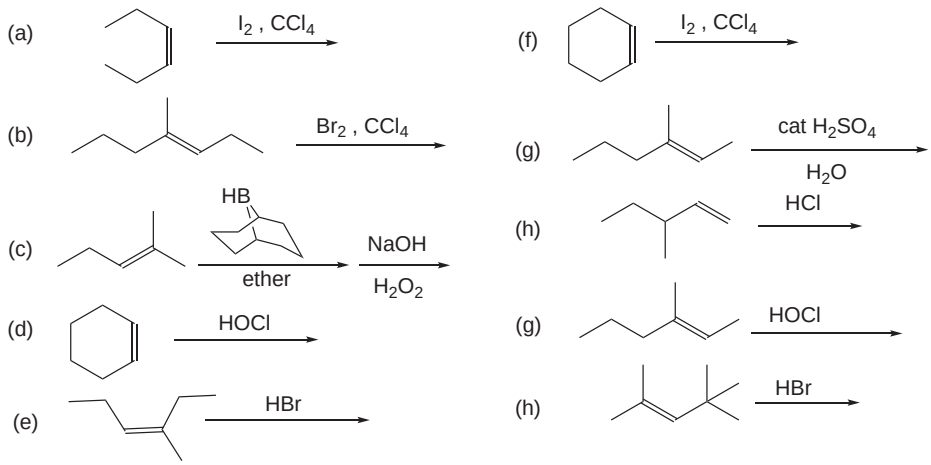
33. Give the major product of the following reactions:



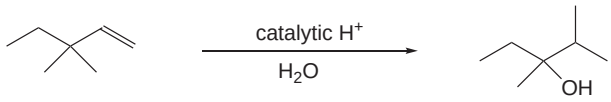
34. Give the major product formed from each of the following reactions:
    (a) Cyclohexene + 1. $Hg(OAc)_2$, H_2O 2. $NaBH_4$
    (b) 6-Phenyl-2,3,4-trimethyl-hex-1-ene + 1. $Hg(OAc)_2$, MeOH 2. $NaBH_4$
    (c) 1-Ethylcyclohexene + 1. $Hg(OAc)_2$, H_2O 2. $NaBH_4$
    (d) Hex-1-yne + 1. $Hg(OAc)_2$, EtOH 2. $NaBH_4$
35. Give a complete mechanism for the following reaction:



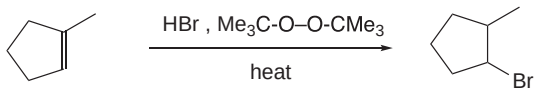
36. Explain why the reaction of *trans*-hex-3-ene and bromine is diastereospecific. Draw the product of this reaction.
37. Give the major product(s) for each of the following reactions: If there is no reaction, indicate by N.R. Remember stereochemistry where it is appropriate.



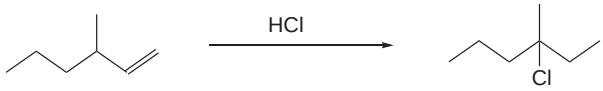
38. Give the complete mechanism for the following transformation.



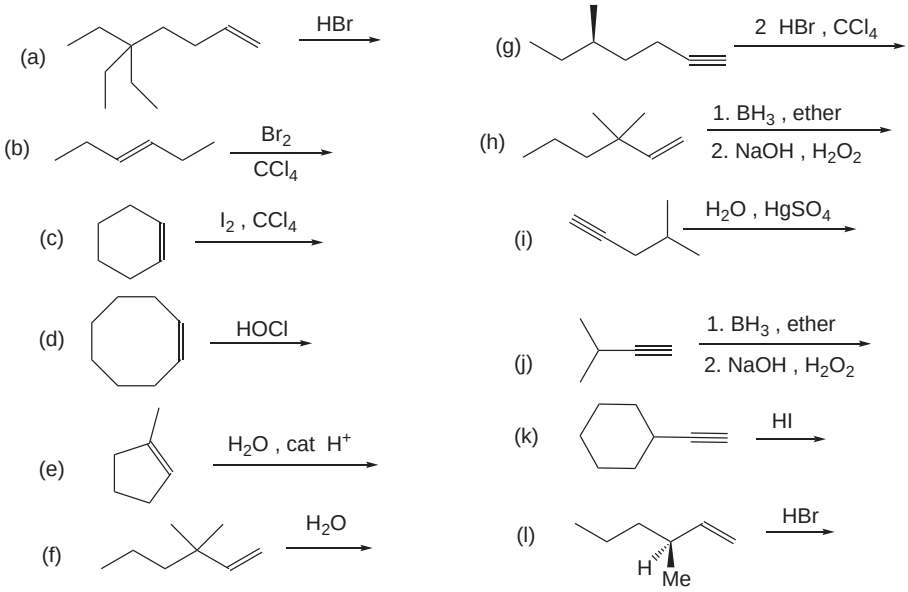
39. Briefly explain why the reaction of 3,3-dimethylpent-1-ene and BH_3 in ether leads to a borane with the boron atom at C1 rather than C2. Draw this product.
40. Give a detailed mechanism for the following reaction:



41. Give a complete mechanism for the following reaction:



42. Give the mechanism for the acid catalyzed conversion of 3,4-dimethylhexane-3,4-diol to 4,4-dimethylhexan-3-one.
43. What are the products form when 1,2-di(but-3-en-1-yl)cyclohexane is treated with the Grubbs II ruthenium catalyst (**25**)?
44. Why are dienes with two terminal C=C units used in ring closing metathesis reactions?
45. What is the product of the reaction of 1,2,3-triphenylethane-1,2-diol with an acid catalyst?
46. Give the major product for each reaction:



Spectroscopy Problems. Chapter 13 must be read and understood before attempting these problems.

47. Draw both possible products for the oxymercuration-demercuration of 3-phenyl-pent-1-ene. Use differences in the IR and ^{1}H NMR to compare the unrearranged and the rearranged products in order to distinguish them.
48. Hydroboration and oxidation of pent-2-yne can lead to two possible products. Draw both of them and briefly discuss differences in their IR and ^{1}H NMR that would allow one to distinguish them.
49. Methylenecyclopentene reacts with HBr and a peroxide. Draw both the regioisomeric products of this reaction and use IR and ^{1}H NMR to distinguish between them.
50. Identify the following molecule:(MS), IR, and ^{1}H NMR data: MS: 82 (M, 100%), 83 (M+1, 6.66%), 84 (M+2, 0.22%). IR: 2960–2840, 2054 (weak), 1430, 1340, and 1270 cm^{-1}. ^{1}H NMR: 1.05 (t, 3H), 1.62 (m, 2H), 1.80 (s, 3H) and 2.41 (t, 2H) ppm.
51. Identify the following molecule: MS: 164 (M, 100%), 165 (M+1, 6.66%), 166 (M+2, 98%) 41 (25), 43 (93), 55 (59), 56 (15), 57 (11), 71 (32), 85 (100), 135 (8), 137 (7). IR: 2964-2864, 1515-1435, 1382-1344, 1302, 1271-1263, 1166-1168, 1048-1014, 615-610 cm^{-1}. ^{1}H NMR: 3.46 (d, 2H), 1.45 (m, 1H), 1.43 (m, 4H), 0.9 (broad t, 6H) ppm.
52. Identify the following molecule: MS: 140 (M, 100%), 141 (M+1, 6.66%), 142 (M+2, 68%), and 144 (M+4, 35%) 41 (37), 42 (44), 55 (100), 68 (48), 69 (23), 104 (9), 106 (3). IR: 2994-2845, 1459-1436, 1348-1248, 1053-1000, 981-836, 1048-1014, 663, 469 cm^{-1}. ^{1}H NMR: 3.55 (broad t, 4H), 2.0-1.35 (broad m, 6H) ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-11.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

11

Substitution Reactions

In Section 6.9, a nucleophile was defined as a species that donates two electrons to carbon to form a new covalent σ-bond. Using a Lewis base analogy, a nucleophile is a two-electron donor, but the product is not an "ate" complex. Nucleophiles react with a variety of molecules that have electrophilic carbon atoms in a reaction where one atom or group replaces another. These are substitution reactions.

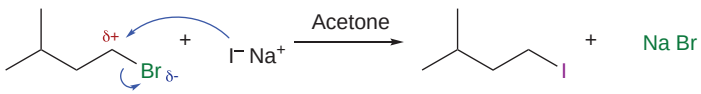
To begin this chapter, you should know the following points:

- Alkyl halides, ethers, alcohols, and alkynes (Sections 4.3, 5.1–5.6).
- Bond polarization and dipoles in a $^{\delta+}C—X^{\delta-}$ species (Section 3.8).
- Conformation of both acyclic and cyclic molecules of ring sizes of 3-6 atoms (Sections 8.1–8.7).
- An alkene reacts with HCl, HBr, or HI to form a carbocation (Sections 10.2 and 10.3).
- The relative stability of carbocation intermediates (Sections 7.2 and 10.1).
- Transition states (Section 7.6).
- Mechanisms (Section 7.10).
- Absolute configuration and stereoisomers (Sections 9.1–9.3).
- Diastereomers (Section 9.5).

11.1 ALKYL HALIDES, SULFONATE ESTERS, AND THE ELECTROPHILIC C—X BOND

Alkyl Halides & Sulfonate Esters

An old experiment mixed 1-bromo-3-methylbutane with sodium iodide (NaI) using acetone as a solvent. This mixture was heated to the boiling point of acetone and the isolated product was found to be 1-iodo-3-methylbutane, in 66% yield.[1] Sodium bromide (NaBr) was formed as a second product during the course of reaction as the sodium iodide was consumed. In terms of the structural changes, the iodide ion reacted as a nucleophile with the $C^{\delta+}$ of the alkyl halide, displacing for the bromine to form the bromide ion (Br^-). In other words, iodine substituted for bromine. This reaction is a nucleophilic substitution reaction, represented by the symbol S_N. The reaction follows second-order kinetics, so it is a *bimolecular reaction*, as described in Section 7.11.2, and the symbol "2" is used. This type of substitution is therefore known as a *S_N2 reaction (nucleophilic bimolecular substitution)*.



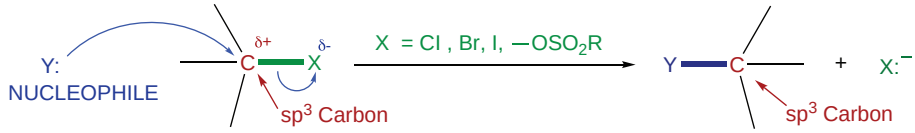
An alkyl halide (R—X) has a halogen atom attached to a carbon atom (C—Cl, C—Br, or C—I). These bonds are polarized (Section 3.8.1) and the carbon atom is electrophilic (δ^+). Chlorine, bromine and iodine are rather large atoms, so the C—X bond is elongated. Longer bonds are generally weaker and relatively easy to break. When an aliphatic (sp^3) carbon atom in C—X bond reacts with a nucleophile, Y^-, X is displaced as the X^- ion. The displaced X^- ion

[1] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.62, p. 572.

DOI: 10.1201/9781003174929-11

is a halide in this example and it is referred to as a *leaving group*. In a halide ion, the charge is dispersed over a large surface area, so it is rather stable. Greater stability is linked to poor reactivity, which is characteristic of a good leaving group. Note that a leaving group does not spontaneously "fly off" or "leave." It is displaced by the nucleophile after collision with the electrophilic carbon atom. In other words, the incoming nucleophile effectively "kicks out" the leaving group after collision with the electropositive carbon. Note that X cannot be hydroxyl in the reaction shown since *OH is a very poor leaving group*, in part because the OH is easily deprotonated if the nucleophile is basic.

Nucleophiles



Sulfonate esters (X is $-OSO_2R$) are derived from sulfonic acids (RSO_3H, Sections 6.2.2 and 18.3). The C—O bond of the alkyl sulfonate is polarized such that the carbon is electrophilic, analogous to alkyl halides. As with halides, the C—O bond is weaker. Once displaced the sulfonate anion (RSO_3^-) is stabilized by resonance and not very reactive. A sulfonate group is a good leaving group.

11.1 (a) Draw all resonance forms for the hydrogen sulfate anion, the conjugate base of sulfuric acid. (b) Replace the OH of the hydrogen sulfate anon with OMe and draw all resonance forms associated with the methanesulfonate anion.

Defining S_N2 Reactions

11.2 THE S_N2 REACTION

There are certain important characteristics of the S_N2 reaction shown in Section 11.1. To understand this reaction, each of these characteristics will be discussed.

11.2.1 NUCLEOPHILIC APPROACH TO AN ELECTROPHILIC CARBON

A simple example of an S_N2 reaction is the reaction of bromomethane with sodium iodide to give iodomethane and sodium bromide, as shown in Figure 11.1. This reaction follows second order kinetics so the iodide anion *must collide* with the polarized sp^3 carbon atom bearing the bromine atom. The electrophilic carbon is part of a three-dimensional molecule with a tetrahedral geometry. If the electron-rich iodide ion approaches the δ^+ carbon atom from the direction of the polarized δ^- bromine (Figure 11.1), there is steric repulsion between the iodide ion and the bromine atom. There is also electrostatic repulsion because both atoms are electron rich.

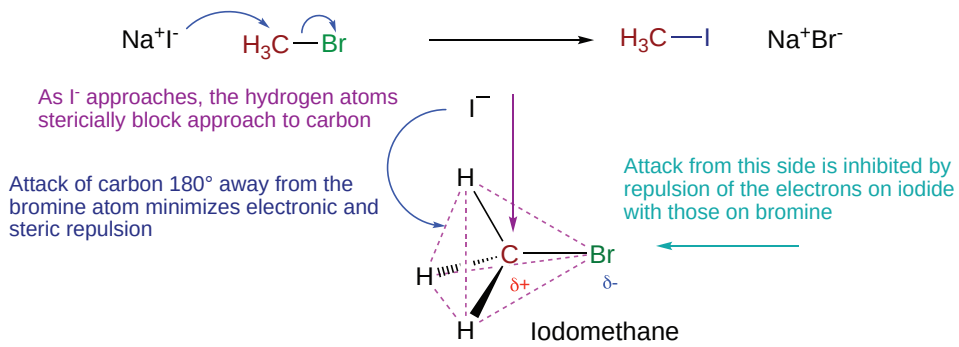


FIGURE 11.1 Nucleophilic attack on an aliphatic carbon.

If the iodide ion approaches carbon over one of the hydrogen atoms there is steric hindrance. The lowest energy approach that *minimizes both electronic and steric effects* is from the "bottom of the tetrahedron," or 180° (anti-) relative to the bromine atom. This approach angle constitutes the characteristic *backside attack* of a S_N2 reaction. Backside attack imposes an important stereochemical consequence. *The reaction must proceed by complete inversion of configuration.* Indeed, complete inversion of configuration is characteristic of an S_N2 reaction.

Pentacoordinate Transition State

In many years of experimentation, an intermediate has *never* been found in a S_N2 reaction such as that of NaI and bromomethane. An understanding must therefore focus on the *transition state*, which is the midpoint of the reaction, **1** in Figure 11.2. When the iodide ion collides with the bromine-bearing carbon via backside attack, the C—I bond begins to form. As the C—I bond begins to form, the three hydrogen atoms on carbon are "pushed away" from the incoming iodine atom, toward the departing bromine atom. In **1** the incoming iodine atom, the departing bromine atom and the three coplanar hydrogen atoms all surround the central carbon. Therefore, **1** has five atoms or groups around the central carbon and is known as a *pentacoordinate transition state*.

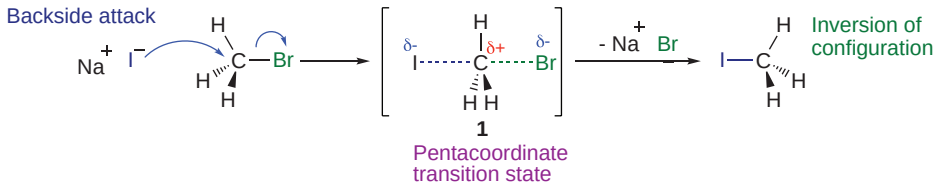
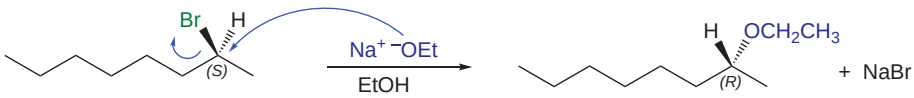


FIGURE 11.2 Pentacoordinate transition state for the reaction of sodium iodide and bromomethane.

All S_N2 reactions proceed by a pentacoordinate transition state. Once this transition state is achieved, the C—I bond continues to form and the bromide ion "leaving group" departs. Since NaI is the source of iodide, the sodium counterion migrates to the bromide ion, so the product is NaBr. It is important to point out that there are not five covalent bonds to carbon in a pentacoordinate transition state**,** but rather three covalent bonds with one bond being made as another is being broken. Remember that **1** is not an intermediate but a transition state so it is not isolated or even observed. Note that the conversion of bromomethane to iodomethane as shown in Figure 11.2 proceeds with inversion of configuration. There is no stereogenic carbon, so this inversion is not obvious. This inversion can only be observed if the S_N2 reaction occurs at a stereogenic carbon, as in the reaction of (+)-(2*S*)-bromooctane with sodium ethoxide (NaOEt) in ethanol. The product is an ether, (2*R*)-ethoxyoctane.[2] The starting material has a (*S*) stereogenic carbon and the ether product has an (*R*) configuration so reaction proceeds with inversion of configuration. Paul Walden (Latvia; 1863–1957)] first showed that the reaction of a nucleophile and a chiral alkyl halide led to inversion of configuration at the stereogenic center. The "inversion model" developed by his experiments is called *Walden Inversion* in his honor. Inversion of stereochemistry is conveniently determined by specific rotation measurements of the starting material and the product.



11.2 Draw the acid-base reaction of ethanol with the base sodium amide, $NaNH_2$.

11.2.2 REACTION RATE AND ENERGY REQUIREMENTS

Substitution and Structure

In an S_N2 reaction, the "2" indicates it follows second order kinetics. It is a bimolecular nucleophilic substitution, so there is a *collision* of the nucleophile with the electrophilic carbon

[2] Hughes, E.D.; Ingold, C.K.; Masterman, S. *Journal of the Chemical Society* 1937, 1196–1201.

atom of the alkyl halide. The rate is proportional to the concentration of both components: Rate (S_N2) ∝ [nucleophile] [halide]. Experimental determination of a proportionality constant k changes the equation to: Rate (S_N2) = k [nucleophile] [halide]. This proportionality constant is the second-order *rate constant* (Section 7.11.2). If the S_N2 reaction is slow, increasing the concentration of either the nucleophile or the halide substrate will increase the rate of the reaction. If one molar equivalent of KI reacts with one molar equivalent of 2-bromopentane at a given rate, for example, the identical reaction of one molar equivalent of 2-bromopentane with 10 molar equivalents of KI will increase the rate of reaction by a factor of 10.

11.3 Determine how much faster the rate will be if 1 molar equivalent of bromomethane is treated with 2.5 molar equivalents of KI in THF.
11.4 Draw the transition state and final product when (3*S*)-chloro-2-methylhexane reacts with KI.

The reaction of bromomethane was shown in Section 3.7 to be an endothermic reaction. When iodide and bromomethane collide, the energy transferred must be equal to the energy of activation (E_{act}) in order to initiate a S_N2 reaction. The bond-making and bond-breaking process begins, and the mid-point of the reaction is the pentacoordinate transition state, **1**. In other words, the reaction does not begin until the energy of activation (E_{act}) for the reaction is applied, as shown in Figure 11.3. Once the transition state is achieved the reaction continues with formation of the C—I bond and displacement of the bromide ion to give iodomethane.

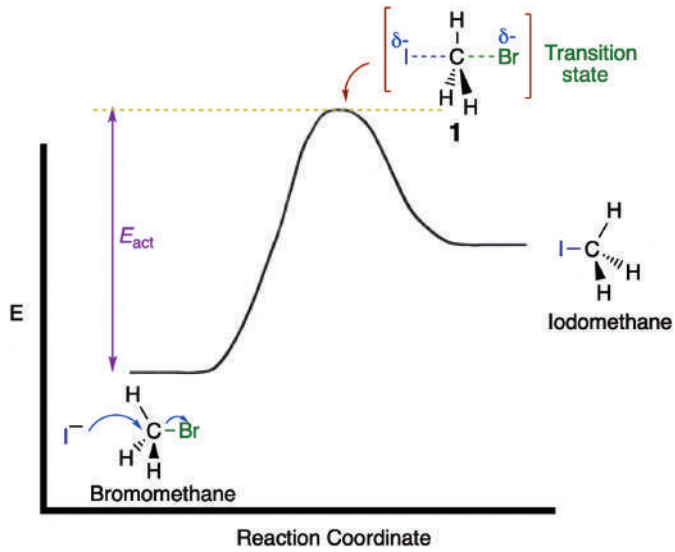


FIGURE 11.3 Energy of activation for the reaction of iodide with bromomethane.

Whether the alkyl halide in a putative S_N2 reaction is primary, secondary, or tertiary a pentacoordinate transition state is required. There are differences in the reactivity of alkyl halides with the nucleophilic iodide ion that are explained by the S_N2 transition state, **2**, where R^1, R^2, or R^3 are alkyl groups. There is more steric hindrance in the transition state as the number of alkyl groups increase. Figure 11.4 shows that the E_{act} required to attain transition state **2** increases as the number of alkyl groups around the electrophilic carbon increases. For a reaction with a halomethane (R^1, R^2, R^3 = H) there is minimal steric hindrance in **2**. Replacing hydrogen atoms with alkyl groups (R) will slightly increase the energy of transition state **2**. If a haloethane is used (R^1 = Me, R^2 and R^3 = H) the methyl group attached to the electrophilic carbon will increase the steric hindrance in **2** and E_{act} is higher. The reaction is slightly slower because the transition state energy is higher. In a secondary haloalkane (R^1 and R^2 = Me, R^3 = H), the two methyl groups provide even more steric crowding in **2**. The E_{act} is higher (higher) and the reaction significantly slower, but still facile. For a tertiary halide (R^1, R^2, R^3 = Me), there is great steric crowding in the pentacoordinate transition state **2** and

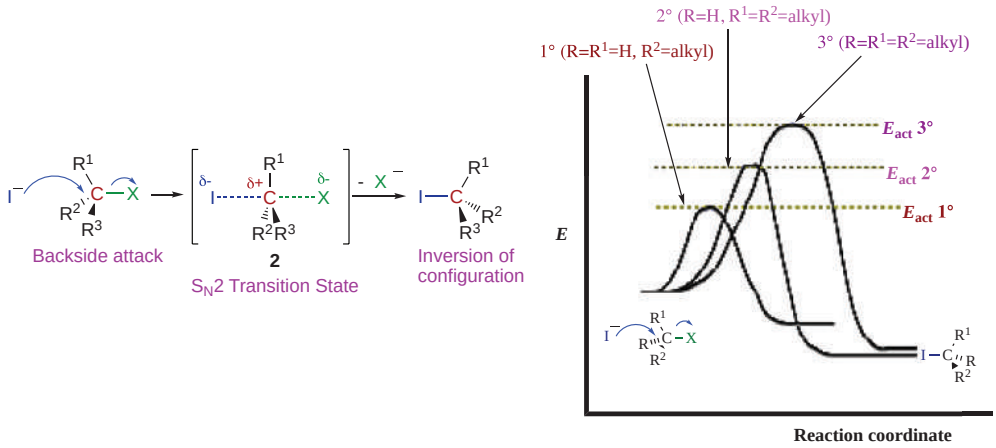
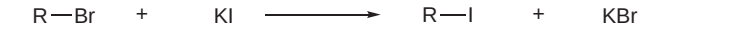


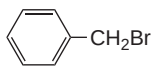
FIGURE 11.4 Energy of activation for the S_N2 transition state as a function of the reacting halide.

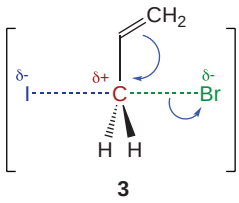
E_{act} is very high. *Indeed, the reaction does not occur.* The steric hindrance that impedes the reaction is *in the transition state*, and *not* at the electrophilic carbon of the alkyl halide. In other words, the nucleophile may collide with a tertiary carbon atom, but the activation energy for the reaction is so high that the S_N2 reaction does not occur.

A relative order of reactivity for alkyl halides in the S_N2 reaction is *methyl > 1° > 2° >>>> 3°* as shown by the data in Table 11.1.[3] In this figure the rate of reaction for bromomethane is used as a standard to compare the rate of reaction of the other halides in an S_N2 reaction. A

TABLE 11.1 The Reaction of KI with Primary, Secondary, and Tertiary Bromides [Reprinted in part with permission from Streitwieser Jr., A. *Chemical Reviews, 1956, 56*, 571. Copyright 1956 American Chemical Society.]



R–X	Relative Rate
CH_3Br	1
CH_3CH_2Br	3.3×10^{-2}
$(CH_3)_2CHBr$	8.3×10^{-4}
$(CH_3)_3Br$	5.5×10^{-5}
$(CH_3)_3C\text{-}CH_2Br$	3.3×10^{-7}
$CH_2{=}CHCH_2Br$	2.3
	4.0



3

smaller number for the relative rate means the reaction is *slower*, and a *larger* number indicates that the rate of reaction is *faster*. The relative rate for bromomethane (k_{Me}) is taken to be 1, and the reactions of 2-bromopropane or 2-bromo-2-methylpropane are slower. The molecule neopentyl bromide (1-bromo-2,2-dimethylpropane; 5th entry in Table 11.1) is interesting because it is a primary halide, but it reacts even slower than the tertiary halide. Although it is a primary alkyl halide, $C(CH_3)_3$ is a very large group that leads to enormous steric hindrance in the transition state **2** (Figure 11.4) making the reaction very difficult. In other words, neopentyl bromide reacts even slower than the tertiary bromide because the transition state is more sterically crowded and higher in energy. Both allyl bromide (3-bromoprop-1-ene, $CH_2{=}CHCH_2Br$) and benzyl bromide ($PhCH_2Br$), react faster than bromomethane. The π-bond participates in the transition state of the reaction in both molecules to help expel

[3] Streitwieser, Jr., A. *Chemical Reviews* 1956, 56, 571–752.

the bromide in the transition state, as illustrated by **3**. The three π-bonds in benzene ring of benzyl bromide provide greater assistance so benzyl bromide reacts faster.

11.5 Draw the transition state for the reaction of neopentyl bromide and KI.

Solvent Effect in S_N2 Reactions

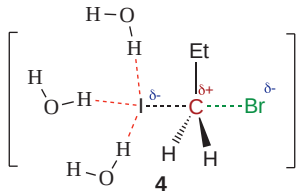
11.2.3 THE ROLE OF THE SOLVENT

Ethanol was used as a solvent in the reaction that converted (2*S*)-bromooctane to (2*R*)-ethoxyoctane in Section 11.2.1. The solvent is an essential component to most reactions. Not only does the solvent modulate energy gain and loss, but it also solubilizes the reactants to keep them in one phase, at least in most cases. The solvent also plays a subtle yet profound role in the S_N2 reaction.

Common solvents may be organized as to *polar or nonpolar* and then *protic* or *aprotic*.[4] A *polar solvent* is one with a substantial dipole and a *nonpolar solvent* tends to have a small dipole, or none at all. An important measure of polarity is the *dielectric constant*, which is the ability of a solvent to conduct charge. It is a good measure of the ability to solvate and separate ions. For substitution reactions, a high dielectric constant is associated with a polar solvent and a low dielectric is associated with a less polar solvent. Water has a dielectric constant of 78.5, for example, compared to 24.55 for ethanol, 32.7 for methanol, 16.9 for ammonia, and 6.15 for acetic acid.[4] Common aprotic solvents include carbon tetrachloride with a dielectric constant of 2.24, diethyl ether (4.34), THF (7.58), acetone (20.7), acetonitrile (37.5), DMF (36.71), and DMSO (46.68).[4] A further solvent classification defines a *protic solvent* as one that contains an acidic hydrogen (O—H, N—H, S—H) and it is essentially a weak Brønsted-Lowry acid. An *aprotic solvent* does not contain an acidic hydrogen.

In order to understand the role of a solvent in these reactions, common table salt (sodium chloride, NaCl) can be examined in water. When NaCl is added to H_2O, the electropositive hydrogen atom of water is attracted to the negative chloride ion. The electronegative oxygen atom of water is attracted to the positive sodium. As the polarized hydrogen atom in water hydrogen bonds to the chloride it "pulls" on the chloride. The polarized oxygen atom of water is attracted to and thereby "pulls" on the sodium. The water begins to separate the ions and pull them apart. Eventually, water molecules encroach between the two atoms and the sodium ion is completely surrounded by water (a solvated sodium), as is the chloride ion (a solvated chloride ion). This phenomenon is called *solvation*.

The polar and protic water can be contrasted with an aprotic solvent (e.g., ether). The oxygen atom is δ^-, and it can certainly coordinate to cations. The δ^+ atom is a tetrahedral carbon, however, and it is difficult for a negative anion or a negatively polarized atom to approach the carbon due to steric repulsion between the atoms. An aprotic solvent (e.g., diethyl ether) can solvate cations but not anions so *there can be no separation of charges (ions).*



4

An S_N2 reaction does not involve ionization such as that described for NaCl. It does involve a polar transition state that is influenced by the solvent. A charged nucleophile reacts with a neutral alkyl halide to generate a pentacoordinate transition state such as **1**. For the reaction of NaI and bromoethane, the S_N2 transition states has a charge distribution in the transition state where the nucleophile is δ^-, the central carbon is δ^+, and the leaving group is

[4] Lowry, T.H.; Richardson, K.S., *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, New York, 1987, pp. 297–298.

δ^-. If the solvent contains water, a charged nucleophile will be solvated (surrounded by water molecules as in **4**), which will inhibit collision with the sp^3 carbon atom. Since collision of iodide with the carbon atom is impeded, the S_N2 reaction is slower in an aqueous medium. If the solvent is changed to the aprotic diethyl ether, the negatively charged nucleophile is not well solvated, so it is easier for the nucleophile to approach and collide with the carbon atom. The most common polar aprotic solvents used in S_N2 reactions are diethyl ether, THF, dimethyl sulfoxide (DMSO; $Me_2S{=}O$), and *N,N*-dimethylformamide (DMF).

11.6 Draw the idealized solvated transition state for the reaction of $PhCH_2Cl$ with KI if H_2O is the solvent.

A different solvent effect is observed for the S_N2 reaction of 1-bromopropane with dimethylamine, as shown in Figure 11.5. The product of the reaction is the ammonium salt, propane-1-(*N,N*-dimethylammonium) bromide. The transition state for this reaction is shown as **5**.

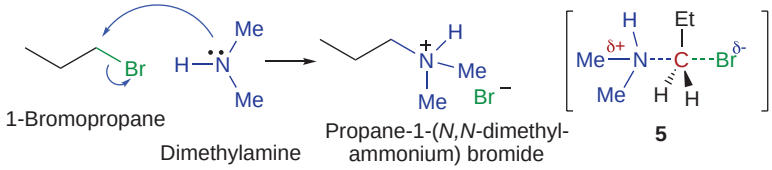


FIGURE 11.5 The reaction of dimethylamine with an alkyl bromopropane.

Examination of **5** shows a different charge distribution when compared with **4**. *The incoming nucleophile is neutral*. Transition state **5** shows that the nitrogen takes on a δ^+ dipole and the bromide takes on a δ^- dipole. A solvent such as water separates charge, and this separation facilitates conversion of **5** to the ionic products. This charge separation will *increase* the rate of reaction. Therefore, if the reaction of 1-bromopropane and dimethylamine to yield an ammonium salt product is carried out in an aqueous medium, the rate of the reaction is faster than when it is carried out in an aprotic solvent (e.g., THF). This acceleration of the reaction stands in sharp contrast to the reaction of potassium iodide and 1-bromopropane, a normal S_N2 reaction, which is faster in the aprotic solvent THF than it is in a protic solvent (e.g., H_2O).

11.7 In which solvent is the reaction of 1-iodobutane and diethylamine faster, aq THF or anhydrous THF?

11.8 Comment on the relative order of leaving group ability for these fragments: Cl, CH_3, OCH_3, NMe_2.

11.9 Draw the transition state and final product when the methanesulfonate ester of 4-phenyl-(2*S*)-butanol reacts with KI in THF.

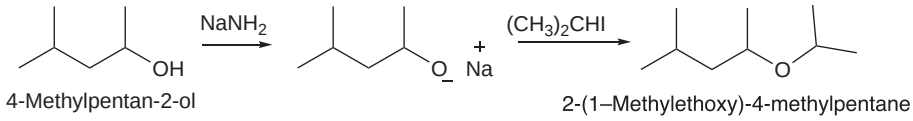
11.3 FUNCTIONAL GROUP TRANSFORMATIONS VIA THE S_N2 REACTION

Functional Group Transformations. Halide and O Nucleophiles

The S_N2 reaction is one of the more important transformations in organic chemistry since one functional group can be transformed into a different functional group. Halide ions are important nucleophiles to interconvert the halogen of alkyl halides. Alkyl chlorides with a Cl leaving group are less reactive in the S_N2 reaction and occasionally alkyl chlorides react so slowly as to be essentially useless. However, there is a synthetic "trick" that will increase the reactivity. When an alkyl halide is treated with NaI in the solvent acetone (propan-2-one; Section 5.6.2), an S_N2 reaction occurs to exchange the iodide ion with the less reactive chloride. Any subsequent S_N2 reaction is more facile. This transformation is known as the *Finkelstein reaction*, named after Hans Finkelstein (Germany; 1885–1938). Iodide can displace bromide or chloride, but bromide or chloride will *not* displace iodide. In general

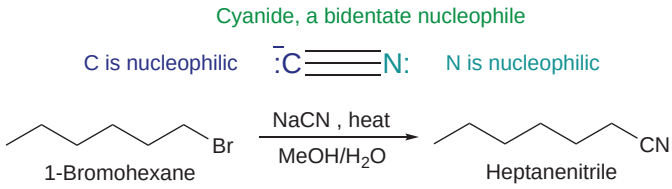
fluoride is a poor leaving group in the S_N2 reaction and it will not be used. The order of nucleophilic strength in S_N2 reactions is $I^- > Br^- > Cl^- > F^-$.

11.10 Offer an explanation to explain why the fluoride ion is a poor nucleophile.



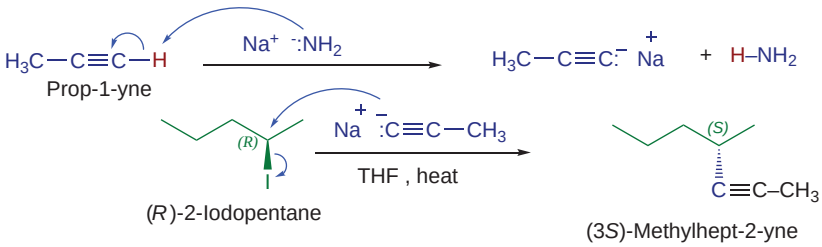
Alcohols can be converted to ethers. When an alcohol (ROH) reacts with a base the product is an alkoxide (RO^-), the conjugate base of the alcohol. In addition to sodium amide, sodium hydride (NaH) or sodium metal are commonly used as bases. An alkoxide is a nucleophile that reacts with alkyl halides in an aprotic solvent to form ethers. This transformation is known as the *Williamson ether synthesis*, named after Alexander W. Williamson (England; 1824–1904). An example is the reaction of 4-methylpentan-2-ol with sodium amide to give the conjugate base, the alkoxide. Subsequent reaction with 2-iodopropane gives 2-(1–methylethoxy)-4-methylpentane in a S_N2 reaction. Since the Williamson ether synthesis is an S_N2 reaction, a primary or secondary halide must be used but alkoxides from 1°, 2°, and 3° alcohols can be used.

11.11 What is the product when 1-chloro-3-phenylpentane reacts with KCN?



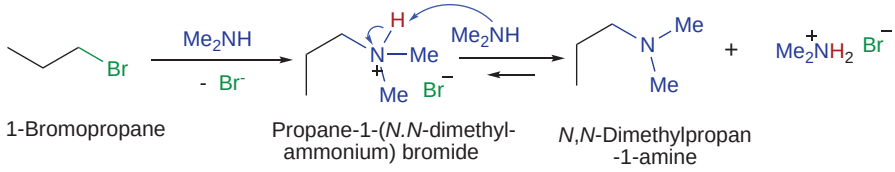
Alkyl halides can be converted to nitriles by reaction with the cyanide ion. Since both the carbon and the nitrogen have unshared electrons, each may react as a nucleophile. A nucleophile with two nucleophilic centers is called a *bidentate nucleophile*, but the formal charge is -1 on the carbon of the cyanide ion. Most reactions of cyanide as a nucleophile occur via carbon when NaCN or KCN are used, ^-CN. Therefore, sodium cyanide (NaCN) and potassium cyanide (KCN) react with alkyl halides via a S_N2 reaction to give a nitrile, RCN. An example is the reaction of 1-bromoheptane with NaCN in ether to give heptanenitrile. Nitriles are discussed in Section 18.12.

Functional Group Transformations. N and C Nucleophiles

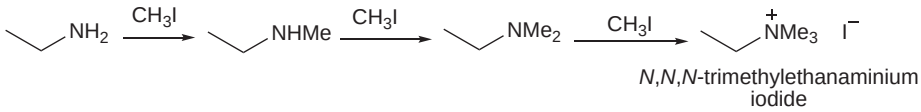


Alkyl halides can be converted to alkynes. As introduced in Section 6.6.1, the hydrogen atom of a terminal alkyne is a weak acid. The reaction of a terminal alkyne with sodium amide or another strong base generates the alkyne anion, which is a carbanion. Alkyne anions react as a carbon nucleophile with alkyl halides via a S_N2 reaction. An example is the reaction of (2*R*)-iodopentane with the propyne anion to give (3*S*)-methylhept-2-yne with the expected inversion of configuration.

11.12 Draw the final product when (2*S*)-iodo-(3*R*)-methylheptane reacts with the anion generated from 3,3-dimethylpent-1-yne.



Alkyl halides can be converted to amines. Primary and secondary amines react as nucleophiles with alkyl halides in S_N2 reactions. An example is the conversion of 1-bromopropane to propane-1-(*N,N*-dimethylammonium) bromide. This ammonium salt is a weak acid that is formed in the presence of dimethylamine, which is a base as well as a nucleophile. An acid-base reaction occurs between the acidic ammonium salt and the basic secondary amine to generate the neutral amine (*N,N*-dimethylpropan-1-amine) as the isolated product, along with dimethylammonium bromide. There are problems when primary amines react with structurally simple alkyl halides. If a primary amine (e.g., ethanamine) reacts with iodomethane, the initial product is *N*-methyethan-1-amine via the corresponding ammonium salt.



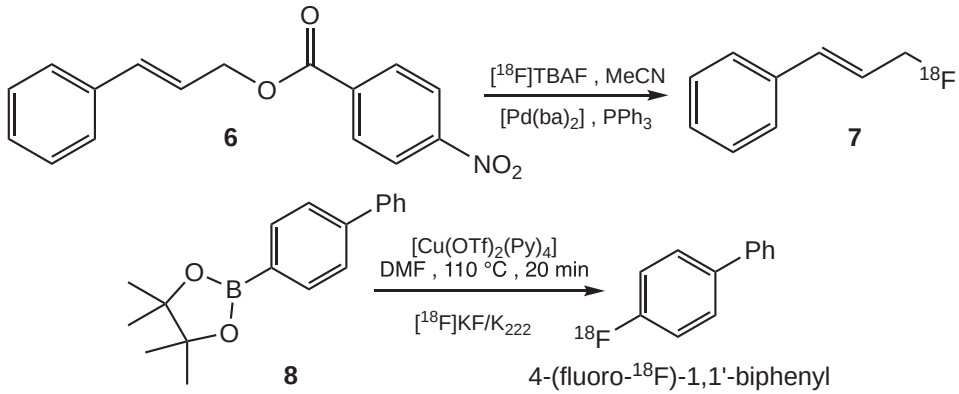
This secondary amine is *more reactive* than primary amine butan-1-amine since it is stronger nucleophile and a stronger base. It competitively reacts with iodomethane to form a tertiary amine (*N,N*-dimethylethan-1-amine), also via an ammonium salt. The *N,N*-dimethylethan-1-amine reacts with iodomethane to yield *N,N,N*-trimethylethanamminium iodide. This sequence is called *exhaustive methylation*. This is an example of *polyalkylation* of the amine, which should always be considered in reactions with alkyl halides.

11.13 Draw the final product when benzylamine ($PhCH_2NH_2$) is treated with a large excess of iodoethane.

Véronique Gouverneur

Substitution reactions that involve the fluoride ion are typically difficult. Fluorides have been categorized as poor nucleophiles. Véronique Gouverneur (Belgium-England), a professor of chemistry at the University of Oxford, has developed a transition metal catalyzed reaction that facilitates allylic fluorination reactions. Professor Gouverneur's interdisciplinary research

lies at the interface of chemistry and medicine. Her work in fluorine chemistry focuses on late-stage fluorination using both the naturally occurring isotope ^{19}F and the cyclotron-produced positron emitting radioisotope ^{18}F. Fluorine compounds have many applications, including in pharmaceutical drugs. These advances have found direct applications in the pharmaceutical sector and in clinical imaging, particularly Positron Emission Tomography (PET). PET is a diagnostic nuclear imaging modality that relies on automated protocols to prepare agents labeled with a positron-emitting radionuclide (e.g., ^{18}F). Professor Gouverneur developed the first ^{18}F carbon bond formation using a palladium-catalyzed method for the formation of allylic C—F bonds from allylic *p*-nitrobenzoates.[5] Allylic ester **6** was converted to allylic fluoride **7** in good radiochemical yield, for example, by reaction with tetrabutylammonium fluoride in acetonitrile, 5 mol% of $Pd(dba)_2$ and 15 mol% of triphenyl phosphine.[5] She has extended this work for the copper-mediated nucleophilic ^{18}F-fluorination of arenes.[6] The reaction of arylboronic ester **8** with $[Cu(OTf)_2(Py)_4]$, in DMF at 110 °C, with $[^{18}F]KF/K_{222}$ as the fluorinating agent gave 4-(fluoro-^{18}F)-1,1'-biphenyl in 74% radiochemical yield. Note that dba is dibenzylideneacetone, Py is pyridine, OTf is $-OSO_2CF_3$, DMF is dimethylformamide and K_{222} is Kryptofix 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane).

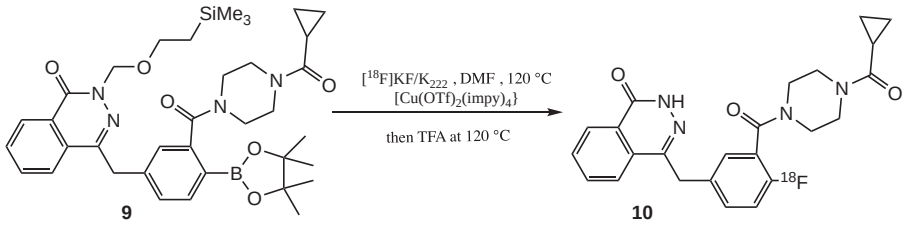


Poly(ADP-ribose) polymerase (PARP) inhibitors are increasingly being studied as cancer drugs, as single agents, or as a part of combination therapies. Imaging of PARP using a radiolabeled inhibitor such as the ^{18}F-labeled equivalent of Olaparib (**9**) allows direct prediction of the distribution of the drug. Olaparib is a medication for the maintenance treatment of BRCA-mutated advanced ovarian cancer in adults. Professor Gouverneur prepared $[^{18}F]$olaparib from the protected N-[2-(trimethylsilyl)ethoxy]methyl (SEM) arylboronate ester precursor in 17% yield.[7] The ^{18}F -labeled, SEM-protected (trimethylsilylethoxymethyl) borylated precursor of Olaparib with $Cu(OTf)_2(impy)_4$ [tetrakis(imidazo[1,2-b]'pyridazine) copper(II) triflate] in DMI (1,3-dimethyl-2-imidazolidinone, a cyclic urea), at 120 °C for 20 min followed by deprotection afforded the $[^{18}F]$olaparib derivative **10** in 17% radiochemical yield. Automation of the copper-mediated ^{18}F -fluorodeboronation followed by deprotection, was achieved on an Eckert & Ziegler Modular-Lab radiosynthesis platform, affording $[^{18}F]$ olaparib in a 6% radiochemical yield. ^{18}F-Fluorodeboronation was achieved with excess trifluoroacetic acid (TFA) at 120 °C followed by *N*-SEM deprotection. The $[^{18}F]$olaparib was isolated, dissolved in a solution of 10% (vol/vol) dimethyl sulfoxide (DMSO) in phosphate-buffered saline (PBS), and used for imaging experiments.

[5] Hollingworth, C.; Hazari, A.; Hopkinson, M.N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A.D.; Brown, J.M.; Gouverneur, V. *Angewandte Chemie International Edition* 2011, 50, 2613–2617.

[6] Tredwell, M.; Preshlock, S.M.; Taylor, N.J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. *Angewandte Chemie International Edition* 2014, 53, 7751–7755.

[7] Guibbal, F.; Isenegger, P.G.; Wilson, T.C.; Pacelli, A.; Mahaut, D.; Sap, J.B.I.; Taylor, N.J.; Verhoog, S.; Preshlock, S.; Hueting, R.; Cornelissen, B.; Gouverneur, V. *Nature Protocols* 2020, 15, 1525–1541.



9 10

11.4 THE S_N1 REACTION

Ionization of Tertiary Halides

In Section 11.2.2, the rate of reaction for a tertiary halide in an S_N2 reaction is shown to be prohibitively slow due to steric hindrance in the requisite pentacoordinate transition state. Therefore, when 2-bromo-2-methylpropane is heated in anhydrous THF (no water) with KI, there is no reaction. However, when 2-bromo-2-methylpropane is heated at reflux in a H_2O/THF mixture, 2-methylpropan-2-ol is isolated. The term reflux similarly means heating the solution at the boiling point of the solvent. This transformation is clearly a substitution reaction (Br for OH) at the tertiary carbon, but it cannot be a S_N2 reaction. The OH unit in 2-methylpropan-2-ol must be derived from water since hydroxide ion is not present, nor is it added. Alkyl halides are essentially insoluble in pure water (Section 5.8.2), however. To get around this problem, *aqueous solvents* (a mixture of water and an organic solvent) are used to provide sufficient solubility for the halide and also provide a source of water. The water efficiently solvates both anions and cations and facilitates ionization. Indeed, water is essential for ionization of the halide.

The reaction of 2-bromo-2-methylpropane is not an S_N2 reaction, so substitution can only occur if the leaving group departs *before* water reacts with carbon. In other words, the halide must ionize first and the reaction in water follows *first-order kinetics* rather than second-order kinetics. Ionization gives an intermediate carbocation. The bromine in this reaction is a leaving group, but it is not "kicked out" by the water nucleophile. In other words, the C—Br bond in 2-bromo-2-methylpropane does not spontaneously fly away from the carbon. Water "pulls" off the bromine via ionization to give a carbocation intermediate.

The δ^+ hydrogen of water coordinates with the δ^- bromide atom, and "pulls" off that atom to generate a carbocation intermediate. Water is present in excess and reacts as a nucleophile with the carbocation to form the oxonium ion shown in Figure 11.6. The acidic protons of the oxonium ion react with water in an acid-base reaction to give 2-methylpropan-2-ol and

The S_N1 Reaction

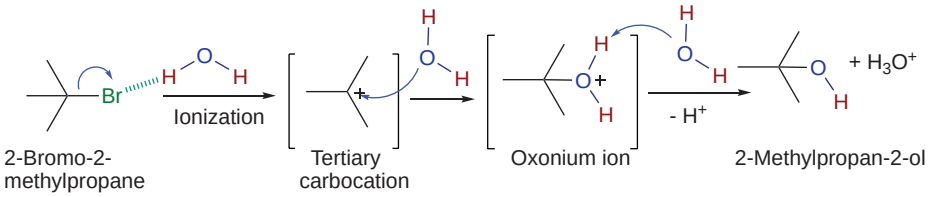


FIGURE 11.6 Mechanism for ionization of 2-bromo-2-methylpropane and reaction with water.

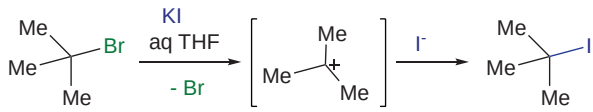
the hydronium ion. The ionization sequence shown is the mechanism for the overall transformation of an alkyl halide to an alcohol. This reaction is a nucleophilic substitution that follows first order kinetics, and it is a *S_N1 reaction*. The 1 indicates it is a first order reaction and it is said to be *unimolecular* (Section 7.11.1). The rate of the reaction is described by both reactions: Rate = k_1 [2-bromo-2-methylpropane] + k_2 [carbocation][I^-]. For all alkyl halides the general expression is Rate = k_1 [halide] + k_2 [carbocation][nucleophile].

The rate constant for the first reaction (ionization) is k_1, and the rate constant for the second reaction is k_2. The rate of ionization of the alkyl halide to a carbocation is very slow when compared to the very fast rate of reaction of the iodide ion with the carbocation. Therefore

$k_2 >>>> k_1$, and a simplified equation for this reaction is *rate = k_1 [halide].* The overall rate of conversion of the starting material (the bromide) to the product (in this example, the iodide) depends *only* on the concentration of the starting halide, and not on the concentration of the nucleophile (iodide in this case). Obviously, 2-iodo-2-methylpropane cannot be formed if iodide does not react with the carbocation. However, if $k_2 >>>> k_1$ then the slow ionization of 2-bromo-2-methylpropane is quite slow and determines the rate of the overall process. The slow step is known as the *rate-limiting or rate-determining step.* This is an ionization reaction and the general order of stability for carbocations is tertiary > secondary > primary > methyl. Therefore, a tertiary alkyl halide will react via a S_N1 mechanism faster than a secondary, which reacts faster than a primary. A methyl halide should react slowest of all, and in fact methyl halides and primary alkyl halides rarely if ever react via ionization.

Ionization is possible in protic solvents other than water (e.g., ethanol and acetic acid). Ionization and solvation are inefficient and much slower, however. Solvation of this type is very efficient in water or solvents mixed with water but not in other protic solvents (e.g., ethanol) when water is not present. For reactions discussed in this book, *assume* that water is the only solvent that efficiently solvates and separates both cations and anions.

Water is a weak nucleophile and while it reacts with a carbocation in a S_N1 reaction it does not react with alkyl halides in a S_N2 reaction. Once an intermediate carbocation is formed via ionization in an aqueous medium, however, it may be possible for it to react with a nucleophile such as water. A nucleophile that is more reactive than water can be added to generate a different product. If 2-bromo-2-methylpropane is heated with KI in aqueous THF solvent, for example, the product is not 2-methylpropan-2-ol, but rather 2-iodo-2-methylpropane. In the presence of water, the tertiary halide will ionize to a tertiary carbocation, but iodide is a better nucleophile when compared with water. The overall process is substitution (iodide substitutes for bromide) via a carbocation intermediate so it an S_N1 reaction.



A S_N1 reaction proceeds via formation of an intermediate carbocation. If the alkyl halide has a stereogenic center, the chirality of the molecule is lost since a *carbocation is planar.* If (3*R*)-bromo-3-methylhexane reacts with KI in aq THF, for example, the major product is 3-iodo-3-methylhexane, but it is a racemic mixture, (3*R*)- and (3*S*)-iodo-3-methylhexane as shown in Figure 11.7. The intermediate carbocation **11** has a planar sp^2 hybridized carbon, so all facial selectivity is lost in subsequent reactions. When iodide approaches **11**, it can approach equally well from the "top" or from the "bottom" because there is nothing to

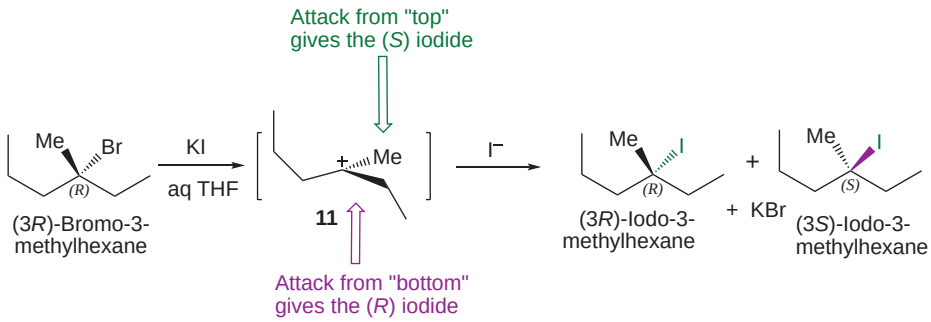


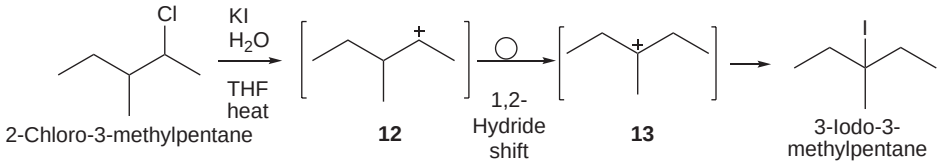
FIGURE 11.7 Ionization and loss of stereochemistry for 3(R)-bromo-3-methylhexane.

Stereochemistry and S_N1 Reactions

make one "face" of the carbocation different from the other. If iodide approaches **11** from the "bottom," (3*R*)-iodo-3-methylhexane is formed, but if iodide approaches from the "top" (3*S*)-iodo-3-methylhexane is formed so the final product is racemic. A characteristic of an *S_N1 reaction is that it produces racemic products.* This sharply contrasts with the S_N2 reaction that proceeded with 100% inversion of configuration due to backside attack.

Carbocation rearrangements were first discussed in Section 10.3, in connection with the reaction of an alkene with an acid. However, *all* carbocation intermediates generated in a S_N1 reaction can rearrange if the charge can be shifted to an adjacent carbon to give a potentially more stable carbocation. An example is the reaction of 2-chloro-3-methylpentane with KI in aq THF.

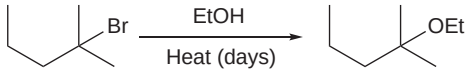
Rearrangement and S_N1 Reactions



In the presence of water, ionization of the chloride will give the secondary carbocation, **12**, but the final product, 3-iodo-3-methylpentane does not arise from this intermediate. A 1,2-hydride shift gives the more stable tertiary carbocation, **13**, which reacts with iodide to give the observed product. Because a carbocation is an intermediate, skeletal rearrangement is a potential issue in any S_N1 reaction. If a primary or secondary cation is generated on a carbon adjacent to a carbon that give a more stable cation rearrangement will occur.

11.14. Draw the mechanism and the final product formed when (2*S*)-bromo-2-phenylpentane is treated with KI in aq THF.

Alkyl halides undergo S_N1 reactions to give an alcohol by heating in an aqueous medium. If 2-bromo-2-methylpentane is heated in anhydrous ethanol (no water) for several hours, or for several days there is a reaction and a poor yield of 2-ethoxy-2-methypentane is obtained. This tertiary halide *cannot* react by an S_N2 mechanism because the activation energy barrier for that transition state is too high. There is no water in this medium, but ethanol is a protic solvent.



2-Bromo-2-methylpentane 2-Ethoxy-2-methylpentane

Although ionization and stabilization of charge (solvation) is not as facile in ethanol as in water (i.e., it is *slow*), it does occur. Prolonged heating leads to slow ionization of the halide to a tertiary carbocation, which reacts quickly with ethanol to yield an oxonium ion intermediate. Loss of the proton to ethanol in an acid-base reaction yields the ether product, 2-ethoxy-2-methylpentane. Replacement of alkyl halides with solvent in this way is called *solvolysis*, and it occurs most often with protic solvents (e.g., alcohols). This reaction is a reminder that water is *not* the only solvent that will facilitate ionization, but the rate of solvolysis reaction varies greatly. Indeed, solvolysis is usually slow if water is not present, but it can occur given sufficient time.

11.15. Write out the mechanism for reaction of ethanol with 4-bromo-3-ethyl-3-methylhexane and then the acid-base reaction of the resulting oxonium salt with ethanol to produce 3-ethoxy-3-ethyl-4-methylhexane.

11.5 SUBSTITUTION REACTIONS OF ALCOHOLS

The leaving group used most often in substitution reactions is the halogen of an alkyl halide, which are readily prepared from alcohols. In the discussions of both S_N1 and S_N2 reactions, the OH unit is a very poor leaving group and nucleophiles do *not* react directly with an alcohol via an S_N2 reaction. Therefore, the OH unit must be converted to a good leaving group for substitution reactions. Alcohols can be converted to sulfonate esters, which are good leaving groups (Section 11.1) but this reaction will not be described until Sections 18.3,6.

Alcohols React H—X Acids

11.5.1 ALCOHOLS REACT WITH MINERAL ACIDS

The reaction of an alcohol with a suitable acid converts the R–OH unit (a poor leaving group) to $R–OH_2^+$, an oxonium ion intermediate that is essentially a water molecule bound to an alkyl group. Water is a stable and neutral molecule and therefore a good leaving group, ROH_2^+. When butan-1-ol was treated with 48% HBr, in the presence of H_2SO_4, a 95% yield of 1-bromobutane was obtained.[8] When 2-methylpropan-2-ol (*tert*-butyl alcohol) was treated with concentrated HCl, 2-chloro-2-methylpropane (*tert*-butyl chloride) was isolated in 90% yield.[9] In both reactions, the alcohol first reacts with HCl to form an oxonium ion, as shown in Figure 11.8, along with the halide counterion of the acid (the conjugate base). The oxonium

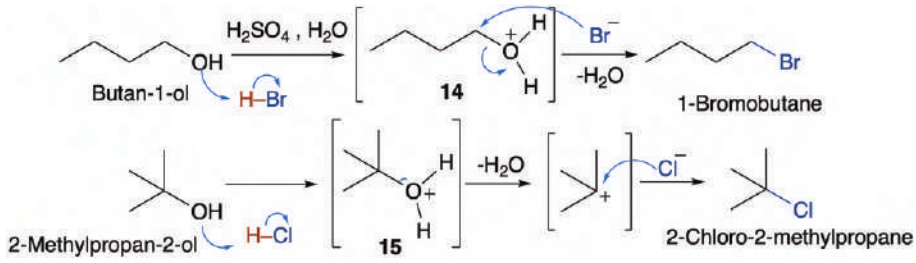


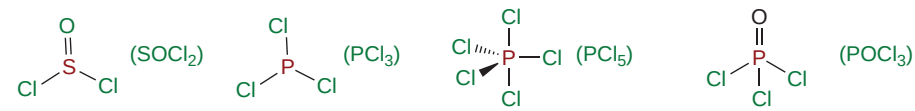
FIGURE 11.8 The reaction of primary alcohols and tertiary alcohols with HCl or HBr.

ion **14** derived from butan-1-ol is a primary system. Ionization to a primary cation is very slow but an S_N2 reaction with the bromide counterion rapidly gives 1-bromobutane. The oxonium ion **15** is derived from a tertiary alcohol and it ionizes in the protic medium to give a tertiary carbocation via loss of water. Once formed, a rapid S_N1 reaction with the nucleophilic chloride ion gives 2-chloro-2-methylpropane. Secondary alcohols may react by *both* the S_N2 and the S_N^1 pathway, depending on the solvent. If an S_N1 mechanism operates in the conversion of a secondary alcohol to the corresponding halide, rearrangement is a distinct possibility and must be considered.

11.16 Write the final product via S_N1 when 2,2-dimethylpentan-3-ol is treated with conc HCl.

11.5.2 SULFUR AND PHOSPHOROUS HALIDE REAGENTS

There are times when the use of mineral acids in chemical reactions must be avoided because of deleterious effects to other functional groups in the molecule. Other inorganic reagents are available that convert alcohols to alkyl chlorides, bromides or iodides. The most common inorganic chlorinating reagents are sulfur and phosphorous halides. The sulfur reagent thionyl chloride is used quite often but phosphorus trichloride, phosphorus pentachloride, and phosphorus oxychloride are also common. The structures of these compounds are shown. The common names are provided along with the IUPAC names. Shorthand notation for these reagents is shown with each structure ($SOCl_2$, PCl_3, PCl_5, and $POCl_3$). Fluoride reagents will not be discussed.



Thionyl chloride (sulfurous dichloride) | Phosphorus trichloride (trichlorophosphine) | Phosphorus pentachloride (pentachlorophosphine) | Phosphorus oxychloride (phosphoryl trichloride)

[8] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.54, pp. 561–562.

[9] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.49, p. 556.

S_Ni Reactions

Primary, secondary, or tertiary alcohols react with these reagents to give an alkyl chloride, ROH ⟶ RCl, or an alkyl bromide, ROH ⟶ RBr. The sulfur or the phosphorus atom in these reagents react as Lewis acids with the electron-donating oxygen atom of an alcohol. A typical experiment heats heptan-1-ol with thionyl chloride for 4 hours at reflux to give 1-chloroheptane in 77% yield.[10] Thionyl chloride reacts with the oxygen atom of heptan-1-ol to give oxonium ion **16**, as shown in Figure 11.9. A second reaction regenerates the S=O bond as HCl is lost, forming a *chlorosulfite* product (heptane chlorosulfite; the IUPAC name is heptyl sulfochloridite), **17**. Alternative mechanisms are possible for loss of HCl, including an intermolecular process to lose HCl, but this one will be used for simplicity. The intramolecular reaction of the chlorine atom at carbon generates 1-chloroheptane with loss of sulfur dioxide, O=S=O. The gaseous HCl and SO_2 escape from the reaction medium.

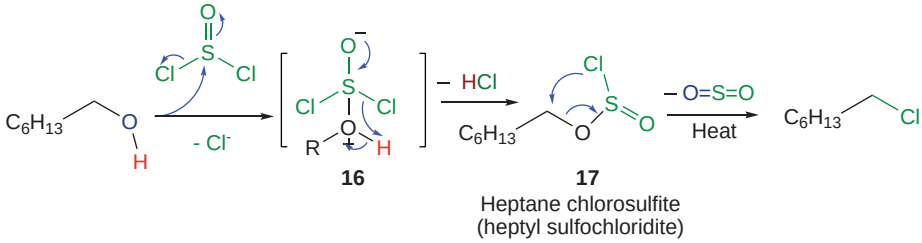
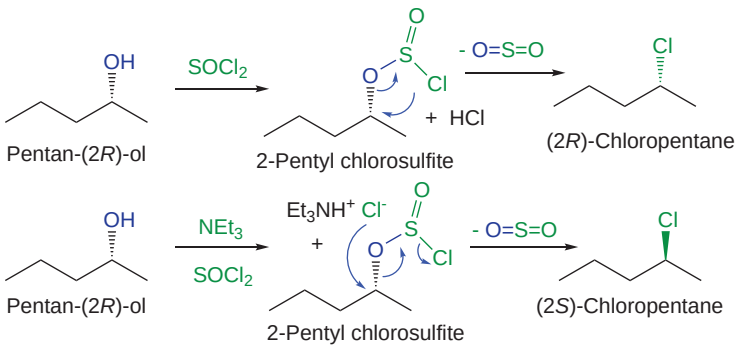


FIGURE 11.9 Mechanism of the reaction of an alcohol with thionyl chloride.

Reactions such as this are classified as *internal nucleophilic substitution*, which is abbreviated by the symbol S_Ni. This chlorination reaction can be done with 1°, 2°, or 3° alcohols. The phosphorus reagents PCl_3, PCl_5, and $POCl_3$ also convert alcohols into alkyl chlorides. The mechanism is slightly different for the phosphorus reagents and will not be presented here. However, the overall transformation is essentially the same in that the oxygen atom of the alcohol donates electrons to phosphorus to form a P—O bond with transfer of the halogen to carbon.

11.17 Draw the final product formed (a) when cyclopentanol reacts with PCl_3, (b) when 3-ethyl-3-pentanol reacts with PCl_5, and (c) when cyclopentanemethanol reacts with $POCl_3$.

When the alcohol contains a stereogenic carbon as in pentan-(2*R*)-ol, reaction with thionyl chloride gives a chlorosulfite and the subsequent S_Ni reaction generates a chiral product, (2*R*)-chloropentane. The reaction proceeds with *retention of configuration*. In other words, the absolute configuration of the alcohol is retained in the chloride product when thionyl chloride is used and no other reagents are added. A different experiment repeats the reaction of pentan-(2*R*)-ol with thionyl chloride, but triethylamine is added and (2*S*)-chloropentane is the isolated product. This reaction occurs with *inversion of configuration* rather than retention of configuration, which suggests an S_N2 reaction. 2-Pentyl chlorosulfite is formed as the intermediate in both reactions and when the amine is present it reacts with the HCl byproduct to generate triethylamine hydrochloride, $Et_3NH^+Cl^-$.



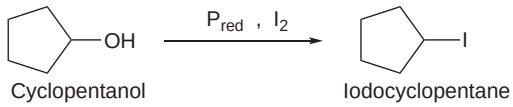
[10] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.52, p. 558.

With the nucleophilic chloride ion in the reaction medium, a S_N2 reaction is facile. Displacement of the chlorosulfite unit by the nucleophilic chloride ion proceeds with inversion of configuration to give (2*S*)-chloropentane. Thionyl bromide ($SOBr_2$) is the bromine analog of thionyl chloride, and it reacts essentially the same way to convert alcohols to bromides. The reaction of $SOBr_2$ with a chiral alcohol produces a mixture of enantiomers rather than an enantiopure product. Only thionyl chloride gives the stereoselectivity mentioned for generation of a chiral alkyl chloride. The reactions of a chiral alcohol with thionyl bromide, PCl_3, PCl_5, $POCl_3$, PBr_3, or PBr_5 do *not* give clean inversion or retention.

11.18 Draw the final product formed when 5,5-dimethylhexan-(2*S*)-ol is heated with thionyl chloride.

11.19 What is the product formed when (4*R*)-methylheptan-(2*S*)-ol reacts with (a) $SOCl_2 + NEt_3$?, (b) with $PBr_3 + NEt_3$?, (c) with $POCl_3$?, (d) with $SOBr_2$?

Sulfur and phosphorus iodides are not very stable, but an alcohol can be converted to an alkyl iodide using a mixture of reagents. The most common method reacts an alcohol (e.g., cyclopentanol) with elemental iodine and red phosphorus to give iodocyclopentane. The active reagent is probably PI_3, formed in situ (produced during the reaction without isolation) because it decomposes when stored. Note that white phosphorus is pyrophoric, which means that it spontaneously ignites in air, so it is important to use *red phosphorus* in this reaction.

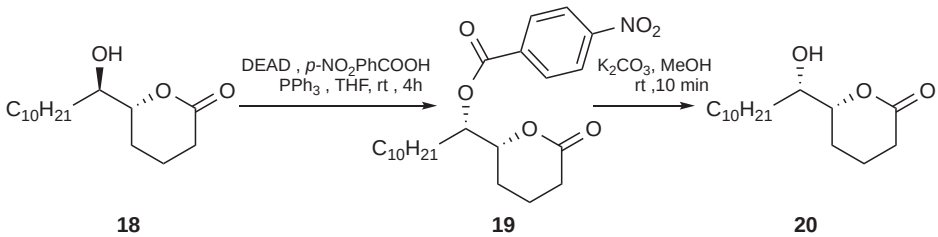


11.20 What is the product formed when hexan-3-ol reacts with iodine and red phosphorus?

Mitsunobu Reaction

11.5.3 THE MITSUNOBU REACTION

It is often necessary to generate an alcohol with either an (*R*) or an (*S*) absolute configuration. However, many reactions that generate an alcohol give the incorrect stereochemistry. In such a case, a reaction that inverts the stereochemistry of a given stereogenic center is required. One important method for inverting the stereochemistry of an alcohol is the *Mitsunobu reaction*.[11] The reaction is named for Oyo Mitsunobu (Japan; 1934–2003), who first discovered this reaction. A synthetic example shows the conversion of (*R*)-alcohol **18** to (*S*)-alcohol **20** in 72% overall yield by reaction with diethyl azodicarboxylate ($EtO_2C–N=N–CO_2Et$, DEAD), 4-nitrobenzoic acid (Section 18.2) and triphenylphosphine (PPh_3). Using this mixture, the alcohol is converted to a phosphonium salt, which has the $Ph_3P–O–C$ unit with the putative leaving group, $Ph_3P=O$. Subsequent S_N2 reaction at the carbon of the phosphonium salt with the carboxylate anion generated from 4-nitrobenzoic acid ($4\text{-}NO_2PhCO_2^-$) gives ester **19** with clean inversion of configuration. Hydrolysis of the resulting ester **19** (Section 18.5) with potassium carbonate in methanol gives **20** in a synthesis of the main mosquito oviposition attractant pheromone.[12]



[11] Mitsunobu. O. *Synthesis* 1981, 1–28.

[12] Dong, H.-B.; Yang, M.-Y.; Zhang, X.-T.; Wang, M.-A. *Tetrahedron: Asymmetry* 2014, 25, 610–616.

The mechanism for this reaction is shown in Figure 11.10 and begins with the reaction of diethyl diazodicarboxylate (DEAD) with triphenylphosphine (Ph_3P) to form **21**. Product **21** is a dipolar ion, and it reacts with RCO_2H to yield phosphonium salt **22**. In the presence of an alcohol R'OH, alkoxyphosphonium salt **23** is formed along with the carboxylate anion counterion and diethyl hydrazine-1,2-dicarboxylate. The RCO_2^- reacts as a nucleophile at

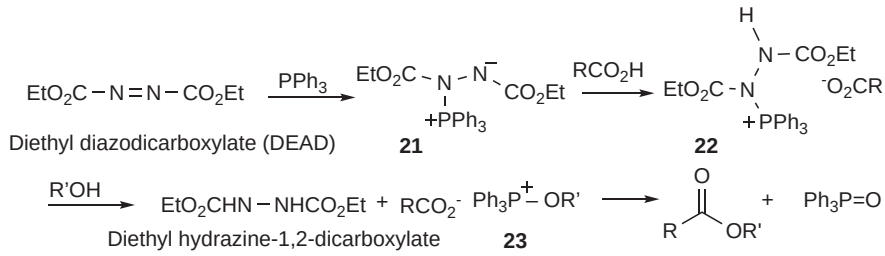


FIGURE 11.10 Mechanism of the Mitsunobu reaction.

carbon in **23**. Displacement of triphenylphosphine oxide (an excellent leaving group) gives the substitution product, the ester. Hydrolysis of the ester gives the alcohol (Section 18.4).

11.21 What is the product formed when hexan-3*R*-ol reacts with (a) $CH_3CH_2CO_2H$, DEAD, PPh_3 (b) aqueous K_2CO_3, heat?

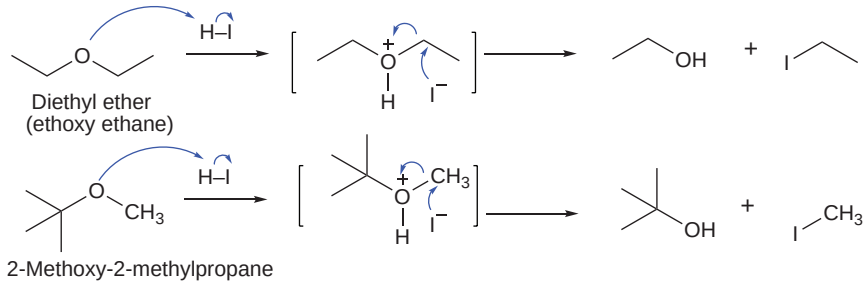
11.6 REACTIONS OF ETHERS

In general, ethers are unreactive to most chemical reagents, and they are often used as solvents. However, ethers react as bases with the strong mineral acids HI or HBr. They are much less reactive with HCl, however. The poor reactivity of most ethers stands in contrast to the reactions of three-membered ring ethers, epoxides (oxirane is the IUPAC name; Section 15.4). Relief of the strain inherent to the three-membered ring makes them susceptible to ring-opening and they are very reactive.

11.6.1 ETHERS REACT AS BRØNSTED-LOWRY BASES

Ethers React with Strong Acids

Ethers such as diethyl ether and THF are commonly used as solvents because they do not react with alkoxide bases or with hydroxide, or with most other reagents that will be encountered in later chapters. Ethers do react as bases, but only with strong acids such as HI and HBr to give an oxonium ion with an iodide or bromide counterion.



The $-OHEt_2^+$ unit in the oxonium ion derived from the reaction with diethyl ether is a putative leaving group since the neutral molecule ethanol is lost. In the diethyl ether reaction, the iodide attacks one of the ethyl groups of the oxonium ion to give iodoethane. The S_N2 reaction also give ethanol. When *tert*-butyl methyl ether (2-methyl-2-methoxypropane)

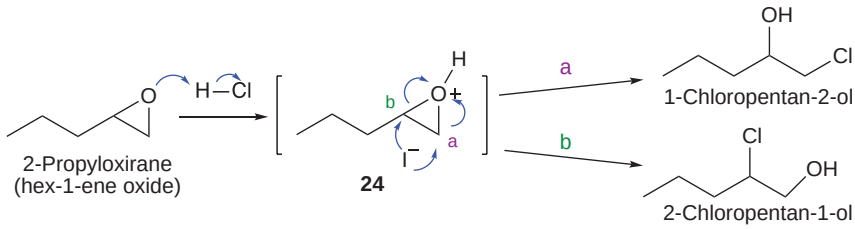
reacts with HI, the product is an unsymmetrical oxonium ion. An S_N2 reaction is possible only if iodide attacks the less sterically hindered methyl carbon of the oxonium ion. The S_N2 product is iodoethane and the leaving group is *tert*-butyl alcohol. With unsymmetrical ethers, nucleophilic attack by the iodide or bromide ion occurs at the less substituted carbon atom via an S_N2 reaction to give an alkyl halide and an alcohol.

11.22 Draw the oxonium ion formed by reaction of Me_3COMe and HBr and give a brief explanation why the bromide attacks the methyl group in that oxonium ion.

Epoxides React By S_N2 and S_N1 Reactions

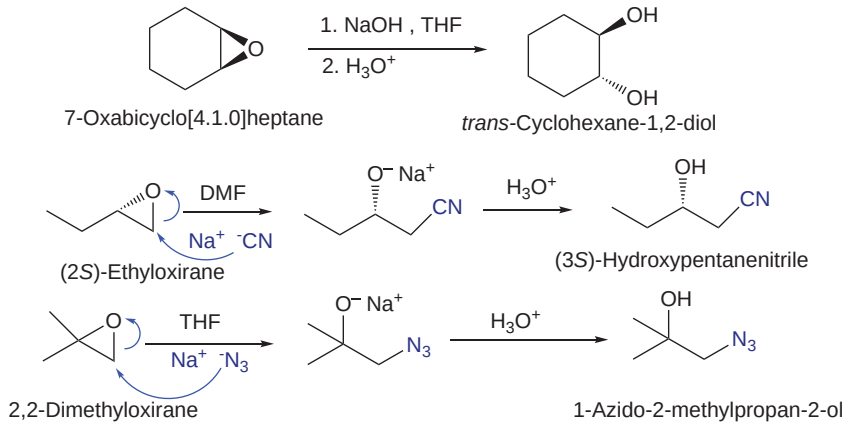
11.6.2 REACTIONS OF EPOXIDES

Epoxides (Section 15.3.2) are a distinct exception to the poor reactivity of most ethers. Ring opening reactions are facile due to relief of the strain inherent to that small ring. When 2-propyloxirane (hex-1-ene oxide) reacts with HCl, oxonium ion (**24**) is formed in the initial reaction. There are two different electrophilic sites on the three-membered ring, C^a or C^b. The main reaction with the nucleophilic chloride ion gives 1-chloropentan-2-ol via a S_N2-like reaction at the less substituted carbon, C^a via path (a). If the reaction is done is an aqueous solvent, however, ionization of the oxonium ion gives the secondary carbocation. Reaction with the chloride ion at the more substituted carbon atom, C^b via path (b) gives 2-chloropentan-1-ol.



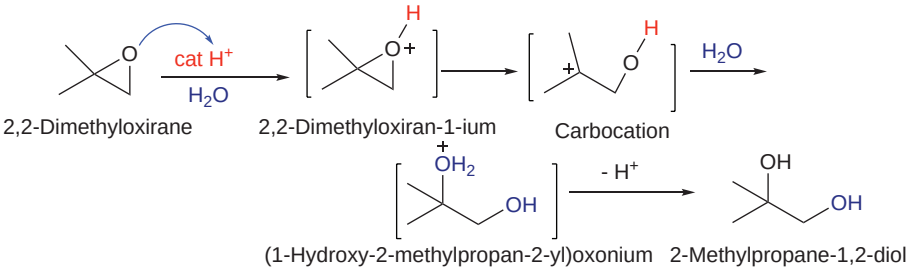
11.23 Draw the expected major product formed when 2-propyloxirane reacts with HCl.

Epoxides react with good nucleophiles even without an acid catalyst. An example is the reaction of 7-oxabicyclo[4.1.0]heptane with NaOH followed by an aqueous hydrolytic workup gives *trans*-cyclohexane-1,2-diol. The reaction of (2*S*)-ethyloxirane with NaCN in DMF solvent gives (3*S*)-hydroxylpentanenitrile, a cyanohydrin, after reaction with H_3O^+. The alcohol shows retention of the stereogenic center at C2 because attack occurs at the less substituted C1 atom. Sodium azide is another good nucleophile and reaction with 2,2-dimethyloxirane at the less hindered carbon gives 1-azido-2-methylpropan-2-ol.



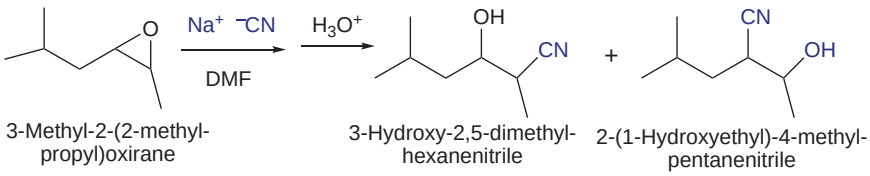
11.24 Draw the reaction and final product formed when 2,2-dimethyloxirane reacts with KI in THF. With NaCN in THF.

In aqueous media, protonation of the epoxide oxygen and ring opening of the resultant oxonium ion leads to a carbocation. The reaction of 2,2-dimethyloxirane with an acid catalyst and water will initially generate oxonium ion 2,2-dimethyloxiran-1-ium. In water solvent, ionization of the oxonium ion gives a tertiary carbocation, and reaction with water gives an oxonium ion (1-hydroxy-2-methylpropan-2-yl)oxonium. Loss of the proton in an acid-base reaction yields 2-methylpropane-1,2-diol and regenerates the acid catalyst.



11.25 Draw the mechanism and final product formed when 2,2-dimethyloxirane reacts with ethanol and an acid catalyst.

When an epoxide does not have a less substituted carbon atom, reaction with a nucleophile will lead to a mixture of products. When 3-methyl-2-(2-methylpropyl)oxirane reacts with NaCN in DMF, attack will occur at both carbon atoms to give two products, 3-hydroxy-2,5-dimethylhexanenitrile and 2-(1-hydroxyethyl)-4-methylpentanenitrile after the aqueous hydrolytic workup. Assume that the reaction of a nucleophile with an unsymmetrical epoxide will give a mixture of regioisomeric products.



11.7 FREE RADICAL HALOGENATION OF ALKANES

Radical Halogenation

There is another method for preparing alkyl halides that involves radical intermediates and reaction with elemental chlorine or bromine. This reaction uses a radical initiator such as a peroxide. As noted in Section 7.2.3, *homolytic cleavage* generates radical intermediates. Radicals react with alkanes to generate carbon radicals, which react with Cl_2 or Br_2 to give an alkyl halide.

Dihalogens (X—X) undergo homolytic cleavage when heated or irradiated with ultraviolet light to generate two radicals: Cl_2 to 2 Cl• and Br_2 to 2 Br•. In Figure 11.11, a radical Cl• is generated by photolysis of chlorine. Subsequent reaction with a H atom of methane gives HCl and a methyl radical in a reaction known as an *atom exchange reaction*. Once a methyl radical is formed, it is also highly reactive and can react with Cl_2 in another atom exchange reaction to generate chloromethane and a new Cl•. These two reactions are repeated, Cl• with methane and the methyl radical with the Cl_2, to give HCl and chloromethane until all Cl_2 and all methane has been depleted. This sequence is the *radical chlorination* of methane.

Irradiation of diatomic chlorine first produces the radicals in what is called an *initiation step*. Three reactions are shown in Figure 11.11 that generate a radical product, which

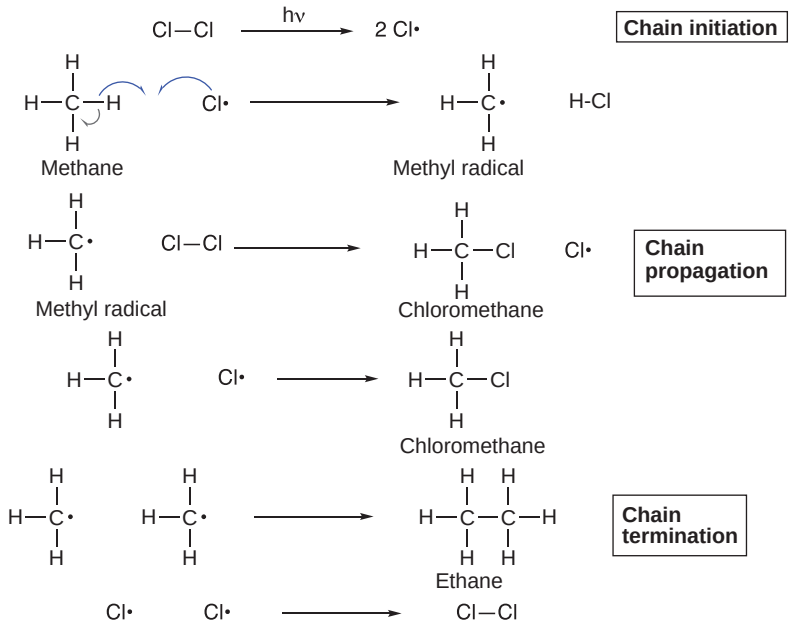


FIGURE 11.11 The radical chain reaction of methane with chlorine.

allows the radical reactions to proceed to the products. These reactions are called *propagation steps.* The coupling of two radicals to yield a neutral product, but not another radical, is called a *termination step*. A methyl radical can couple with the chlorine radical to yield chloromethane, two methyl radicals can couple to give ethane and two chlorine radicals can couple to yield diatomic chorine. This chain halogenation reaction be applied to virtually any alkane and the Cl• or Br• radicals will exchange with every hydrogen atom in an alkane.

For an alkane with the formula C_8H_{18}, all 18 hydrogen atoms will exchange with the radical. The primary, secondary and tertiary C—H units of an alkane will react at different rates depending on the stability of the carbon radical that is formed. The stability of carbon radicals is dependent on the number of substituents, similar to carbocations. A tertiary carbon radical is more stable than a secondary carbon radical, which is more stable than a primary carbon radical.

Order of carbon radical stability: $R_3C\bullet > R_2HC\bullet > RH_2C\bullet >>> H_3C\bullet$

Rate of Substitution of Different H Atoms

The more stable the carbon radical formed by removal a hydrogen, the faster the rate of atom exchange with a halogen radical. In other words, Cl• or Br• will react faster with a tertiary hydrogen atom (R_3C—H) than with a secondary hydrogen atom (R_2HC—H) and a primary hydrogen atom (RH_2C—H) will react slowest of all. Since primary, secondary, and tertiary hydrogen atoms in an alkane react at different rates, a mixture of isomeric alkyl halides will be formed. An example is the radical halogenation of 2-methylbutane and chlorine gas under photochemical conditions (*hν* means irradiation with light). In the *radical chlorination* of 2-methylbutane, four different isomeric products were isolated as shown in Figure 11.12.[13] There are six primary hydrogen atoms marked in red on two methyl groups that give a primary radical and 1-chloro-2-methylbutane as the product. All six are identical and constitute one type of hydrogen atom. Removal of the one tertiary hydrogen in blue leads to a tertiary radical and 2-chloro-2-methylbutane. There are two identical secondary hydrogen atoms marked in green that give a secondary radical that leads to 2-chloro-3-methylbutane. Finally, there are three identical primary hydrogen atoms for the remaining methyl group in violet, giving a primary radical and 1-chloro-3-methylbutane. The relative percentages of products were given for the reaction of 2-methylbutane based on experimental results.

[13] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry*, Reinhold Publisher, New York, 1961, pp. 120–121.

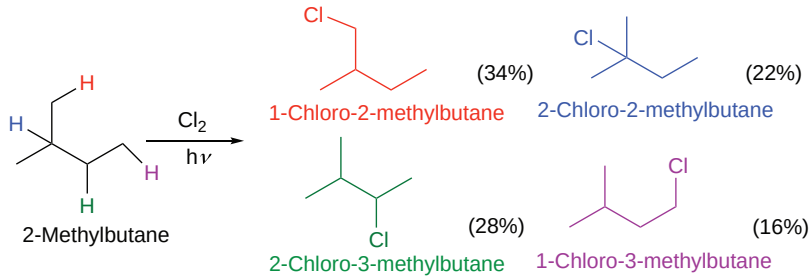


FIGURE 11.12 Radical chlorination of the four different types of hydrogen atom in 2-methylbutane.

11.26 Speculate on the relative stability of a primary radical and a tertiary radical, and which would have the lower activation barrier to formation.

The percentage of each product can be estimated. The rate for removal of a primary hydrogen from an alkane by Cl• is $k_{primary}$; the rate for a secondary hydrogen is $k_{secondary}$ and that for a tertiary hydrogen is $k_{tertiary}$. From various experiments it is known that the relative rates are 1° = 1, 2° = 3.9, and 3° = 5.2. Relative percentages of each product may be *estimated* using the number of hydrogen atoms and the relative rate for that type of hydrogen atom. For a given alkane, the relative rate for chlorination of all hydrogen atoms is:

$$\text{Relative \%} = \left[\frac{\text{No 1° H atoms}}{\text{Total No H atoms}} \times 1\right] + \left[\frac{\text{No 2° H atoms}}{\text{Total No H atoms}} \times 3.9\right] + \left[\frac{\text{No 3° H atoms}}{\text{Total No H atoms}} \times 5.2\right]$$

Of the twelve hydrogen atoms, there are six of one type of primary hydrogen atoms and three of the different primary hydrogen atoms. There are two secondary hydrogen atoms and one tertiary hydrogen in 2-methylbutane. The relative % of 1-chloro-2-methylbutane is (6/12)(1); the relative % of 2-chloro-2-methylbutane is (1/12)(5.2); the relative % of 2-chloro-3-methylbutane is (2/12)(3.9); and, the relative % of 1-chloro-3-methylbutane is (3/12)(1). This calculation leads to a mixture of all four products in a 0.5:0.43:0.65: 25 ratio. This corresponds to a predicted mixture of 27.3% of 1-chloro-2-methylbutane, 23.5% of 2-chloro-2-methylbutane, 35.5% of 2-chloro-3-methylbutane and 13.7% of 1-chloro-3-methylbutane. The predicted values do not exactly match the experimental values, but the predicted values clearly show that no one product predominates in this reaction.

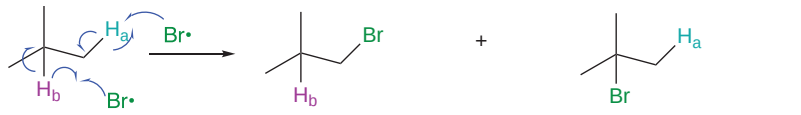
11.27 Calculate the relative percentages of products for the reaction of 2-methylbutane with chlorine and compare it with the actual percentages given above.

Radical Bromination of Alkanes

In the radical bromination of 2-methylpropane there are only two different types of hydrogen atoms, so only two products are expected. There are nine identical primary hydrogen atoms and only one tertiary hydrogen atom. Photolysis of Br_2 will generate Br•, and the products are 1-bromo-2-methylpropane formed in < 1%, and 2-bromo-2-methylpropane formed in ~ 99% yield. It seems obvious that the reaction with bromine is more selective for the tertiary hydrogen than the reaction with chlorine. Reaction with chlorine yields 1-chloro-2-methylpropane and 2-chloro-2-methylpropane in a ratio based on 9/10(1) and 1/10(5.2), which does not predict 99% of the tertiary chloride.

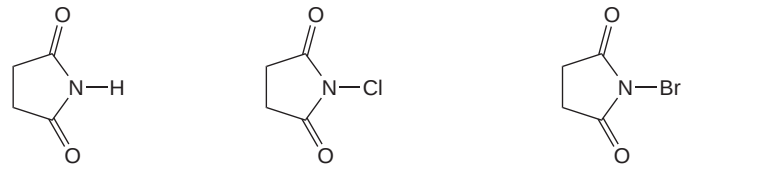
Allylic Halogenation

The experimentally determined rates for bromine radical reactions with alkanes are 1° = 1, 2° = 82, and 3° = 1640. Using this rate data, the relative % of 1-bromo-2-methylpropane is 9/1649 = 0.0055 and that of 2-bromo-2-methylpropane is 1640/1649 = 0.9945 or 0.55% of 1-bromo-2-methylpropane and 99.45% of 2-methylpropane-2-methylpropane. Due to these rate differences, radical bromination is a selective and useful reaction. Radical chlorination is not very useful since there is only a small rate difference between different types of hydrogen atom. The rationale for the greater selectivity of the bromine radical relative to the chorine radical is based on the Hammond postulate that predicts a later transition state for the bromination. This statement means that in radical atom transfer reactions, the stability of the radical product (3° > 2° > 1°) is more important in determining the product distribution.



2-Methylpropane 1-Bromo-2-methylpropane 2-Bromo-2-methylpropane

The use of chlorine gas or liquid bromine in simple chemical reactions can be inconvenient, and sometimes dangerous. Therefore, a "solid form" of chlorine and bromine is very attractive. There are two reagents that can be used in this way, *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS).



Succinimide *N*-Chlorosuccinimide (NCS) *N*-Bromosuccinimide (NBS)

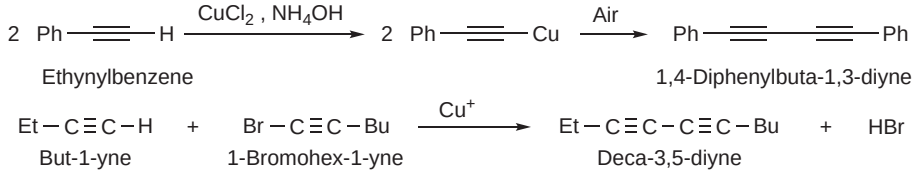
Both of these reagents are derivatives of succinimide (Section 18.11), which is the imide derivative of succinic acid (1,4-butanedioic acid; Section 18.11). The NBS and NCS are readily available and easy to handle. Both reagents react with light to release diatomic chlorine or bromine, which subsequently reacts with the light or another radical to produce chlorine or bromine radicals. Therefore, NCS is a chlorine surrogate and NBS is a bromine surrogate. Cyclohexene, for example, reacts with NBS in the presence of light to give 3-bromocyclohexene in 45% yield by the radical substitution mechanism presented in Figure 11.11, via generation of diatomic bromine.[14]

11.28 Write out the reaction of cyclohexene with NBS, showing reactants and product.

11.8 C—H SUBSTITUTION

Functionalization of the C—H bond in organic molecules has been accomplished for alkynes using transition metals. The C—H unit of terminal alkynes is activated by copper derivatives to give a diyne product. One procedure used cuprous salt [copper (I) chloride or copper (I) bromide] catalysis in the presence of aqueous ammonia or ammonium chloride and an oxidant such as oxygen. This reaction is called the *Glaser reaction*.[15] The reaction forms an alkyne-copper intermediate, which reacts with oxygen and ammonium hydroxide to give the diyne. An example is the reaction of two molar equivalents of ethynylbenzene to generate two equivalents of called the by *Cadiot-Chodkiewicz coupling*[16] prepared unsymmetrical diynes using a copper-catalyst. The reaction of terminal alkynes with 1-bromoalkynes generates unsymmetrical diynes. An example is the copper catalyzed reaction of but-1-yne and 1-bromohex-1-yne to give deca-3,5-diyne and HBr.

Alkyne Coupling



Ethynylbenzene 1,4-Diphenylbuta-1,3-diyne

But-1-yne 1-Bromohex-1-yne Deca-3,5-diyne

[14] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.68, pp. 578–579.
[15] (a) Glaser, C. *Berichte* 1869, 2, 422–424; (b) Glaser, C. *Annalen* 1870, 154, 137–171.
[16] Chodkiewicz, W.; Cadiot, P. *Comptes Rendus de l'Académie des Sciences* 1955, 241, 1055–1057.

11.29 Predict the product of the reaction of hex-1-yne with (a) CuCl and ammonium hydroxide (b) air.

M. Christina White

The C—H alkylation reaction of less activated C—H bonds such as allylic or aliphatic C—H bonds has been a very difficult transformation to do selectively and preparatively. Recent developments in transition metal catalysis, however, has led to useful methodology that is being developed for the synthesis of important molecules. Professor M. Christina White (USA) of the University of Illinois, Urbana-Champaign has developed the first general method for intermolecular allylic C—H alkylation of terminal alkenes with tertiary and secondary nucleophiles. The $Pd(II)(OAc)_2$/sulfoxide catalysts are critical for effecting a heterolytic cleavage of the allylic C—H to form an electrophilic π-allylPd intermediate **25** (Section 20.7.4). Additives like DMSO and $Zn(OAc)_2$ promote functionalization of tertiary carbon nucleophiles, in some cases by promoting their *in situ* deprotonation.[17] The reaction has recently been rendered asymmetric by replacing the achiral Pd(II)/BisSO (BisSO = bis-sulfoxide) catalyst with chiral Pd(II)/SOX catalysts (SOX = sulfoxide oxazoline), so C—C bonds

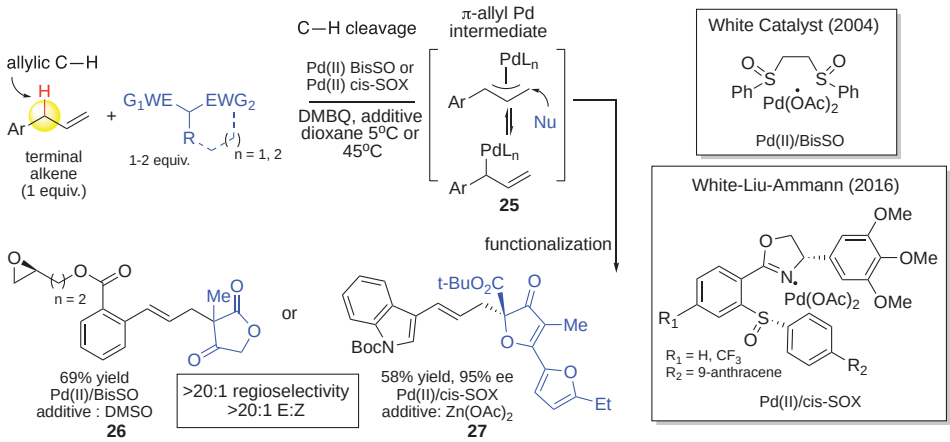
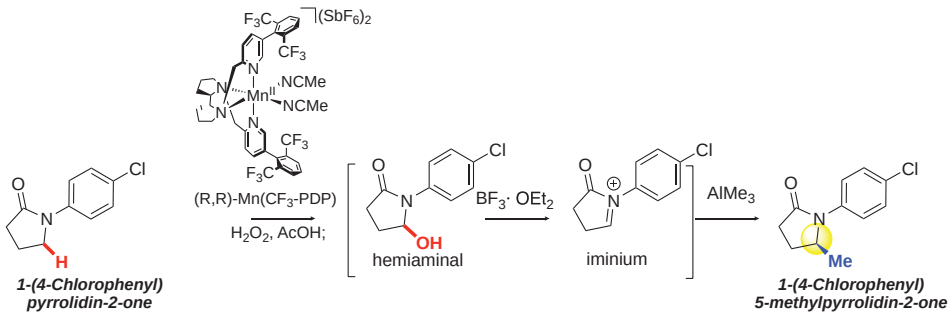


FIGURE 11.13 C—H Methylation of allylic alkenes. With permission from Professor M. Christina White.

[17] (a) Young, A.J.; White M.C. *Journal of the American Chemical Society* 2008, 130, 14090–14091; (b) Young, A.J.; White, M.C. *Angewandte Chemie International Edition* 2011, 50, 6824–6827; (c) Howell, J.M.; Liu, W.; Young, A.J.; White, M.C. *Journal of the American Chemical Society* 2014, 136, 5750–5754.

can be formed in high enantiomeric excess (ee).[18] Both allylic C–H alkylations proceed with excellent regioselectivity (>20:1 linear:branched, **26**:**27**) and >20:1 *E:Z* stereoselectivity as shown in Figure 11.13. In addition to what is shown, aliphatic terminal olefins containing reactive functionalities and cyclic and acyclic tertiary as well as secondary nucleophiles are viable. The versatility of this reaction has enabled the alkynyl copper reagent. Exposure to air gives the diyne, 1,4-diphenylbuta-1,3-diyne. A newer procedure C—H alkylation generates intermediate products that can undergo secondary reactions to rapidly construct complex molecules. Aliphatic terminal alkenes containing reactive functionalities and internal olefins are viable substrates, as are allylarenes. Cyclic and acyclic tertiary nucleophiles that have a variety of functionalization can be used. The versatility of this reaction has enabled C—H alkylation to generate intermediate products that can undergo intramolecular secondary reactions to rapidly construct complex molecules.

The C—H methylation reaction is a highly desirable reaction, particularly next to nitrogen in aromatic drugs as this modification been shown to increase drug potency (magic methyl effect). Professor White has developed a chemoselective manganese catalyst, Mn(CF_3PDP), described in Section 15.4, that is able to selectively oxidize aliphatic C—H bonds in preference to functional groups generally more prone to oxidation (aromatics, alcohols).[19] Using this catalyst, her group developed the first oxidative late-stage C(sp^3)–H methylation. The reaction uses low catalyst loadings of Mn(CF_3PDP) with hydrogen peroxide and acetic acid to perform a C—H hydroxylation alpha to nitrogen to furnish a hemiaminal. The hemiaminal can be eliminated using various Lewis acids (for example boron trifluoride etherate or TMSOTf) to furnish a highly electrophilic iminium intermediate. The iminium is then alkylated with a mildly nucleophilic, non-basic, commercial organometallic reagent trimethylaluminum.[20] The reaction of 1-(4-chlorophenyl)pyrrolidin-2-one, for example, gave the methylated product 1-(4-chlorophenyl)-5-methylpyrrolidin-2-one in 71% yield upon reaction with 0.5% of the Mn(CF_3PDP) catalyst, in acetonitrile with acetic acid and hydrogen peroxide, with trimethylaluminum and boron trifluoride etherate. Methylation was successfully carried on 41 substrates housing 16 different medicinally important cores that included electron-rich aryls, heterocycles, carbonyls and amines. Professor White developed iron and manganese catalysts that were used for C—H oxidation reactions, described in Section 15.4.



11.9 ORGANIZATION OF REACTION TYPES

Substitution reactions can be organized as follows.

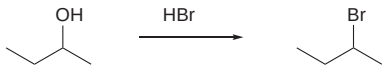
What reactions are possible for alkyl halides?

1. Alkyl halides undergo substitution reactions with various nucleophiles. Other halides, ethers, nitriles, and alkynes can be prepared.

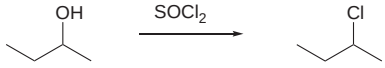
[18] Liu, W.; Ali, S.Z.; Ammann, S.E.; White, M.C. *Journal of the American Chemical Society* 2018, 140, 10658–10662.
[19] Zhao, J.; Nanjo, T.; de Lucca Jr. E.C.; White, M.C. *Nature Chemistry* 2019, 11, 213–221.
[20] Feng, K.; Quevedo, R.E.; Kohrt, J.T.; Oderinde, M.S.; Reilly, U.; White, M.C. *Nature* 2020, 580, 621–627.

What reactions are possible for alcohols?

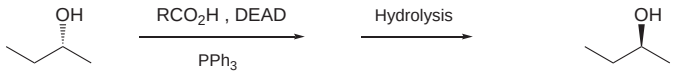
1. Alcohols react with HBr or HCl to form alkyl bromides or alkyl chlorides.



2. Alcohols react with sulfur or phosphorus halides to form alkyl halides.

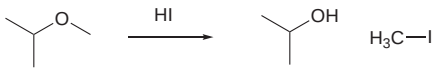


3. The stereochemistry of chiral alcohols can be inverted using the Mitsunobu reaction.

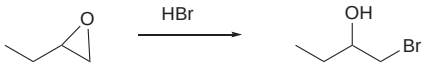


What reactions are possible for ethers?

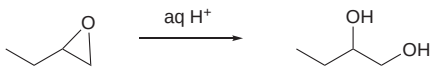
1. Ethers are generally unreactive, but they react with HI or HBr to form alcohols and alkyl halides.



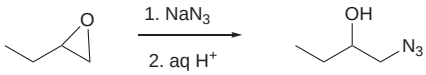
2. Epoxides are reactive ethers that react with acids to form halo-alcohols.



3. Epoxides react with water and acid to yield diols.

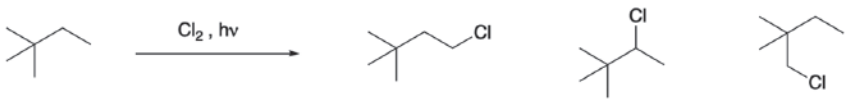


4. Ethers react with nucleophiles at the less substituted carbon in nonaqueous solvents.



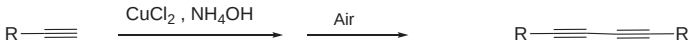
What reactions are possible for alkanes?

1. Alkanes are generally unreactive, but they react with bromine or chloride under radical conditions to yield alkyl halides.

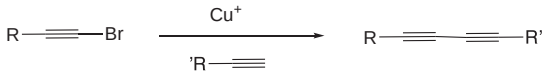


What reactions are possible for alkynes?

1. Terminal alkynes can be coupled to give diynes using a copper catalyst.



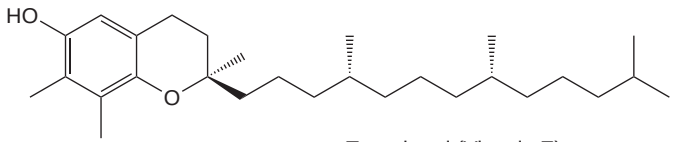
2. Haloalkynes are coupled with terminal alkynes using a copper catalyst.



11.10 BIOLOGICAL RELEVANCE

Substitution reactions occur in many biological processes. Bis(2-chloromethyl)sulfide [$ClCH_2CH_2SCH_2CH_2Cl$], otherwise known as *mustard gas*, is a sulfide (a thioether) with primary alkyl chloride units and it is highly reactive. It was used as a poison gas in World War I as a vesicant, since exposure causes large blisters on exposed skin. It is also cytotoxic and mutagenic. These latter effects arise by a reaction with heterocyclic bases in DNA. As this compound was studied, chemical modification led to an amine derivative, 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine, a so-called *nitrogen mustard*. It is one of the first clinically useful anti-cancer drugs. The anti-cancer activity arises from reaction as a DNA intercalating agent. An intercalating agent inserts itself into the DNA structure of a cell and binds to the DNA, causing damage. The nitrogen mustard first reacts via the N^9-nitrogen of a guanine that is part of a DNA strand (**28**), and a S_N2-like reaction at the aziridinium salt leads to **29**, as shown in Figure 11.13.[21] Aziridines are discussed in Section 23.7. The three-membered ring is susceptible to attack by nucleophiles, similar to the reactivity of epoxides. Hence, 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine is classified as an alkylating agent. The cross-linking (intercalating) ability arises when the tertiary amine unit in **29** reacts with the other primary alkyl chloride to give aziridinium salt **30**. A second molecule of DNA (**28**) reacts to form **31**. As suggested by **31**, reaction with double stranded DNA leads to intercalation of the nitrogen mustard (Figure 11.14).

Radical reactions appear in biological systems. Reactive oxygen and nitrogen species are formed regularly as a result of normal organ functions, or as a result of excess oxidative stress. Normal metabolic pathways of the human organs[22] generate the reactive species superoxide (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical (HO•), nitrogen oxide (NO•), peroxynitrite ($ONOO^-$), and hypochlorous acid (HOCl). If these radicals are produced in excess, they may be harmful. Antioxidants can combat these harmful effects. The tocopherols, (e.g., γ-tocopherol, vitamin E), are an important class of antioxidants.[23] Tocopherols work in the lipid phase of cell membranes, breaking the chain reaction of radical processes, scavenging a peroxyl radical by donating an electron to the peroxyl radical of the fatty acid. This introduces a chain termination step to stop radical propagation steps.[24]



γ-Tocopherol (Vitamin E)

[21] Rajski, S.R.; Williams, R.M. *Chemical Reviews* 1998, 98, 2723–2796.
[22] Vaya1, J.; Aviram, M. *Current Medicinal Chemistry - Immunology, Endocrine & Metabolic* 2001, 1, 99–117.
[23] Pryor, W.A. *Free Radical Biology and Medicine* 2000, 28, 141–164.
[24] Burton, G.W.; Joyce, A.; Ingold, K.U. *Lancet* 1982, 320, 2(8293), 327.

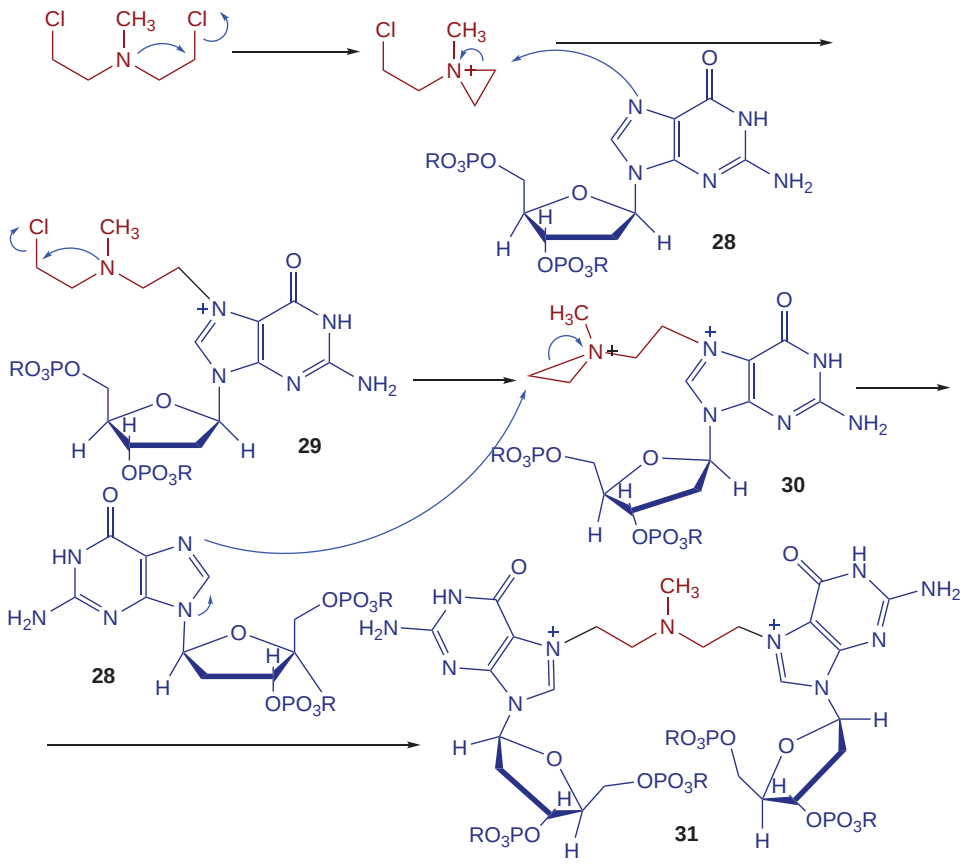


FIGURE 11.14 Intercalation of nitrogen mustard in DNA. (Reprinted with permission from Rajski, S.R.; Williams, R.M. *Chemical Reviews 1998, 98*, 2723. Copyright 1998 American Chemical Society).

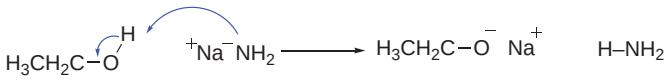
CORRELATION OF HOMEWORK WITH CONCEPTS

- Nucleophiles react with primary and secondary alkyl halides, displacing the leaving group in what is known as aliphatic, bimolecular nucleophilic substitution, the S_N2 reaction: 2, 3, 4, 6, 11, 12, 13, 32, 36, 37, 40, 41, 45, 46.
- Leaving groups, X, are characterized by weak C—X bonds that are easily broken and generate stable ions or molecules: 1, 8, 9, 35, 37.
- S_N2 Reactions proceed by a pentacoordinate transition state: 4, 5, 6, 36.
- S_N2 Reactions are faster in aprotic solvents and slower in protic solvent; S_N1 reactions require water: 7, 9, 38.
- Many nucleophiles are known, including halide ions, alkoxides, amines, phosphines, azides, cyanide, acetylides, and enolate anions: 10, 11, 12, 13, 36, 39, 40, 41, 45, 46.
- Carbocation intermediates can be trapped by nucleophiles in an S_N1 reaction: 14, 15, 16, 31, 36, 42, 46.
- Carbocations are subject to rearrangement to a more stable cation via 1,2-H or alkyl shifts: 14, 2, 43, 44, 46.
- Alcohols are converted to alkyl halides with mineral acids (HCl and HBr), thionyl chloride, thionyl bromide, PX_3, and PX_5: 16, 17, 18, 19, 20, 34, 45.
- Ethers are generally unreactive except with strong acids (e.g., HI and HBr), which leads to cleavage of the ether to an alcohol and an alkyl halide: 22, 43, 46.
- Epoxides are particularly reactive with good nucleophiles. They also react with an acid catalyst and weak nucleophiles: 23, 24, 25, 48.

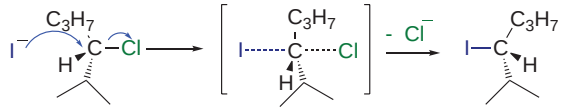
- Chlorine and bromine radicals react with alkanes, removing hydrogen atoms via a radical process that leads to substitution and formation of alkyl chlorides and alkyl bromides: 26, 27 28, 30, 45, 47.
- Spectroscopy is used to determine the structure of a particular molecule (see Chapter 13): 49, 50, 51, 52, 53.

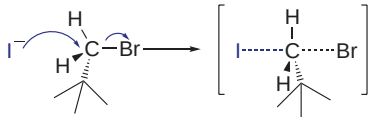
ANSWERS TO IN-CHAPTER QUESTIONS

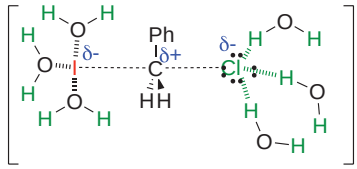
11.1 

11.2 

11.3 Two and one-half times faster.

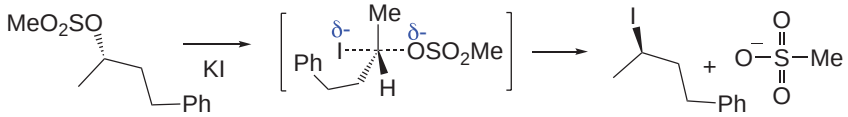
11.4 

11.5 

11.6 

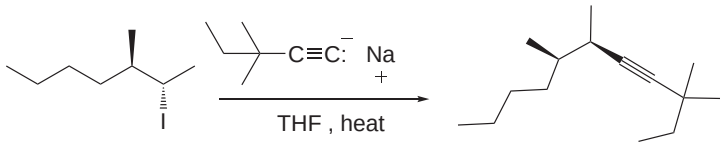
11.7 The reaction should be faster in aq THF. The transition state develops a positive charge on nitrogen and a negative change on the leaving group, so water will accelerate charge separation, which leads to the product.

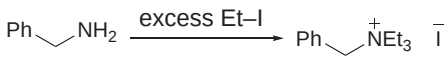
11.8 Of these four fragments, Cl is the most electronegative and best able to accommodate charge. Therefore, the C—Cl bond is weaker, and Cl^- will be very stable with the charge dispersed over the relatively large atom. This leads to Cl being the best leaving group. The C—CH_3 bond is strongest, and the anion formed after methyl "leaves" is $^-CH_3$ making this very unfavorable. Methyl will be the worst leaving group. The Me_2N^- group is less stable and more reactive than MeO^-, but the C—O bond is weaker than the C—N bond. Since OR is a better leaving group than NR_2, the final order of leaving group ability should be Cl >> OMe > NMe_2 >>> Me.

11.9 

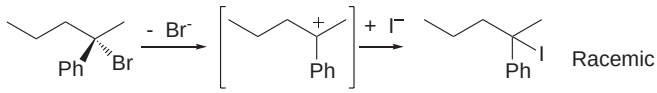
11.10 Fluorine is a very electronegative atom. The fluoride ion effectively holds electrons because of this electronegativity. If fluoride "holds" electrons, they are not available for donation to a carbon atom: the definition of a nucleophile. Therefore, the high electronegativity of fluoride makes it unable to donate electrons effectively, which makes it a poor nucleophile.

11.11 The product is 4-phenylhexanenitrile.

11.12 

11.13 

11.14



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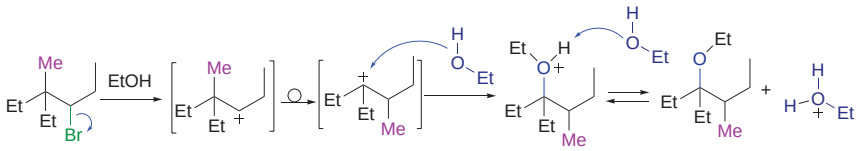
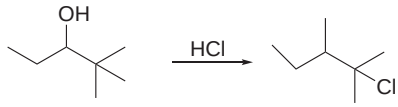


11.16



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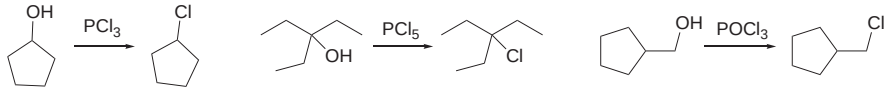
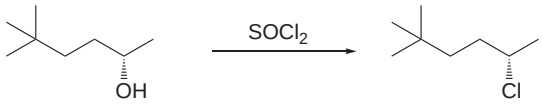
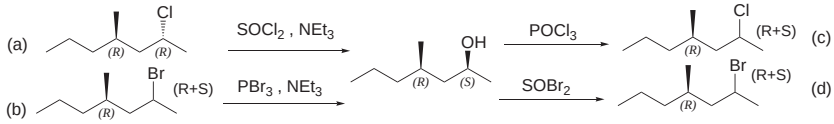


11.18



(*S*)-5,5-Dimethylhexan-2-ol (*S*)-5-Chloro-2,2-dimethylhexane

11.19



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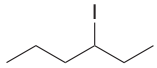
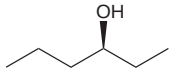
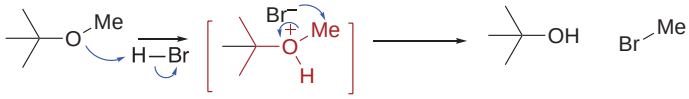


11.21

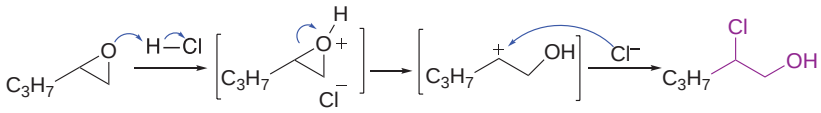


Hexan-3*S*-ol

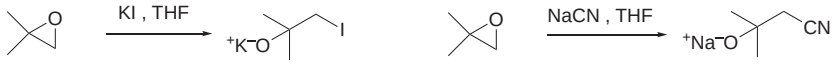
11.22 Formation of the oxonium ion is accompanied by formation of the nucleophilic bromide ion. The bromide ion attacks the less hindered methyl group in an S_N2 reaction rather than the tertiary carbon of the *tert*-butyl group. Therefore, the product is bromomethane and *tert*-butanol.



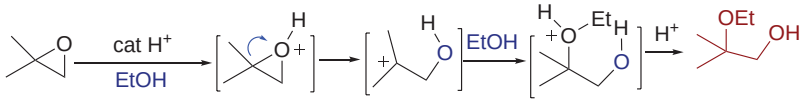
11.23



11.24



11.25

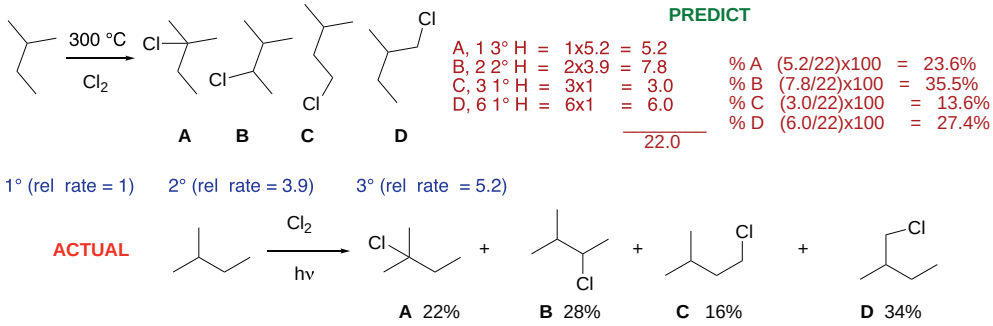


In both reactions, the product is an alkoxide. A second step is required, treatment with dilute aqueous acid, to convert the alkoxide to the alcohol.

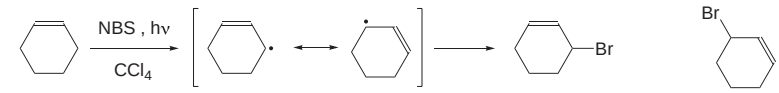
11.26 The larger number of carbon groups on the tertiary radical **B** should lead to greater stability. Therefore, **B** should be more stable than **A.** If **B** is more stable, it should be easier to form, which suggests that **B** should have a lower E_{act} relative to **A.**

11.27 The predicted values are not accurate, and the actual major product is **D** rather than the predicted **B**. Nonetheless, the prediction indicates that there will be a mixture,

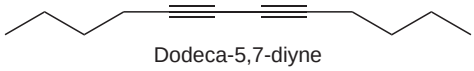
and the predicted numbers show a higher percentage of **A** from the tertiary hydrogen atom, which is generally correct.



11.28



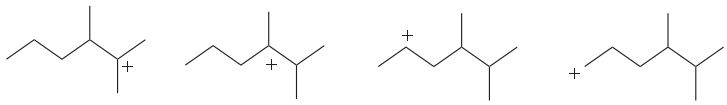
11.29



HOMEWORK

30. Which of the following alkanes give only one alkyl chloride upon reaction with chlorine and light?

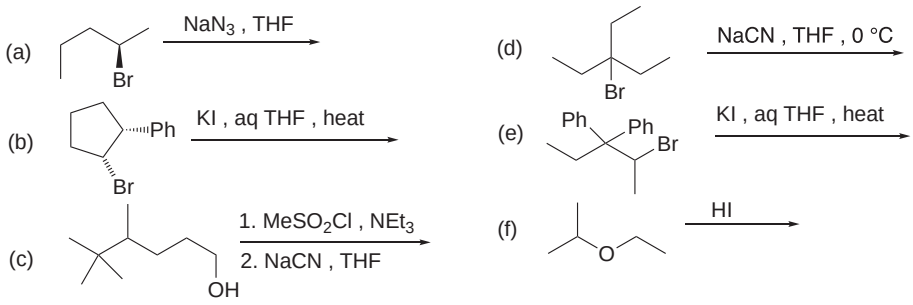
31. Which of the following is the least stable carbocation? Justify your choice.



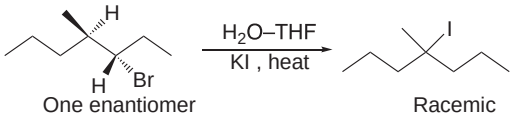
32. Which of the following reactions will proceed with 100% inversion of configuration? Explain.

33. Draw the transition state that would be required for the S_N2 reaction of 2-bromo-2-methylpropane and KI in diethyl ether. Use this transition state to explain *why* this combination of reactants yields *no reaction under these conditions.*
34. What is the product formed when butan-(2*S*)-ol is treated with thionyl chloride and triethylamine?

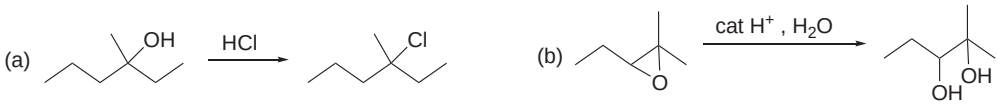
35. Briefly explain why methoxide (MeO^-) is a relatively poor leaving group but methanesulfonate ($MeSO_3^-$) is a good leaving group in nucleophilic substitution reactions.
36. Give the major product for each of the following reactions:



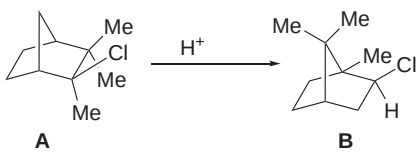
37. When 1,3-dibromo-4,4-dimethylpentane is treated with KI in THF, the product formed results from reaction with only one of the two C—Br units. Draw the product and discuss why that bromine reacts preferentially.
38. Briefly explain why diethylamine is a stronger nucleophile with 1-bromopentane when water is used as a solvent when compared to THF.
39. The nitrate anion (NO_3^-) is not a very good nucleophile in the S_N2 reaction. Briefly explain why this is the case.
40. A common "trick" used by organic chemists when a S_N2 reaction has a slow rate of reaction is to add NaI. When 2-bromo-3-methylhexane reacts with NaCN, for example, the reaction rate can be significantly increased by adding NaI to the reaction. Why and how does this help the reaction?
41. Draw the major product for the reaction of pent-1-yne + $NaNH_2$, THF followed by reaction with (2*R*)-bromopentane.
42. Explain the following observation. Give the complete mechanism as part of your answer.



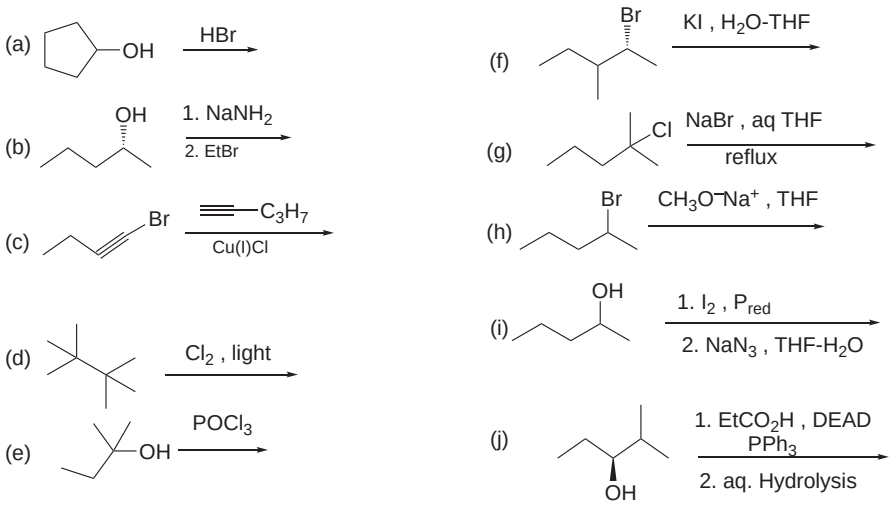
43. Give a complete mechanism for the following reactions:



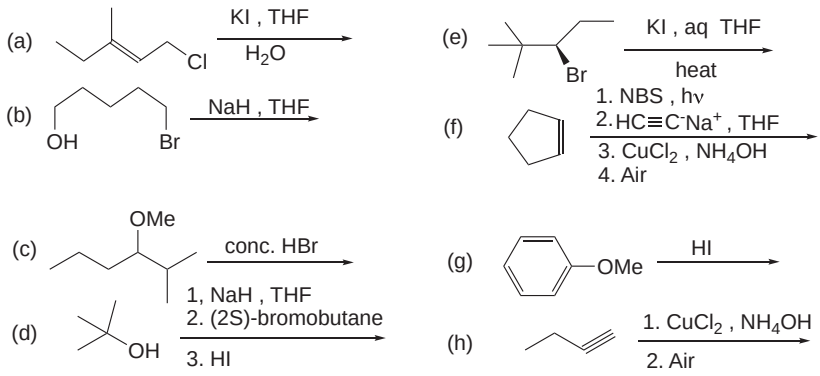
44. The Wagner-Meerwein rearrangement occurs when **A** is treated with acid. The product is **B**. This is a classical reaction in organic chemistry. Offer a mechanism that will convert **A** to **B**.



45. Give the major product expected from each of the following reactions:



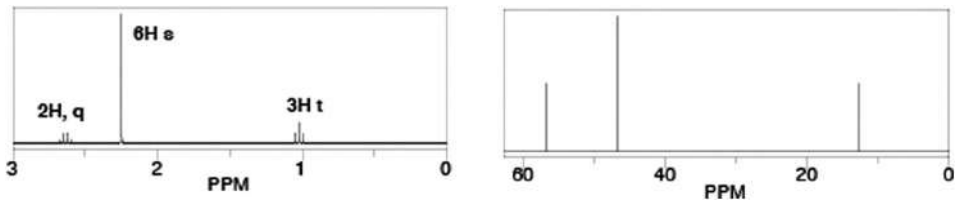
46. Give the major product for each of the following reactions:



47. Treatment of pent-2-ene with NBS and light can yield three different products. Draw them and explain this lack of selectivity.
48. What is the product formed when 2-propyloxirane reacts with (a) NaCN (b) NaN_3 (c) catalytic H^+ in water (d) HCl (e) $CH_3C{\equiv}C^-Na^+$?

Spectroscopic problems. Do not attempt these problems until you have read and understood Chapter 13.

49. Briefly describe differences in the IR and ^1H NMR that will allow you to distinguish between pent-2-ene and pent-1-ene.
50. Given the spectral data shown, provide a structure. The formula is $C_4H_{11}N$. Infrared: 3050-2850, 2800-2650, 1500-1490, 1080-1020 cm^{-1}.



51. Provide a structure given the following spectral data. MS: M 118 (100%), M+1 119 (6.66%), M+2 120 (0.62%): 43 (36), 45 (100), 55 (29), 69 (29), 70 (89), 71 (20), 87 (22), 118 (very small); IR: 3270, 2870-2854, 1472-1438, 1410, 1068-1028 cm^{-1}; ^1H NMR:

3.54 (broad s, 2H; this peak is greatly diminished when the sample is washed with D_2O), 3.49 (broad s, 4H), 1.34 (q, 2H), 0.86 (7, 3H), 0.8 (s, 3H) ppm.

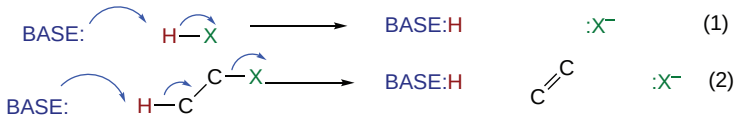
52. Molecule **A** has the formula C_5H_{10} and shows a sharp peak at 2080 cm^{-1} and a moderate peak at 1826 cm^{-1}; MS: M=164 (100%), M+1=165 (6.66%), M+2=165 (98%); ^1H NMR: 5.81 (m, 1H), 4.97 (m, 1H), 4.93 (m, 1H), 2.0 (m, 2H), 1.43 (m, 2H), 0.91 (t, 3H) ppm. The reaction of this molecule with a catalytic amount of H_2SO_4 in aq THF gives a modest yield of a new molecule **B** that has the formula $C_5H_{12}O$. This new molecule shows a very strong peak in the IR at 3683-2933 cm^{-1}. It has a ^1H NMR: 3.8 (m, 1H), 1.92 (broad s; this peak is diminished when treated with D_2O, 1H), 1.52-1.29 (m, 2H), 1.28 (m, 2H), 0.93 (broad t, 3H) ppm. When **B** reacts with NaH in THF, a slightly exothermic reaction occurs. This solution is then treated with iodomethane, and the final product is **C**, which has a formula of $C_6H_{14}O$, no prominent peaks in the IR and the ^1H NMR is: 3.30 (s, 3H), 3.01 (m, 1H), 1.42 (m, 2H), 1.33 (m, 2H), 1.18 (broad d, 3H), 0.90 (broad t, 3H) ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-12.php

12

Elimination and π–Bond-Forming Reactions

An alkyl halide contains a C—X bond, where X is F, Br, Cl, or I. In an alkyl halide the acidic proton and the leaving group are separated by two carbon atoms. The bond polarization for this system is $H^{\delta+}—C^{\delta-}—C^{\delta+}—X$ and this δ^+ proton is a weak acid. A traditional Brønsted-Lowry acid-base reaction is shown in reaction (1), where the base donates electrons to the proton, which is directly connected to the leaving group X. In (2) reaction of the acidic proton with a base leads to formation of an alkene (C=C) as the X^- group leaves to form the conjugate base, X^-. The conjugate acid is BASE:H. The elements of H and X are lost in this reaction as the C=C unit is formed, so it is known as an *elimination reaction*. Alkyl fluorides are typically not used in these reactions.



To begin this chapter, you should know the following points:

- The structure and nomenclature of alkyl halides (Section 4.3.3).
- The structure and nomenclature of alkenes and alkynes (Sections 5.1–5.3).
- Brønsted-Lowry acid-base reactions (Sections 2.1–2.6, 6.1–6.3, and 6.7).
- Bond polarization and dipoles in a $^{\delta+}C—X^{\delta-}$ species (Section 3.8).
- S_N2 and S_N1 reactions (Sections 11.2 and 11.4).
- Nucleophiles (Sections 6.9 and 11.1).
- Intermediates (Sections 7.2 and 10.3).
- Transition states (Section 7.6) and kinetics (Section 7.11).
- Conformations (Sections 8.1–8.6).
- Stereogenic centers and absolute configuration (Sections 9.1 and 9.2).
- Diastereomers (Section 9.5).

Alkenes from Alkyl Halides

12.1 BIMOLECULAR ELIMINATION

Alkoxides (RO^-) are important nucleophiles, and the S_N2 reaction of an alkoxide with an alkyl halide is the basis of the Williamson ether synthesis (Section 11.3). Since tertiary halides do not react with nucleophiles in the S_N2 reaction, mixing with sodium ethoxide in a solvent such as tetrahydrofuran (THF) does *not* give an ether product. If the solvent is ethanol, however, there is a reaction. As shown in Figure 12.1, 2-bromo-2-methylpropane reacts with sodium ethoxide to give 2-methylprop-2-ene, along with sodium bromide and ethanol.[1]

As an electron donor, sodium ethoxide is most attracted to the electrophilic carbon that bears bromine. The ethoxide anion does indeed collide with that carbon. However, the activation barrier for a S_N2 reaction with a tertiary halide is too high due to steric hindrance in the transition state (Section 11.2). The collision is unproductive and there is no reaction.

[1] Biale, G.; Cook, D.; Lloyd, D.; Parker, A.J.; Stevens, I.D.R.; Takahashi, J.; Winstein, S. *Journal of the American Chemical Society* 1971, 93, 4735–4749.

DOI: 10.1201/9781003174929-12

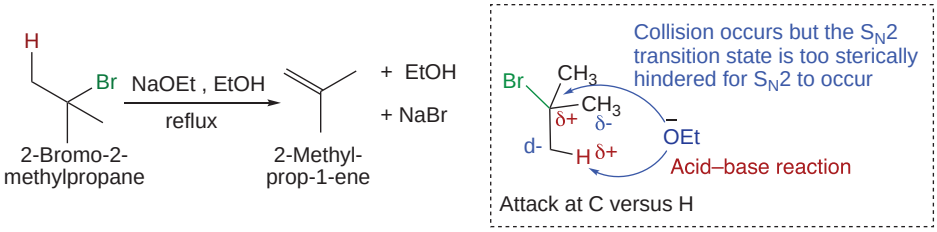


FIGURE 12.1 Elimination of 2-bromo-2-methylpropane.

Remember that sodium ethoxide is a base as well as a nucleophile. Ethoxide is also attracted to the weakly acidic β hydrogen and collision initiates an acid-base reaction. Removal of the β hydrogen converts ethoxide to ethanol and gives 2-methylbut-2-ene, as shown in Figures 12.1 and 12.2.

This is an *elimination reaction* (E) and loss of H and Br gives a π-bond between the α- and β- carbons. This reaction is *second-order* (Section 7.8.2) and it is called an *E2 reaction*, a bimolecular elimination. The bases used to initiate an E2 reaction rely on the old adage, a strong acid yields a weak conjugate base, and a weak acid yields a strong conjugate base. In general, the bases used for an E2 reaction are NaOH or KOH in a protic solvent or the alkoxide RO^- derived from the alcohol solvent. In other words, use $NaOCH_3$ in CH_3OH, $NaOCH_2CH_3$ in CH_3CH_2OH, or $(CH_3)_3CONa$ in $(CH_3)_3CHOH$.

*No intermediate has been detected for this reaction. A*ll of the bond making and breaking occurs simultaneously, so this is a *synchronous* reaction. With no intermediate, the characteristics of the reaction are described by the *E2 transition state* shown in Figure 12.2.

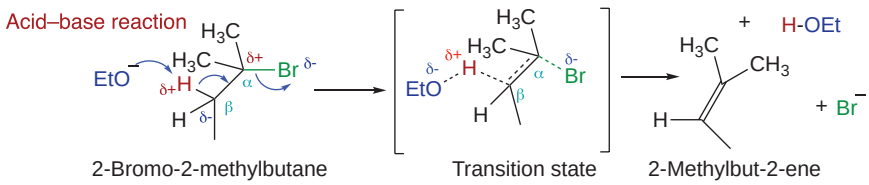


FIGURE 12.2 The conversion of 2-bromo-2-methylbutane to 2-methylbut-2-ene.

As the β-hydrogen is pulled off by the base and the C—H bond begins to break, electron density increases on the β carbon and migrates toward the δ^+ carbon (the α carbon) to form a second bond to carbon, a π-bond. The bromine leaving group is expelled. Drawing the transition state can be correlated with the reaction arrows. To represent the transition state a dashed line replaces the arrow, as shown for the developing bond between the base and the β-hydrogen. A dashed line also replaces the arrows for breaking the C—H bond and formation of the π-bond, and finally for cleavage of the C—Br bond.

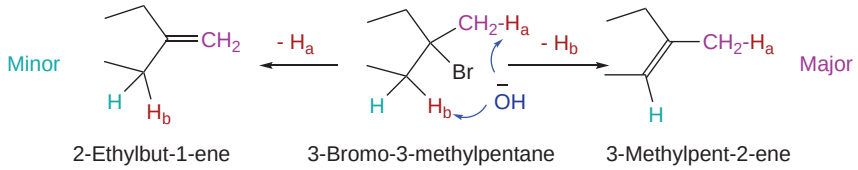
The E2 Reaction

12.1 Show all positively polarized hydrogen atoms, relative to the iodine atom, in 3-iodo-2,3-dimethylpentane.

Alkenes usually have different β hydrogen atoms so an E2 reaction can lead to isomeric alkenes. In general, an E2 reaction gives the *more highly substituted alkene* as the major product. Alexander Mikhaylovich Zaytsev (also spelled Saytzeff, or Saytzev; Russia; 1841–1910) recognized the selectivity of elimination reactions to give the more substituted product. He formulated what is known as *Zaytsev's rule* (also known as Saytzeff's rule or Saytsev's rule), which states "if more than one alkene can be formed by an elimination reaction, the more substituted alkene is the major product." An E2 reaction is therefore *regioselective* since one alkene is formed as the major product of two or more possible alkene products.

3-Bromo-3-methylpentane has two β hydrogen atoms (H_a and H_b), so there are two possible products, 3-methylpent-2-ene and 2-ethylbut-1-ene. The carbon bearing H_a has fewer carbon substituents and therefore H_a is a slightly stronger acid than H_b. The carbon bearing

H_b has more carbon substituents therefore H_b is a weaker acid. If H_a were removed faster in the acid-base reaction, then 2-ethylbut-1-ene should be the major product, but it is not. The E2 reaction of 3-bromo-3-methylpentane gives 3-methylpent-2-ene as the major product by removal of H_b. Acidity of the β hydrogen atom in the starting material *cannot* be the most important factor for generation of the major product in an E2 reaction. Another factor must drive the reaction.



12.2 Draw the elimination product expected when 2-bromo-3,3-dimethylbutane is treated with hydroxide ion and heated.

Removal of each different β-hydrogen leads to a different transition state in the reaction of 3-bromo-3-methylpentane and sodium ethoxide. Transition state **1** leads to 3-methylpent-2-ene, and **2** leads to 2-ethylbut-1-ene, as shown in Figure 12.3. Removal of the more acidic

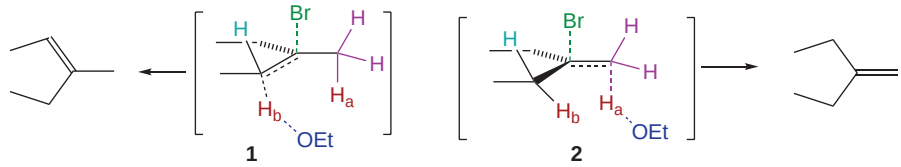


FIGURE 12.3 Transition states for the reaction of sodium ethoxide and 3-bromo-3-methylpentane.

hydrogen leads to transition state **2**. Energetically, **2** is more like the starting materials since removal of the more acidic proton is faster. Formation of the more substituted and more stable alkene proceeds by transition state **1**. Energetically, **1** is more like the isolated product, which is the more substituted alkene. The Hammond postulate states, "the transition state for a given step resembles the side of the reaction to which it is closer in energy."[2] In this reaction, **1** is a late transition state (more like the product) and **2** is an early transition state (more like the starting materials). Transition state **1** leads to the major product, consistent with a late transition state for E2 reactions. *An E2 reaction always gives the more stable alkene.* Therefore, factors that influence the stability of the products are more important than acidity in the starting material.

12.3 Draw the major product expected when KOH is heated with 3-bromo-2,3-dimethylhexane, in a suitable solvent.

In the E2 reaction of 3-bromo-4-ethyl-2-methylhexane and potassium *tert*-butoxide ($Me_3CO^-K^+$) two alkene products are formed, 4-ethyl-2-methylhex-2-ene and 4-ethyl-2-methylhex-3-ene. Both are trisubstituted alkenes, and they should be roughly equal in energy and formed in approximately equal amounts. Indeed, if there are two products of equal substitution and presumed equal stability, *assume they are formed as close to a 1:1 mixture.* Primary halides (e.g.,1-bromopentane) usually do not give E2 reactions. It is not impossible, just very slow and depending on the nucleophile and the substituents on the primary halide, so a competitive S_N2 reaction is usually faster. The reaction of 1-bromopentane with sodium ethoxide in ethanol will likely give the S_N2 product, 1-ethoxypentane and not an alkene.

[2] Hammond, G.S. *Journal of the American Chemical Society* 1955, 77, 334–338; (b) Farcasiu, D. *Journal of Chemical Education* 1975, 52, 76–79.

12.4 Draw the reaction and product predicted to form when sodium methoxide reacts with 1-bromobutane.

E/Z-Selectivity of the E2 Reaction

12.2 STEREOCHEMICAL CONSEQUENCES OF THE E2 REACTION

Examination of transition states **1** and **2** in Figure 12.3 reveals another important characteristic of the E2 reaction. For an E2 reaction to occur the β-hydrogen removed by the base must be anti- to the leaving group. In other words, for the reaction to proceed to the requisite transition state, the leaving group must be 180° opposite the β hydrogen being removed. This can only occur via an anti-rotamer where backside attack of the migrating electrons at the bromine-bearing carbon can expel the leaving group. If an anti-rotamer is not possible, an E2 reaction is *not* possible. This requirement determines the stereoselectivity of the E2 reaction.

12.5 Draw the two possible transition states that lead to an alkene product when KOH is heated with 2-bromo-3-ethylpentane, in a suitable solvent. Indicate which one leads to the major product.

When (2*R*)-bromo-(3*R*)-methylpentane is treated with KOH in ethanol, the more highly substituted alkene predicted by Zaitsev's rule is 3-methylpent-2-ene. However, there are

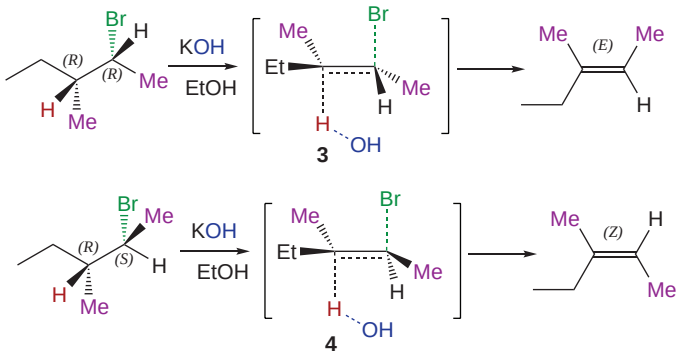


FIGURE 12.4 The E2 reactions of diastereomeric 2-bromo-3-methylpentanes.

two isomeric 3-methylpent-2-enes, the *E*- and the *Z*-isomer. As shown in Figure 12.4, only 3-methylpent-2*E*-ene is formed so this reaction is *diastereospecific*. In other words, no 3-methylpent-2*Z*-ene is observed. The bond making-breaking process begins once the anti-rotamer is achieved for (2*R*)-2-bromo-(3*R*)-methylpentane. Once transition state **3** is achieved, the stereochemical position of all groups are "locked" in position. If the two methyl groups are on the same side in transition state **3** they will be on the same side in the alkene product, which is 3-methylpent-(2*E*)-ene. Conversely, the E2 reaction of (2*S*)-bromo-(3*R*)-methylpentane via the anti-rotamer leads to transition state **4**. The methyl groups are locked on opposite sides, which gives 3-methylpent-(2*Z*)-ene.

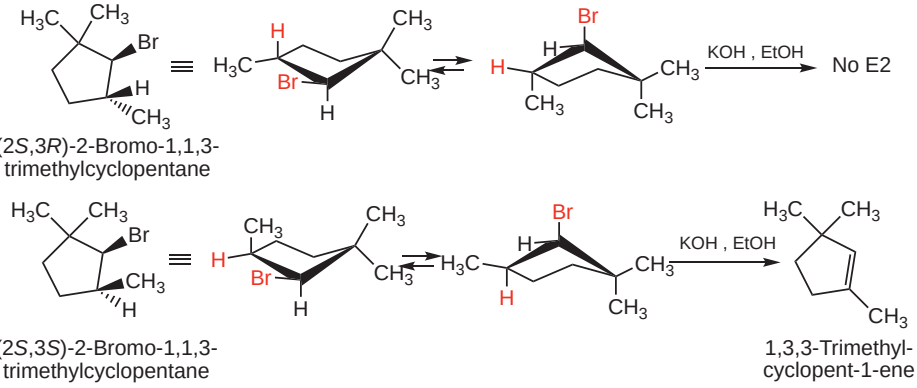
12.6 Draw the E2 transition state and final major product formed when (3*S*)-iodo-(4*R*)-(1-methylethyl)heptane reacts with sodium ethoxide in ethanol at reflux.

Racemic 2-bromopentane undergoes an E2 reaction when treated with KOH to give pent-2-ene as the major product. The E2 reaction is regiospecific as expected. However, there are two β hydrogen atoms on the C3 carbon. Removal of one β hydrogen atom leads to pent-(2*Z*)-ene, whereas removal of the other β hydrogen atom leads to pent-(2*E*)-ene. Therefore, a *racemic hali*de leads to a mixture of (*E*)- and (*Z*)-alkenes.

12.3 THE E2 REACTION IN CYCLIC MOLECULES

The E2 Reaction with Cyclic Molecules

Cyclic halides with a secondary or tertiary center undergo E2 reactions when treated with base. The requirement for an anti-relationship (180° apart) of the leaving group and the β hydrogen atoms raises conformational issues in cyclic compounds. Cyclic compounds cannot rotate by 360° about any C—C bond, but pseudorotation is possible as described in Section 8.5. In addition, cyclic halides can have the β-hydrogen and leaving group on the same side of the ring or on the opposite sides.



An E2 reaction of cyclopropane derivatives to give a cyclopropene is difficult in large part because it is highly strained. Therefore, other methods are used to prepare cyclopropene derivatives. There is sufficient flexibility in a four-membered ring that trans-substituted halocyclobutanes react with a base to give a cyclobutene via an E2 reaction. An E2 reaction in halocyclopentane derivatives is facile. It is possible that certain substitution patterns can limit the reactivity of cyclopentane derivatives, however. The reaction of isomeric 2-bromo-1,1,3-trimethylcyclpentanes with KOH in ethanol is an example. Two envelope conformations of (2*S*,3*R*)-2-bromo-1,1,3-trimethylcyclpentane and (2*S*,3*S*)-2-bromo-1,1,3-trimethylcyclpentane are shown to emphasize the flexibility of the five-membered ring. In (2*S*,3*R*)-2-bromo-1,1,3-trimethylcyclpentane, the β-hydrogen and the bromine cannot achieve an anti-orientation so an E2 reaction is not possible. In (2*S*,3*S*)-2-bromo-1,1,3-trimethylcyclopentane the β-hydrogen and the bromine have a trans relationship but only one of the envelope conformations has the β-hydrogen and the leaving group with the required orientation to give 1,3,3-trimethylcyclopent-1-ene.

There is greater conformational flexibility in cyclohexane derivatives and both cis- and trans-derivatives react. The only way a β-hydrogen and a leaving group can have the needed anti-relationship, however, is when those atoms have a *trans-diaxial* relationship. This requirement is shown by an E2 reaction of both *cis*- and *trans*-1-bromo-2-methylcyclohexane, in Figure 12.5. In both compounds the bromine is axial in one chair conformation

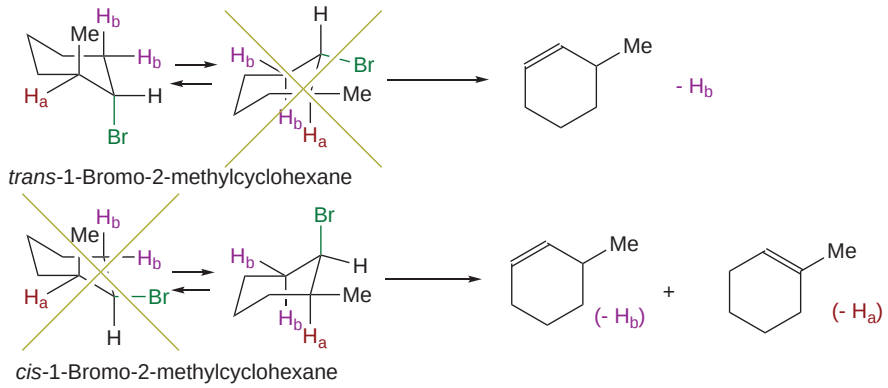
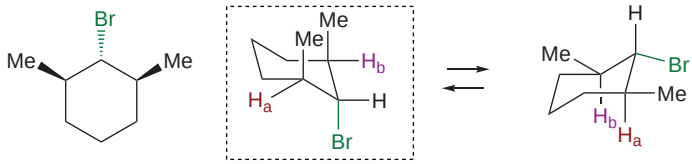


FIGURE 12.5 E2 reaction of *trans*- and *cis*-1-bromo-2-methylcyclohexane.

but not the other. If the bromine is equatorial, it is impossible to achieve an anti-relationship with a β hydrogen atom. This conformation is crossed out to show that it cannot lead to an alkene. Note that *trans*-1-bromo-2-methylcyclohexane can *only* give the less substituted alkene 3-methylcyclohex-1-ene. Therefore, this halide does not follow Zaitsev's rule. In *cis*-1-bromo-2-methylcyclohexane the bromine is axial when both H_a and H_b are trans diaxial so *both* will be removed by KOH to yield both 3-methylcyclohex-1-ene and 1-methylcyclohex-1-ene.

12.7 Draw the E2 transition state for the reaction of bromocyclopentane with KOH.

If the limitations described above are taken to their ultimate conclusion, there should be halocyclohexanes for which an E2 reaction is impossible. When (1*R*,3*S*)-2-bromo-1,3-dimethylcyclohexane is treated with KOH, the conformation where the bromine atom is axial has two axial methyl groups. Both β hydrogen atoms (H_a and H_b) are equatorial so there are no β- hydrogen atoms that are trans, diaxial to an axial bromine. Therefore, an E2 reaction is not possible. In addition, the carbon bearing the bromide in (1*R*,3*S*)-2-bromo-1,3-dimethylcyclohexane is very sterically hindered so an S_N2 reaction is slow and unlikely. Treatment of (1*R*,3*S*)-2-bromo-1,3-dimethylcyclohexane with base is expected to give no reaction.



(1*R*,3*S*)-2-Bromo-1,3-dimethylcyclohexane

No E2 reaction is possible

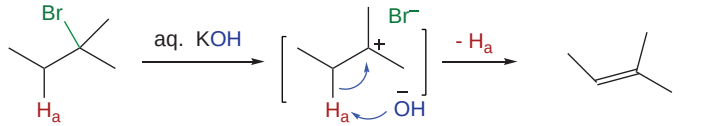
Note that halocycloheptane derivatives and halo derivatives of larger ring compounds that have greater flexibility for pseudorotation are expected to give E2 reactions without serious complications. The cyclic alkene product should form without a problem in most cases.

12.8 Draw the major product, if any, formed when (1*R*)-bromo-(2*R*)-ethyl-(5*R*)-methylcyclohexane is heated with KOH in ethanol.

The E1 Reaction

12.4 UNIMOLECULAR ELIMINATION: THE E1 REACTION

Both the S_N2 reaction in Section 11.2 and the E2 reaction discussed in Sections 12.1–12.3 follow second-order kinetics (Section 7.11.2), and they are bimolecular reactions. The S_N1 reaction described in Section 11.4 is a unimolecular reaction in which slow ionization of the halide to a carbocation is facilitated by water. Subsequent reaction with a nucleophile is a very fast second step so the reaction follows first-order kinetics. Therefore, it is not a surprise that reaction of a tertiary halide with base in an aqueous medium will lead to ionization and formation of a carbocation. The hydrogen atoms on the carbon atoms attached to C^+ of the carbocation are polarized δ^+ and therefore weak acids. Under these reaction conditions, the β-hydrogen atoms (H_a) can react with the base to give the more substituted alkene. This two-step process of ionization followed by an acid-base reaction is termed an *unimolecular elimination, E1*.



2-Bromo-2-methylbutane

Tertiary carbocation

2-Methylbut-2-ene

If 2-bromo-2-methylbutane is heated with KOH in aq THF, an S_N2 reaction is not possible due to steric hindrance, but an E2 reaction is possible. Water is the solvent in this reaction, and it facilitates ionization, which leads to the tertiary carbocation with a bromide counter-ion. The carbon adjacent to the positively charged is polarized δ^-, which leads to polarization of the β hydrogen as δ^+. The β hydrogen of the carbocation is more polarized and more acidic when compared to the β hydrogen atom in 2-bromo-2-methylbutane. The β hydrogen reacts with hydroxide to give water as the conjugate acid and 2-methylbut-1-ene. The acid-base reaction is fast compared to ionization and the reaction follows first-order kinetics (Section 7.11.1). Ionization is the rate-determining step, and the overall reaction is an *E1 reaction (unimolecular elimination)*. Although an E1 reaction is possible, it is important to note that ionization is slower than a bimolecular process. An E2 reaction to give the alkene is possible even in water. Indeed, the E2 is usually faster than the E1, but the alkene formed by both E2

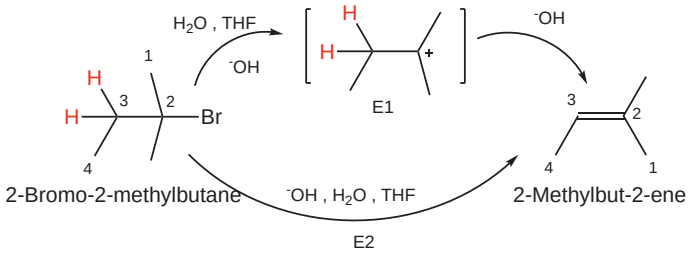
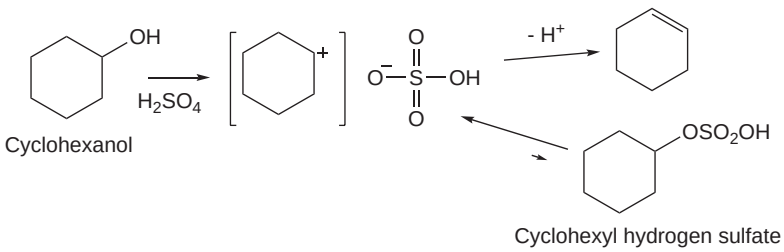


FIGURE 12.6 Competition between E2 and E1 reactions for 2-bromo-2-methylbutane.

and E1 reactions is the same, as shown in Figure 12.6. In general, E2 > E1 so in aqueous media the E2 reaction will produce more product than the E1 reaction.

There is another problem. Once the carbocation intermediate is formed, both the nucleophilic hydroxide ion and water can collide with the positive carbon of the carbocation. These nucleophilic S_N1 reactions will afford 2-methylbutan-2-ol. In a protic solvent such as water, substitution of the carbocation via a S_N1 reaction is usually faster than elimination via an E1 reaction. Therefore, it is difficult to find a "clean" E1 reaction. Exceptions occur when the base used in the reaction is a poor nucleophile, or if the S_N1 product is unstable and leads to a reversible reaction. If cyclohexanol is treated with concentrated sulfuric acid, for example, the observed product is cyclohexene in a fast reaction. The mechanism involves an acid-base reaction of the oxygen from the OH unit with the sulfuric acid to form an oxonium ion. Loss of water from the oxonium ion yields a secondary carbocation and the hydrogen sulfate anion.



The hydrogen sulfate anion is highly stabilized due to resonance and is not very nucleophilic (Section 10.2). Even if the S_N1 reaction occurs, the cyclohexyl hydrogen sulfate product is unstable under these reaction conditions, so a substitution reaction is reversible and unfavorable. In other words, the instability of cyclohexyl hydrogen sulfate leads to an equilibrium that favors the carbocation. The hydrogen sulfate anion is sufficiently basic, however, to remove a β-hydrogen from the carbocation intermediate to give cyclohexene, the E1 product. For the most part, the E1 reaction is a "nuisance" in that E1 products are formed as minor products when a carbocation is generated, even when the S_N1 product is the major one.

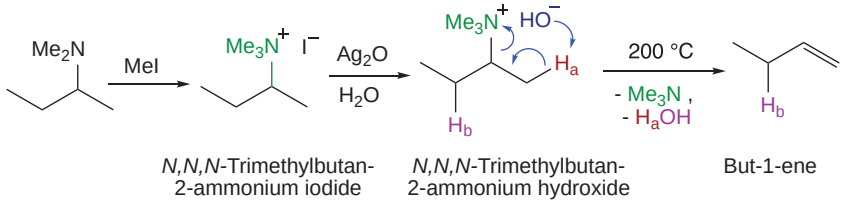
12.9 Draw the oxonium ion formed when cyclohexanol reacts with sulfuric acid.

12.5 INTRAMOLECULAR ELIMINATION

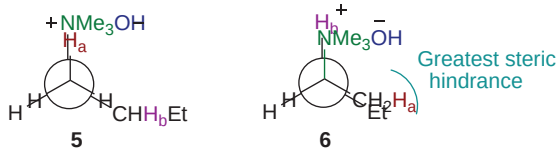
Intramolecular elimination reactions are possible in addition to the intermolecular E2 reaction. An example of this elimination uses a trimethylammonium salt with a basic counterion. When *N,N,N*-trimethylbutan-2-ammonium hydroxide is heated to ~ 200 °C, neat (no solvent), the major product is but-1-ene in 95% yield.[3] Hydroxide is the base in this reaction and trimethylamine is the leaving group. Formation of this ammonium hydroxide requires several chemical steps. The reaction of *N,N*-dimethylbutan-2-amine with iodomethane affords *N,N,N*-trimethylbutan-2-ammonium iodide. The iodide counterion is not basic enough to remove the proton and must be exchanged for a basic counterion. The reaction of *N,N,N*-trimethylbutan-2-ammonium iodide with silver oxide and a *trace* of water leads to exchange of the iodide ion for a hydroxide ion and formation of *N,N,N*-trimethylbutan-2-ammonium hydroxide. If there is no solvent, the positive and negative charges attract to form a *tight ion pair* where the hydroxide counterion is tethered to the ammonium ion. As noted, heating gives but-1-ene. The transformation of *N,N*-dimethylbutan-2-amine to but-1-ene is called *Hofmann elimination*, named after August Wilhelm Hofmann (Germany; 1818–1892).

Since but-1-ene is the less thermodynamically stable alkene when compared to but-2-ene, the reaction does not follow the Zaitsev rule and the reaction is clearly not E2. There are two β hydrogen atoms in *N,N,N*-trimethylbutan-2-ammonium hydroxide, H_a and H_b, and removal of either will generate water and triethylamine. However, only removal of H_a will give but-1-ene. Therefore, the hydroxide ion must react intramolecularly with a β-hydrogen to give but-1-ene.

Hoffman Elimination



An intramolecular process can occur only when the C—H bond of a proton on the methyl unit and the ammonium unit eclipse. They have a syn relationship. Greater steric interactions make an eclipsed rotamer higher in energy than the staggered rotamer required for an E2 reaction. Therefore, this intramolecular reaction does not occur at ambient or low temperatures. Heating to 200°C or greater is necessary. Eclipsed or syn rotamer **5** is required for removal of H_a and syn rotamer **6** is required for removal of H_b. Of the two eclipsed rotamers, **6** has greater steric hindrance due to the methyl-ethyl interaction and is therefore higher in energy. The lower energy eclipsed rotamer **5** is easier to form and leads to preferential removal of H_a and formation of but-1-ene as the major product. This acid-base reaction is an *intramolecular elimination (an Ei reaction),* defined as a reaction in which two groups leave simultaneously as a π-bond is formed.



12.10 Draw the syn rotamer that is required to remove H_a in *N,N,N*-trimethylbutan-2-ammonium hydroxide.

If *N,N,N*-trimethylbutan-2-ammonium hydroxide is heated in an aqueous solvent, the water facilitates ionization of the ammonium hydroxide. In aqueous ethanol, for example,

[3] Cope, A.C.; Trumbull, E.R. *Organic Reactions* 1960, 11, 317–493 (see p. 334).

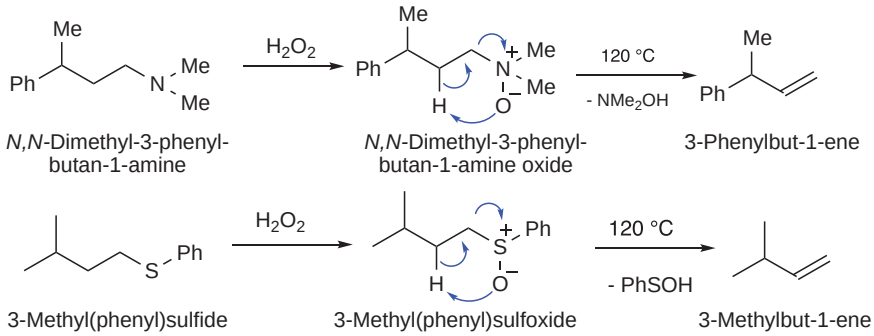
the positively charged ammonium ion and the negatively charged hydroxide ion are solvent separated. The hydroxide ion reacts via an intermolecular E2 reaction with formation of but-2-ene as the major product. The intramolecular Hofmann elimination can occur only in nonaqueous solvents via an eclipsed rotamer. In aqueous solvents the reaction proceeds via an E2 pathway.

Other Intramolecular Elimination Reactions

12.11 Write out the reaction of the ammonium salt with hydroxide ion as solvent separated ions in aqueous media, giving the expected E2 transition state and E2 product.

12.12 Draw the product formed when 2-iodo-3-methylpentane is reacted with (1) NMe_3, (2) Ag_2O/H_2O, and (3) heat to 200°C.

Other syn-elimination reactions are possible if the molecule has a basic atom or group that is part of the leaving group. Arthur C. Cope (USA; 1909–1966) found that conversion of an amine to an amine *N*-oxide ($R_3N^+—O^-$) unit satisfied this criterion. The oxygen atom is a negative dipole that reacts as a base. Removal of the β hydrogen via a syn conformation leads to cleavage of the C—N bond with loss of a neutral leaving group, a hydroxylamine. Heating amine oxides to produce alkenes is known as *Cope elimination*.[4] A typical reaction temperature is 120°C, significantly lower than that required for the Hofmann elimination. The *N*-oxides are prepared by oxidation of the corresponding amine precursor with hydrogen peroxide or *m*-chloroperoxybenzoic acid[5] (Section 15.4). The example shown begins with the hydrogen peroxide oxidation of *N,N*-dimethyl-3-phenylbutan-1-amine to give the N-oxide, *N,N*-dimethyl-3-phenylbutan-1-amine oxide. Subsequent heating leads to loss of *N,N*-dimethylhydroxylamine and formation of the less substituted alkene, 3-phenylbut-1-ene.



Another syn elimination precursor incorporates the polarized oxygen of a sulfoxide.[6] If a sulfide is oxidized with hydrogen peroxide or with sodium *meta*-periodate ($NaIO_4$),[7] the resulting sulfoxide (an *S*–oxide) has a polarized S—O bond. The negatively polarized oxygen reacts as a tethered base. Heating leads to an eclipsed conformation for the β hydrogen and the S—O moiety. Intramolecular reaction with the β-hydrogen gives the alkene with loss of PhS—OH (benzenesulfenic acid where sulfur is bonded to a phenyl group). This product is unstable to the reaction conditions and decomposes, facilitating formation of the alkene. The temperature required for elimination is only about 75–140°C. An example is the reaction of 3-methyl(phenyl)sulfide with H_2O_2 to give 3-methyl(phenyl)sulfoxide. Subsequent heating to 120°C gave 3-methylbut-1-ene and benzenesulfenic acid.

12.13 What product is formed when (1-bromoethyl)cyclopentane reacts with (a) PhS^-Na^+ (b) H_2O_2 (c) 80°C?

[4] (a) Cope, A.C.; Foster, T.T.; Towle, P.H. *Journal of the American Chemical Society* 1949, 71, 3929–3934; (b) Cope, A.C.; Pike, R.A.; Spencer, C.F. *Journal of the American Chemical Society* 1953, 75, 3212–3215.

[5] (a) Cope, A.C.; Ciganek, E. *Organic Synthesis Collective Volume 4*, 1963, 612–622.

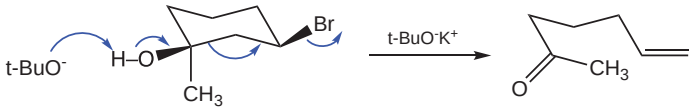
[6] (a) Grieco, P.A.; Reap, J.J. *Tetrahedron Letters* 1974, 1097–1100; (b) Kingsbury, C.A.; Cram, D.J. *Journal of the American Chemical Society* 1960, 82, 1810–1814.

[7] (a) Reich, H.J.; Renga, J.M.; Reich, I.L. *Journal of Organic Chemistry* 1974, 39, 2133–2135; (b) Sharpless, K.B.; Young, M.W. *Journal of Organic Chemistry* 1975, 40, 947–949.

12.14 What product is formed when *N,N*,4,4-tetramethylhexan-3-amine reacts with (a) H_2O_2 (c) 120°C?

All E2 or E1 reactions as well as the Ei reactions are 1,2-elimination reactions. Other elimination reactions have been developed. One such reaction requires that an electron-donating species and a leaving group be separated by at least three carbons, so it is a *1,3-elimination*. The bonds that are made and broken must assume an anti-relationship before elimination is possible. The atoms involved in this elimination therefore assume a "W" conformation. Vladimir Prelog (Croatia-Switzerland; 1906–1998) first observed such an elimination reaction in work that solved the structure of quinine and other Cinchona alkaloids.[8] Cyril Grob (England; 1917–2003) later expanded this work to include amino halides and amino sulfonates.[9] Although the reaction was discovered by Prelog, Grob's contributions to this reaction led to its bearing his name, the *Grob fragmentation*.[10] An example is the reaction of 3*R*-bromo-1-methylcyclohexan-1*S*-ol with *tert*-butoxide. The acid base reaction with the acidic proton of the alcohol generates an alkoxide that is anti to the bromine leaving group. Electron transfer generates a carbonyl with concomitant cleavage of the adjacent C—C bond to form an alkene and expel the bromine leaving group. The product of this Grob fragmentation is hept-6-en-2-one.

Grob Fragmentation



3*R*-Bromo-1-methylcyclohexan-1*S*-ol Hept-6-en-2-one

Richmond Sarpong (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Elimination type reactions are important tools in the synthesis of biologically important molecules. Professor Richmond Sarpong (Ghana-USA) at the University of California Berkeley develops new synthetic methods in the pursuit of the total synthesis of biologically active and architecturally complex natural products. Professor Sarpong's synthesis of phomactin uses a C—C bond cleavage strategy using a rhodium mediated strategy.[11] Phomactin A is a

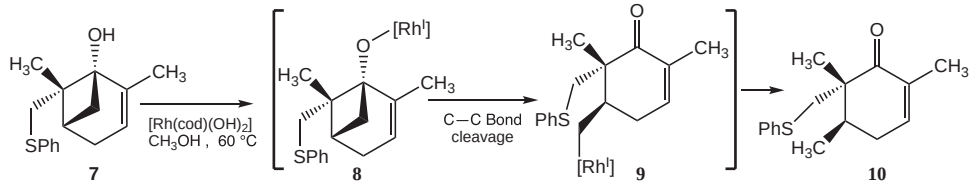
[8] (a) Klyne, W.; Prelog, V. *Experientia* 1960, 16, 5210–5523; (b) Grob, C.A. *Angewandte Chemie International Edition* 1969, 8, 535–546 and references cited therein.

[9] Grob, C.A.; Kiefer, H.R.; Lutz, H.J.; Wilkens, H.J. *Helvetica Chimica Acta* 1967, 50, 416–431.

[10] (a) Grob, C.A.; Baumann, W. *Helvetica Chemica Acta* 1955, 38, 594–610; (b) Prantz, K.; Mulzer, J. *Chemical Reviews* 2010, 110, 3741–3766.

[11] (a) Wang, B.; Perea, M.A.; Sarpong, R. *Angewandte Chemie, International Edition* 2020, 59, 18898–18919; (b) Leger, P.R.; Kuroda, Y.; Chang, S.; Jurczyk, J.; Sarpong, R. *Journal of the American Chemical Society* 2020, 142, 15536–15547.

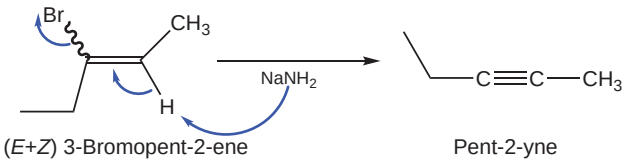
terpenoid secondary metabolite first isolated from a Phoma species of marine fungus in 1991 during a search for fungal metabolites that display platelet-activating factor receptor antagonism.[12] Many derivatives have been isolated in this small class of terpenoids. His synthesis uses a hydroxylated pinene derivative **7** obtained from carvone (Section 5.4). Reaction with 7.5 mol% of $[Rh(cod)OH]_2$ gave the rhodium complex **8** and C—C bond fragmentation led to formation of the carbonyl and the carbon-rhodium complex in **9**. In methanol solvent, ketone **10** was isolated in 75% yield. Note that cod is cyclooctadienyl.



12.15 What product is formed when (1*R*,3*S*)-3-iodocyclopentan-1-ol reacts with sodium amide?

12.6 ELIMINATION REACTIONS OF VINYL HALIDES: FORMATION OF ALKYNES

Formation of Alkynes



Alkynes are important compounds in organic chemistry, as shown in Section 10.8 for the reaction of alkynes with various reagents. Alkynes are prepared from other alkynes via an alkyne anion that reacts via a S_N2 reaction (Section 11.3). Alkynes can also be prepared from vinyl halides by an elimination reaction. In one example, 3-bromopent-2-ene is treated with sodium amide ($NaNH_2$) to give pent-2-yne. The hydrogen atom on the alkene unit is removed in an E2-like acid-base reaction. Loss of bromide ion leads to formation of a new π-bond in pent-2-yne and concomitant formation of the conjugate acid, ammonia. As noted, only a powerful base (e.g., sodium amide) can remove the vinyl hydrogen atom. In this reaction the hydrogen is on a carbon β- to the leaving group and the hydrogen removed is anti to the leaving group. This is a useful method if a vinyl halide is available as a starting material.

12.16 Draw the reaction that generates 3-bromopent-2-ene from an appropriate alkyne.

12.7 SUBSTITUTION VERSUS ELIMINATION

Substitution Competes with Elimination

The S_N2 and E2 reactions are bimolecular reactions, and the S_N1 and E1 reactions are unimolecular. These reactions can compete with each other in a given reaction, but it is not always clear which will predominate. However, for a given halide and set of conditions it is possible to predict which of these four reactions will predominate *if* a few simplifying assumptions

[12] Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *Journal of the American Chemical Society* 1991, 113, 54630–5464.

are made. The nature of the alkyl halide (1°, 2°, or 3°) is important, as is the strength of the nucleophile and whether or not that nucleophile can also react as a strong base. When substitution and elimination reactions compete, the solvent plays an important role. In reactions of tertiary halides, unimolecular processes dominate in water and aqueous solvents, and S_N1 reactions is usually faster than E1 reactions. There is competition between bimolecular substitution (S_N2) and bimolecular elimination (E2) for alkyl halides that react with a nucleophile that is also a base.

Water facilitates ionization due to the ability to separate ions. Solvents with a high dielectric, such as water, are more efficient at conducting a current, which is one measure of their ability to solvate and separate ions.[13,14] In general, ionization is very slow in aprotic, nonpolar solvents that do not contain water. In polar aprotic solvents ionization is usually slow. The essential difference between protic and aprotic solvents is the ability of protic solvents to solvate both cations and anions, whereas aprotic solvents efficiently solvate only cations. If no water is present, it can be safely assumed that the reaction proceeds by a bimolecular mechanism S_N2 or E2. If water is the solvent or a cosolvent, ionization is assumed to be favored. Therefore, assume that the reaction proceeds by a unimolecular mechanism; S_N1 or E1.

If the nucleophile is a weak base, elimination is very slow, and substitution is usually the major process. However, if the nucleophile is also a strong base, *both* substitution *and* elimination are possible. For the purposes of this book, a compound classified as a strong base that can be used in an E2 reaction must fit the old axiom "a weak acid gives a strong conjugate base." A compound that does not fit this criterion is considered a weak base and will not induce an E2 reaction.

12.17 Draw the conjugate base of nitric acid. Is this base strong enough to induce an E2 reaction with an alkyl halide? What is the conjugate base of methylamine? Is it a strong enough base to induce an E2 reaction?

To compare substitution versus elimination, the structure of the halide must be examined to see if it is compatible with the predicted reaction type. Substitution is much faster than elimination for primary halides, which usually react via a S_N2 reaction. Under most reaction conditions a primary halide cannot undergo an E2 reaction. Primary carbocations are very unstable relative to a tertiary carbocation and the transition state energy required to form a primary carbocation is too high in energy. For this reason, primary carbocations effectively do not form under solvolysis conditions so S_N1 and E1 reactions of primary halides do not occur.

12.18 Draw the S_N2 transition state for the reaction of sodium methoxide with 1-bromopropane. Draw the E2 transition state for these reactants.

The reactivity for primary and tertiary halides is well defined. However, secondary halides can undergo both bimolecular or unimolecular reactions; i.e., both substitution or elimination. For a secondary halide in a reaction with a base, with water as the solvent, ionization is a competitive process and both bimolecular and unimolecular reactions are observed. The S_N2 reaction is usually faster than the S_N1 reaction since direct attack at the α-carbon is more facile than ionization. In an aprotic solvent, both S_N2 and E2 reactions are favorable for a secondary halide in the presence of a strong base. Aprotic solvents favor bimolecular reactions since substitution is a faster process than elimination, but if the solvent is protic, elimination is known to be faster than substitution.

12.19 Draw the product of a reaction between sodium ethoxide and 2-bromobutane in THF. In ethanol.

[13] Parker, A.J. *Chemical Reviews* 1969, 69, 1–32.
[14] Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. *Journal of the Chemical Society* 1937, 1252–1254.

12.8 STRENGTH AND LIMITATIONS OF THE SIMPLIFYING ASSUMPTIONS

Four Assumptions

The previous discussion generates four questions that can be used to predict the major product of a reaction with an alkyl halide, based on an analysis of reaction conditions, the substrate, and reactants. Note that 1° is a primary halide, 2° is a secondary halide and 3° is a tertiary halide.

1. Does the solvent contain water? Yes or No!

If yes, assume that unimolecular processes (S_N1, E1) are faster than bimolecular processes (S_N2, E2).
If no, and particularly in aprotic solvents, assume that bimolecular processes (S_N2, E2) are faster than unimolecular processes (S_N1, E1).

2. Is the nucleophile categorized as a strong base? Yes or No!

If yes, assume that elimination reactions are possible (E2, E1), but other factors are required to determine whether elimination is faster or slower than substitution.
If no, then assume that elimination (E2, E1) is not possible.

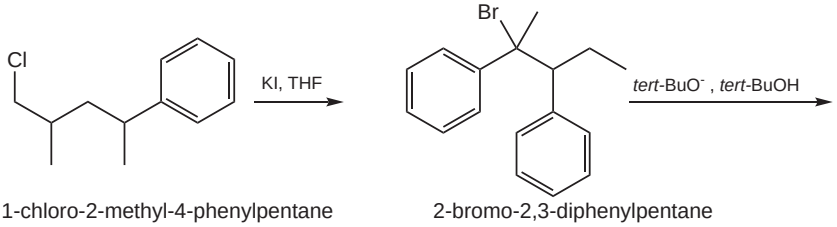
3. Is the alkyl halide 1°, 2°, or 3°?

If 1°, assume S_N2 predominates, regardless of solvent and that S_N1, E1, and E2 do not occur.
If 3°, assume S_N2 is impossible, but S_N1, E1, or E2 are possible, depending on the answers to questions 1 and 2.
If 2°, all reactions are possible, but if the answer to question 2 is Yes, see question 4.

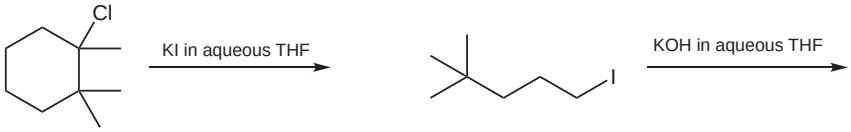
4. Is the solvent protic or aprotic?

If protic, assume that elimination is faster than substitution. If aprotic, assume that substitution is faster than elimination.

The assumptions listed here are based on mechanistic observations for each reaction. The utility of these assumptions can be examined with a few examples. If 1-chloro-2-methyl-4-phenylpentane is treated with KI in THF, first ask if the solvent contain water. No! Therefore, assume a bimolecular reaction (S_N2 or E2). Is the nucleophile a strong base? No! Iodide is not very basic and E2 is not competitive. The halide is primary, so the major product of this reaction should result from an S_N2 reaction, *1-iodo-2-methyl-4-phenylpentane*.



1-chloro-2-methyl-4-phenylpentane — 2-bromo-2,3-diphenylpentane



1-chloro-1,2,2-trimethylcyclohexane — 1-iodo-4,4-dimethylpentane

When 2-bromo-2,3-diphenylpentane reacts with potassium *tert*-butoxide in *tert*-butanol, first ask if the solvent contains water. No! The solvent is protic but does not contain water, so assume a bimolecular reaction (S_N2 or E2). Is the nucleophile a strong base? Yes! Alkoxides are good bases and an E2 reaction is competitive, so *both* E2 and S_N2 are possible. 2-Bromo-2,3-diphenylpentane is a tertiary halide, which means that E2 is possible but not S_N2. In addition, the solvent is protic, which favors elimination over substitution. The major product is predicted to be *2,3-diphenylpent-2-ene*.

In the reaction of 1-chloro-1,2,2-trimethylcyclohexane with KI in aqueous THF, first ask if water is present. The term aq THF indicates a mixture of water and the solvent THF (an ether), so the answer to question 1 is Yes. Therefore, *assume* that S_N1 or E1 is faster than S_N2 or E2. Is iodide a strong base? No. Therefore, assume that E1 is not competitive, so reaction conditions point to an S_N1 reaction. The halide is tertiary and an S_N1 reaction is feasible. Therefore, it is predicted that that iodide will replace chloride in an S_N1 reaction to give *1,2,2-trimethylcyclohexene*. Since the intermediate carbocation is tertiary, no rearrangement is anticipated. Another example is the reaction of 1-iodo-4,4-dimethylpentane with KOH in aqueous THF. The solvent is water, but primary halides do not undergo unimolecular reactions, so a bimolecular process is predicted, contrary to the rules listed. Further, E2 reactions are not facile so a S_N2 reaction is predicted to give *4,4-dimethylpentan-1-ol*.

It is important to remember that all of these "questions" are based on assumptions and are not universally correct. Understanding each possible mechanism and trying to apply those principles to the given reaction is essential. These four questions are useful tools, and they work most of the time, at least in this book, *but not always*. It is important to understand that these working assumptions apply *only* to reactions of alkyl halides and alkyl sulfonate esters. They work quite often but may fail for primary halides in aqueous media and for solvolysis reactions of tertiary halides in particular.

12.20 Briefly discuss what changes would occur in the product if 2-chloro-1,1-dimethylcyclohexane were heated with KI in aq THF. Draw the product.
12.21 Draw the formal mechanism for ionization of 2-bromo-2-methylbutane and reaction with ethanol to yield the ether.

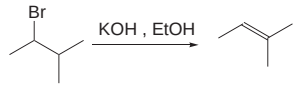
Examples of the Four Working Assumptions

12.9 ORGANIZATION OF REACTION TYPES

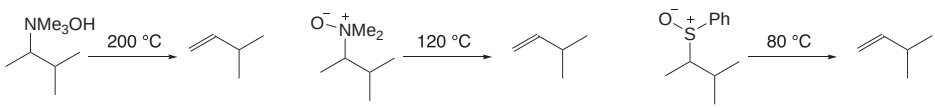
Substitution reactions were summarized at the end of Chapter 11. Elimination reactions can be organized as follows:

What reactions are possible for alkyl halides?

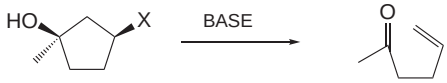
1. Alkyl halides undergo elimination reactions with a strong base to yield an alkene



2. Trialkylammonium hydroxides, amine oxides and sulfoxides yield the less substituted alkene upon heating

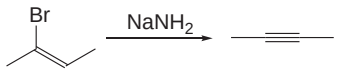


3. β-Halo alcohols react with a base to give the alkoxide and bond cleavage accompanies loss of the leaving group X to give an alkene-carbonyl compound.



What reactions are possible for vinyl halides?

1. The reaction of a vinyl halide with a strong base yields an alkyne



12.10 BIOLOGICAL RELEVANCE

In the sequence shown in Figure 12.7,[15] 1-aminocyclopropane-carboxylic acid uses Fe(II), dioxygen ascorbate, and CO_2 for a radical reaction. This reaction transfers one electron to form a radical cation and a reduced form of iron, iron(III) from iron (IV). The three-membered ring is strained (Section 8.5.2) and opens to form the radical. This radical reacts with the Fe(III) species to generate an iron intermediate, and an internal acid-base reaction generates the OH group on iron and an imine unit, C=NH, in (3-carboxylato-3-iminopropyl)(hydroxy) tetramethyliron. In the presence of a biological unit that can react as a base (e.g., water or a nitrogen atom from a different molecule), the hydrogen atom from the C=NH unit reacts,

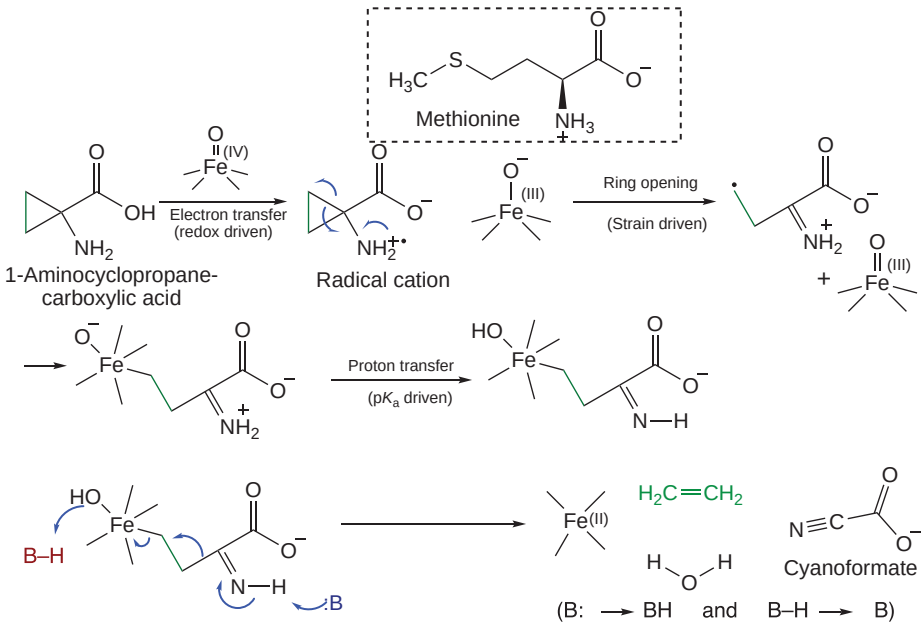


FIGURE 12.7 Ethylene biosynthesis. [Reprinted in part with permission from Pirrung, M.C. *Accounts of Chemical Research*, 1999, 32, 711 (see p. 716). Copyright 1999 American Chemical Society.]

transferring electrons to carbon (forming a CN unit; a nitrile), and this electron-transfer process leads to an elimination reaction that forms ethylene, and Fe(II),with transfer of the OH unit to a suitable acid. The products are ethylene and cyanoformate, which then decomposes to HCN + CO_2. Ascorbic acid is utilized in this transformation. This sequence is one example in which an elimination process plays a key role in a biosynthetic transformation.

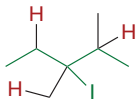
[15] Pirrung, M.C. *Accounts of Chemical Research* 1999, 32, 711–718 (see p. 716).

CORRELATION OF HOMEWORK WITH CONCEPTS

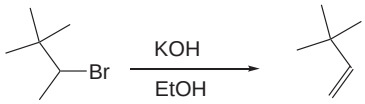
- When alkyl halides are heated with a base in protic solvents, an E2 reaction occurs to give an alkene. The E2 reaction is diastereospecific: 1, 2, 3, 4, 5, 6, 22, 23, 24, 25, 26, 29, 30, 34, 40, 41.
- Elimination reactions in a cyclic halide is dependent on the conformations of that ring system: 7, 8, 29, 34, 41.
- Ionization to a carbocation, in the presence of a base, can give unimolecular elimination to the more substituted alkenes, the E1 reaction: 9, 10, 27, 31.
- When a base is tethered to a leaving group, removal of a β-hydrogen occurs via an intramolecular process and a syn rotamer to give the less substituted alkene: 11, 12, 13, 14, 28, 29, 32, 33, 41.
- Elimination can occur when a β-halo alcohol reacts with base: 15, 35, 41.
- When vinyl halides are heated with a strong base, an E2 reaction occurs to yield an alkyne: 16.
- Four assumptions can be used to distinguish E1, E2, S_N1 and S_N2 reactions: 17, 18, 19, 20, 21, 29, 36, 37, 38, 39, 41.
- Spectroscopy can be used to determine the structure of a particular molecule (Chapter 13): 42, 43, 44, 45, 46.

ANSWERS TO IN-CHAPTER QUESTIONS

12.1 The positively polarized hydrogen atoms are marked in red.

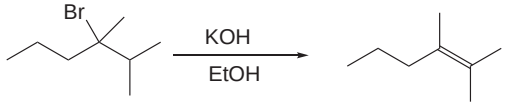


12.2



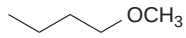
The methyl hydrogen atoms are the only β-hydrogen atoms, so only one alkene is possible

12.3

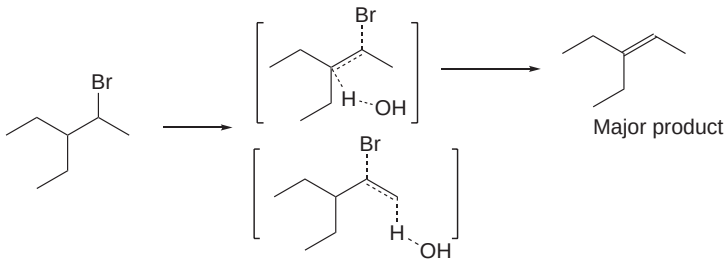


The more highly substituted alkene

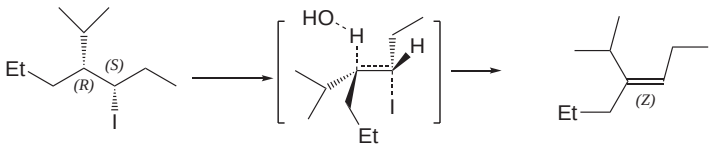
12.4



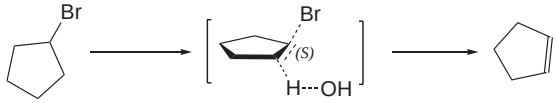
12.5



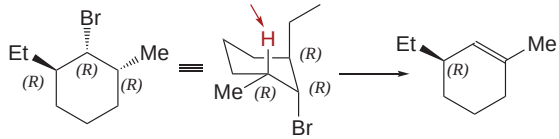
12.6



12.7

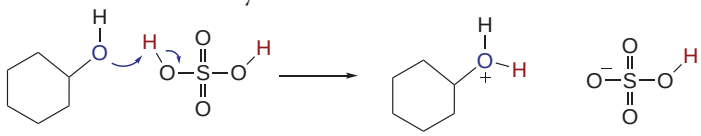


12.8

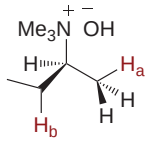


This is the only *trans*-diaxial β-H relative to Br, so it is the only one removed by the base and it leads exclusively to the alkene shown.

12.9



12.10



12.11

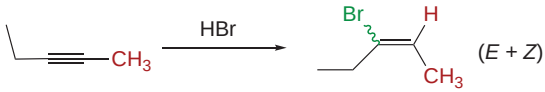
12.12 Via Hofmann elimination

12.13 Via Cope elimination

12.14 Via sulfoxide elimination

12.15 Via Grob fragmentation

12.16



12.17

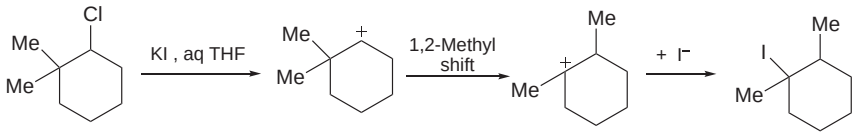
Resonance-stabilized nitrate anion — Amide anion

The nitrate anion is a resonance stabilized conjugate base of a strong acid. It is a weak base and should not induce an E2 reaction under normal conditions. On the other hand, the amide base derived from methylamine is a strong base (methylamine has a pK_a of ~ 25), and this powerful base should easily induce an E2 reaction.

12.18

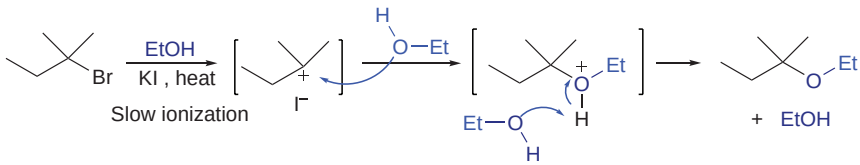
12.19

12.20



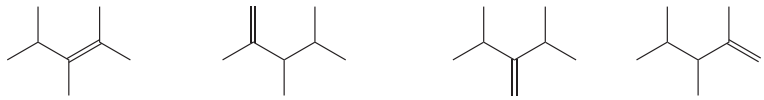
Ionization of the chloride to yield a secondary carbocation under the S_N1 conditions is followed by a rearrangement (a 1,2-methyl shift), to yield the more stable tertiary carbocation. Trapping the nucleophilic iodide yields the indicated product. Note that initial ionization leads to a carbocation that can rearrange.

12.21



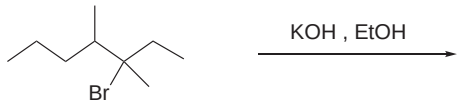
HOMEWORK

22. Which of the following is the more stable alkene? Justify your answer.

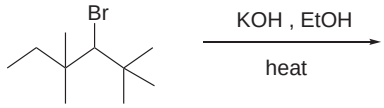


23. Which of the following yields 2,3,4-trimethylpent-2-ene upon reaction with KOH in ethanol?

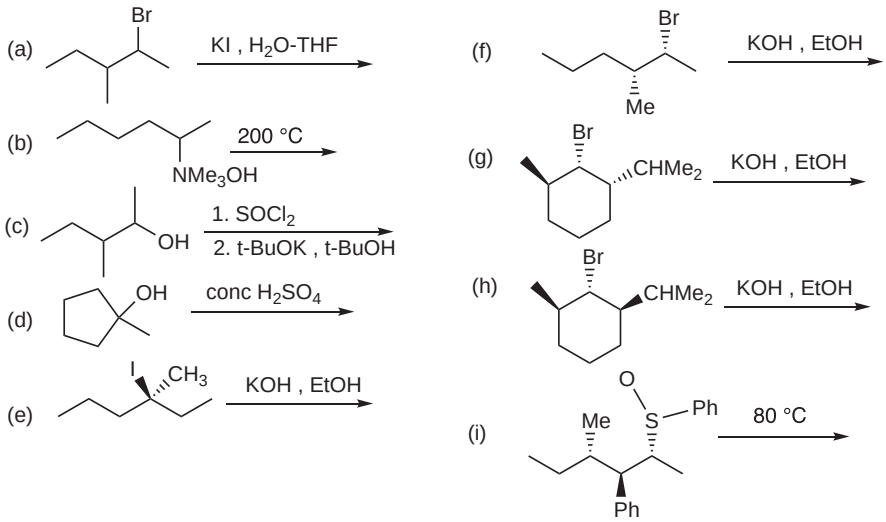
24. When (2*S*)-bromopentane is treated with KOH and ethanol, a mixture of (2*E*)- and (2*Z*)-pentene is formed as the major product. Explain why a mixture of stereoisomers is formed from this enantiopure halide.
25. For this reaction, draw all products that result from an E2 reaction, and the transition state for removal of the hydrogen that leads to the major product. Ignore *E* and *Z* isomers as being different products.



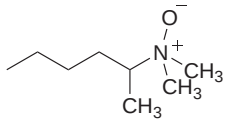
26. The following gives no reaction after 24 h. Use mechanistic arguments for the two possible reaction pathways to explain why neither one gives a product.



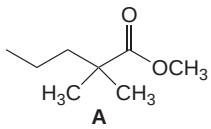
27. Explain why the reaction of cyclohexanol + concentrated HBr yields 1-bromocyclohexane but the reaction of cyclohexanol + concentrated sulfuric acid yields cyclohexene.
28. Briefly explain why 3-methylhept-1-ene is formed from 2-bromo-3-methylheptane by the Hofmann elimination sequence rather than 3-methylhept-2-ene.
29. Draw the major product expected from each of the following reactions.



30. 2,3-Dibromo-2,4,4-trimethylpentane does not undergo generate an alkene when heated with an excess of KOH in ethanol. Explain.
31. When $Ph_3C—OH$ is exposed to acid, the product is the extremely stable trityl cation. Draw this cation and offer an explanation for the stability.
32. Heating the amine *N*-oxide leads to an alkene. Suggest a mechanism that will explain this elimination reaction and suggest a major product.

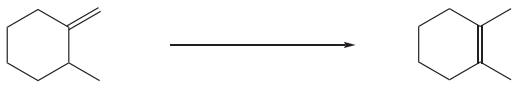


33. Heating **A** (a carboxylic acid ester; Section 18.6) to ~450 °C leads to elimination to give 2-methylbut-1-ene. Suggest a mechanism for the reaction and speculate on why the elimination requires such high temperatures when compared to the Hofmann elimination.



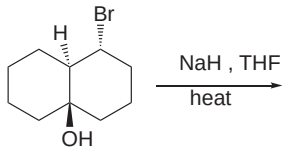
A

34. Provide a reaction sequence that will convert **A** into **B**.

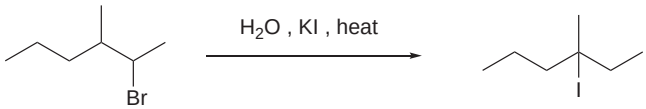


A **B**

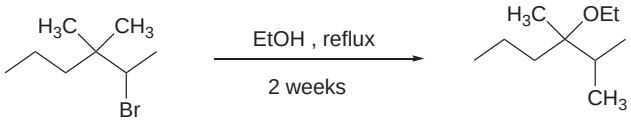
35. When the bromo-alcohol shown reacts with the base sodium hydride (NaH), the reaction produces an alkoxide. Suggest a mechanism that will lead to a ketone-alkene cyclic product.



36. Offer an explanation for why 2-bromobutane undergoes an S_N2 reaction, but 2-bromo-2-methylbutane does not when reacted with KI in ether.
37. Briefly explain why the presence of water favors first-order reactions.
38. Give the complete mechanism for the following reaction:

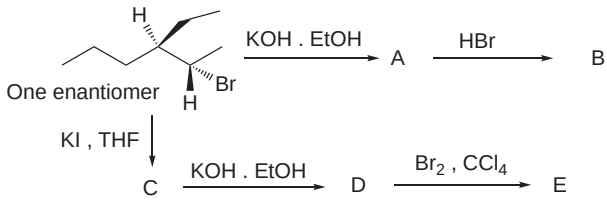


39. Give a complete mechanism for the following reaction:

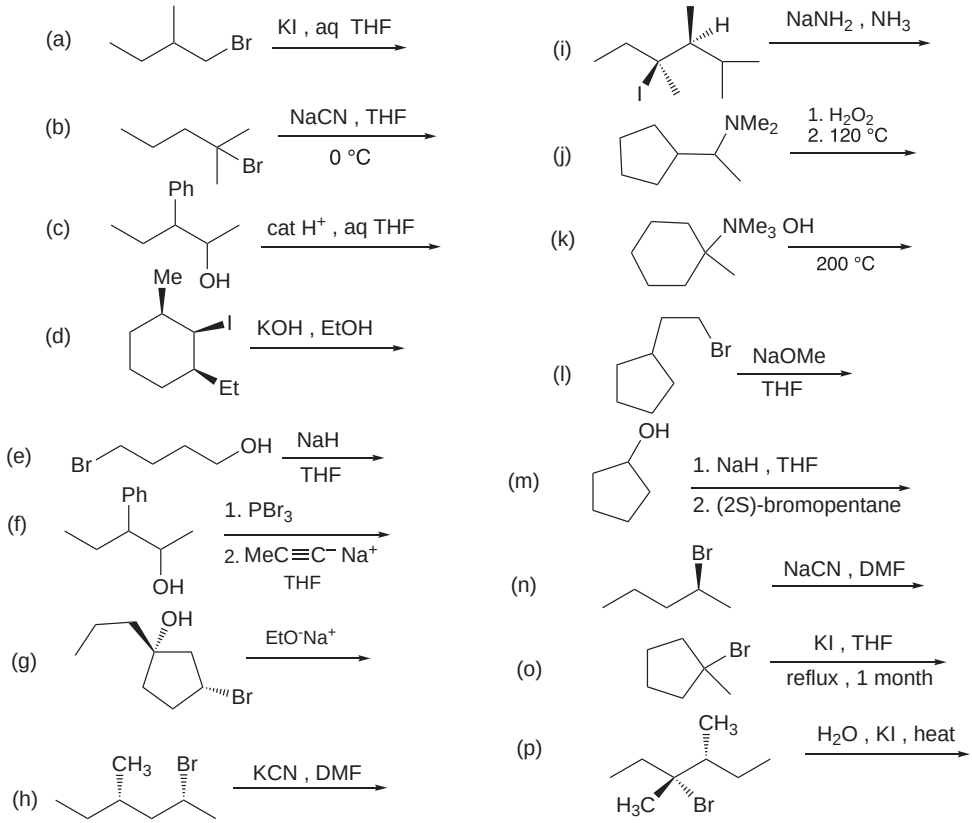


40. Give the major product for each of the following transformations, with the correct stereochemistry where appropriate. Give the structure of **A**, then react **A** with the reagent shown to give **B.** React the bromide with KI to give **C**, and then react **C** with the reagent shown to give **D**. Finally, react **D** with the reagent shown to give **E**. In

addition, determine if product **B** is racemic or is it one enantiomer. Determine if product **E** is racemic or if it is one enantiomer.

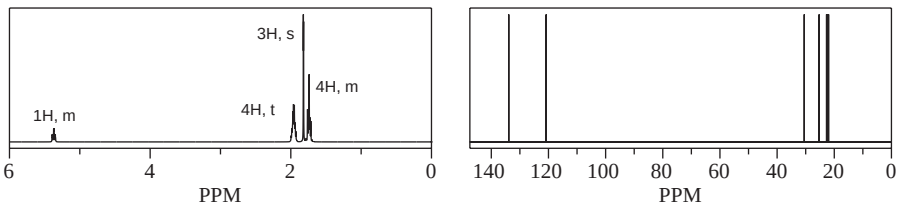


41. Predict the major product for each of the following reactions. Indicate no reaction by N.R. if that is appropriate.

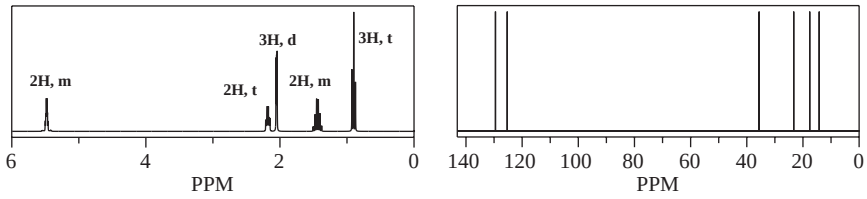


Spectroscopic problems. Do not attempt until you have read and understood Chapter 13.

42. Identify the following molecule given the following spectral data: Mass spectral data: M=96, 100%. M+1 = 97, 7.77%. M+2=98, 0.30%. Infrared: 2850-3010, 1651, 1450, 1390, 1360 and 700 cm^{-1}.



43. Identify the following molecule given the following spectral data. MS: M (112, 100%), M+1 (113, 8.88%), M+2 (114, 0.39%), 43 (100), 55 (59), 70 (15), 71 (95), 83 (12), 97 (7), 112 (very small). IR: 3077, 2964-2882, 1820, 1640, 1464-1438 cm^{-1}. ^1H NMR: 5.81 (m, 1H), 5.00 (m, 1H), 4.99 (m, 1H), 1.93 (m, 2H), 1.23 (q, 2H), 0.83 (s, 9H) ppm.
44. Molecule **A** has a formula $C_6H_{14}O$. IR: 3373 cm^{-1}. ^1H NMR: 2.04 (broad s, 1H), 1.44 (t, 2H), 1.38 (m, 2H), 1.20 (s, 6H), 0.93 (t, 3H) ppm. Compound **A** reacts with PBr_3 to give **B**, which reacts with KOH in hot ethanol to give **C**: MS. Parent ion at m/*z* 84. IR: 1676-1667 cm^{-1}. ^1H NMR: 5.11 (m, 1H), 1.97 (m, 2H), 1.68 (d, 3H), 1.60 (s, 3H), 0.93 (t, 3H) ppm. Identify the structures of **A–C**.
45. Identify the following molecule given the following spectral data. The formula is C_6H_{12}.Infrared: 2860-3010, 1660, 404, 1020, 992 and 980 cm^{-1}.



The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-13.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

13

Spectroscopic Methods of Identification

If a molecule is subjected to enough energy to break bonds, the molecule fragments into smaller pieces. These fragments provide structural information. Exposure to infrared (IR) light causes the bonds in a molecule to vibrate, but not break. Analyzing these vibrations provides structural information. The number and type of hydrogen atoms or the number and type of carbon atoms within a molecule is determined by analysis in a magnetic field. When the information from all three techniques is combined, the structure of a given molecule can be determined. The interaction of a molecule with ultraviolet (UV) light also yields information about the structure of conjugated molecules but this technique be not discussed until Section 21.3.

To begin this chapter, you should know the following:

- The electromagnetic spectrum (from general chemistry).
- All functional groups (Sections 4.3, 5.1–5.3, 5.6, and 5.7).
- The strength of covalent bonds (Sections 3.7 and 3.8).
- Isomers (Section 4.2.2).
- Rotamers, pseudorotation, and conformations (Sections 8.1–8.3).
- Radicals (Section 7.2.3).
- Magnetism (from general chemistry).

13.1 LIGHT AND ENERGY

Light and Energy

Spectroscopy techniques analyze how radiation of a particular energy is altered by interaction with a molecule. Since "light" is energy, examining the electromagnetic spectrum is the logical place to begin a discussion. Electromagnetic radiation is energy transmitted through space in the form of waves. Two energy waves are drawn in Figure 13.1, labeled as ***A*** and ***B***. *Wavelength* is defined as the distance between the crests of each wave. The amount of time it takes to complete one cycle of the wave, or the distance required to complete one wave is the *frequency* of the wave, measured in centimeters (cm) so one cycle/cm = 1 cm^{-1}. When the cycle or frequency is displayed in seconds, 1 cycle/sec is measured in hertz (Hz). If both ***A*** and ***B*** show a frequency of 1 cm^{-1}, it takes more time for one cycle of ***A*** than for one cycle ***B***. A higher frequency wave will have more waves per second, so the shorter wavelength, ***B***, is higher in energy than the longer wavelength, ***A***. Frequency is given the symbol ν (in Hz) and wavelength is given the symbol λ (in cm). Wavelength and frequency are inversely proportional: $\nu = c/\lambda$ where c is the speed of light $3x10^{10}$ cm s^{-1}. Energy (E) is proportional to frequency (ν) and it is related by Planck's constant (h, where $h = 6.626x10^{-34}$ J Hz^{-1}), so that $E = h\nu$.

An energy continuum stretches from low energy radio signals to high energy X-rays and gamma rays, as shown in Figure 13.2. Radio waves are low in energy and have a long wavelength whereas gamma rays are extremely high in energy with a very short wavelength. The passage of visible (vis) light through a prism reveals the visible spectrum, with the lower energy red on one end and the higher energy violet on the other. The energy of red light in this spectrum is measured to be ~ 35.75 kcal (149.6 kJ) mol^{-1}, whereas the energy of the violet light is ~ 71.5 kcal (299.2 kJ) mol^{-1}. If the wavelength energy is converted from kcal mol^{-1} to

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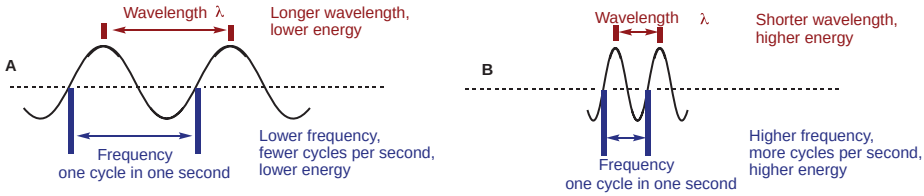


FIGURE 13.1 Long wavelength and short wavelength energy waves.

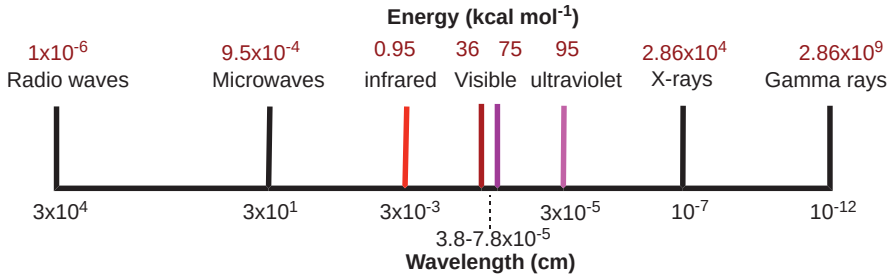


FIGURE 13.2 Electromagnetic spectrum measured in wavelength (cm) and energy (kcal mol^{-1}).

angstroms (Å; $1x10^{-8}$ cm), red light appears at 8000 Å (800 nm) and violet light appears at 4000 Å (400 nm; nm or ν; $1x10^{-7}$ cm). The 800 nm light is lower in energy than 400 nm light.

13.2 MASS SPECTROMETRY

Marie Curie

Nobel laureate Marie Curie (Poland-France; 1867–1934) co-discovered the radioactivity of elements and several radioactive isotopes. She also developed methodology for the separation of isotopes. Later, physicist Arthur Jeffrey Dempster (Canada-USA; 1886–1950) discovered the uranium isotope ^{235}U and was able to separate isotopes based on their mass. He developed the first mass spectrometer as part of that study. This separation technique was expanded by others to an analytical technique called *mass spectrometry* and it is used to examine many types of molecules. A *mass spectrometer* generates radical cations from a molecule. These are detected and displayed as a plot of intensity versus the mass-to-charge ratio of each radical cation. This plot is called a *mass spectrum*.

Mass Spectrometry

Radical Cations

A diagram for a basic electron impact mass spectrometer is shown in Figure 13.3. In a mass spectrometer, a molecule is bombarded with a high-energy electron beam (~70 electron volts, 70 eV, or greater). A *radical cation* is generated that is missing one electron from the original molecule, so it has the same mass as the original molecule, minus one electron. This initially formed radical cation is known as the *molecular ion* (M), although is used to be called the *parent ion (*P). Note that 1 eV (one electron volt) is a unit of energy where 1 eV = 23.06 kcal (96.5 kJ) mol^{-1}. If a molecule such as acetone is bombarded with electrons, an electron is ejected to give the molecular ion of acetone (**1**) with the molecular weight of

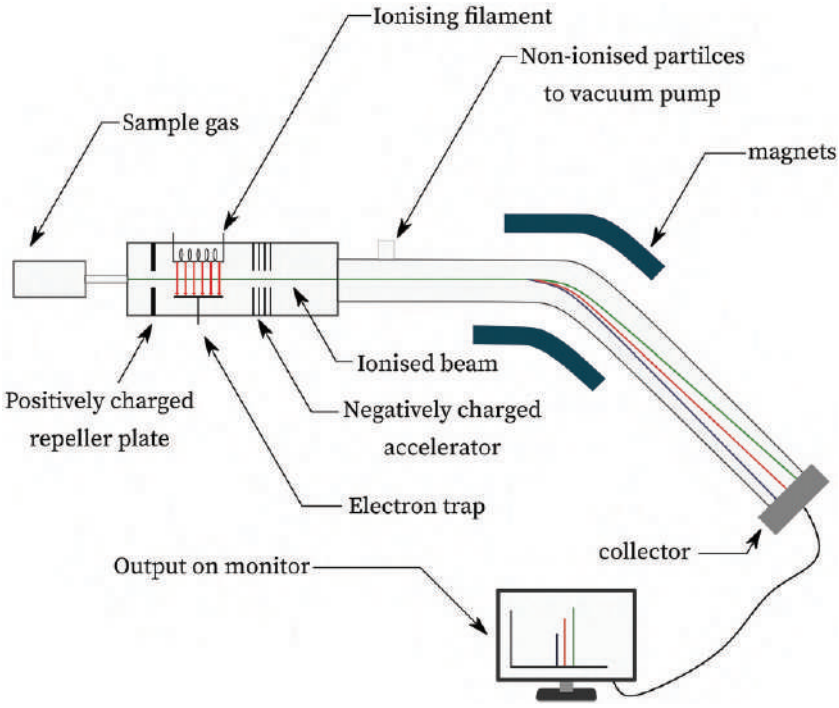
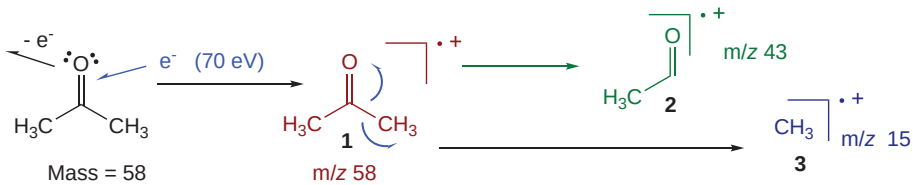


FIGURE 13.3 Schematics of Mass Spectrometer Measurement of Atomic Mass. Reprinted from the Shutterstock illustration ID: 1826468333.

acetone minus one electron. It is usually difficult to know exactly which electron is removed in the mass spectrometer so the radical cation is represented with partial bracket and the symbol (•+). A radical cation has mass (*m*) of course, but it is charged and is reported as *m/z*, where *z* is the charge As long as the charge (*z*) on the ion is +1, the mass of the molecular ion taken to be that of the original molecule. The initially formed ion of acetone in the mass spectrometer is the molecular ion *m/z* 58 (**1**). This is a high-energy species that usually undergoes homolytic fragmentation of a C—C bond into smaller mass radical cations. For example, fragmentation of **1** leads to new radical cations, **2** with *m/z* 43, and **3** with *m/z* 15. An arcane term for the molecular ion **1** is the *parent ion*, and fragmentation ions **2** and **3** are referred to as *daughter ions. The*y are formed by fragmentation of the parent ion (the molecular ion).

Daughter ions are typically formed by fragmentation of the weakest bonds of the molecular ion. Such fragmentation is analogous to the cleavage of bonds in organic chemical reactions to give more stable products. Indeed, more stable radical cations will be formed in greater abundance relative to less stable ions. For example, fragmentation to a tertiary radical cation occurs more readily than fragmentation to a primary radical cation.



13.1 What is the m/*z* for the molecular ion of hexane, pentan-3-one, and diethyl ether?

Fragmentation of the molecular ion of acetone in the electron bombardment chamber of the mass spectrometer leads to a mixture of **1**, **2** and **3**. This mixture is swept into the acceleration chamber (see Figure 13.3) and then into a curved magnetic sector. Each radical cation has a different mass, and the accelerating voltage can be changed so that ions of only *m/z* 15 will make it through the curved magnetic sector to be detected. In that example, the heavier mass ions **1** and **2** have insufficient kinetic energy to pass through the magnetic sector. They "crash" into the sides of the curved sector and do not reach the detector. The accelerating voltage is then varied so that only **2** with *m/z* 43 is detected. Finally, the voltage is adjusted so only the heavier mass **1** with *m/z* 58 can be detected. In other words, the accelerating voltage is varied in a stepwise manner such that all radical cations are separated based on differences in their mass-to-charge ratio, m/*z*. As each separated radical cation is swept into a detector, it is recorded as a peak.

When the m/*z* values for all three radical cations (**1**-**3**) produced from acetone are plotted against their abundance, a mass spectrum is generated as shown in Figure 13.4. The highest mass ion in the mass spectrum is assumed to be the molecular ion, which is the

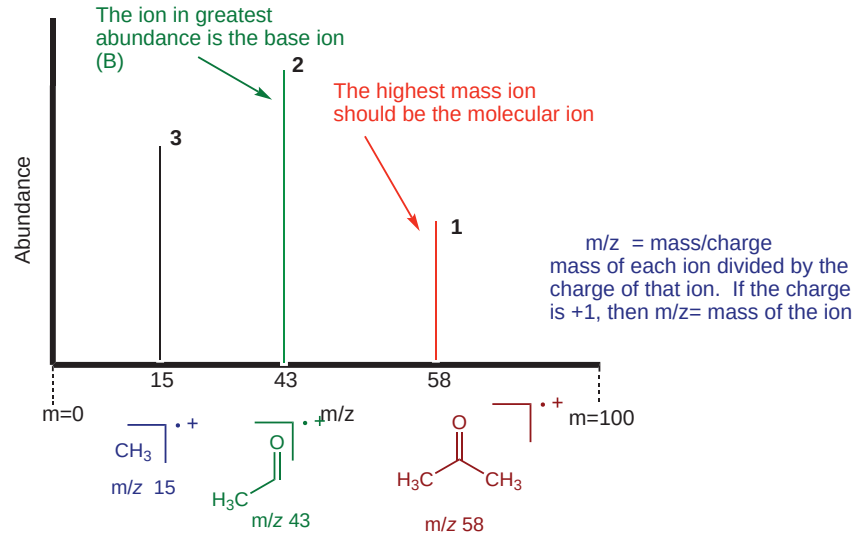


FIGURE 13.4 Mass spectrum of acetone.

mass of the original molecule. For acetone, two daughter ions at m/*z* 43 and m/*z* 15 arise via fragmentation of the molecular ion. The ion with the highest relative abundance is called the *base ion (B).* The base ion (B) is associated with accumulation of ions from the most facile fragmentation(s). *T*he abundance of all other ions are reported as a ratio of B.

The Mass Spectrum

Detection of the mass of radical cation fragments to four or five decimal places is possible in modern mass spectrometers. Data such as 100.12516 is used to determine the "*exact mass*" of a molecular ion or a daughter ion. This technique is called *High Resolution Mass Spectrometry (HRMS).* With this level of accuracy, only a small number of formulas are possible for a molecule being examined. Therefore, it is possible to estimate a reasonable empirical formula directly from the molecular ion.[1] Such an analysis is only possible if a library of possible choices is generated during the analysis.

Before the structure of a molecule can be determined, the empirical formula must be known. Predating HRMS is a method for determining an empirical formula that takes advantage of the fact that a mass spectrometer separates ions by mass, including the separation of

[1] (a) Marshall, A.G.; Hendrickson, C.L. *Annual Review of Analytical Chemistry* 2008, 1, 579–599; (b) Kind, T.; Fiehn, O. *BMC Bioinformatics* 2006, 7, 234–244; (c) Kind, T.; Fiehn, O. *Bioanalytical Reviews* 2010, 2, 23–60; (d) Pluskal, T.T.; Uehara, T.; Yanagida, M. *Analytical Chemistry* 2012, 84, 10, 4396–4403.

TABLE 13.1 Isotopic Abundance Of Common Isotopes And Isotopic Masses

Isotope	Relative Abundance (%)	Isotope Mass
^{12}C	100	12.00000
^{13}C	1.1	13.00336
^{1}H	100	1.00782
^{2}H	0.106	2.01410
^{14}N	100	14.00307
^{15}N	0.38	15.00010
^{16}O	100	15.99491
^{17}O	0.14	16.99913
^{18}O	0.20	17.99916
^{32}S	100	31.97207
^{33}S	0.78	32.9716
^{34}S	4.40	33.96786
^{35}Cl	100	34.96885
^{37}Cl	32.5	36.96590
^{79}Br	100	78.91839
^{81}Br	98.0	80.91642

isotopes. The molecular ion of a molecule will be composed of the *lowest mass and highest abundance isotopes:* ^{12}C, ^{1}H, ^{14}N, ^{16}O, and so on. Table 13.1 lists the isotopes along with the relative abundance for elements that commonly appear in organic molecules. The most abundant carbon isotope is ^{12}C. There are also small amounts of ^{13}C and ^{14}C isotopes. The most abundant isotope of hydrogen is ^{1}H, but there are tiny amounts of the deuterium (^{2}H) and tritium (^{3}H) isotopes. Oxygen is primarily ^{16}O but has an ^{18}O isotope. Likewise, ^{14}N is the most abundant isotope for nitrogen, but there is a ^{15}N isotope. The most abundant isotope for chlorine is ^{35}Cl. For bromine it is ^{79}Br, and for sulfur it is ^{32}S. All three have significant isotopes, ^{37}Cl, ^{81}Br and ^{34}S. Fluorine (^{19}F), phosphorus (^{31}P), and iodine (^{127}I) are common, but they do not have important isotopes.

As noted, the molecular ion of acetone is composed of the most abundant isotopes ^{12}C, ^{1}H, and ^{16}O, but there are higher mass isotopes. The molecular ion (**1**, *m/z*, 58) for acetone is expanded (Figure 13.5) to show peaks at m/z 59, *a M+1 peak,* and m/z 60 peak, *a M+2 peak*. The atoms found in organic chemicals have the fixed ratio of isotopes listed in Table 13.1.

Isotopic Peaks

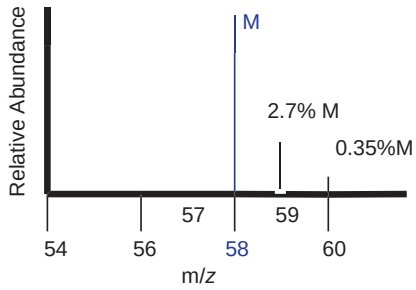


FIGURE 13.5 Expansion of the molecular ion region for acetone.

In the mass spectrometer the ^{13}C isotope appears as a peak one mass unit higher than the molecular ion, or M+1. For acetone, the *M+1 ion* (*P+1 ion* in older notation) has a mass of *m/z* 59. There are three carbon atoms in acetone and the relative abundance of ^{13}C is ~ 1% for each carbon. Therefore, there is 3x1.1% = 3.3% ^{13}C in the molecule. In other words, the M+1 peak for acetone is 3.3% relative to 100% for the molecular ion (M). Each carbon in the molecule also has a small amount of ^{14}C, and this peak appears at two mass units greater than the molecular ion, or M+2, which is m/*z* 60 for acetone. The abundance of ^{14}C in an M+2 peak is [(number of C)(1.11)]^2/200, so for acetone, M+2 is [(3)(1.11)]^2/200 or 0.055 of M.

The hydrogen atoms in the molecular ion are due to 1H. There is a small amount of the ^{2}H isotope so the ^{2}H atoms appear as a M+1 peak. There are six hydrogen atoms in acetone and the relative abundance of deuterium is only 0.106, so 6x0.106 = 0.6% of deuterium is in

the molecule. This small amount of deuterium is usually undetectable unless the molecule has a very large number of hydrogen atoms. For the most part, the deuterium contribution to the M+1 is ignored. Acetone also has an oxygen atom, and the molecular ion is composed of ^{16}O, but there is an ^{18}O isotope that appears as a M+2 peak. The relative abundance of the ^{18}O isotope is 0.20 of ^{16}O, so with one oxygen there is 1x0.2 = 0.2% of ^{18}O. In acetone this peak appears at *m/z* 60, the *M+2 peak* (the *P+2* peak). The intensity of the M+1 and M+2 ion peaks are measured against the molecular ion, M, where the abundance of M is arbitrarily set to 100%. For acetone, the measured relative abundance of M+1 is 2.7/100, and M+2 is 0.35/100 (see Figure 13.5). The M+1 peak at *m/z* 59 has an abundance of 2.7% relative to the molecular ion, M, and the M+2 peak at *m/z* 60 has an abundance of 0.35% relative to M.

13.2 Predict the M, M+1, and M+2 pattern for butan-2-one; for triethylamine.

The mass of the molecular ion (M) is used to give the molecular weight of a sample. The intensity of the M+1 peak relative to M is due the presence of ^{13}C and depends on the number of carbon atoms in a molecule. Therefore, the number of carbon atoms in the molecule can be calculated. Similarly, the number of nitrogen atoms can be estimated using the M+1 ratio. The number of oxygen atoms can be calculated using the M+2 data. An empirical formula can be calculated using the m/*z* value of M and the isotope ratio of M+1 and M+2. For molecules that contain *only* C, H, N, O, two formulas are used to calculate an empirical formula:

$$\text{M+1} = (\text{Number of C})\,(1.11) + 0.38\,(\text{Number of N})$$

and

$$\text{M+2} = \frac{[(\text{Number of C})\,(1.11)]^2}{200} + 0.20\,(\text{Number of O})$$

Once the identity and number of these atoms are determined, the number of hydrogen atoms is calculated by subtracting the mass of all atoms from the molecular weight of the molecule.

The M+1 formula uses the isotopic ratio for ^{13}C relative to ^{12}C, but the ^{15}N isotope relative to ^{14}N must also be considered. The M+2 formula determines the amount of ^{14}C relative to ^{12}C, and also the amount of ^{18}O relative to ^{16}O. Note that the M+1 formula has two unknowns, the number of carbon and the number of nitrogen atoms. There are many molecules that have both carbon and nitrogen, and many that contain no nitrogen atoms at all. To analyze a molecule that does or does not contain nitrogen, working *assumptions* must be made.

1. *Since N has an odd valence, assume that if a molecule contains an* **even** *number of nitrogen atoms (0, 2, 4, etc.), the molecule will have an even mass.*
2. *Since N has an odd valence, assume that if a molecule contains an* **odd** *number of nitrogen atoms (1, 3, 5, etc.), the molecule will have an odd mass.*

To solve the M+1 formula for relatively simple compounds, assume that even mass compounds have zero nitrogen atoms and odd mass compounds have one nitrogen. In the M+1 formula, insert a 0 or 1 in the (0.38)(number of N) term. The equation may be solved for the number of carbon atoms.

The discussion of M+1 and M+2 isotope peaks has ignored chlorine, bromine, and sulfur, which are also found in many organic molecules. Bromine is composed of two isotopes (^{79}Br and ^{81}Br) in almost equal amounts. The near 1:1 mixture of ^{79}Br and ^{81}Br leads to an atomic mass of ~ 80 (listed as 79.904) in the periodic table. However, molecules with bromine have both isotopes. These isotopes are separated and observed in the mass spectrum. The ^{79}Br isotope is the lower mass isotope that is incorporated in the molecular ion M and the ^{81}Br isotope is found in the M+2 ion. Therefore, a molecule containing one bromine will show a M+2 ion that is 90–100% of M. Therefore, smaller abundance isotopes in the M+2 peak such

as oxygen cannot be observed. In other words, no calculation is necessary because if the M+2 peak is 90–100% of M, the molecule contains one bromine atom.

Chlorine has an atomic mass of 35.453 in the periodic table because it is a 3:1 mixture of ^{35}Cl and ^{37}Cl isotopes. Both are detected in the mass spectrum, however. The ^{35}Cl isotope is part of the molecular ion M, and the ^{37}Cl isotope is part of the M+2 ion. A molecule that has one chlorine atom will have an M+2 ion in the mass spectrum that is ~30–35% of M. Once again, the M/M+2 ratio is obvious, and the formulas are not used. Finally, ^{34}S is ~4.4% of ^{32}S, so the M+2 ion of a molecule containing one sulfur atom will be ~4 to 5% of M. As noted, when Cl, Br or S are present in a molecule, the M+2 formula cannot be used to detect the small abundance of the ^{18}O isotope.

Determining a Molecular Formula

WORKED PROBLEM

An example of empirical formula determination uses the M+1 and M+2 formulas. Determine the empirical formula for a molecule whose mass spectrum is

M (129) 100 M+1 (130) 9.49 M+2 (131) 0.39_4

This data shows the mass for the molecular ion is *m/z* 129, and the M+1 is *m/z* 130 and the M+2 is *m/z* 131. If the abundance of the molecular ion is taken as the standard, the M+1 ion is 9.49% of M and M+2 is 0.39% of M. Note that one N is assumed because of the odd mass of the molecular ion and solving the M+1 equation leads to eight carbons. The M+2 calculation is shown, using the eight carbons found from the M+1 calculation. In this example, the solution to the M+2 equation shows there are no oxygen atoms, and the formula is $C_8H_{19}N$.

M+1 = 9.49 = 1.11(No. C) +0.38(No. N). Odd mass for parent (129), so assume 1 N

9.49 = 1.11(No. C) + 0.38, 9.49 - 0.38 = 8.88/1.11 = 8 C so C_8N

M+2 = 0.39 = $[8 \times 1.11]^2/200$ + 0.2 (No. O) 0.39 = 0.39 + 0.2 (No. O),

so 0.39 - 0.39 = 0/0.2 = zero O. Calculate H by difference with mass of M

C_8N = 110. 129 - 110 = 19, so 19 H. $C_8H_{19}N$

In modern mass spectrometry the limitations imposed by different isotope ratios as just described are not a problem and assumptions are not necessary. The instruments that are capable of HRMS also provide accurate determination of an empirical formula. The M, M+1 and M+2 method shown here is intended to familiarize the reader with the isotope peaks encountered in mass spectrometry.

13.3 Determine the formula of an unknown molecule that shows the following information in the mass spectrum: M (m/z 126) 100%, M+1 (m/z 127) 8.88%, M+2 (m/z 128) 0.59%.

If relatively small mass daughter ions are lost from the molecular ion it is possible to equate that small mass with a specific molecular fragment. A limited number of structures are possible for each fragment and these structures are easily correlated with known organic fragments. The structure and mass of several fragments that commonly appear in organic molecules are shown in Table 13.2.[2] In a mass spectrum the difference in mass between the *m/z* of the molecular ion and the *m/z* of a given daughter ion can be determined. If the difference in mass is 15, for example, the small fragment that most closely matches the *m/z* 15 is a methyl group. If a difference in mass of 29 is found, it is assumed that either an aldehyde unit

[2] McLafferty, F.W. *Mass Spectral Correlations, Advances in Chemistry Series*, Gould, R.F., Ed., American Chemical Society, Washington, DC, 1963.

TABLE 13.2 Mass of Common Structural Fragments in Organic Molecules

Mass	Fragment	Mass	Fragment
15	CH_3	29	CH_3CH_2
16	NH_2	31	CH_3O
17	NH_3	41	$CH_2{=}CHCH_2$
18	H_2O	43	C_3H_7
27	$CH_2{=}CH$	44	CO_2
28	N_2	57	C_4H_9
28	$CH_2{=}CH_2$	77	C_6H_5
29	CHO	91	C_7H_7

(CHO) or an ethyl group has been lost. If the fragment lost is m/*z* 18 it assumed that water is lost from the molecule, which is common for alcohols.

An imaginary mass spectrum for a molecule with an empirical formula of C_5H_{12} and a molecular ion of *m/z* 72 is shown in Figure 13.6. Three fragmentations are shown for this imaginary molecule and the difference in mass relative to *m/z* 70 is shown for each fragment.

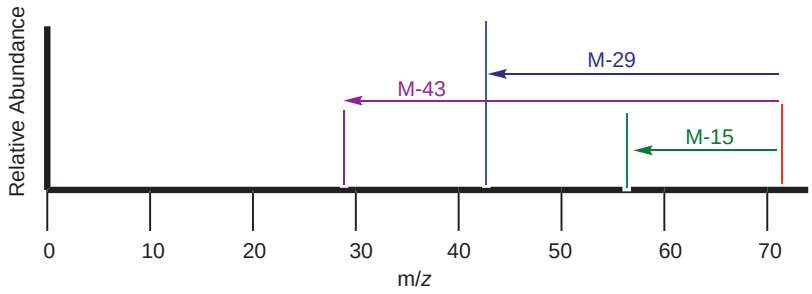


FIGURE 13.6 Loss of methyl, ethyl and propyl fragments from the molecular ion.

Loss of 15 m/z, loss of 29 m/z, and loss a 43 m/z fragments from the molecular ion are shown. Loss of 15 mass units should correlate with a methyl group in the original molecule. Loss of a mass unit of m/z 29 can correlate with loss of an ethyl if the formula is C_5H_{12}, and loss of 43 mass units with a propyl unit, either $-CH_2CH_2CH_3$ or $-CH(CH_3)_2$. This information can help with identification of an unknown structure.

Absorption of Infrared Light

13.3 INFRARED SPECTROSCOPY

When irradiated with infrared light a molecule absorbs energy that will induce molecular vibrations, but this energy is not sufficient to break bonds. The energy absorbed and molecular vibrations that dissipate the excess energy from the molecule will vary with each bond in the molecule. The correlation of absorption frequencies with individual functional groups is therefore possible.

13.3.1 ABSORBING INFRARED LIGHT AND THE INFRARED SPECTROPHOTOMETER

Organic molecules interact with infrared light at frequencies between 4000–400 cm^{-1}. Infrared radiation is essentially an alternating electrical field, and due to changes in vibrational frequency there is good absorption when the dipole moment of a molecule fluctuates. When there is a large electronegativity difference between two atoms in an unsymmetrical bond, there is a larger dipole moment and a stronger absorption in the infrared. Symmetrical

bonds with no dipole have little or no change in dipole moment and so do *not* absorb infrared light very well and will give a weak absorption peak.

When a molecule absorbs IR energy, the resulting vibrations will have a characteristic frequency (ν) that depends on the mass of the two atoms in the bond and the strength of that bond. A bond in a diatomic molecule will have two masses (m_1 and m_2) connected by a bond separated by distance r_o. Since Δr is small in a diatomic molecule, there is simple harmonic motion, and this type of system is referred to as a *harmonic oscillator*. The bond effectively acts as a spring between the atoms of two masses. Absorption of that bond can be estimated using *Hooke's law*: $F = -f\,\Delta r$, where F = force, f = a proportionality factor (the *force constant*) and Δr is the change in distance between the two atoms of the molecule. Hooke's law is named after Robert Hooke (England; 1635–1703). Assuming this vibrational motion in a molecule is a harmonic oscillator, the frequency of the oscillation can be calculated by

$$\nu = \frac{1}{2\pi}\sqrt{\frac{f}{\mu}} \qquad \mu = \frac{m_1 m_2}{m_1 + m_2}$$

In this equation, ν = the frequency of the stretching vibration f = force constant, and μ = reduced mass. The mass (m) used in this equation is the mass of the atom, given by $m = \frac{\text{atomic weight}}{\text{Avagadro's number}}$, where Avogadro's number = 6.02252×10^{23} g mol^{-1}. The force constant (f) is proportional to the strength of the covalent bond linking m^1 and m^2. This Hooke's Law model indicates that as the spring becomes stronger the force constant increases, and the frequency of the vibration will increase. In a molecule, as a bond becomes stronger the frequency of the vibration will increase. As the reduced mass (μ) increases, the vibrational frequency will decrease. By analogy with different masses connected by a spring, atoms of different masses with different bond strengths will have different absorption frequencies in the IR. The C—O bond will absorb at a different frequency than a C—N bond. A C≡C bond will absorb differently than a C=O bond or a C=C bond.

13.4 Comment on which bond will have the greater force constant, C≡C or C=C. Which will absorb at lower energy?

When irradiated with IR light between 4000 and 400 cm^{-1} absorption leads to bending and stretching vibrations for various bonds in organic molecules. Bonds in a molecule can be represented by a two-atom, one-bond system (•–•) or a three-atom, two-bond system (•–•–•). A *stretching vibration* of a one-bond system occurs at a particular frequency, is usually rather strong and is the easiest to observe. Indeed, functional groups such as O—H, C=O or C—O have a polarized bond, and each stretching absorption gives a strong signal. The frequency of the stretching vibration depends on the mass of the two atoms, as well as the strength of the bond. A double bond is stronger than a single bond, and the stronger the bond the more difficult it will be to stretch that bond. Therefore, a C≡C bond absorbs at a higher frequency than a C=C bond, which absorbs at a higher frequency than a C—C bond. Likewise, a C=O stretching signal requires more energy so it is at a higher frequency relative to a C—O stretching signal. With a three-atom, two-bond system, there are several symmetrical and asymmetric bending vibrations in addition to the stretching vibrations of each bond. Each of these vibrations will occur at a different frequency. Bending vibrations are usually lower in energy and in intensity than the stretching vibrations.

Each absorption described will generate a "peak" in the IR spectrum and several "peaks" are possible for an individual bond due to stretching, bending or other vibrations. The real point of this discussion is to show that for a given diatomic or triatomic unit (a functional group), there are several different vibrational modes (bending, stretching, etc.) each with a unique frequency.

An Infrared Spectrophotometer

A schematic of the basic components of an infrared spectrophotometer is shown in Figure 13.7. Once the sample is ready it is irradiated with infrared light. Before passing

through the sample, the light is split by a prism into two beams of equal intensity. Each beam is continuously passed through the sample and a reference chamber (usually air). The instrument scans frequency by frequency and compares the intensity of the two light beams. In other words, the sample is scanned with IR light that is varied from 4000–400 cm^{-1}, recording any absorption for each wavelength. The instrument recombines the two beams and the signal that emerges from the reference cell is electronically subtracted from the signal that emerges from the sample cell. This signal is transmitted to the detector. The amount of IR light absorbed at each wavelength is displayed as an absorption peak. The absorptions obtained for each wavelength obtained by the scan is the *infrared spectrum*.

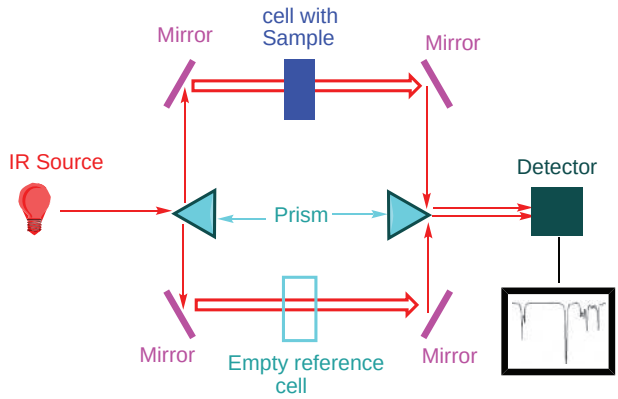


FIGURE 13.7 Schematic for a simple IR spectrophotometer.

The sample cell is often two clear plates made of pressed NaCl or KBr, and a liquid sample is sandwiched between the plates. These salts are soluble in water so the plates can be damaged by exposure to water. Any contact with water should be avoided during handling the plates and during sample preparation, including handling the plates. If the compound of interest is a liquid, a drop is placed on the salt plates *neat* (no solvent) and placed in the spectrophotometer. If the compound of interest is a solid or another liquid, it can be dissolved in a *solvent* that will have minimal interfering IR absorption. The solvent should not contain water. Chloroform or carbon tetrachloride are commonly used since the absorptions associated with halogens do not interfere with functional groups that are commonly found in organic molecules.

Characteristics of an Infrared Spectrum

13.5 Comment on the possibility of using acetone to wash KBr or NaCl infrared plates.

13.3.2 THE INFRARED SPECTRUM AND FUNCTIONAL GROUP ABSORPTIONS

Recording absorption peaks obtained by scanning a range of IR light frequencies (4000–400 cm^{-1}) gives an infrared spectrum. The spectrum can be viewed as a series of "peaks" or "valleys." The spectrum is typically obtained by starting at the "top" and as *absorption* of IR light occurs at a given frequency the absorption signal increases toward the "bottom," a *peak*. The IR spectrum of heptane is shown in Figure 13.8 and the two horizontal scales are in cm^{-1} (the frequency scale, ν) and in μ (the wavelength scale in microns or micrometers, which is 10^{-6} meters). There are two vertical scales: absorbance (A) and % transmittance (%T). If all of the IR light is absorbed by the molecule, the value of $A = 100\%$ so no light is transmitted (0 %T) and there is a strong "peak." When there is 100% transmittance (%$T = 100$) no light is absorbed so there is 0% A and no peak. The greater the absorbance, the stronger and larger is the "peak." The spectrum of heptane in

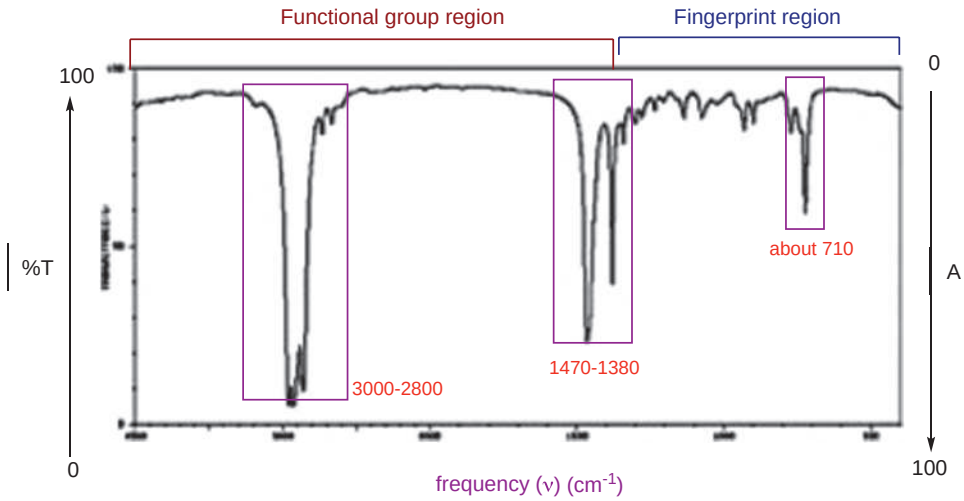


FIGURE 13.8 Infrared spectrum of heptane.

Figure 13.8 shows a cluster of strong peaks at ~ 3000–2800 cm^{-1}, a moderately strong set of peaks at 1470–1380 cm^{-1}, another weak peak at ~ 710 cm^{-1} and many small peaks. The strong absorptions in this molecule are due to C—H stretching and bending vibrations and the weaker peaks are likely due to minor C—H vibrations and C—C vibrations. The stronger peaks are of interest and the weaker peaks are usually ignored. In effect, these stronger peaks constitute the "hydrocarbon backbone." Virtually all organic molecules contain C—H bonds. Therefore, these peaks appear in the IR spectra of virtually all organic molecules. The smaller peaks are usually due to bending or other vibrations, but the stretching absorptions highlighted are the stronger signals.

For molecules with a functional group, an IR spectrum is analyzed using two distinct regions. That region between 4800 and 1400 cm^{-1} (higher energy) is called the *functional group region*. That region between 1400–400 cm^{-1} (lower energy) is called the *fingerprint region*. The signals in the functional group region of the IR are due to unique stretching vibrations of functional groups and can be used to distinguish them. The signals in the fingerprint region are due to bending and other vibrations that are characteristic of an individual molecule. As with any fingerprint, if there is a library of IR spectra on file, an unknown can be examined with the goal of identification.

13.6 Briefly explain why the C=O absorption is at higher energy than the C—O absorption.

IR of Common Functional Groups

There are two ways to display an IR spectrum, linear in wavelength or linear in frequency. Functional groups are more easily discernable when the spectrum is linear in frequency because the functional group region is expanded. Conversely it is easier to see individual vibrational variations for a molecule when the spectrum is linear in frequency, where the fingerprint region is expanded. A spectrum that is linear in frequency is useful for identifying one specific compound when compared to another or to a library of possibilities. Note that the micron scale (linear in wavelength) is used less often in modern spectroscopy but it is common in the older literature.

Table 13.3 shows the major absorptions for common functional groups. Most of these absorptions appear in the functional group region of the IR spectrum (4800–1400 cm^{-1}). A few will be seen in the fingerprint region (1400–400cm^{-1}) but few of these absorptions are used to identify a functional group.

TABLE 13.3 Infrared Frequencies For Common Functional Groups

Functional Group		ν in cm^{-1} (μ)	Functional Group		ν in cm^{-1} (μ)
C—H	Alkanes	2850–2960 (3.38–3.51) 1350–1470 (6.80–7.41)	C=C—H	Alkenes	3020–3080 (3.25–3.31) 675–1000 (10.00–9.81)
C—H	Aromatic rings	3000–3100 (3.23–3.33) 675–870 (11.49–9.81)	C≡C—H	Alkynes	3300 (3.03)
			O=C—H	Aldehydes	2817 (3.55)
C=C	Alkenes	1640–1680 (5.95–6.10)	C≡C	Alkynes	2100–2260 (4.42–4.76)
C=C	Aromatic rings	1600 (6.25) 1500 (6.75)	C=C	Dienes	1650 + 1600
O—H	Alcohols	3610–3640 (2.75–2.77) monomeric 3200–3600 (2.78–3.13) hydrogen bonded	C—O	Alcohols, ethers acids, esters, etc.	1080–1300 (7.69–9.26)
			C=O	Aldehydes, ketones acids, esters	1690–1760 (5.68–5.92)
	RCO_2H	2500–3000 (3.33–4.00)		Acid chlorides	1802 (5.55)
				Anhydrides	1818 (5.50) 1750 (5.71)
				Conjugated carbonyls	1695 (5.90)
N—H	Amines	3300–3500 (2.86–3.03)	C—N	Amines	1180–1360 (7.35–8.48)
	1° = 2 peaks 2° = 1 peak 3° = 0 peaks (no H)		C≡N	Nitriles	2210–2260 (4.43–4.52)

Out-of-Plane Bending Vibrations

$RCH=CH_2$	990 + 910	Aromatic, 5 adjacent H	770–730 + 710–690
$R_2C=CH_2$	890	Aromatic, 4 adjacent H	770–735
RCH=CHR		Aromatic, 3 adjacent H	810–750
cis	730–765	Aromatic, 2 adjacent H	860–800
trans	965	Aromatic, isolated H	900–860
$R_2CH=CHR$	840–800		

The more important points can be summarized.

1. A terminal alkene unit (—$CH=CH_2$) is easily detected by the two bands at 990 and 910 cm^{-1}.
2. The signal at 2850–2960 cm^{-1} and the signals at 1350–1470 cm^{-1} correlate with the C—H unit.

   Alkenes and alkynes have a C—H absorption at 3030–3080 and 3300 cm^{-1}, respectively, that is useful for identification. The C≡C—H absorption is at lower energy than the C=C—H absorption, which is lower in energy than the C—C—H absorption for alkanes.
3. The hydrogen absorption for an OH of an alcohol is at 3610–3640 cm^{-1}

   Hydrogen bonding for the O—H unit changes the effective O—H bond distance, which leads to a range of absorption frequencies. The result is that a hydrogen-bonded OH signal is rather broad and very strong. The hydrogen absorption for NH is in generally the same position as that for OH, but is weaker and not as broad since N—H cannot hydrogen bond as effectively as an O—H.
4. Aldehydes have a hydrogen atom attached to the carbonyl. This absorption appears at ~ 2817 cm^{-1}.
5. The signals for C—C single bonds appear at 1200–800 cm^{-1} (they are not listed in Table 13.3), but they are very weak and of little value for compounds discussed in this book.
6. The C=C unit of an alkene gives a moderate-to-strong signal in the IR, at 1640–1680 cm^{-1}.

7. The alkyne unit (C≡C) also gives rise to a moderate-to-weak signal, at 2100–2260 cm^{-1}. It is higher in energy than the C=C signal since the alkyne unit is stronger.

   Internal alkynes often have a weak C≡C absorption because there is only a small change in dipole moment for the vibration. A symmetrical internal alkyne (e.g., but-2-yne) may show no signal at all.
8. In alcohols, ethers, and in esters, the C—O stretching modes are usually found between 1080 and 1300 cm^{-1} as strong or moderate peaks.

   The C—O absorption appears in the fingerprint region, which means it may be obscured by other peaks. In most simple alcohols, and ethers, the C—O absorption is strong and usually easy to find. In many cases, however, there is sufficient ambiguity that its identification can be problematic.
9. The C=O unit of aldehydes, ketones, carboxylic acids, and esters absorbs at 1690–1760 cm^{-1}, and it is a strong absorption peak. For most aliphatic derivatives, the C=O absorption is centered ~ 1725 cm^{-1}.
10. When a carbonyl is conjugated to a C=C unit or a benzene ring it is a conjugated carbonyl derivative. The absorption is shifted to lower energy and the C=O stretch is found at ~ 1695 cm^{-1}.
11. The carbonyl of an acid chloride absorbs at higher energy, at ~ 1802 cm^{-1}.
12. An anhydride will show *two* absorption peaks in this region, for the two carbonyl units, usually centered on 1818 and 1750 cm^{-1}.
13. The carbonyl unit of a carboxylic acid absorbs ~ 1725 cm^{-1}. The carboxyl unit (COOH) also contains an OH unit, which absorbs between 2500–3000 cm^{-1} as a *very* broad and strong absorption. The O—H of the acid unit is more extensively hydrogen bonded than that of an alcohol.
14. The N—H signal of an amine absorbs essentially in the same place as the O—H signal, at 3300–3500 cm^{-1}. It is usually weak or moderate in strength because amines do not hydrogen-bond as extensively as an alcohol.

    A primary amine has the NH_2 unit, and asymmetric vibrations of the two N—H units lead to *two* N—H absorptions. Therefore, a primary amine should show a doublet (two peaks) in this region. Since a secondary amine has only one N—H unit, it absorbs as a singlet (one peak) in this region. Tertiary amines do not have an N—H, and there is no absorption in this region.
15. Imines (Section 16.7.1) have a C=N unit, which absorbs at 1690–1640 cm^{-1} and is usually strong enough to be observed.
16. The C≡N unit of a nitrile absorbs at 2210–2260 cm^{-1}, usually as a moderate-to-strong, sharp peak.

The information from Table 13.3 is of limited value unless one knows what the actual absorption peaks for a given functional groups look like. What constitutes a strong, a weak or a medium absorption peak and when is a peak strong enough to be considered? It is important to know what types of absorption to look for, *vis-à-vis* a given functional group. Figure 13.9 shows the IR spectra for an alkane (**A**, heptane), an alkene (**B**, pent-2-ene), and an alkyne (**C**, hex-1-yne). Note that the C—H region is essentially the same in all three spectra. There is a moderate C≡C—H signal for hex-1-yne at ~ 3300 cm^{-1}. The C=C signal for pent-2-ene in Figure 13.9 is clearly visible but tends to be weak to moderate. The absorption for the C≡C unit for hex-1-yne at 2100–2260 cm^{-1} appears in a unique region and is moderate for unsymmetrical alkynes but can be very weak for symmetrical alkynes.

Figure 13.9 also shows the IR spectrum of a common alcohol (**D**, butan-2-ol) with an usually strong and prominent OH absorption at 3610–2640 cm^{-1}. There is also a strong C—O absorption in the fingerprint region at 1080—1300 cm^{-1}. A hydrogen-bonded OH is usually broad and strong and is very characteristic of an OH. If the peak is sharper it is associated with a non-hydrogen-bonded OH. Example (**E**) is the IR spectrum of dipropyl ether, with a

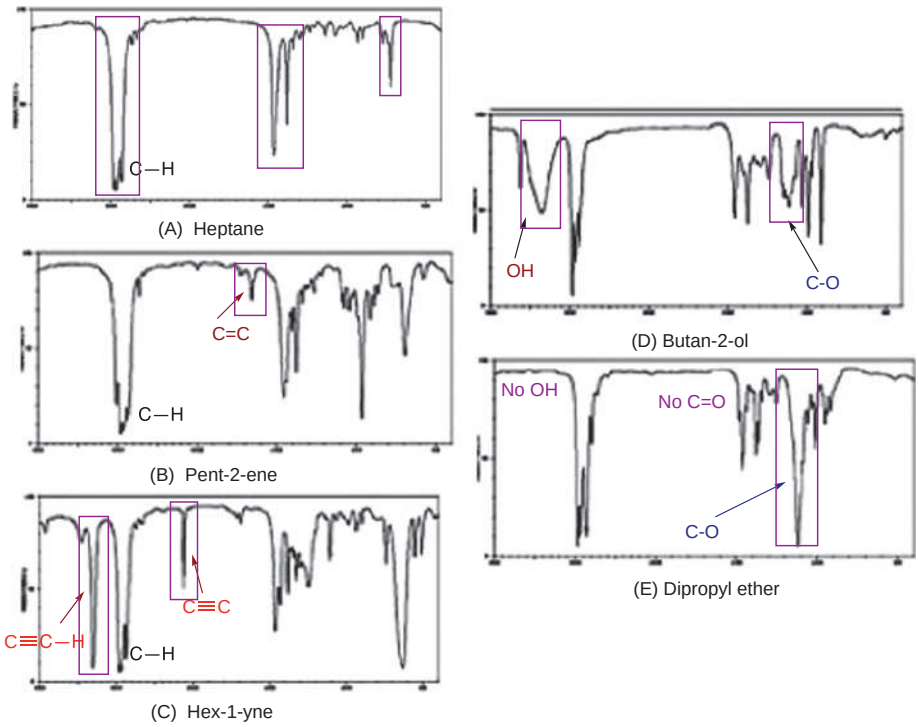


FIGURE 13.9 Infrared spectra of (**A**) an alkane, (**B**) an alkene, an (**C**) an alkyne, an alcohol (**D**) and an ether (**E**).

more prominent C—O absorption in the 1080–1300 cm^{-1} region. Note that for a molecule that has a molecular formula with a single oxygen atom. The presence of an ether unit must be inferred by the absence of an OH signal and the absence of a C=O signal. The C—O units in **D** and **E** are not always obvious because they appear in the fingerprint region, so the *absence* of the OH and C=O peaks are important clues that this compound is an ether. Note the C—H peaks in the functional group region of both the alcohol and the ether.

Figure 13.10 shows the IR spectra of several carbonyl compounds as well as several amines and a nitrile. Ketones, aldehydes, alcohols and ethers have only one oxygen, which is apparent from the empirical formula. Esters and carboxylic acids will have two oxygen atoms in the empirical formula. The carbonyl absorption at ~ 1730 cm^{-1} is characteristic of a ketone an aldehyde or a carboxylic acid. 4-Methylpentan-2-one (**A**) and 2-methylpentanal (**B**) both have a carbonyl signal but the aldehyde has a hydrogen atom attached directly to the carbonyl that absorbs at lower energy (2817 cm^{-1}) than the C—H units of a typical alkyl fragment. This weak signal can usually be seen and it is sufficient to distinguish an aldehyde from a ketone. Carboxylic acids have a carbonyl group but the carbonyl is part of the carboxyl group (COOH). The carboxyl has both a carbonyl and an O—H unit, and both absorb in the functional group region of the IR. Ketones and aldehydes do not have an O—H absorption, which is very broad and distinctive, and they are easily distinguished from a carboxylic acid such as 3-methylpentanic acid. Figure 13.10 shows the IR spectrum of 3-methylpentanoic acid (**C**) and the O—H absorption (2500–3300 cm^{-1}) is very broad due to the extensive hydrogen bonding and partly obscures the C—H absorption. Esters are carboxylic acid derivatives that will be discussed in Sections 18.2 and 18.7. Esters also have a carbonyl absorption at ~ 1730 cm^{-1} as seen in the spectrum of 2-methylbutyl 2-methylpropanoate (**D**). Therefore, the carbonyl absorption does not distinguish this compound from an aldehyde or a ketone. It can be difficult to identify the C—O peak for an ester from alcohols, ethers, or carboxylic acids since these signals appear in the fingerprint region. If the formula is known, it is easy to distinguish an ester or a carbolic acid because they have two oxygen atoms, whereas an aldehyde, ketone, alcohol or ether has only one. A carboxylic acid has the strong –OH peak and an ester does not.

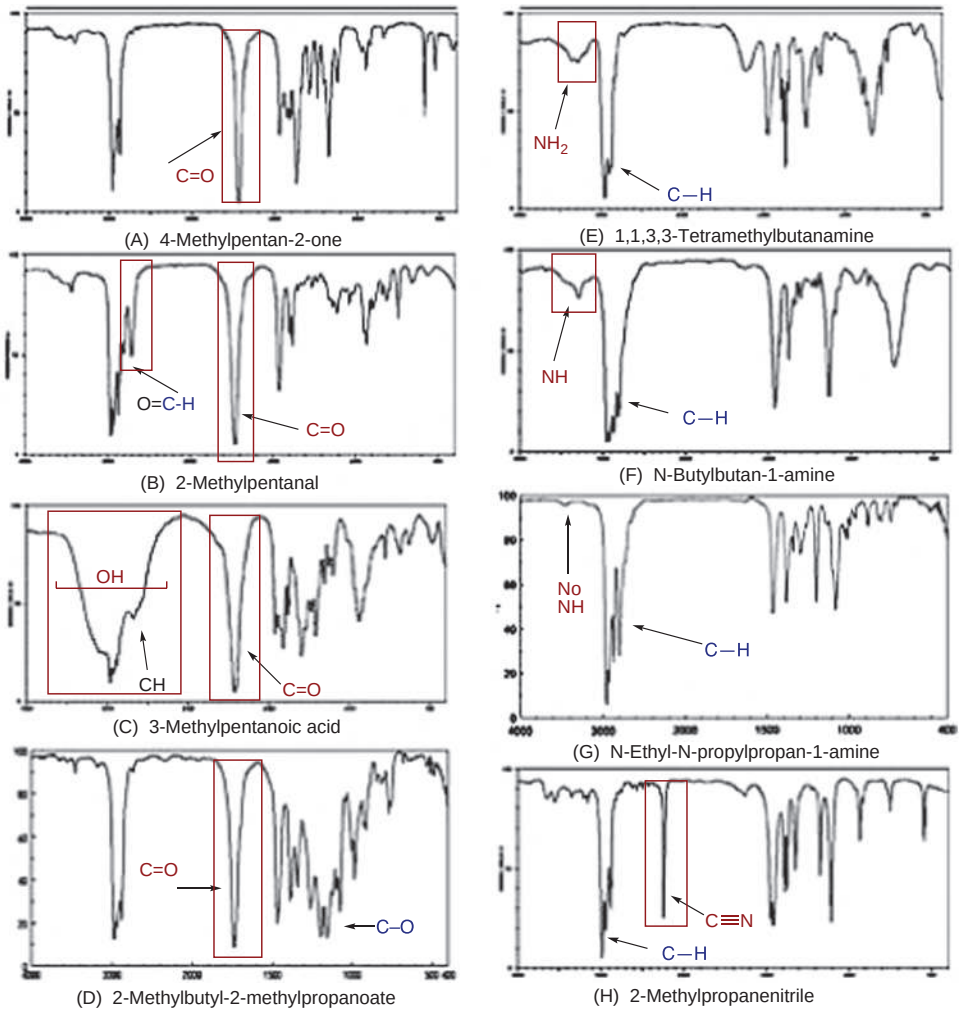


FIGURE 13.10 Infrared spectra of carbonyl-containing compounds, amines and a nitrile.

There are three fundamental types of aliphatic amines, primary amines with a NH_2 unit, secondary amines with an N—H unit, and tertiary amines, which have no N—H at all. The IR spectra of the primary amine 1,1,3,3-tetramethylbutanamine, **E**, the secondary amine dibutylamine (*N*-butylbutan-1-amine, **F**, and tertiary amine ethyldiisopropylamine (*N*-ethyl-*N*-propylpropan-1-amine, **G**, are shown in Figure 13.10. Although the absorption is at about the same frequency as the O—H unit in an alcohol, the N—H absorption is relatively weak compared to the O—H absorption. The primary amine (**E**) shows a weak, but discernable doublet in the N—H region, whereas the secondary amine shows only a weak singlet. This doublet is sufficient to distinguish the NH_2 unit of a primary amine from the N—H singlet of a secondary amine in **F**. For the tertiary amine, **G**, there is no N—H unit and that region of an IR spectrum shows no signal. The identity of the tertiary amine must be inferred from the presence of one nitrogen atom in the formula and the lack of N—H absorption or a C≡N unit. In a case such as this, negative evidence is compelling.

Another possible functional group for a molecule that contains a single nitrogen atom is the cyano group found in nitriles. The cyano functional group (C≡N) has a very distinctive absorption in the "triple-bond region" similar to that for alkynes. This absorption occurs at ~ 2260 cm^{-1} as a moderately strong and sharp peak, as seen in Figure 13.10 (**H**, 2-methylbutanenitrile). There is a slight difference in the absorption frequency between a C≡C and a C≡N unit, as seen in Table 13.3. The C≡N absorption is sharp and relatively strong, whereas the alkyne C≡C peak is weak. Further, a molecule containing one nitrogen atom in the formula showing this absorption is very likely a nitrile.

13.4 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Modern organic chemists rely on nuclear magnetic resonance (NMR) spectroscopy for day-to-day identification of organic molecules. Proton NMR (^{1}H NMR) is a powerful technique that allows one to "count" protons by identifying their different magnetic environment. This provides insight into the chemical environment of those protons. Other nuclei may be probed by NMR, including carbon, nitrogen and fluorine, but this section will focus on ^{1}H NMR with a brief discussion of ^{13}C NMR. Using various NMR experiments as well as the empirical formula and information obtained from MS and IR, the structure of organic molecules can usually be determined.

H is a Magnet

13.4.1 THE NUCLEAR MAGNETIC RESONANCE EXPERIMENT

A hydrogen nucleus is a charged particle (a proton) possessed of a property called "spin." The spin quantum number *I* is used to describe the intrinsic angular momentum of the hydrogen nucleus in a molecule. The value of *I* is determined by the number of protons and neutrons in a given nucleus. If the number of protons *plus* the number of protons is *odd*, the nucleus has a half-integer spin = ½, 3/2, 5/2, and so on. Both the proton (^{1}H) and ^{13}C nuclei have spin = ½. If the number of protons and neutrons are *both* odd, the nucleus has an integer spin (1, 2, 3,

TABLE 13.4 Common Nuclei and Their Spin Quantum Numbers

Nucleus	Number of Protons	Number of Neutrons	Spin (I)
^{1}H	1	0	$\frac{1}{2}$
^{2}H	1	1	1
^{12}C	6	6	0
^{13}C	6	7	$\frac{1}{2}$
^{15}N	7	8	$\frac{1}{2}$
^{16}O	8	8	0
^{18}O	9	9	1
^{19}F	10	9	$\frac{1}{2}$

etc.). Deuterium (^{2}H) will have spin = 1. If the number of protons and neutrons is *even* (as in ^{12}C), the nucleus has a spin of zero. Table 13.4 shows several common nuclei, the number of protons and neutrons, and the spin quantum number.

A hydrogen nucleus with the property of spin rotates and is electrically charged, which creates a magnetic moment. The magnetic moment of the nucleus forces it to behave as a tiny bar magnet. The magnetic moment of the hydrogen nucleus is proportional to the spin quantum number *I*. The proportionality constant that links the magnetic moment and *I* is called the *gyromagnetic ratio*, with the symbol γ. The value of γ will change with each type of nuclei (^{1}H, ^{2}H, ^{13}C, ^{15}N, etc.).

Spin Quantum Number

In the NMR experiment, an organic molecule is placed in a strong magnetic field, H_o. In that molecule, each hydrogen nucleus will behave as a small bar magnet that can assume more than one orientation *I* relative to H_o. The number of different orientations = $2I + 1$. The orientations for $I = ½$ and $I = 1$ are shown graphically in Figure 13.11. If $I = ½$ then there are $2(0.5) + 1 = 2$ orientations: spin = +½ and spin = -½. With two orientations there is only one possible transition of the nucleus when it absorbs energy. There is *one transition (one signal)*

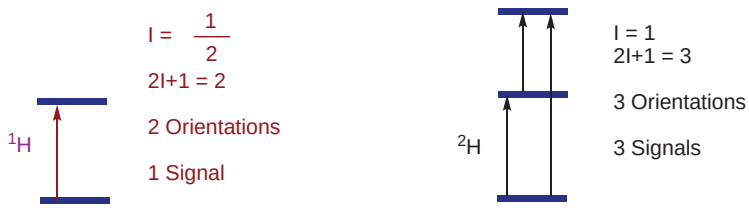


FIGURE 13.11 Orientations and signals per nucleus as a function of spin.

per absorption so a proton (^{1}H) shows one signal per proton. For a nucleus with $I = 1$, there are three orientations, spin = +½, spin = 0 and spin = -½. Absorption of energy leads to three orientations with three possible transitions. There are *three signals per absorption* so a deuterium (^{2}H) shows three signals per deuterium. Deuterochloroform, ($CDCl_3$, C^2HCl_3), for example, shows three signals (three lines) for that one ^{2}H nucleus. The spectrum of a molecule with many ^{2}H nuclei will be difficult to interpret. If a molecule contains many ^{1}H nuclei, however, each different hydrogen will give a unique absorption signal.

The specific magnetic field associated with a hydrogen atom is H_H. When the hydrogen atom with a spin of ½ is placed in the large magnetic field, H_o, there are two nonrandom orientations for H_H. The proton magnetic field H_H may be aligned with H_o, which is a lower energy orientation (Figure 13.12). The proton magnetic field H_H may be opposed to H_o, which

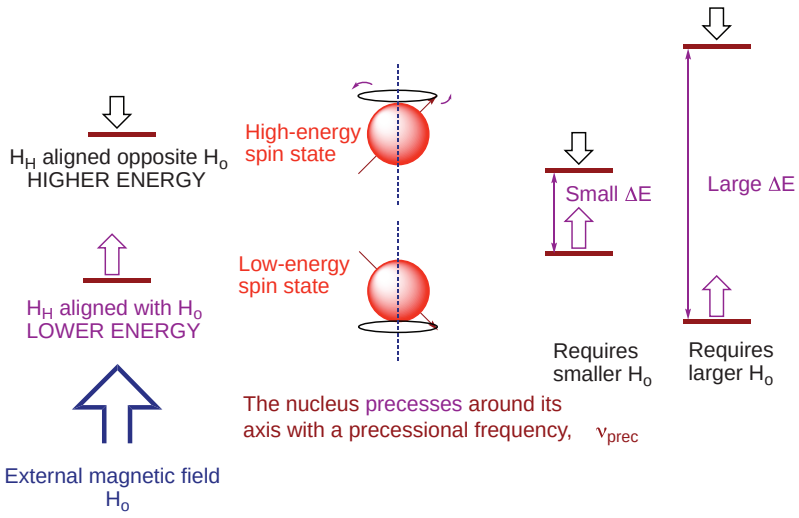


FIGURE 13.12 The energy gap generated when a spinning proton changes its spin state relative to an external magnet field, H_o.

is the higher energy orientation. There is an energy gap (ΔE) for the transition of H_H from the lower energy orientation to the higher energy. A reasonable analogy for this phenomenon uses two small bar magnets, with N and S poles. While N and S attract (low energy), N–N and S–S repel (high energy). The N–S alignments is analogous to H_H aligned with H_o, while the N–N or S–S alignment is analogous to H_H opposed to H_o. As the external magnetic field increases, H_H, increases, ΔE will increase and *the magnetic field at the nucleus increases.* As the external magnetic field decreases, ΔE decreases and *the magnetic field at the nucleus decreases*.

A proton (a hydrogen nucleus) spins "off-axis" and it precesses around the axis at a certain frequency, the *precessional frequency,* ν_{prec} (see Figure 13.12). The precessional frequency is equal to the product of the gyromagnetic ratio and the strength of the applied magnetic field ($\nu_{prec} = \gamma + H_o$). In other words, the precessional frequency is the rate of precession of the magnetic moment of the proton around the external magnetic field. When energy (ΔE) is absorbed by the spinning nucleus the spin is perturbed and the precession angle will change. The proton is said to "flip its spin state." This means that the precession angle changes from the low-energy spin state (aligned with H_o) to the high-energy spin state (opposed to H_o) as shown in Figure 13.12. This absorption of energy is registered as a peak in the ^{1}H NMR. A given nucleus can *only* absorb energy equal to ΔE for a given strength of H_o. At this point, the external frequency (ΔE, which is ν_{rf}) is said to be in *resonance* with the precession frequency of the proton (ν_{prec}), and the energy is absorbed. Note that as the external magnetic field increases, H_H, increases and ΔE increases. As the external magnetic field decreases, H_H, decreases and ΔE decreases. As noted, when the proton absorbs ΔE, it is recorded as a "peak."

The NMR spectrum for an organic molecule is obtained by first dissolving the sample in a suitable solvent. The sample is placed in a sample tube, which is inserted into a radio

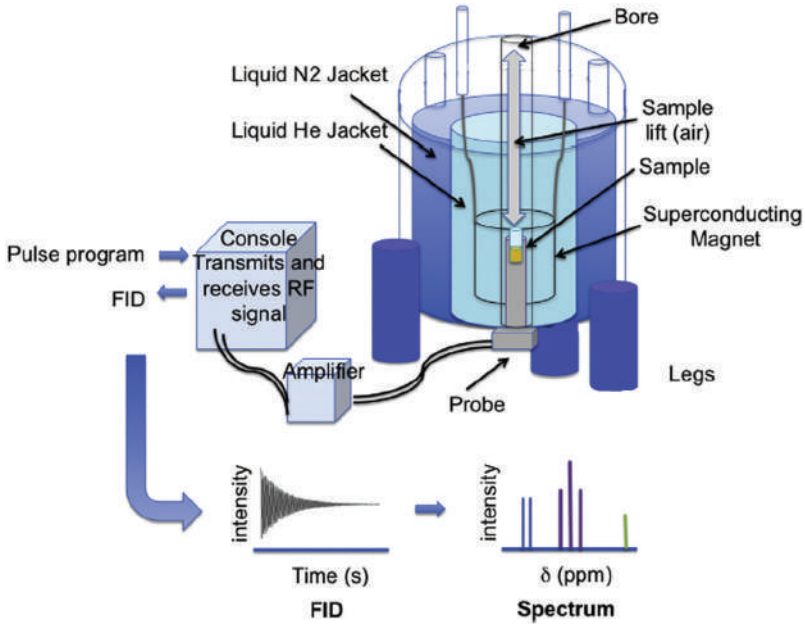


FIGURE 13.13 Diagram of a modern NMR spectrometer. Rankin, N.J.; Preiss, D.; Welsh, P.; Burgess, K.E.V.; Nelson, S.M.; Lawlor, D.A.; Sattar, N. *Atherosclerosis*, 2014, 237, 287–300. See p. 289 and Figure 1 therein. An open access article distributed under the terms of the Creative Commons CC-BY license.

frequency (R_f) coil inside a powerful magnet. The instrument used for this experiment is known as an NMR spectrometer. A diagram of a modern NMR spectrophotometer is shown in Figure 13.13.[3] In the instrument depicted in this diagram, the sample is lowered into the center of a superconducting magnet where the sample tube is encircled by a R_f coil. There are many molecular orientations (rotamers) for a molecule once it is in the magnetic field, so the sample tube is spun to normalize these orientations. In the presence of a strong magnetic field the R_f coil sends R_f pulses to excite the protons when they absorb the energy. A short R_f pulse has a range of frequencies centered about the carrier frequency and the range of excitation. As they relax back to equilibrium the *free-induction decay (FID)* is collected. The FID is processed by a computer, the signals are amplified and Fourier transforms the FID. It is mathematically deconvoluted. The FID is the time-domain signal obtained from the NMR spectrometer and the Fourier transform converts the signal from the time domain to the frequency domain. In other words, a the Fourier transform conversion of the FID generates a ^{1}H NMR spectra of intensity versus chemical shift (δ).

NMR Instrument and the NMR Spectrum

Extremely powerful magnets are used in NMR, and to keep the magnetic field stable the larger ones must be cooled in liquid helium, which requires a liquid nitrogen jacket. Typical magnetic fields are 14,092 Gauss (1.41 Tesla; 1.41. T), 46,973 Gauss (4.7 T), and 140,920 Gauss (14.1 T). Note that 1 T = 10,000 Gauss. Increasing the magnetic field strength (H_o) will require a larger ΔE as illustrated in Figure 13.12. The ΔE for a proton discussed previously is in the radio frequency (rf) range. Radio waves generally have energy in the 3-kHz–300-GHz range, but in modern NMR instruments, ΔE is in the 60-MHz (4.99×10^{9} nm; 5.72×10^{-6} kcal) to 1000-MHz (2.998×10^{8} nm; 9.54×10^{-5} kcal) range. The radio frequency is linked to the external magnetic field strength so a 14,092 Gauss (1.41 Tesla) magnet requires a 60 MHz rf signal. Likewise, a 46,973 Gauss (4.7 Tesla; 4.7 T) magnet requires a 200 MHz rf signal, and a 600 MHz 140,920 Gauss (14.1 T) magnet requires a 600 MHz rf signal.

[3] Rankin, N.J.; Preiss, D.; Welsh, P.; Burgess, K.E.V.; Nelson, S.M.; Lawlor, D.A.; Sattar, N. *Atherosclerosis* 2014, 237, 287–300. See p. 289 and Figure 1 therein.

To summarize, when a radio signal of the proper energy (ΔE) is applied at a particular external magnetic field strength, H_o, a proton with the correct precessional frequency will absorb this energy, $\Delta E = \nu_{rf}$. This absorption of energy is detected as a signal (a peak) that is a function of the magnetic field strength and ΔE. The display of all peaks associated with different hydrogen atoms in a molecule is the *NMR spectrum*. The energy required for this process is quite small but modern instruments generate a NMR spectrum in a few minutes or a few hours with very small samples.

The discussion of absorption of energy by a proton in Section 13.4.1 is misleading in one sense. This technique does not examine a "free" proton, but rather hydrogen atoms attached to carbon or another atom in an organic molecule. Most organic molecules have many hydrogen atoms, and different structures have different hydrogen atoms in a slightly different environment. Therefore, there are slightly different local magnetic fields for the various protons. First the number of *different* hydrogen atoms must be identified. As a mnemonic, imagine replacing every hydrogen atom in a molecule with a chlorine atom, which will lead to different isomers. Replacing the eight hydrogen atoms in butan-2-one, for example, will lead to three different chlorinated isomers, 1-chlorobutan-2-one, 3-chlorobutan-2-one and 4-chlorobutan-2-one, indicative of the fact that there are three different types of hydrogen atoms. For example, replacing any of the three hydrogen atoms on the methyl group attached to the carbonyl ($H_3C—C=O$) will give 1-chlorobutan-2-one, so all three of those hydrogen atoms are chemically identical. Likewise, replacing the two hydrogen atoms on the -CH_2-unit will give 3-chlorobutan-2-one and replacing all three hydrogen atoms on the other methyl group will give 4-chlorobutan-4-one.

Assume that chemically identical protons are magnetically identical protons. Assume that chemically identical protons are magnetically identical and give one signal in the ^{1}H NMR. Assume that chemically different protons are magnetically different and give different signals in the ^{1}H NMR. If each different type of proton generates a different magnetic field, each localized magnetic field will have a different strength, each coming into resonance with a different ΔE. In other words, different types hydrogen atoms will give different signals in the proton NMR. Conversely, identical hydrogen atoms will all give one signal. Taking butan-2-one as an example, there are three chemically different kinds of hydrogens. An NMR spectrum with three different peaks is expected and it is possible to distinguish the different types of hydrogen atoms in a molecule. As noted in Section 13.4.1, the proton nucleus (^{1}H) has a spin of ½, so there is one signal per absorption. Therefore, each different type of hydrogen atom in a molecule will yield only one signal per absorption.

13.7 How many signals are expected for each carbon nucleus in a molecule using ^{13}C?

13.4.2 THE PROTON NMR SPECTRUM

When a proton NMR spectrum for a molecule is obtained, ΔE is held constant in a continuous wave NMR instrument (60, 200, 600 MHz, etc.) and the magnetic field (h_o) is changed incrementally. When a proton comes into resonance for a given H_o, absorption of ΔE leads to a signal for that type of proton. If ΔE is constant, the change in magnetic field will be very small because each proton generates only a tiny H_H measured in hertz (Hz) while the applied ΔE is measured in megahertz (MHz). The signal is recorded in millionths of hertz relative to ΔE.

Chemical Shift

In ^{1}H NMR experiments two issues must be addressed. To establish a zero-point, a compound is added to the sample. This compound must generate a signal in a position that does not interfere with most signals from organic compounds. It should also be volatile and easily removed from any precious sample. *Tetramethylsilane [$(Me_3)_4Si$; TMS]* is used as an internal standard because it satisfies these requirements. All twelve protons of TMS absorb as one signal that appears upfield of virtually all signals associated with organic molecules, as shown

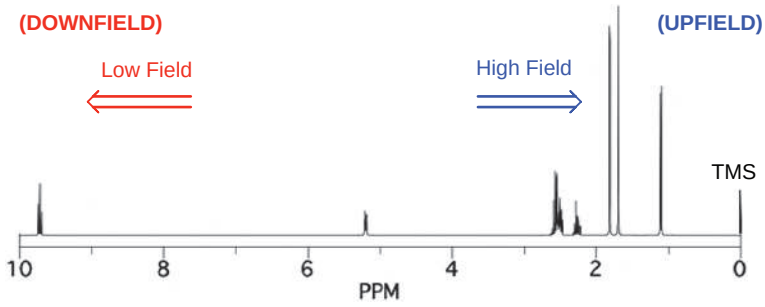
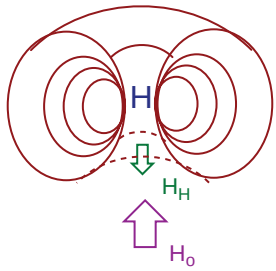


FIGURE 13.14 A typical ^{1}H NMR spectrum.

in Figure 13.14. This signal is set equal to zero in the NMR instrument. The position of each signal of a sample is recorded relative to TMS, in hertz.

A second problem is apparent when a sample in a 60-MHz instrument shows an absorption signal at 60 Hz but that same sample shows a signal at 200 Hz in a 200-MHz instrument. This fact creates a problem for establishing the scale used for the NMR spectrum since using two different NMR instruments (60 and 200 MHz) leads to two different signals relative to TMS. These signals must be ***normalized*** before they can be compared. The ratio of the signal measured in hertz to the applied ΔE measured in megahertz leads to the δ *scale* (also known as the *ppm scale*), where $\cdot = \frac{(\text{Frequency shift from TMS in Hz})}{(\text{Frequency of the instrument in Hz})}$. In a 60-MHz instrument, a signal that appears at 60 Hz can be normalized: $60/60\text{x}10^6 = 1 \text{ x } 10^{-6}$ or 1 *part per million (ppm)* or 1 δ. For the 200 MHz instrument, a signal at 200 Hz is $200/200\text{x}10^6 = 1 \text{ x } 10^{-6} = 1$ ppm. This procedure converts a signal in hertz to a normalized signal in ppm. Therefore, a signal for a given hydrogen atom is reproducible in any NMR instrument of any field strength. The *ppm scale* is used in Figure 13.14. The position of a peak in ppm, relative to TMS, is known as the *chemical shift* for that peak.

13.8 Determine the position of a signal in ppm that appears at 438 Hz in a 500-MHz instrument, relative to TMS.



When placed in a uniform magnetic field (H_o) the electrons surrounding any individual proton will circulate in a manner that generates the tiny magnetic field (H_H) described previously. In other words, the hydrogen atom is a spinning charge surrounded by electrons so it is *a tiny electromagnet*. This magnet field H_H is illustrated in cross section. The small magnetic field H_H precesses in opposition to the applied field, H_o. If H is the magnetic field strength required for resonance and absorption, then $H = H_o + H_H$ when H_H is opposed to H_o. In other words, a greater magnetic field is required to make the proton come into resonance for a given ΔE, so the signal will be at higher field, or upfield relative to the TMS signal.

A hydrogen atom that shows a signal in a NMR spectrum is not a "proton" but rather a hydrogen atom covalently bonded to carbon or to another atom. Depending on the atom it

is bonded to, the electron density is different for each different covalently bonded hydrogen. Therefore, each different type of hydrogen will give rise to a signal with a different chemical shift. In other words, a hydrogen atom on a primary carbon atom will show a signal with a different chemical shift than a hydrogen atom on a secondary or a tertiary carbon atom. A hydrogen atom in an ether or an alcohol, H—C—O, will have a different chemical shift relative to a hydrogen atom in a ketone or aldehyde, H—C—C=O. The chemical shift (in ppm) relative to the zero point of TMS is therefore a function of molecular structure.

When a higher electron density surrounds the nucleus of a proton it is *shielded* and *a larger magnetic field is required to bring it into resonance*. A proximal electron releasing carbon group (an alkyl group) will increase the electron density around H_a, as shown in Figure 13.15. A higher magnetic field is required for resonance of that proton and the signal is said

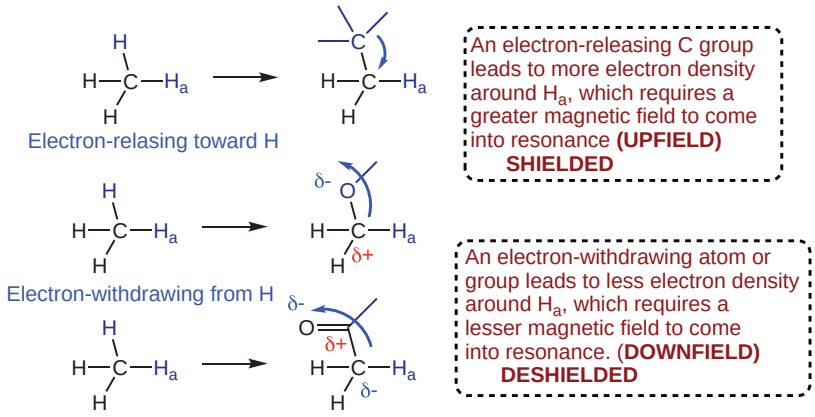


FIGURE 13.15 Shielding and deshielding in ^{1}H NMR.

to appear at a higher magnetic field, or *upfield* (closer to the TMS signal). The proton nucleus is *shielded*. The higher the electron density around the proton, the more shielded it will be, requiring a larger value of H_o.

While alkyl groups are electron releasing as described, the different ^{1}H NMR signals for protons in an alkane appear to be an anomaly. A tertiary carbon atom has three alkyl substituents, a secondary carbon has two and a primary carbon has one. Although a tertiary carbon has more electron releasing substituents, a hydrogen on a tertiary carbon resonates at about 1.5 ppm, *downfield* of a proton on a primary carbon at 0.9 ppm. Clearly, another phenomenon influences the chemical shift. A tertiary C—H bond is known to be weaker than a primary C—H bond (Sections 7.4,5). The H_o for H_3C—H is 103.4 kcal (432.7 kJ) mol^{-1}, H_3CH_3C—H is 101.1 kcal (423 kJ) mol^{-1}, $(CH_3)_2HC$—H is 98.6 kcal (412.5 kJ) mol^{-1} and $(CH_3)_3C$—H is 96.5 kcal (403.8 kJ) mol^{-1}. Because a tertiary C—H bond is weaker, there is less electron density associated with the hydrogen. The signal is therefore downfield of hydrogen on a primary carbon. Indeed, a methyl signal, with a hydrogen on a primary carbon appears at 0.9 ppm, a hydrogen on a secondary carbon appears at 1.2 ppm and a hydrogen on a tertiary carbon is at 1.5 ppm.

An alternative situation has an electron-withdrawing group (X) such as an oxygen or a carbonyl attached to carbon bearing a hydrogen atom, as in X—C— H_a. The electron withdrawing atom draws electron density away from H_a so there is less electron density around it (Figure 13.15). A proton with less electron density is less shielded (*deshielded*) so a smaller magnetic field will be required to bring it into resonance. The signal appears at a lower magnetic field, or *downfield* relative to TMS. An electron-withdrawing group will deshield a proton, making it absorb at a lower magnetic field.

The relative position of protons connected to various functional groups in the ^{1}H NMR are shown in Figure 13.16. The carbonyl group shifts the signal downfield to about 2.1 ppm relative to methyl, and oxygen shifts the signal to ~3.3 ppm relative to methyl. A hydrogen

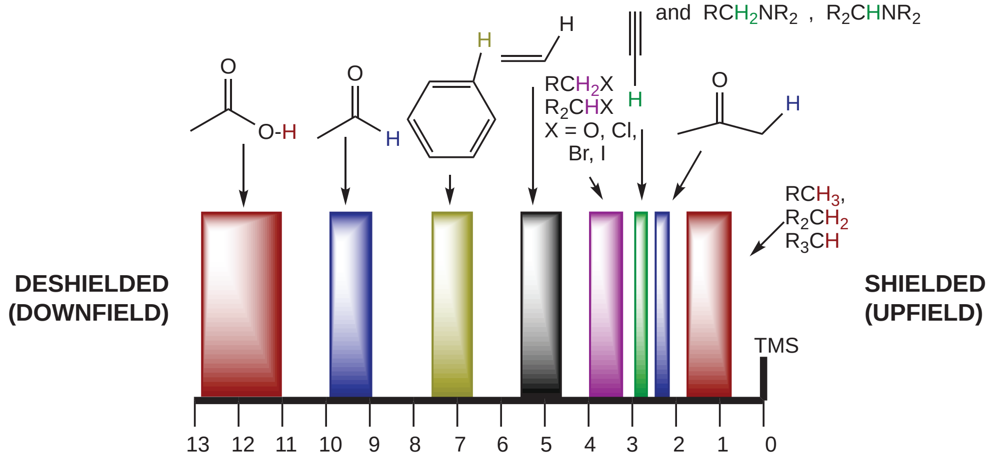


FIGURE 13.16 General absorption patterns for protons attached to functional groups in the ^1H NMR.

atom attached to a carbon that is connected to an oxygen or to a halogen will also shift the signal downfield by similar amounts, and it can be difficult to distinguish these signals using only ^1H NMR. A C=C unit is not polarized, yet in Figure 13.16 the alkene protons (H—C=C) are downfield relative to C—O, C—halogen or other functional groups. An aldehyde proton (H—C—C=O) is further downfield than an alkene proton. Note that the alkyne proton is upfield of the alkene. These chemical shifts are due to *magnetic anisotropy*, associated with the presence of a π-bond. The π-electrons generate a *secondary magnetic field* that influences H_o. The OH proton of an alcohol is also polarized and appears between 1 and 5 ppm. The signal for the O—H proton of a carboxylic acid resonates at ~ 11–15 ppm according to Figure 13.16. The carboxyl proton appears so far downfield because the acidic proton has a large δ^+ hydrogen atom and it is extensively hydrogen bonded. The increased bond polarization makes the proton even more deshielded.

Magnetic Anisotropy

Protons on a carbon with a π-bond show downfield chemical shifts, as noted in Figure 13.16. If ethylene (ethene) is examined, the π-electrons generate a secondary magnetic field

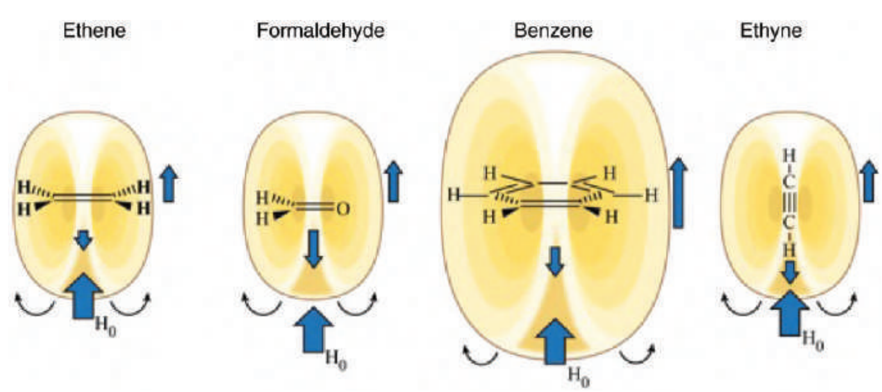


FIGURE 13.17 Magnetic anisotropy for ethene, ethyne, formaldehyde, and benzene.

as shown in Figure 13.17 that opposes H_o in the region of the π-bond. The field generated by the π-electrons is greater than that of the sigma electrons, so this π-secondary field dominates the interaction with H_o. This leads to a nonrandom orientation of the planar ethylene molecule such that the carbon and hydrogen atoms are perpendicular to H_o. This secondary field only influences those hydrogen atoms ***directly attached*** to a sp^2 hybridized carbon, H—C=C. Hydrogen atoms that are not directly attached will not be affected. The secondary field H_π augments H for the nucleus, so less of a magnetic field is required $[H = H_o - H_\pi]$. Protons directly attached to a sp^2 hybridized atom are therefore *deshielded* by the secondary

magnetic field so the signal will appear *downfield (lower field),* between 5 and 6 ppm in most cases. As noted, this phenomenon is called *magnetic anisotropy*. The six π-electrons of benzene have a larger secondary field. The interaction of the π-electrons orients the benzene molecule such that all six hydrogen atoms are perpendicular to H_o. The protons on the benzene ring are therefore more deshielded by the larger the secondary field. Therefore, protons on a benzene ring resonate even further downfield when compared with the proton attached to the C=C unit of an alkene, at ~ 7.1 ppm.

A proton connected directly to a carbonyl occurs only in an aldehyde functional group and this proton resonates at ~ 9 to 10 ppm, far downfield from the alkene proton. There is magnetic anisotropy induced by the two π-electrons in a carbonyl in formaldehyde as shown in Figure 13.17. The carbonyl is also polarized but the C=C unit is not. The anisotropy effect of the π-electrons and the electron-withdrawing properties of the carbonyl are additive so this proton is even more deshielded. The aldehyde proton is therefore far downfield (9–10 ppm) relative to an alkene proton (5–6 ppm).

Terminal alkynes show an apparent anomaly in the anisotropy arguments since this proton resonates at ~ 2.3 ppm. It is upfield of the alkene protons, although there are two π-bonds rather than one. However, the two π-bonds are orthogonal, one to the other. The two π-bonds will orient parallel to H_o so all four electrons (both π-bonds) can interact with the external magnetic field to generate the secondary magnetic field. This orientation is shown in Figure 13.17. Since the secondary magnetic field opposes H_o along the line of the H—C—C—H bonds the proton of the terminal alkyne is in the shielding portion of the secondary field and *upfield relative to the alkene*.

The factors that influence chemical shift are summarized as follows:

1. Sigma electrons shield the nucleus and the proton absorbs at higher field.

   Alkyl groups are electron donating but a tertiary C—H bond is weaker than a primary C—H bond, so the tertiary signal is more downfield. Methyl groups usually absorb at 0.9 ppm, —CH_2— groups (methylene) are found at ~ 1.1–1.3 ppm, whereas methine protons (—CH—) are found at ~ 1.5 ppm.

2. Electronegative atoms deshield the nucleus and the proton absorbs at low field (downfield).

   When the proton is connected to a carbon connected to an electron-withdrawing oxygen, nitrogen, halogen, or sulfur, the bond polarization is such that the proton has less electron density. It is deshielded. That proton will appear downfield relative to methyl, methylene, and methine of an alkane. The more polarized the C—X bond, the further downfield the proton will appear. Cyano, carbonyl-bearing functional groups, and nitro groups are all electron-withdrawing since they have a δ^+ atom connected to the carbon bearing the proton of interest. The electron-withdrawing effect pulls electron density away from the proton, deshields it, and that signal will appear downfield.

3. π Electrons have spin and generate a magnetic field (H_π) that opposes.

   Just as sigma electrons generate a secondary field (have a magnetic moment), π-electrons also generate a secondary magnetic field that influences H_o. The greater the concentration of π-electrons, the greater will be the secondary magnetic field.

Influence of Functional Groups on Chemical Shift

The ability to correlate a proton signal with its attachment to or proximity to a functional group is important. As noted the position of each signal relative to TMS is known as the *chemical shift* and Table 13.5 gives chemical shift ranges for hydrogen atoms attached to various functional groups. A range of signals is necessary since a hydrogen atom attached

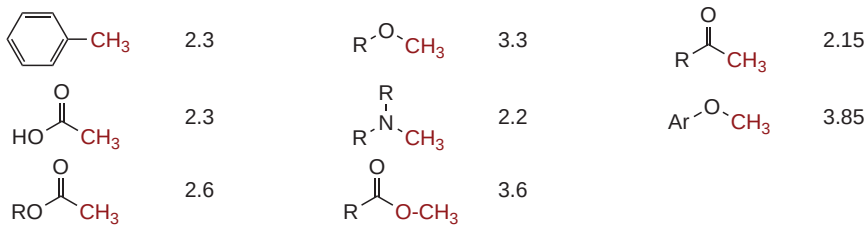
TABLE 13.5 The ^{1}H NMR Spectroscopy Correlation Table

^{1}H NMR Chemical Shifts

Cyclopropane	0.2	Primary, RCH_3	0.9
Secondary, R_2CH_2	1.3	Tertiary, R_3CH	1.5
Vinylic, C=C—H	3.5–5.9	Alkynyl, C≡C–H	2.0–3.0
Aromatic, Ar—H	6.0–8.5	Benzylic, Ar—C—H	2.2–3.0
Allylic, C=C—C—H	1.7	Fluorides, F—C—H	4.0–4.5
Chlorides, Cl—C—H	3.0–4.0	Bromides, Br—C—H	2.5–4.0
Iodides, I—C—H	2.0-4.0	Alcohols, HO—C—H α-H of alcohols	3.4–4.0
Ethers, C—O—C—H	3.3–4.0	Esters, RCOO—C—H H on carbon of alcohol unit	3.7–4.1
Carboxylic acids, HOOC—C—H α-H of acids	2.0–2.2	Esters, ROOC—C—H α-H of esters	2.0–2.7
Carbonyls, O=C—C—H α-H of aldehydes and ketones	2.0–2.7	Aldehydes, O=C—H Aldehyde proton	9.0–10.3
Hydroxyl, O—H	1.0–5.5	Phenols, ArO—H	4.0–12.0
Enols, C=C—O—H	15.0–17.0	Carboxylic acids, RCOO—H Acidic proton of the OH	10.5–15.0
Amino, R—N—H Proton on nitrogen	1.0–5.0	Amines, N—C—H α-H of amines	2.5

Methyl Signals for Common Fragments

To determine signals for funtional groups to a methylene, add 0.4 to these numbers
To determine signals for funtional groups to a methine, add 0.6 to these numbers



to a tertiary carbon is further downfield (1.5 ppm) than when attached to a secondary carbon (1.25 ppm), which is further downfield that a primary carbon (0.9 ppm). Table 13.5 also shows the chemical shift data for methyl groups attached to various functional groups at the bottom to give a quick reference for the downfield shift effect of various functional groups.

The signals listed for a methyl group attached to various functional groups can be used to calculate chemical shifts for a given functional group. The differences in chemical shift for a proton attached to a primary, secondary and tertiary carbons are illustrated in Figure 13.18 for groups attached to a carbonyl group. The methyl signal is 2.15 ppm when attached to a

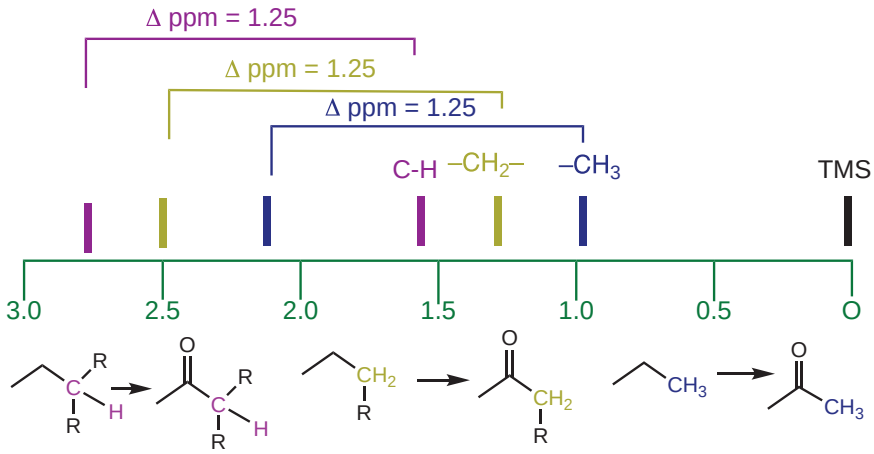


FIGURE 13.18 Chemical shift for a carbonyl as a function of hydrogen substitution.

carbonyl, which is 1.25 ppm downfield from the "alkane" methyl signal of about 0.9 ppm. A carbonyl therefore shifts a signal downfield by 2.15-0.9 = 1.25 ppm. A methylene for an alkane normally resonates at 1.25 pm but connection to a carbonyl also shifts the signal by 1.25 ppm downfield. The methylene signal attached to a carbonyl is therefore predicted to be 1.25+1.25 ppm or 2.5 ppm. A methine ($-CHR_2$) attached to a carbonyl is predicted to be 1.25+1.5 ppm, or 2.75 ppm. These predicted chemical shifts of 2.15–2.75 correlate well with the 2.0–2.7 pp chemical shift range in Table 13.5 for a carbonyl. Comparing the methyl signals in Table 13.5 with the 0.9 methyl signal for an alkane provides an estimate for the chemical shift associated with each functional group.

The estimation of chemical shift for a given functional group can be used when a proton is connected to more than one functional group. If a $—O—CH_2—C=O$ unit is part of a molecule, the chemical shift of that methylene can be estimated. The chemical shift of a methylene group of an alkane is 1.25 ppm. The shift for each functional group shift is added to 1.25 ppm to predict the position of the functionalized proton. For a $—O—CH_2—C=O$, the shift for a carbonyl is 2.15-0.9 = + 1.25. The shift for a methyl group attached to an oxygen atom is 3.3-0.9 =+ 2.4. Therefore, the predicted chemical shift for the $—O—CH_2—C=O$ methylene protons will be 1.25+1.25+2.4 = 4.9 ppm. Clearly, the signal appears much further downfield because it is influenced by two functional groups. This approach is useful for the prediction of proton signals attached to a variety of functional groups.

Integration

Figure 13.19 shows an ^1H NMR spectrum of a compound that has four different types of hydrogen atoms and four different signals. The Integration of the area under each signal is

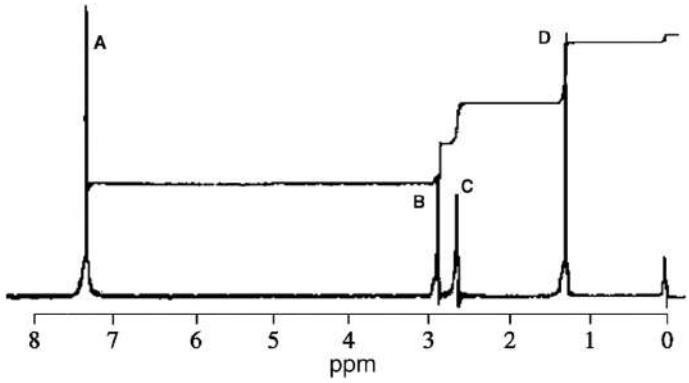


FIGURE 13.19 The integration of a typical ^1H NMR spectrum with four different signals representing four different kinds of protons.

proportional to the number of hydrogen atoms that contribute to a given absorption signal. The larger the integration, the greater the number of hydrogen atoms. Mass spectrometry provides the empirical formula for an unknown molecule and the total number of hydrogen atoms. The ratio of integration values for the different peaks gives the ratio of different hydrogen atoms. This ratio and the total number of hydrogen atoms from the empirical formula provides the number of hydrogen atoms that correlate with each signal. Each signal can therefore be identified as one or more methine, methylene or methyl groups.

An old-style NMR spectrum is shown in Figure 13.19. There are horizontal line traces along with the proton peaks and at each peak the line trace begins to rise to a new plateau. If the height of these traces is measured, beginning where the peak starts to rise and ending where the peak levels out again, a number is obtained that correlates with the peak area. This number is the *peak integration.* Modern instruments integrate each signal electronically and report the integration directly in digital form, but this older method is shown to illustrate the methodology. In Figure 13.19, peak A integrates for 26 mm, peak B for 9.2 mm, peak C for 9.1 mm, and peak D for 9.7 mm. If all numbers are divided by the smallest integration (9.1 mm), the ratio of A:B:C:D = 2.86 : 1 : 1 : 1.6. There are no fractional hydrogen atoms, so the numbers are multiplied by an integer that will give close to whole numbers. Multiplication by 2 leads to a ratio of 5.7:2:2:3.2. The ratio is not exact due to experimental error, so both 5:2:2:3 or 6:2:2:3

should be considered. Before, the correct ratio can be determined for the NMR integration data the empirical formula must be determined from mass spectral data. For the problem at hand, the formula is $C_{10}H_{12}O$ so there are twelve hydrogen atoms. Therefore, the ratio must be 5+2+2+3 hydrogen atoms, which fits this empirical formula.

If the empirical formula has a larger number of atoms, then a multiple of the 5:2:2:3 must be considered. If the empirical formula is $C_{20}H_{24}O_2$, for example, then the integration for this molecule is (5+2+2+3)x2 = 10:4:4:6. For any molecule, establish the integration ratio and compare it with the empirical formula that correlates with the number of hydrogen atoms match.

13.9 For a formula of $C_9H_{10}O_2$, the ^{1}H NMR spectrum shows three signals with the following integration values: 71.5:28.6:42.9. Determine the relative ratio of these three signals.

In Figure 13.19 the four signals correspond to four different kinds of hydrogen atoms and all four are single peaks (singlets). A different example is shown in Figure 13.20 where there are *three different signals* that correspond to *three different kinds of hydrogen atoms* in the nitrile, 2,2-diphenylbutanenitrile. The three hydrogen atoms on the methyl group constitute one signal (A), the two hydrogen atoms of the methylene give a different signal (B), and the 10 hydrogen atoms on the two identical benzene rings constitutes the third signal (C). Each different *signal* is a *cluster of peaks* rather than one single peak. In other words each different type of hydrogen atom gives rise to one signal but there are several peaks per signal. These multiple peaks are due to the presence of *neighboring hydrogen atoms*. Upon integration, the ratio of A:B:C is 1.5:1:5 with an empirical formula of $C_{16}H_{15}N$, so the ratio of A:B:C must be 3:2:10.

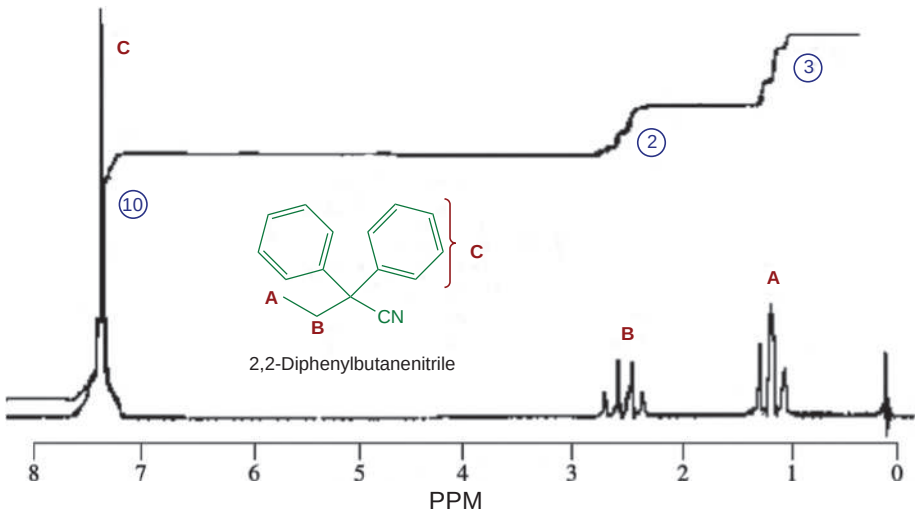


FIGURE 13.20 The ^{1}H NMR spectrum of 2,2-diphenylbutanenitrile.

The three peaks for signal A in Figure 13.20 is called a *triplet* that integrates to 3 protons. The four peaks for signal B is called a *quartet* that integrates to 2 protons, and the one peak signal C is called a *singlet* that integrates to 10 protons**.** The three hydrogen atoms labeled **A** are attached to a carbon that is also connected to the carbon bearing the two hydrogen atoms B. Protons H_A and H_B are separated from each other by three covalent bonds, H—C—C—H. The *protons **A** and **B** are on adjacent carbon atoms*, and they are classified as *neighbors.* When hydrogen atoms are neighbors, the magnetic field H_H of one will influence the magnetic field of the other.

Non-First Order Coupling

Why do protons on neighboring carbon atoms led to multiple peaks? Remember that H_A functions as a small magnet in the presence of the external field (H_o), but H_B is also a small magnet. If H_A and H_B are close enough, it is reasonable that the magnetic field exerted by H_B will influence that of H_A and vice-versa. The H_A field may be aligned or opposed to the field of H_B, in addition to its interaction with H_o. The net result is that the signal for H_A will be *"split" into two signals* by its interaction with H_B and the signal for H_B will also be split into two signals by H_A.

13.10 Identify those protons that are neighbors in 2,5-dimethylhexan-3-one.

If two neighboring hydrogen atoms are chemically identical, it is assumed they have identical magnetic environments. Therefore, "n" identical neighbors will split each adjacent proton into "n+1" peaks, the *n+1 rule*. Following this n+1 rule, a proton with one neighbor appears as a *doublet*; two neighbors lead to a *triplet*; three neighbors lead to a *quartet*; four neighbors lead to a *pentet*. If a proton has no neighbors, it will appear as a *singlet* (one single peak).

13.11 What is the multiplicity of the —CH_2— group in ethyl methyl ether? Of the —CH_2— group in propane? Of the —CH_3 group in ethanol?

n+1 Rule

This *n+1 splitting* is graphically illustrated in Figure 13.21 using Pascal's triangle to estimate how many peaks should appear for a given signal that follows first-order behavior. The

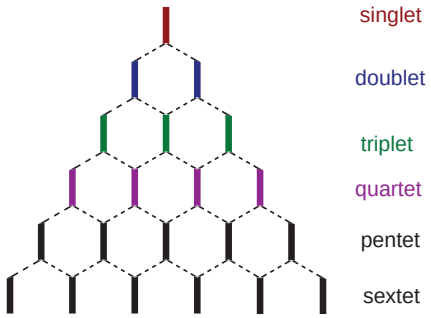


FIGURE 13.21 Pascal's triangle, used in conjunction with the *n*+1 rule.

n+1 rule and the use of Pascal's triangle *assumes that all neighboring hydrogen atoms are chemically identical*. The initial signal is equally split by each neighbor and the distance between the peaks is the same. Therefore, the peaks split symmetrically and the "inner" peaks overlap. The overlap leads to a triplet with a 1:2:1 ratio for three peaks, a 1:3:3:1 ratio for four peaks, a 1:4:6:4:1 ratio for five peaks, and so on.

The appearance of these peak clusters is very characteristic for protons that follow first order behavior. The observation of four peaks in the proton NMR means there are three neighboring hydrogen atom, three peaks means two neighbors, two peaks means one neighbor and one peak means zero neighbors. When there are several peaks in a signal, but the number is unknown or cannot be determined, such a peak is called a *multiplet*.

1. *For a molecule where all the neighbors are identical, a proton with "n" neighbors will appear as "n+1" peaks in the ^{1}H NMR.*
2. *If there are "n" peaks for a signal in the ^{1}H NMR spectrum, there are "n-1" neighbors.*
3. *Molecules that exhibit this behavior are said to exhibit first order behavior.*

The separation between peaks is measured in hertz, and this distance is called the *coupling constant* (given the symbol *J*). The neighboring hydrogen atom effect described is actually called *spin-spin coupling*. Returning to 2,2-diphenylbutanenitrile in Figure 13.20, there is an equidistant separation of the three peaks of the triplet for H_A and the four peaks for H_B. The coupling constant for the neighboring protons (H_A and H_B) is J_{AB}. Typically, the value of

J ranges from close to zero to 8-10 Hz. The value of *J* depends on the *dihedral angle* of separation between the two neighbors protons. The H—H vicinal coupling constants is a function of dihedral angle of the C—H bond. The coupling constant is calculated using the $\cos^2$ function, $J = a\cos^2 \Phi - 0.28$, which is known as the *Karplus-Conroy equation*. The equation is named in honor of Martin Karplus (Austria/USA; 1930-) and Harold Conroy (USA). In the cases cited, a dihedral angle of 10° corresponds to a *J* of ~ 7–8 Hz, whereas a dihedral angle of 60° corresponds to *J* of ~ 1.5-2 Hz. In other words, a H—C—H unit with a dihedral angle of 10° shows a coupling constant of 7-8 Hz. When a proton (A) is coupled to another proton (B), then J_{AB} is the same for the H_A signal and also the H_B signal. This finding shows that they are *neighbors* and their *spins are coupled* and they will have the same coupling constant.

13.12 What is the multiplicity for the —CH_2— units in 1,2-diphenylethane?

There are certain structural fragments that follow *first-order behavior*, which means that they show coupling that follows the *n*+1 rule. Finding examples of these fragments in an unknown NMR spectrum provides useful structural information. For example, in Figure 13.22 the triplet-quartet signal for two types of protons in an ethyl group that integrate to

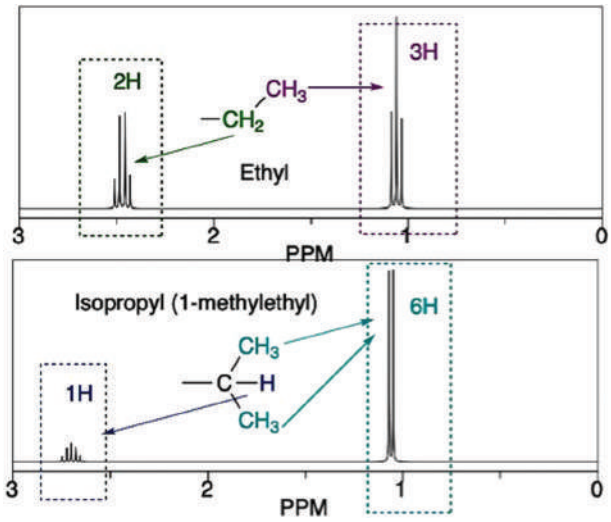


FIGURE 13.22 Ethyl and isopropyl patterns in the ^{1}H NMR.

2:3. Likewise, an isopropyl group, $-CH(CH_3)_2$, clearly shows two signals that integrate 6:1 as a doublet and a downfield heptet. A *tert*-butyl group, $-C(CH_3)_3$, has nine identical protons and appears as a singlet at about 0.9–1.0 ppm. A broad singlet that integrates to five hydrogen atoms at ~ 7.0–7.2 ppm is usually a monosubstituted phenyl group.

It is also important to know if proton signals are not neighbors. For examples shown in this book, if protons are separated by four or more bonds, they are not neighbors and there is no coupling and therefore *no splitting*. There is such a thing as long-range coupling but *it will not be discussed in this book*. If protons are attached to a heteroatom (e.g., O—H, N—H, or S—H) assume there is no coupling.

The ^{1}H NMR spectrum of 4,4-dimethylhexan-3-one in Figure 13.23 shows that there are two ethyl groups in the molecule. There is a triplet at 0.9 ppm and another triplet at 1.1 ppm and there is a quartet at 1.55 ppm and another quartet at 2.45 ppm. These signals are due to two different ethyl groups and they are distinguished by their chemical shift differences. The downfield shift for methylene protons proximal to a carbonyl should be around 2.4 ppm, whereas protons next to an unfunctionalized carbon should be around 1.5 ppm, using Table 13.5 as a guide for chemical shift. The downfield quartet and triplet is due to the CH_3CH_2—C=O unit. Likewise, the quartet at 1.55 ppm is associated with the upfield triplet and these signals correspond to the $CH_3CH_2C(C=O)Me_2$ unit. Note that the two identical

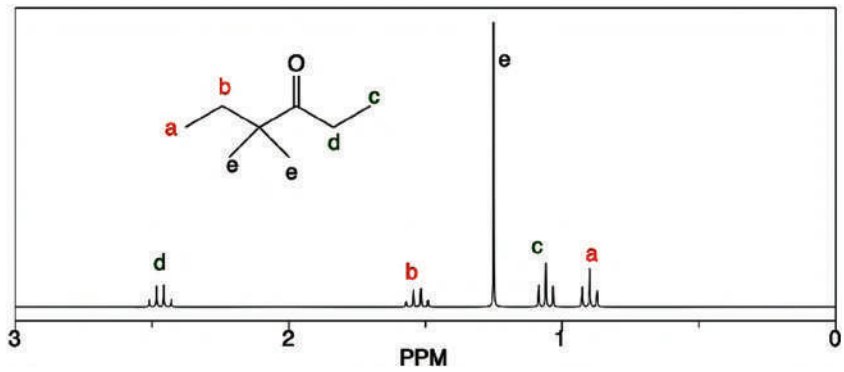


FIGURE 13.23 Distinguishing different ethyl groups in 4,4-dimethylhexan-3-one.

geminal methyl groups (marked *e*) come into resonance as a singlet at ~ 1.5 ppm so they have no neighbors.

13.13 Predict the ^{1}H NMR spectrum for butan-2-one.
13.14 Predict the ^{1}H NMR spectrum for acetophenone (1-phenylethan-1-one).

13.5 IDENTIFYING MONOFUNCTIONAL MOLECULES

Rings or π-Bonds

Structural information is available from the "index of hydrogen deficiency." This analysis is based on the alkane generic formula and there are two types: one for molecules without nitrogen and those for molecules containing nitrogen. The formulas are

$$\Omega_{NoN} = \frac{2(\text{No.C}) + 2 - (\text{No.H}) - (\text{No.Halogen})}{2}$$

$$\Omega_{N} = \frac{2(\text{No.C}) + 3 - (\text{No.H}) - (\text{No.Halogen})}{2}$$

If these formulas are renamed the *"number of rings and/or π-bonds"* in a molecule, a value of one indicates one ring or one π-bond. Knowledge of the number of rings or π-bonds may narrow the choices for a structure when used in conjunction with the IR and ^{1}H NMR data. If there is one ring or π-bond and there is no oxygen or nitrogen, the molecule may be a cyclic alkane or a π-bond may be part of an acyclic alkene. If there is one oxygen, then a value of 1 could indicate ring or an alkene with an alcohol or ether group or the π-bond of a C=O unit (a carbonyl). A value of 2 could mean two C=C units, two C=O units, a C=C and a C=O unit, two rings, or a ring with a C=C or a C=O. A value of 2 could also mean the presence of a triple bond, either C≡C or C≡N depending on whether or not there is a nitrogen in the empirical formula. A value of 3 is indicative of one or two rings and a functional group or two or more functional groups. A value of 4 usually indicates a benzene ring and a value of 8 is consistent with two benzene rings. As the structure becomes more complex the value of this parameter is consistent with many more possibilities so it is less useful.

An unknown can be identified by first obtaining the formula, then using the IR to determine the functional group, and finally using the integration for different types of hydrogen atom, the chemical shift, and the multiplicity obtained from the ^{1}H NMR. The structural fragments obtained from this information can be assembled into a final structure. An analysis of an unknown is shown to illustrate the method.

An unknown with the formula $C_9H_{18}O$ will have one ring or π-bond. With only one oxygen, this molecule must be an alcohol, a ketone, an aldehyde, or an ether. The IR spectral data in Figure 13.24 indicates there is no OH peak, so it cannot be an alcohol. The carbonyl peak a 1609 cm^{-1} correlates with one π-bond. If there is a carbonyl peak it must

be a ketone or an aldehyde, but there is no aldehyde CH peak at 2817 cm^{-1}. Further, the ^1H NMR spectrum does not contain an aldehyde proton between 9 to 10 ppm, so this is a *ketone*. There is a singlet that integrates to nine protons at ~ 0.9 ppm. This signal is consistent with a *tert*-butyl group. There is a methyl group that appears as a triplet, so it has two neighbors as a quartet. That signal is not obvious but there is a multiplet at about 2.4 ppm that could contain four peaks. There is a triplet worth 2H that correlates with a methylene attached to another methylene. That second methylene is also not obvious but could be part of the multiplet at 2.4 ppm. Protons attached to the carbonyl must appear at about 2.14 ppm. Since a 4H signal appears at 2.4 ppm, it is likely that there are two methylene units attached to the carbonyl. The fragments are a $-CH_2CH_3$ unit, a $-CH_2COCH_2-$ unit, and a *tert*-butyl unit. The *tert*-butyl unit must be attached to the $-CH_2CH_2-$ unit since the upfield $-CH_2-$ unit is a triplet and has only two neighbors. Putting the pieces together leads to *6,6-dimethylheptan-3-one*.

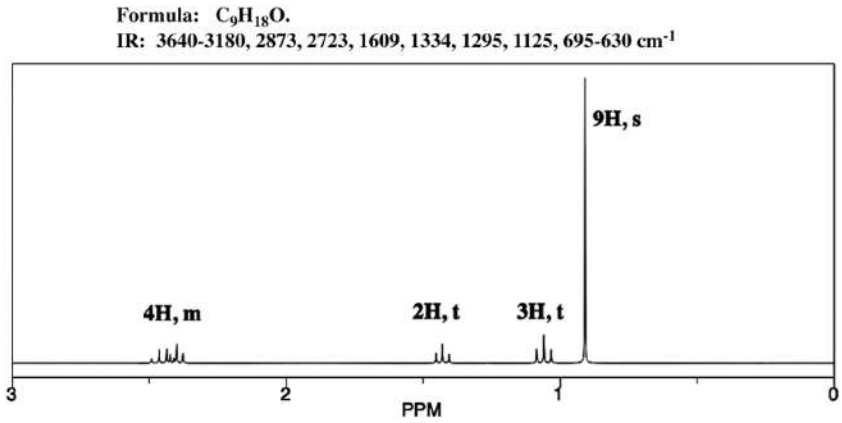


FIGURE 13.24 Spectral data for an unknown with the formula $C_9H_{18}O$.

Carbon-13 NMR

Determine a Structure. Examples 1–3

Determine a Structure. Examples 4–7

13.15 For the formula C_5H_8, determine if there are any rings or π-bonds.
13.16 Are there rings or π-bonds in the molecule with the formula C_3H_9NO?

13.6 CARBON-13 NMR SPECTROSCOPY: COUNTING THE CARBONS

Sections 13.4 and 13.5 focus exclusively on ^1H NMR spectroscopy, but other nuclei with spin = ½ are shown in Table 13.4. One of these is ^{13}C, which accounts for only 1.11% of all carbon atoms. Because ^{12}C is the most abundant isotope, ^{12}C will comprise most of the carbon found in organic molecules. The isotope ^{12}C cannot be used for NMR spectroscopy, however, since it has a spin of zero. The small amount of ^{13}C in a molecule will give an NMR spectra that allows the number and type of carbon atoms in a molecule to be identified. The gyromagnetic constant for ^{13}C is different from that for a ^1H (Section 13.4.1). Therefore, the ΔE is different and the position of the carbon signals is different relative to hydrogen atoms. In other words, signals for ^{13}C appear at a different energy and magnetic field strength relative to signals for ^1H. The low natural abundance of ^{13}C initially made it difficult to detect the absorption peaks but modern computer technology makes ^{13}C NMR a viable and highly useful tool.

As with ^1H NMR, the carbon nucleus absorbs energy (ΔE) within a powerful magnetic field and flips its spin state. This absorption for different carbon atoms is detected and displayed as peaks on a ppm scale. With ^{13}C NMR spectroscopy, the absorption range is 0–220 ppm compared to 0–15 ppm range for most ^1H NMR spectra. The ^{13}C NMR spectrum may be divided into regions where one finds sp^3 carbons, carbons attached to electron withdrawing

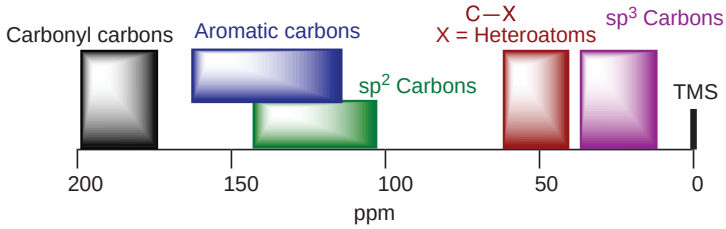


FIGURE 13.25 Structurally different carbon atoms in a typical ^{13}C NMR spectrum.

groups, carbons attached to heteroatoms, sp^2 and sp hybridized carbons, aromatic carbons, and carbonyl carbons. This correlation is shown in Figure 13.25, and this information is used to identify a given type of carbon atom.

14.17 If the ^{13}C NMR spectrum of an unknown molecule shows a signal at 155 ppm, is this consistent with a compound that has a benzene ring? Briefly explain.

A few examples of ^{13}C NMR spectra show the utility of this method. As mentioned, the scale ranges from 0 ppm to ~ 220 ppm relative to TMS in ^{13}C NMR. There is no coupling between adjacent carbon atoms. There is coupling between the hydrogen atoms on carbon that gives rise so a spectrum has many peaks. This coupling makes it difficult to correlate a carbon signal with a structure in a raw ^{13}C NMR spectrum. The ΔE used for proton absorption (^1H NMR) is different from the ΔE used for carbon absorption (^{13}C NMR). To simplify the ^{13}C NMR spectra the entire ΔE region for proton NMR is irradiated, effectively causing all protons to flip their spin states. In other words, all protons are converted from the low energy spin state to the high-energy spin state, so there is no absorption signal for any proton and therefore no coupling with the attached carbon. This action is known as "saturating" the ^1H NMR region and it causes all the proton signals to disappear since all H—C coupling disappears. Therefore, *all carbon signals in ^{13}C NMR appear as singlets.* Because of this experiment, as well as the nature of the ^{13}C NMR signals, the area under each carbon peak does not correspond to the relative number of carbon atoms in the molecule.

Figure 13.26 shows the ^{13}C NMR spectrum for butan-2-one with four carbon signals. Beginning upfield, near the TMS peak at zero, there is a signal at 7.6 ppm that cor-

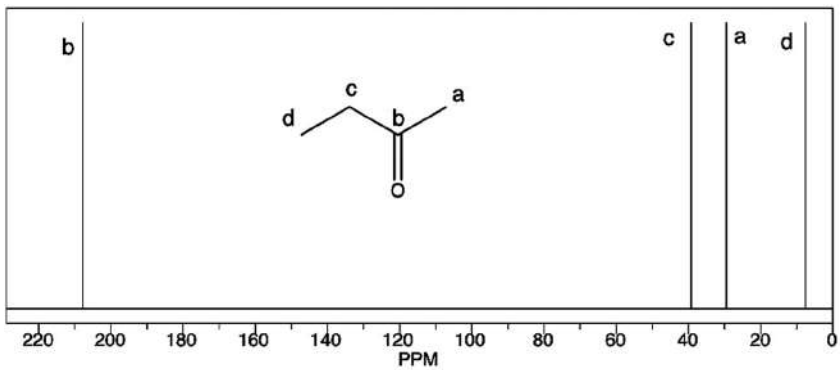


FIGURE 13.26 The **^{13}C** NMR spectrum of butan-2-one.

responding to the methyl group *d*. The signal at 29.5 ppm is also a methyl group that corresponds to carbon *a*. Note that the methyl group closest to the carbonyl is further downfield. The methylene carbon (*c*) appears at 39.3 ppm, and the appearance of methyl groups upfield of methylene groups is common in ^{13}C NMR spectroscopy. In this case, the methylene carbon is further downfield due to its proximity to the carbonyl carbon, but note that it is downfield from the methyl carbon marked *a*. It is anticipated that methine carbons (CH) appear downfield of methylene carbons (CH_2). The carbonyl

carbon *b* is furthest downfield, at 207.7 ppm. This chemical shift is typical for a carbonyl carbon of an aldehyde or a ketone.

Another ^{13}C NMR spectrum is shown in Figure 13.27 for the alkene 3,5-dimethylhex-1-ene. The chemical shifts show a clear distinction between five upfield peaks and two downfield peaks. The downfield peaks are the sp^2 hybridized alkene carbons, with the $=CH_2$ unit at 112.6 ppm and

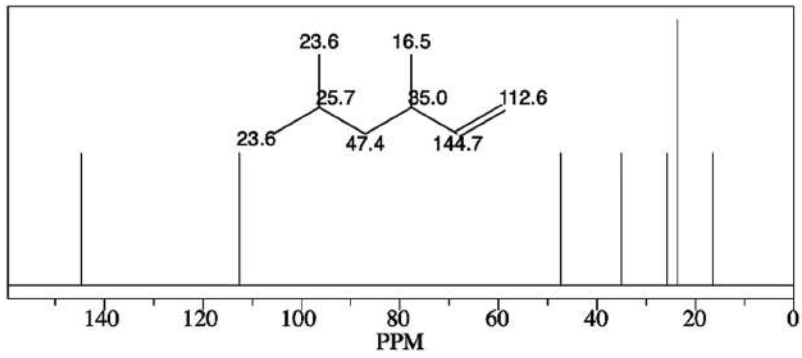


FIGURE 13.27 The ^{13}C NMR spectrum of 3,5-dimethylhex-1-ene.

the C—CH= unit at 144.7 ppm. This downfield shift for alkene carbons is typical, and the more substituted carbon of the C=C unit is further downfield. Note that there are eight carbon atoms in the alkene, but only seven appear. The two identical methyl groups of the isopropyl unit show as a single peak, at 23.6 ppm. The other methyl group appears at 16.5 ppm. It is clear that the aliphatic methyl groups tend to appear further upfield. Note that the two CH units appear at 35.0 and 25.7 ppm for C3 and C5, respectively, whereas the methylene carbon (C4) is at 47.4 ppm. This effect is rationalized by the presence of substituents on neighboring carbon atoms. It is clear that the alkene carbons appear far downfield of the sp^3 carbons, and are usually easy to distinguish.

Carbon-13 NMR spectroscopy is a powerful tool for structural analysis, particularly when it is used in conjunction with ^1H NMR spectroscopy, IR spectroscopy, and MS. There are other NMR spectroscopy techniques that can provide a wealth of information. The objective here is to provide an introduction to spectroscopy, not to give a complete spectroscopy course.

14.18 The empirical formula is C_4H_8O, and the IR and ^1H NMR spectrum are unavailable. The mass spectrum shows a M-15 peak. The ^{13}C spectrum shows peaks at 57.8, 76.8, 136.0, and 118.2 ppm. Is the spectral data provided consistent with $CH_3OCH_2CH{=}CH_2$ or with 2-methyloxetane? Draw both compounds and indicate which molecule is consistent with the ^{13}C NMR.

Two-Dimensional (2D)-NMR

13.7 TWO-DIMENSIONAL (2D)-NMR

Two-dimensional nuclear magnetic resonance spectroscopy (2D NMR) is a NMR method that plots two frequency axes. ^1H-^1H Correlation Spectroscopy (COSY) is one example that shows the correlation between hydrogens that are coupled to each other in the ^1H NMR spectrum. The ^1H spectrum of a molecule is plotted against that identical ^1H spectrum. This plot shows the peak for peak correlation on a diagonal. Those protons with spin-spin coupling show peaks *off the diagonal*. Both 2-bond and 3-bond ^1H-^1H coupling is shown in COSY experiment. A simple example is the COSY experiment for heptan-3-one shown in Figure 13.28.[4] The digonal correlation is marked with a line and the off-diagonal peaks show

[4] Taken from Figure 19, the TOCSY and COSY spectrum of heptan-3-one, in Furoria, N.K.; Furoria, S. *Journal of Analytical & Bioanalytical Techniques, Conference Proceeding*. Open Access. Copyright:© 2013 de Francisco TMG, et al. Copyright:© 2021, OMICS International, an Open Access Publisher. All Rights Reserved. www.omicsonline.org/structural-elucidation-of-small-organic-molecules-by-1d-2d-and-multi-dimensional-solution-nmr-spectroscopy-2155-9872.S11-001.php?aid=12051.

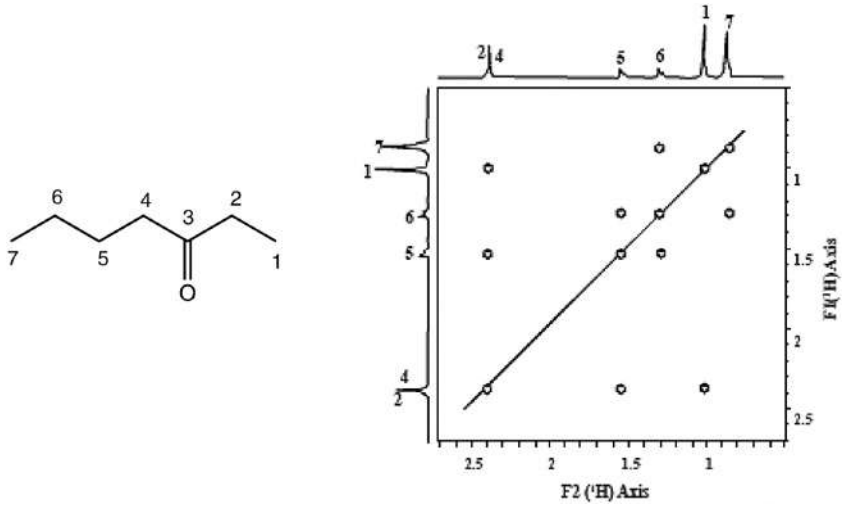


FIGURE 13.28 COSY of heptan-3-one.

the coupling information. If a peak off the diagonal is parallel to a peak on the diagonal, as seen for peak 1 and peak 2, those protons are coupled. The COSY correlations show that peak 4-peak 5, peak 5-peak 6 and peak 6-peak 7 protons are coupled but the peak 4-peak 7 protons and the peak 5-peak 7 protons are not. Good structural information is provided, especially for complex molecules.

There are other 2D experiments, including Total Correlation Spectroscopy (TOCSY) and Nuclear Overhauser Effect Spectroscopy (NOESY). The TOCSY experiment shows correlations between all protons within a given spin system, not just the 1,2- or 1,3- related protons as in COSY. Correlations are seen between distant protons as long as there are couplings between every intervening proton. The NOESY experiment can show signals that arise from protons that are close to each other in space even if they are not bonded

13.8 BIOLOGICAL RELEVANCE

Structural information for large enzyme/inhibitor complexes can be obtained from proton NMR spectra. The spectra are simplified by isotope-editing procedures. Only those protons that are attached to isotopically labeled nuclei (e.g. ^{13}C or ^{15}N) and their scalar or dipolar coupled partners are observed. In addition, two-dimensional Nuclear Overhauser Effect (2D NOE) difference spectra can be obtained by subtracting NOE spectra of two enzyme/inhibitor complexes prepared with either a protonated or a deuterated inhibitor. Only NOEs arising from protons of the inhibitor substituted with deuterium appear in the 2D NOE difference spectra. Deuterated enzymes can be used to eliminate the many proton NMR signals of the enzyme and allow the selective detection of the resonances corresponding to the bound ligand. Heteronuclear three-dimensional NMR spectroscopy in which homonuclear 2D NMR spectra are edited with respect to the heteronuclear chemical shifts. With these methods the complete three-dimensional structures of large enzyme/inhibitor complexes can be obtained.

Proteomics

Proteomics is a broad field but it often refers to the large-scale experimental analysis of proteins and proteomes. The term is often is used specifically to refer to protein purification and to mass spectrometry (MS) techniques that are useful for protein profiling. One mass spectrometry method uses high resolution, two-dimensional electrophoresis to separate proteins from different samples in parallel. This is followed by selection and staining of differentially expressed proteins to be identified by mass spectrometry. Electrophoresis is the movement of charged particles in a fluid or gel under the influence of an electric field. However, this mass spectrometry method is not very useful to resolve all the proteins within a sample. A different approach uses stable isotope tags to differentially label proteins from two different complex mixtures. The proteins within a complex mixture are labeled and

then digested to yield labeled peptides. The labeled mixtures are combined, the peptides separated by multidimensional liquid chromatography and analyzed by tandem mass spectrometry. Peptide mass mapping or mass fingerprinting compares the experimentally determined mass spectrometric peak mass values with the predicted molecular mass values of the peptides generated by a theoretical digestion of each protein. Collision-induced dissociation (CID) spectra of individual peptides from MS/MS relies on database searching. Searches are based on comparisons between the experimentally observed fragment ions and all predicted fragments for all hypothetical peptides of the appropriate molecular mass, based on known fragmentation rules. Each peptide match can be linked to a protein match. The greater the number of peptides being matched to any one protein and the greater the sequence coverage, the greater the probability of a correct identification. When a protein is not in a database, *de novo* peptide sequencing is used, based on known rules for peptide fragmentation.

Infrared imaging, or thermal imaging, has been used to study a number of diseases where skin temperature can reflect the presence of inflammation in underlying tissues. It is also used to show that blood flow is increased or decreased due to a clinical abnormality.[5] The examples in Figure 13.29[5] include an image in which the left foot shows inflammation due to a sports injury. The second image in Figure 13.29 shows an image of the knees of a patient with rheumatoid arthritis in the right leg.

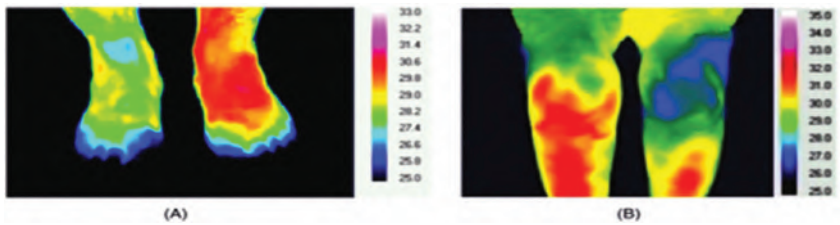


FIGURE 13.29 Infrared images showing (*A*) chronic inflammation of the forefoot following a sports injury (*B*) rheumatoid arthritis of one knee. (Reprinted with permission from Figure 3, Ring, E.F.J.; Ammer, K. *Physiological Measurement*, 2012, 33, R33). Creative Commons license: "© Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved."

A biological application of NMR spectroscopy is known as magnetic resonance imaging (MRI). When a MRI is taken of a person, or a part thereof, the result is a high quality image of the inside of the human body. The MRI of a human brain is shown in Figure 13.30. This

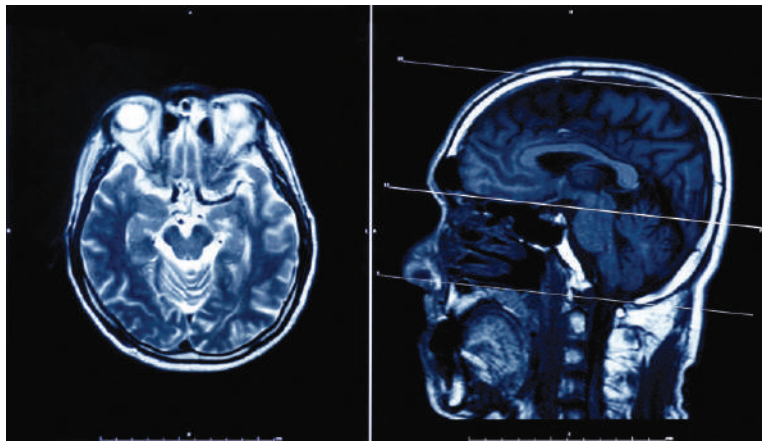


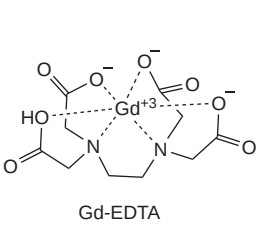
FIGURE 13.30 Magnetic resonance image (MRI) of a human brain. Reprinted from Shutterstock photo ID: 1379585096.

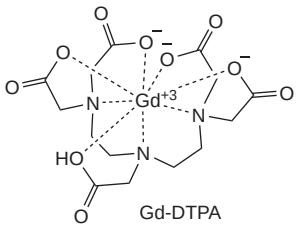
[5] Ring, E.F.J.; Ammer, K. *Physiological Measurement* 2012, 33, R33–R46.

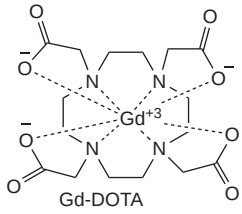
noninvasive technique is a great help to medicine. In many cases, examination of human tissue is complicated because it may be difficult to distinguish one tissue type from another, however, or to bring out detail for one organ or tissue type.

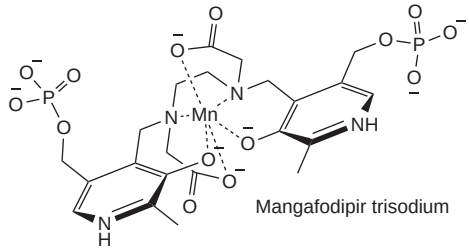
As noted, there are some problems associated with MRI scans. The difference between a cancerous tumor and normal brain tissue may be so small that detection of the tumor may be difficult by MRI. Chemicals that are injected into a patient make it easier to distinguish tissue types. These are known as *contrasting agents*. They typically make one or more tissue types appear brighter and lead to greater contrast. Alternatively, a tissue may appear darker, so there is significant contrast. Some typical contrast agents[6] are Gd-EDTA, Gd-DTPA, and Gd-DOTA. *Gadodiamide* is useful for imaging the central nervous system. *Mangafodipar trisodium* is used for lesions of the liver. Note that the organic fragments of the contrast agents are amino acid derivatives (Section 24.3), phosphates or amides (Sections 18.2 and 18.9). These compounds include ferric ammonium citrate (sold commercially as Geritol), which is used to image the stomach and upper small intestine.

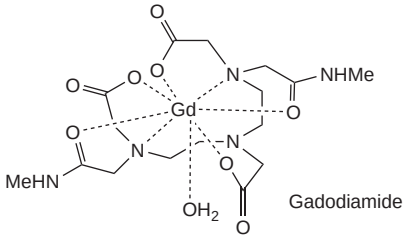
Most contrasting agents are an organic complex of a paramagnetic metal ion (e.g. gadolinium, Gd and Gd^{3+} compounds, ferric compounds, Fe^{3+}, or manganese compounds, Mn^{2+}).[7] Heavy metals are often toxic, but complexation with other molecules or ions often diminishes the toxicity and facilitates clearance of those metals from the body. If one tissue type complexes the metal more than another, that tissue type (or organ) "stands out" from the background. Most tumors, for example, have a greater Gd uptake than the surrounding tissues, leading to a stronger signal since the tumor stands out from the background.[8]











CORRELATION OF HOMEWORK WITH CONCEPTS

- Mass spectrometry bombards a molecule with 70 eV of energy, which leads to formation of a radical cation called the molecular ion. Fragmentation of leads to daughter ions. Determining the mass of lost fragments can assist in structure determination, which is called: 1, 20, 22, 23, 28, 34, 35, 36.
- The M+1 and M+2 isotopic peaks can be used to determine an empirical formula: 2, 3, 19, 21.
- Use the empirical formula to determine the number of rings and/or π-bonds as a prelude to looking for the functional group: 15, 16, 19.
- Absorption of IR light leads to molecular vibrations, and observation of the effects of IR radiation of the molecular vibrations induced by IR light is called IR

[6] Hornak, J.P. *The Basics of MRI*, an online book, 2008. In Chapter 12.
[7] Rajan, S.S. *MRI. A Conceptual Overview*, Springer, New York, 1998, p. 66.
[8] Hornak, J.P. *The Basics of MR*I, an online book, 2008. In Chapter 1.

spectroscopy. Matching peaks in the IR spectrum with functional group correlation tables allows one to determine the presence or absence of functional groups in an organic molecule: 4, 5, 6, 24, 29, 36.

- When an organic molecule is placed in a powerful magnetic field, the nucleus of each hydrogen atom behaves as a tiny magnet and the small magnetic field interacts with radio signal and the resulting absorption of energy is called nuclear magnetic resonance (NMR) spectroscopy: 7, 8, 9, 26, 30, 31, 33.
- π-Bonds react to an applied magnetic field by developing a small opposing local field that orients a molecule in a large magnetic field. This interaction is called magnetic anisotropy: 32.
- Neighboring protons split a proton signal into *n*+1 peaks called multiplicity: 10, 11, 12, 27.
- Carbon-13 NMR spectroscopy can be used to count and classify the number of different carbon atoms in an organic molecule: 17, 18, 25.
- Mass spectral data, infrared and NMR data can be used to identify organic molecules: 13, 14, 36, 37, 38, 39, 40, 41, 42.

ANSWERS TO IN-CHAPTER QUESTIONS

13.1 Hexane has a formula of C_6H_{14} and a molecular ion at *m/z* 86. Pentan-3-one is $C_5H_{10}O$ and a molecular ion at *m/z* 86. Diethyl ether is $C_4H_{10}O$ and a molecular ion at *m/z* 74.

13.2 For butan-2-one, with a formula of C_4H_8O, the parent ion will appear at *m/z* 72 and that will be taken as 100%. Since there are 4 carbons and zero N, M+1 = 1.11 (4) = 4.44. The M+2 is $\frac{4.44^2}{200} + 0.2$ (for 1 O) = 0.30. For triethylamine, with a formula of $C_6H_{15}N$, the parent ion will appear at *m/z* 101 and will be taken as 100%. There are 6 carbons and 1 N, so M+1 = 6 (1.11) + 0.38 = 7.04. There are zero oxygen atoms so M+2 = $\frac{6.66^2}{200} = 0.22$.

13.3 Since the mass of the parent is 126, it is even and there are assumed to be zero N. Taking the M+1 signal, No. C = $\frac{8.88}{1.11} = 8$. Using this in the M+2 we find that $\frac{8.88^2}{200}$ = 0.39. Since M+2 = 0.59, assume there is an oxygen so the number of O = $\frac{0.59 - 0.39}{0.2}$ = 1, or C_8O = 112. Since the molecular ion is 126, the number of H atoms is obtained by difference = 126 - 112 = 9. Therefore, the formula is $C_8H_{14}O$.

13.4 The stronger C≡C bond will have the larger force constant and it will require more energy for vibration. Therefore, the C=C bond will absorb at lower energy.

13.5 Acetone is completely miscible with water so it rapidly absorbs water. Therefore, washing KBr or NaCl plates with acetone will bring water into contact with these water soluble salts. The result will be etching and/or pitting of the plates making them unusable for IR spectroscopy. The pressed salt plates should be washed only with solvents that do not contain water.

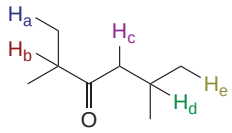
13.6 The C=O bond is stronger than the C—O bond, requiring greater energy for it to vibrate. Therefore, it absorbs at higher energy than the C—O bond.

13.7 Since the spin = ½, there are two orientations and one signal per ^{13}C nucleus.

13.8 The ppm for this signal is determined by ppm = $\frac{438}{500 \times 10^6} = 0.876 \text{x} 10^{-6} = 0.876$ ppm.

13.9 The ratio is taken to be $\frac{71.5}{28.6} + \frac{28.6}{28.6} + \frac{42.9}{28.6} = 2.5{:}1{:}1.5$. This sum adds up to 5 protons. Since the formula indicates that 10 protons are present, multiply this ratio by 2 to obtain 5:2:3. There are three different kinds of hydrogen atoms in this molecule, 5 of one kind, 2 of a second kind, and 3 of a third kind.

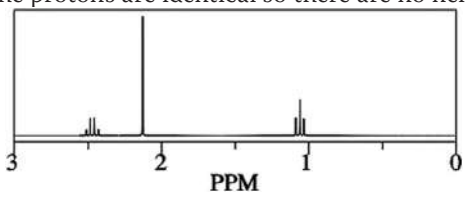
13.10 In 2,5-dimethylhexan-3-one, there are five different kinds of protons, labeled H_a-H_e in the figure below. The six methyl protons H_a and the single proton H_b are neighbors. The methylene protons H_c and proton H_d are neighbors, but H_d is also neighbors with the six methyl protons H_e.



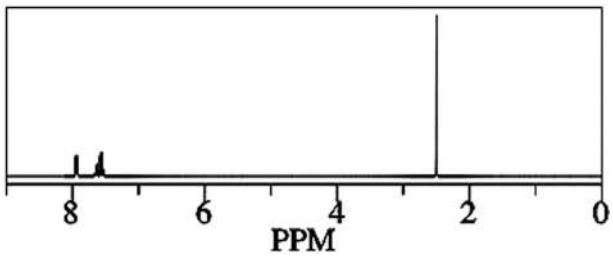
13.11 Quartet; quartet; triplet.

13.12 Singlet. All of the protons are identical so there are no neighbors.

13.13



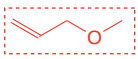
13.14



13.15 The rings or π-bonds is $\frac{2\times3+2-7-1}{2} = 0$. Therefore, there are no rings or π-bonds.

13.16 The rings or π -bonds is $\frac{2\times3+3-9-0}{2} = 0$. Therefore, there are no rings or π-bonds.

13.17 According to Figure 13.36, a signal at 155 ppm is in the range where aromatic carbon are observed, so it is consistent with an unknown compound that has a benzene ring.

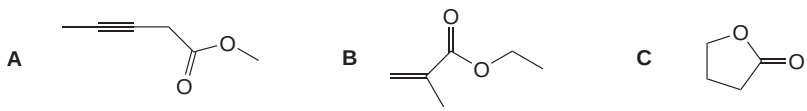
13.18 The signals at 118 and 136 ppm are indicative of a C=C unit  vs  The oxetane has no signals related to the C=C signals

HOMEWORK

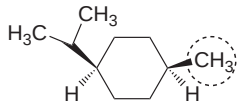
19. Given the following molecular ion region data, determine a formula for each structure. For each formula, calculate the number of rings and/or double bonds.
    (a) M (100) 100% M+1 (101) 6.66% M+2 (102) 0.42%
    (b) M (149) 100% M+1 (150) 11.46% M+2 (151) 0.62%
    (c) M (96) 100% M+1 (97) 7.77% M+2 (98) 0.30%
    (d) M (96) 100% M+1 (97) 6.66% M+2 (98) 0.42%
20. Draw the molecular ion region expected for bromomethane, including *m/z* values and % relative to M.
21. A M:M+1 ratio in a mass spectrum was 100:24. How many carbon atoms are present?

22. Draw the structure for the radical cation formed from pentan-3-one in the mass spectrum. Put the radical and positive charge on appropriate atoms. Draw the daughter ion resulting from cleavage of the X—C^{α} bond and also from the C^{α}—C^{β} bond, where X = C=O.
23. Below is an IR spectrum of a compound that is known to have either structure **A** or **B**. The experimental IR is 3100–3650, 2150–2950, 1657, 1450, 1256, and 920 cm^{-1}. Which structure is *not* consistent with the spectrum? Why?

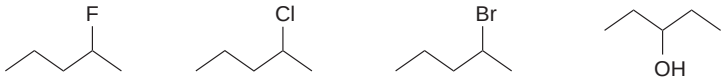
24. The ^{13}C NMR spectrum of a compound that is known to have peaks at 15, 62**,** 128 132 and 167 ppm. and structures **A**, **B**, or **C**. Which structure is consistent with the spectrum? Why?



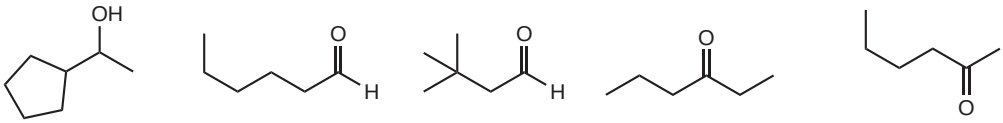
25. Two signals in the ^{1}H NMR spectrum appears at 345 and 350 Hz in a 60-MHz field. Calculate the position of both signals *in hertz* in a 270-MHz instrument. In a 600-MHz instrument. Calculate the position of these signals in ppm.
26. Careful analysis of the ^{1}H NMR spectrum of the molecule shown, obtained at -50 °C, indicates that there are two different doublets for the circled methyl group. Offer an explanation.



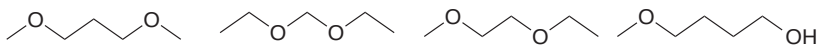
27. Which of the following structures are consistent with a mass spectrum having a M+2 = 98% of M. Explain.



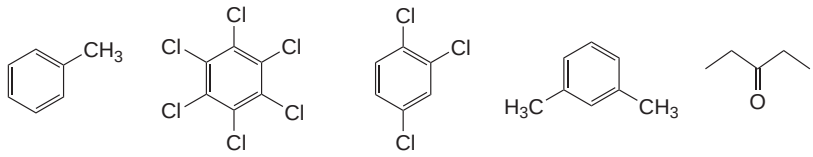
28. A molecule with a formula $C_6H_{12}O$ shows a strong peak at 1725 cm^{-1} and another weaker peak at 2815 cm^{-1}. Which of the following are structures consistent with the data? Briefly explain each choice.



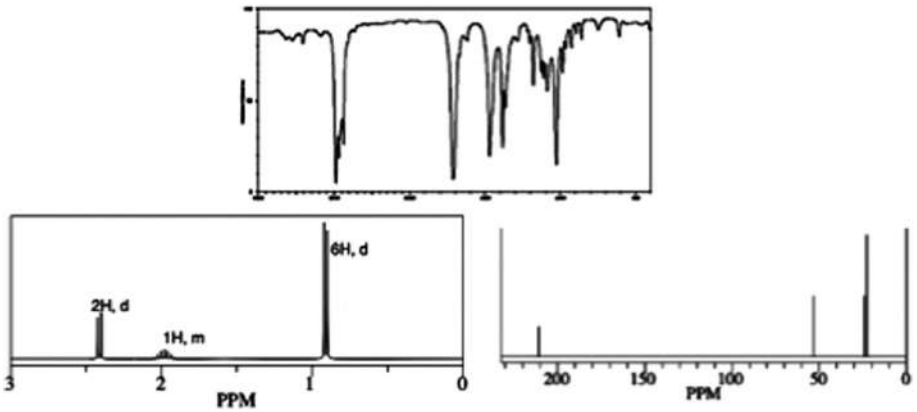
29. One of the four structures shown exhibits a singlet at 5.9 ppm, as well as a triplet at 1.0 ppm and a quartet at 3.5 ppm. Which molecule that is consistent with this ^{1}H NMR? Explain your choice.



30. Which of the following molecules are expected to show *no peaks* in the 7 to 8 ppm region of a ^{1}H NMR spectrum:



31. (a) Briefly explain why the proton for ethene absorbs at ~ 5.4 ppm in the ^{1}H NMR spectrum whereas the proton for ethyne absorbs ~ 2.3. (b) Briefly explain why the H of the aldehyde H—C=O unit appears at ~ 9.4 ppm whereas the H of the alcohol H—C—O appears ~ 3.5 ppm in the ^{1}H NMR spectrum.
32. Which of the following solvents can be used as a solvent in ^{1}H NMR spectrum? Explain.
    CH_3OH D_2O $CDCl_3$ CH_2Cl_2 CCl_4
33. Which of the following atoms contribute to the M+1 signal in the mass spectrum?
    ^{1}H ^{13}C ^{34}S ^{35}Cl ^{81}Br ^{3}H
34. At what *m/z* does the molecular ion for C_5H_9Cl appear? Explain.
    104 105 106 107
35. There are two bottles (A and B), but the labels have fallen off and been lost. One is pentan-3-one and the other is methyl butanoate. A mass spectrum and an IR spectrum of each help determine their identity. Describe how to distinguish A and B.
36. Give the structure for the molecule with a formula of $C_9H_{18}O$ and the following spectra:



37. Give the structure for the molecule with the following spectra: MS: M(164) 100% M+1(165) 12.21% M+2(166) 0.945%. The molecular ion is rather weak, with prominent ions at *m/z* 146 and *m/z* 77. IR: 3050, 3000–3860, 1460 cm^{-1}. ^{1}H NMR: 7.54-7.38 (broad s, 5H), 3.65 (s, 1H; diminished when treated with D_2O), 1.77 (q, 4H), 0.90 (t, 6H) ppm. ^{13}C NMR: 128.8, 128.1, 126.0, 144.4, 78.6, 34.2, 7.8 ppm.
38. Give the structure for the molecule with the following data: M(214) 51.4% M+1(215) 2.3% M+2(216) 100 % M+3 (217) 4.4% M+4 (218) 48.7%. IR: 2980-2950, 2868, 1460, 1380, 1157, 1099, 652 cm^{-1}. ^{1}H NMR: 4.01 (m, 1H), 1.79 (d, 3H) ppm. ^{13}C NMR: 53.9, 22.7 ppm.
39. Give the structure for the molecule with formula C_6H_{10} and the following spectra:
    IR: 2964-2840, 2054, 1465 1456, 1436, 1380, 1340 cm^{-1}. ^{1}H NMR: 2.08 (2H, t), 1.78 (3H, s), 1.50 (2H, m), 0.97 (3H, t) ppm. ^{13}C NMR: 3.42, 13.6, 20.9, 22.7, 75.5, 79.2 ppm.
40. Give the structure for the molecule with the formula C_4H_7N and the following spectra:
    IR: 2986-2881, 2248m, 1476, 1460, 1372, 1323, 1175, 1106 cm^{-1}. ^{1}H NMR: 2.84 (m, 1H), 1.36 (d, 6H) ppm. ^{13}C NMR: 123.83, 20.0, 19.87 ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-14.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

14

Organometallics

Thus far, the organic molecules discussed contain carbon, hydrogen, halogen, nitrogen, oxygen, or sulfur atoms. Many other elements form bonds to carbon, including mercury (Section 10.7) and copper (Sections 11.4 and 11.8). Compounds such as this are important examples of a class of compounds known as *organometallics*. They are organic molecules that incorporate one or more metal atoms. Other important organometallic compounds are discussed in this chapter.

To understand this chapter, you should understand

- Group 1 and 2 metals, as well as group 11 and 12 metals (general chemistry).
- Functional groups with polarized covalent bonds (Sections 3.8, 5.5, and 5.6).
- Alkyl halides (Section 4.3.3).
- Bond polarization and electronegativity (Sections 2.4 and 3.8).
- Acids and Bases (Sections 2.1–2.3, 2.7, 6.2–6.4, 6.7, and 6.8).
- Nucleophiles (Sections 6.9 and 11.2–11.4).
- Intermediates (Section 7.2).
- Radical chemistry (Sections 11.2 and 11.3).
- S_N2 reactions (Sections 11.1 and 11.2).
- Chirality and stereogenic centers (Sections 9.1 and 9.2).

14.1 ORGANOMAGNESIUM COMPOUNDS

Grignard Reagents

Useful organometallic compounds are formed by the reaction of alkyl halides with the alkali metals Na, Li and Mg in groups 1 and 2. *Organomagnesium reagents* are important examples. Magnesium reacts directly with an alkyl halide $R_3C—X$ (X = Cl, Br, or I) to yield R–Mg–X, an organomagnesium halide in an ether solvent. The organometallic shown in Figure 14.1 is known as a *Grignard reagent*, named after Nobel laureate Françoise Auguste Victor Grignard (France; 1871–1935) who prepared and characterized these compounds. In a subsequent reaction, a Grignard reagent reacts with a ketone or an aldehyde in what is now called a *Grignard reaction*, discussed in Section 16.2. The work of Grignard is derived from earlier work by Philippe Antoine Barbier (France; 1848–1922), who studied similar reactions. Barbier reacted magnesium, an alkyl halide and a ketone or aldehyde all in the same flask and isolated an alcohol product but did not fully understand product formation (Section 16.3). Grignard took this work further and discovered how and why the reaction worked. Alkyl halides have a polarized $^{\delta+}C—X^{\delta-}$ bond. The dipole in bromoethane is $^{\delta+}C—Br^{\delta-}$, for example. The reaction with magnesium metal gives a Grignard reagent with a C—Mg—X bond. *Carbon is more electronegative than magnesium, so* carbon is δ^- and magnesium is δ^+ as shown in Figure 14.1. This bond polarization means that carbon can function as a base or a nucleophile.

Formation of a Grignard reagent is facile in the presence of an ether solvent (e.g., diethyl ether or THF). The oxygen of the ether can react as a Lewis base and forms a Lewis acid-Lewis base coordination complex with the magnesium, **1**, as shown in Figure 14.2. This coordination facilitates insertion of magnesium into the C—X bond. Once formed, **1** donates one electron to the halogen atom (X) in the alkyl halide (R—X) to form a radical cation (•+), **2**.

DOI: 10.1201/9781003174929-14

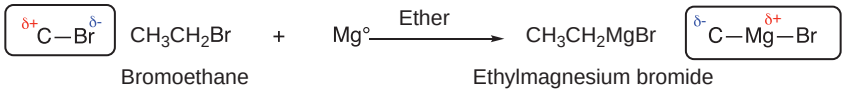


FIGURE 14.1 The reaction of bromoethane and magnesium and bond polarization in ethylmagnesium bromide.

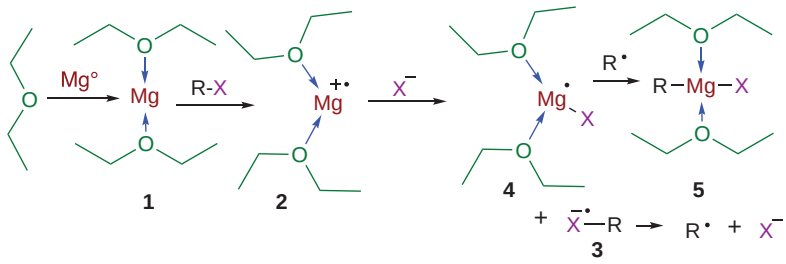


FIGURE 14.2 The mechanism of Grignard reagent formation.

The ether solvent coordinates and stabilizes this radical cation and all radical intermediates. Electron donation to the halogen atom (X) generates a radical anion (•-), **3**, which dissociates to yield a carbon radical, R• and X^-. A Mg—X bond is formed when X^- and **2** react with each other. The $Mg^{\bullet+}$ in **2** reacts with the electron-rich X^- to form radical (**4**). Subsequent reaction of **4** with the carbon radical (R•) gives the Grignard reagent (**5**). Ether stabilizes the C—Mg—X bond. This conversion of an alkyl halide to a Grignard reagent is called a *metal insertion reaction*. The sequence shown in Figure 14.2 is believed to be the *mechanism* of Grignard reagent formation from alkyl halides.[1]

14.1. Draw the product formed when diethyl ether reacts with BF_3.
14.2. Draw the Grignard reagent formed when 3-bromo-3-ethylheptane reacts with magnesium metal in diethyl ether.

Structure of Grignard Reagents

The structure of Grignard reagents is not as simple as the structure RMgX suggests. Depending on the solvent, Grignard reagents exist as an *equilibrium mixture* of several organometallics. For the reaction of bromomethane and magnesium this mixture includes the starting halide as well as the alkylmagnesium bromide RMgX, a dialkylmagnesium compound R_2Mg, and two dimeric forms, as shown in Figure 14.3. In addition, some trimeric forms exist in low concentrations, but they are not shown. This equilibrium mixture

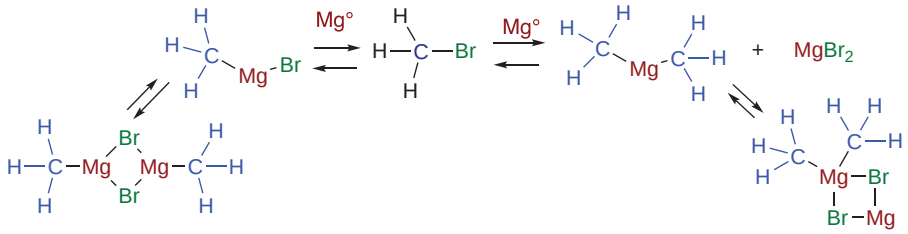


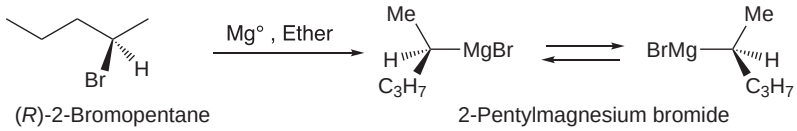
FIGURE 14.3 Schlenk equilibrium for a Grignard reagent.

is called the *Schlenk equilibrium* and it constitutes a more complete representation of the "Grignard reagent" formed when an alkyl halide reacts with magnesium. The position of this equilibrium depends on the solvent. In ether solvents, the alkylmagnesium reagent RMgX predominates so this representation is used when discussing Grignard reagents. This equilibrium is named after Wilhelm Johann Schlenk (German; 1879–1943), who discovered this

[1] Smith, M.B. *March's Advanced Organic Chemistry*, 8th ed. Wiley-Interscience, Hoboken, NJ, 2020, pp. 550–554.

equilibrium. Note that Schlenk is credited as the discoverer of organolithium reagents, discussed in Section 14.3.

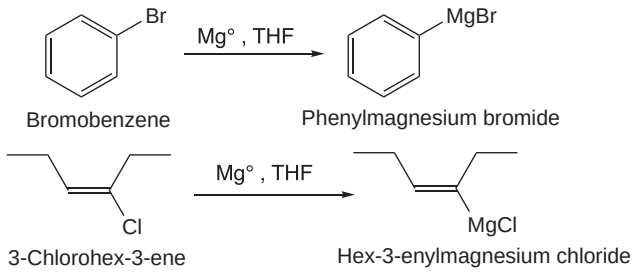
The Schlenk equilibrium suggests that attachment of the Mg to carbon is not fixed with respect to the C—Mg bond. Indeed, when a chiral, nonracemic halide such as (2*R*)-bromopentane reacts with magnesium metal to give the Grignard reagent, the product is *racemic* 2-pentylmagnesium bromide. Grignard reagents such as 2-pentylmagnesium bromide formed from (*R*)-2-bromopentane exist as an equilibrating mixture of both (*R*) and (*S*) enantiomers, a racemic mixture. In other words, the stereogenic center of any chiral alkyl halide is lost during the reaction and the resulting Grignard reagent is racemic.



(*R*)-2-Bromopentane 2-Pentylmagnesium bromide

14.3 Draw the product of a reaction of (2*S*)-iodo-5,5-dimethylhexane and Mg, in diethyl ether.

Virtually any alkyl halide reacts with Mg to form the corresponding Grignard reagent in the presence of an ether solvent, including vinyl halides (Section 10.8.1) and aryl halides (halogen connected to a benzene ring; Sections 19.2.2 and 19.3.1). It is more difficult for the magnesium to insert into the C—X bond of these sp^2 carbon substrates.



Bromobenzene Phenylmagnesium bromide

3-Chlorohex-3-ene Hex-3-enylmagnesium chloride

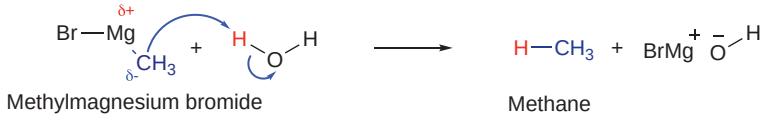
In addition, these Grignard reagents are less stable than those from aliphatic alkyl halides so more stabilization is required from the solvent. For this reason, the most commonly used solvent is tetrahydrofuran (THF). In THF the electrons on oxygen are more available for donation than in diethyl ether, so THF is a stronger Lewis base than diethyl ether. When bromobenzene and Mg react in THF the product is phenylmagnesium bromide. Vinyl halides also react with magnesium in THF. 3-Chlorohex-3-ene gives the vinyl Grignard reagent hex-3-enylmagnesium chloride.

14.4 Draw the structure of the products formed by the reaction of 4-phenyl-1-bromobenzene and Mg, in THF.

14.2 GRIGNARD REAGENTS ARE BASES AND NUCLEOPHILES

Grignard Reagents Are Strong Bases

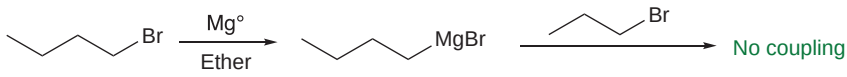
A Grignard reagent is a powerful Brønsted-Lowry base because the carbon of the C—Mg—X unit is polarized δ^-. The base strength can be ascertained by examining the conjugate acid derived from the Grignard reagent base, which is an alkane. An alkane is a remarkably weak acid, so the Grignard reagent is a remarkably strong base.



Methylmagnesium bromide — Methane

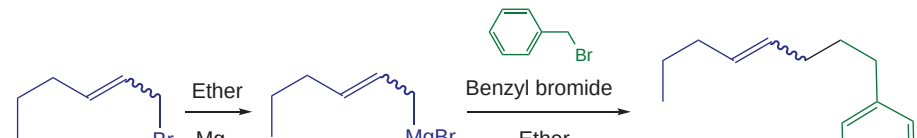
Indeed, water, alcohols, terminal alkynes, and even amines react with a Grignard reagent to form the corresponding conjugate base and an alkane as the conjugate acid. As an example, methylmagnesium bromide reacts with water to form methane (the conjugate acid) and the bromomagnesium hydroxide ion (BrMgOH). Grignard reagents also react with alcohols and carboxylic acids. These acid-base reactions are much faster than any other reaction that is possible for a Grignard reagent. Therefore, a Grignard reagent must be prepared in an aprotic solvent and once formed it must be kept away from water, alcohols, or any acid.

14.5 Draw the conjugate base formed when a Grignard reagent ($CH_3CH_2CH_2MgX$) reacts with (a) water, (b) methanol, (c) prop-1-yne, or (d) dimethylamine.



1-Butylmagnesium bromide

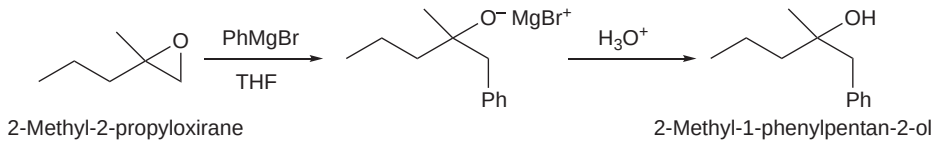
A Grignard reagent has a δ^- carbon atom so in principle it may react as a carbanion nucleophile. An attempted S_N2 coupling reaction of 1-butylmagnesium bromide and 1-bromopropane, however, does *not* give the coupling product heptane. In fact, a Grignard reagent derived from an alkyl halide decomposes or reacts in other ways, but it gives no or a poor yield of coupling product in an S_N2 reaction with a simple aliphatic halide. However, Grignard reagents generated from particularly reactive halides such as benzylic or allylic halides do react, but only with particularly reactive benzylic or allylic halides to give a coupling reaction. If the Grignard reagent derived from 1-bromohex-2-ene reacts with benzyl bromide, for example, the product is 1-phenyloct-4-ene. Assume that all but highly reactive Grignard reagents do *not* yield coupling products. Note that aryl Grignard reagents and vinyl Grignard reagents are *less* reactive than Grignard reagents derived from aliphatic halides.



1-Bromohex-2-ene — Hex-2-enyl-1-magnesium bromide — 1-Phenyloct-4-ene

14.6 Draw the product formed when 1-bromo-3-methylbut-2-ene reacts with Mg in ether, and then reacts with 1-bromo-3-methylpent-2-ene.

Grignard reagents are very reactive with other electrophilic substrates, such as aldehydes or ketones (Sections 16.2 and 16.3) or epoxides (oxiranes; Section 15.3.2). Epoxides are three-membered ring ethers. Due to significant ring strain, they are very reactive with nucleophiles (Section 11.6.2). The reaction of Grignard reagents with epoxides proceeds more or less by an S_N2 type process. Therefore, they react with epoxides at the less sterically hindered carbon atom. The reaction of phenylmagnesium bromide and 2-methyl-2-propyloxirane, for example, generates an alkoxide product. An aqueous acid workup converts the alkoxide to the conjugate acid, and final product, 2-methyl-1-phenylpentan-2-ol.

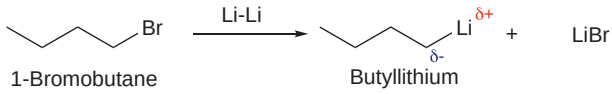


2-Methyl-2-propyloxirane 2-Methyl-1-phenylpentan-2-ol

14.3 ORGANOLITHIUM REAGENTS

Organolithium Reagents

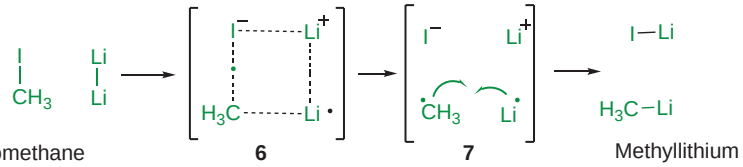
Lithium is a Group 1 alkali metal that reacts with alkyl halides to form an organometallic compound. Virtually any alkyl halide R—X reacts with lithium metal to form an *organolithium reagent* (RLi)[2] and LiX. An example is the reaction of 1-bromobutane to form the organometallic known as butyllithium or 1-lithiobutane, where lithium has replaced bromine. Note that lithium metal exists primarily as dilithium, Li_2. The C—Mg—X bond of a Grignard reagent is the result of the bivalent (forms two bonds) magnesium which is in group 2. Lithium is in group 1 and is monovalent (forms one bond), so an organolithium reagent forms a C—Li bond.



1-Bromobutane Butyllithium

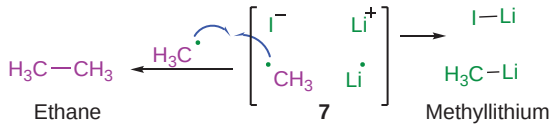
The C—Li bond is polarized with a δ^- carbon and a δ^+ lithium because carbon is more electronegative than lithium. This reaction should be done in aprotic solvents such as diethyl ether or hexane. A primary organolithium reagent is more stable than a secondary or tertiary organolithium reagent. In other words, a tertiary organolithium reagent is much more reactive than the secondary organolithium, which is more reactive than primary organolithium reagents.

The reaction that forms an organolithium reagent (an alkyllithium) proceeds by a slightly different mechanism when compared to the formation of a Grignard reagent. The mechanism of the reaction of iodomethane with lithium metal is shown and the products are LiI and CH_3Li (methyllithium). This mechanism is taken to be the generalized mechanism for the reaction of Li metal with any alkyl halide. When the polarized C—I bond of iodomethane comes close to the Li dimer it polarizes Li—Li and initiates the reaction. The transition state of the reaction is taken to be **6**.



Iodomethane 6 7 Methyllithium

The Li—Li bond breaks with transfer of only one electron to carbon (*homolytic cleavage*; remember that Li is in group 1). This cleavage gives a methyl radical ($\bullet CH_3$) and a lithium radical (•Li), as well as a Li cation and an iodine anion (see **7**). The methyl radical and the lithium radical each donate a single electron to form the organolithium reagent (methyllithium; abbreviated MeLi) and lithium iodide (LiI). The halogen (iodide) and one lithium atom (Li) interchange by this *single electron-transfer mechanism*. It is a *metal-halogen exchange* reaction. The "single-headed" arrows indicate transfer of one electron.



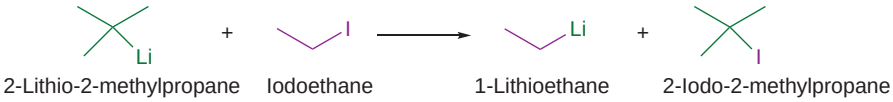
Ethane 7 Methyllithium

[2] Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon, Oxford, UK, 1974.

Since this reaction proceeds via a radical intermediate (•CH_3 in **7**), there is a side reaction in which the two radicals can react via donation of one electron to form a new σ-bond in what is known as *radical coupling*. Apart from coupling of •CH_3 with •Li to form CH_3Li, •CH_3 may couple to another methyl radical to generate ethane (CH_3CH_3), as shown. Radical coupling of two alkyl radicals to form an alkane in the presence of a metal is called *Wurtz coupling*, named after Charles-Adolphe Wurtz (France; 1817–1884). Wurtz coupling often accompanies reactions of Li metal. In the reaction of bromobutane with lithium metal to form *n*-butyllithium, for example, coupling of two butyl radicals leads to octane as a byproduct. Common organolithium reagents such as methyllithium, *n*-butyllithium, *secondary*-butyllithium (also known as *sec*-butyllithium; the correct name is 2-lithiobutane), and *tert*-butyllithium (2-lithio-2-methylpropane) are sold commercially for use as reagents in other chemical reactions.

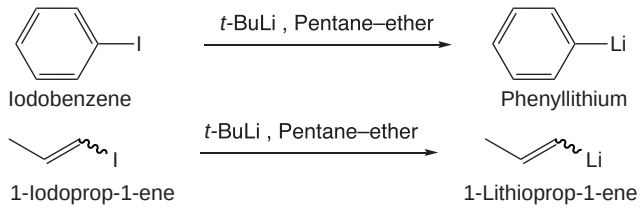
14.7 Draw and name the products that result when Li metal reacts with 2-bromopropane, 2-bromo-1-butene, 1-iodopentane (all in ether).
14.8 Write out the organolithium and the Wurtz coupling products expected during the reaction of lithium with 2-iodopentane.

Grignard reagents typically give poor yields in a coupling reaction with simple alkyl halides, as do organolithium reagents. However, organolithium reagents do react with alkyl halides by what is known as metal-halogen exchange rather than substitution.

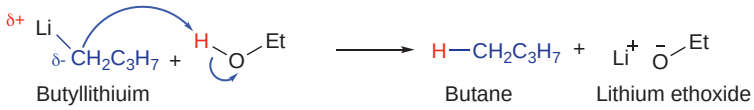


New organolithium reagents can be prepared by the reaction of a less reactive primary alkyl halide with the commercially available and more reactive tertiary 2-lithio-2-methylpropane, commonly known as *tert*-butyllithium. If *tert*-butyllithium is mixed with the primary halide iodoethane, for example, a rapid reaction takes place to produce ethyllithium (1-lithioethane) and *tert*-butyl iodide (2-iodo-2-methylpropane). This *metal-halogen exchange* reaction works well when the tertiary organolithium reagents reacts with a primary iodide (bromides and chlorides are less reactive). Since the primary organolithium reagent is more stable than the tertiary organolithium reagent, the reaction favors formation of the primary organolithium reagent. However, the exchange reaction with secondary halides is much slower and often leads to poor yields.

Aryl halides such as iodobenzene (Section 19.2.2) and vinyl halides such as 1-iodoprop-1-ene react with Li metal. These exchange reactions give the corresponding organolithium reagent (phenyllithium) or 1-lithioprop-1-ene, respectively, as shown. Note that the vinyllithium reagent (1-lithioprop-1-ene) is formed as a mixture of (*E*)- and (*Z*)-stereoisomers, as indicated by the "squiggle" line. The reactions use a shorthand notation for *tert*-butyllithium (*t*-BuLi).



14.9 Draw the starting materials required to prepare 2-lithopent-2-ene.



Organolithium reagents are more reactive and stronger bases relative to a comparable Grignard reagent. Some organolithium reagents are pyrophoric, reacting with air and water

in a violent and exothermic reaction. These acid-base reactions are sometimes called *metal-hydrogen exchange reactions.* Organolithium reagents are such strong bases that they react with most organic compounds that have a polarized hydrogen atom. Alkynes (e.g., 1-propyne) and amines (e.g., diethylamine) are weak acids with pK_a values close to 25 and 36, respectively as shown Figure 14.4. In both cases, *n*-butyllithium (BuLi) reacts to form the anion and butane (H–Bu) as the conjugate acid. Prop-1-yne yields an alkyne anion, 1-lithioprop-1-yne, which is a good nucleophile in S_N2 reactions, as shown in Section 11.3. Diethylamine also reacts with butyllithium to yield the conjugate

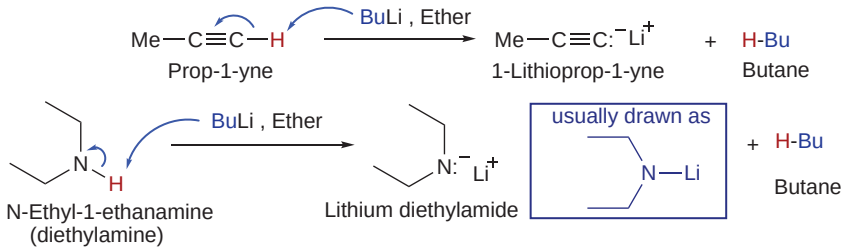


FIGURE 14.4 Terminal alkyne and secondary amines react as acids with butyllithium.

acid, butane. Although lithium diethylamide can be drawn as the salt, the actual structure is probably the covalent structure in the box in Figure 14.4. Lithium diethylamide and related compounds will be discussed in Section 20.2.

14.10 Draw out the reaction of butyllithium and ethanol and show all products.

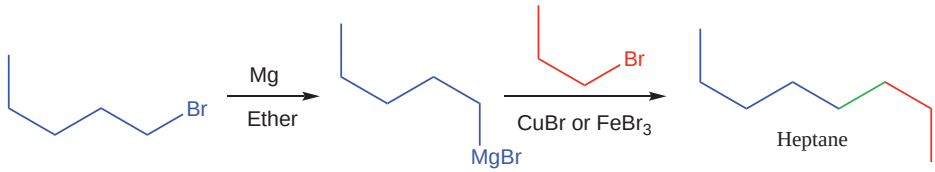
Organolithium reagents are such powerful bases that they slowly react with the normally unreactive ethers. This is a problem since an ether solvent is typically used to form an organolithium reagent. As the organolithium reagent reacts, the concentration of the reagent slowly diminishes. Therefore, once the organolithium reagent is formed, the ether solvent is partially removed and replaced with hexane or another hydrocarbon. This expedient prolongs the shelf-life of an organolithium reagent.

14.11 Draw the reaction formed for each step with buty-1-yne reacts with (1) methyllithium in ether and (2) (2S)-bromobutane.

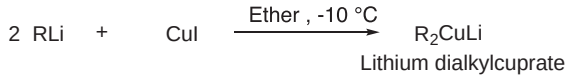
14.4 ORGANOCUPRATES

Organocuprate Reagents

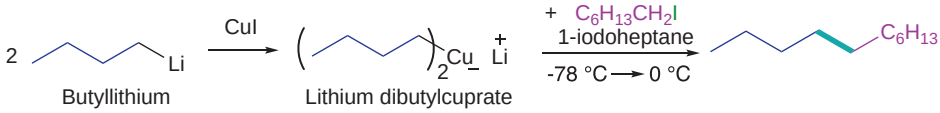
Apart from organomagnesium reagents and organolithium reagents, organocopper reagents are well known. The alkyl-copper reagents used in the Glaser reaction and the Cadiot-Chodkiewicz reactions in Section 11.8 are examples. Although Grignard reagents react poorly with alkyl halides, the addition of transition metal salts such as CuBr or $FeBr_3$ to a Grignard reagent enhances the reactivity by generating a new organometallic. This modification is called the *Kharasch reaction*, named for Morris S. Kharasch (Ukraine-USA; 1895–1957). If a Grignard reagent is mixed with cuprous bromide (CuBr) or ferric bromide ($FeBr_3$), a new organometallic intermediate is formed in situ (in the reaction medium) that is reactive with alkyl halides. In a specific case, the reaction of butylmagnesium bromide and 1-bromopropane, in the presence of either CuBr or $FeBr_3$, yields heptane as the major product.



The observation that greater reactivity is due to formation of a new organometallic species spurred the development of new organometallic species. When an organolithium reagent (RLi) reacts with cuprous iodide (CuI) in ether at -10 °C, a reaction takes place to generate what is called an *organocuprate*, R_2CuLi. Organocuprates with this structure are sometimes called *Gilman reagents* after the chemist who developed them, Henry Gilman (USA; 1893–1986). If the organocuprate has a carbon fragment with a hydrogen atom on the carbon β- to the metal (i.e., with the structural fragment H—C—C—Cu), elimination and decomposition is very fast above 0 °C. Therefore, formation of the organocuprate and reaction with an alkyl halide is done < 0 °C.



Note that the reaction of RLi and CuI requires two molar equivalents of the organolithium reagent to react with one equivalent of copper. The reaction of CuI with two molar equivalents of *n*-butyllithium gives lithium dibutylcuprate. The carbon attached to copper in the organocuprate is δ^- (it is carbanionic) and very reactive with most alkyl halides. The reaction of lithium dibutylcuprate with 1-iodoheptane, for example, gives undecane in 53% yield.[3] Primary, secondary, or tertiary organocuprates similarly react with primary, secondary, and tertiary alkyl halides, vinyl halides, and aryl halides.

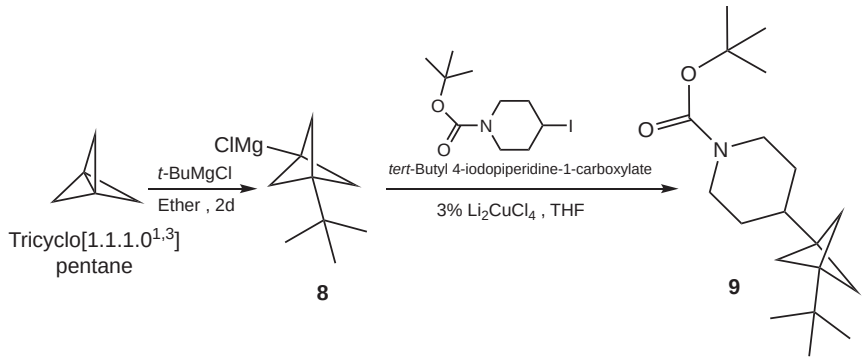


The halide can be a chloride, a bromide, or an iodide, but iodides are more reactive than bromides, which are more reactive than chlorides. The reaction of an organocuprate with an alkyl halide is probably the best method available for coupling an organometallic with an alkyl halide.

Janine Cossy

Janine Cossy (France) is a professor of organic chemistry at ESPCI Paris (École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris). Her work focuses on the total synthesis of natural biologically-active products like antitumor agents, antibiotics, anti-inflammatories or products acting on the central nervous system. She has also conducted research on organometallics, free-radical reactions, and photochemical reactions. Recent work by Professor Cossy focused on the cross-coupling reaction of Grignard reagents derived from bicyclo[1.1.1]pentane derivatives. These compounds appear to be promising *bioisosteres* to replace 1,4-disubstituted phenyls.

[3] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed. Longman, Essex, UK, 1994, Exp. 5.10, p. 483.

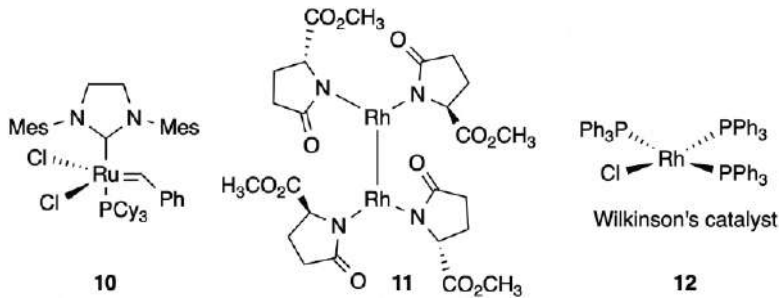


Bioisosteres are chemical substituents or groups with similar physical or chemical properties that produce broadly similar biological properties to another chemical compound. The cross-coupling of both primary and secondary alkyl halides with the bicyclopentyl Grignard reagents tolerated a variety of functional groups. The cross-coupling was applied to the functionalization of *N*-heterocycles (Section 23.5) to prepare putative scaffolds for the design and synthesis of bioactive molecules in the pharmaceutical industry. An example is the preparation of the Grignard reagent **8** by the reaction of tricyclo[1.1.1.01,3]pentane with *tert*-butylmagnesium chloride.[4] Subsequent reaction with *tert*-butyl 4-iodopiperidine-1-carboxylate and the organocopper reagent Li_2CuCl_4 (dilithium tetrachlorocuprate) gave **9** in 77% yield. Although it is commercially available, dilithium tetrachlorocuprate can be prepared from the reaction of lithium chloride and copper (II) chloride.

14.12 Write out the reactions and products formed when benzyl bromide is treated with dipropylcuprate; when 3-bromocyclopentene is treated with dimethyl cuprate.

14.5 OTHER ORGANOMETALLIC COMPOUNDS

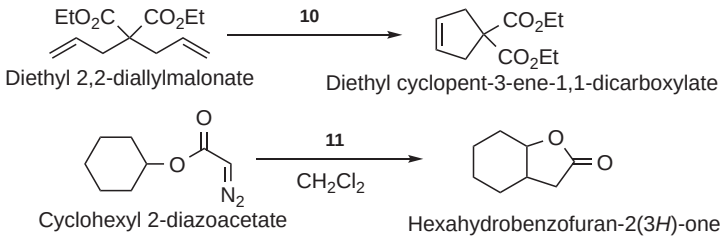
Other Organometallic Compounds



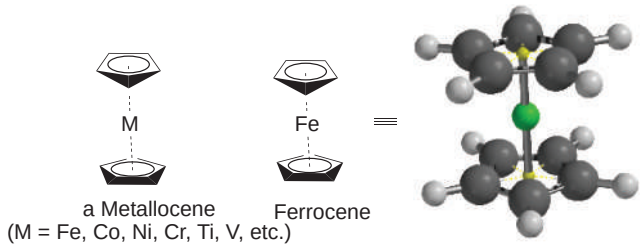
Myriad transition metal catalysts as well as non-metal catalysts have been developed for use in many types of reactions. This area is vast, far too large to do more than a brief survey. Rhodium catalysts such as the *Grubbs II catalyst* (**10**) are a mainstay of alkene metathesis catalysts (Section 10.9). An example of a metathesis reaction is the reaction of diene diethyl 2,2-diallylmalonate with the Grubbs II catalyst (**10**), which gave ethylene and diethyl cyclopent-3-ene-1,1-dicarboxylate in quantitative yield.[5] Several dirodium catalysts have been developed including *Doyle catalysts* such as dirhodium tetrakis(methyl 2-pyrrolidone-5(*R*)-carboxylate)acetonitrile (**11**). They are widely used in cyclopropanation and C—H insertion reactions. An example of a C—H insertion reaction in the presence of the Doyle catalyst **11** is the C—H insertion reaction of cyclohexyl 2-diazoacetate to give the lactone hexahydrobenzofuran-2(3*H*)-one in 30 % yield as a 75:25 cis/trans mixture.[6] In the presence of the rhodium catalyst, the diazo unit generates a carbene that

[4] (a) Andersen, C.; Ferey, V.; Daumas, M.; Bernardelli, P.; Guérinot, A.; Janine Cossy, J. *Organic Letters* ***2020***, *22*, 6021-6025. (b) Guérinot, A.; Cossy, J. *Accounts of Chemical Research* ***2020***, 53, 1351-1363.
[5] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Organic Letters* **1999**, 1, 953-956.
[6] Müller, P.; Polleux, P. *Helvetica Chimica Acta* 1994, 77, 645–654.

undergoes C—H insertion, in this case to form the lactone (Section 18.7). A carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons (RR'C:). Diazoesters can be prepared by the reaction of an α-amino esters (Sections 24.3–24.4) with sodium nitrite ($NaNO_2$) and acid (Section 19.10).



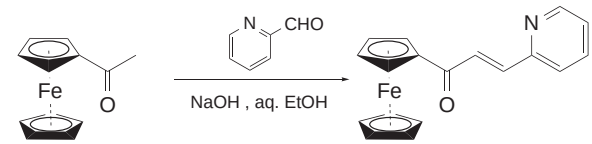
Catalysts for hydrogenation reactions (Section 17.4.3) that are soluble in the reaction medium are known as *homogeneous catalysts*. Homogeneous catalysts have the advantages of better catalyst reproducibility and better selectivity. An example is Wilkinson's catalyst, chlorotris(triphenylphosphine)hydridoruthenium(II), **12**. Many palladium catalysts are important for coupling reactions such as the *Heck reaction*, the *Suzuki-Miyara reaction*, and the *Sonogashira reaction* that will be discussed in Section 19.13, and the *Tsuji Trost reaction* that will be discussed in Section 20.7.4.



The *metallocenes* (also called *sandwich compounds*) constitute another type of organometallic in which two cyclopentadiene rings (Section 19.8) form a sandwich around a metal. The best known of these is *ferrocene*, where the η^5-coordination of the two cyclopentadienyl rings to iron is apparent in the ball-and-stick model. Other metallocenes have been prepared with Co, Ni, Cr, Ti, V, and other metals. Ferrocene has two cyclopentadienyl ligands and it is properly called bis(η^5-cyclopentadienyl)iron(II).

Ingrid Montes-González

Ingrid Montes-González (Puerto Rico) is a professor at the University of Puerto Rico, Río Piedras. Her research involves ferrocene derivatives, which have exhibited a broad range of biological activity. Research in this area has shown that dimethylamino ferrocenyl analogs are very active with chloroquine-sensitive and resistant strains of Plasmodium. Further, Tamoxifen-like frameworks (known as ferrocifens) confer recognition for the estrogen receptor in breast cancer cells, while the presence of ferrocene induces damage to DNA.[7] Other applications of ferrocene derivatives include optical devices, redox mediators for enzyme sensors, biofuel cells and they are useful in drug design. One area of research of Professor Montes' group involved the synthesis of ferrocenyl chalcone ammonium and pyridinium salt derivatives with the goal of improving solubility in aqueous media.[8] Chalcone is (*E*)-1,3-diphenylprop-2-en-1-one and a chalcone derivative generally has the structure of a 1,3-diarylprop-2-en-1-one. Improved aqueous solubility is a valuable aid for decreasing dosage while increasing efficiency. An example is the formation of the ferrocenyl chalcone shown by reaction of acetylferrocene with pyridine carbaldehyde in the presence of NaOH and aqueous ethanol. This reaction is the *Claisen-Schmidt condensation* (Sections 20.3–20.5) of acetylferrocene with benzaldehyde derivatives or pyridine carbaldehyde derivatives.



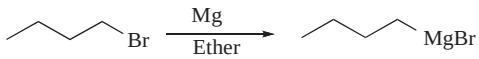
Acetylferrocene Ferrocenyl chalcone

14.6 ORGANIZATION OF REACTION TYPES

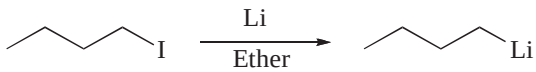
The reaction of organometallics can be organized as follows:

What reactions are possible for alkyl halides?

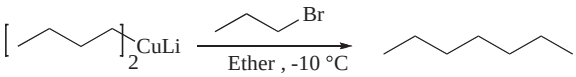
1. Alkyl halides react with magnesium to form organomagnesium reagents (Grignard reagents).



2. Alkyl halides react with lithium to form organolithium reagents.



3. Organocuprate reagents react with virtually any alkyl halide to yield coupling products

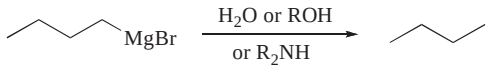


[7] Jaouen, G.; Vessières, A.; Top, S. *Chemical Society Reviews* 2015, 44, 8802–8817.

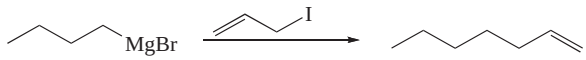
[8] (a) Montes-González, I.; Alsina-Sánchez, A.M.; Aponte-Santini, J.C.; Delgado-Rivera, S.M.; Durán-Camacho, G.L. *Pure and Applied Chemistry* 2019, 91, 653–669. (b) Delgado-Rivera, S.M.; Pérez-Ortiz, G.E.; Molina-Villarino, A.; Morales-Fontán, F.; García-Santos, L.M.; González-Albó, A.M.; Guadalupe, A.R.; Ingrid Montes-González, I. *Inorganic Chimica Acta* 2017, 468, 245–251.

What reactions are possible for Grignard reagents?

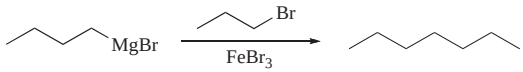
1. Grignard reagents react with acids (e.g., water, alcohols, and amines) to form an alkane.



2. Grignard reagents react only with very reactive alkyl halides to yield coupling products.

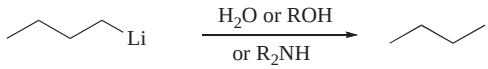


3. Grignard reagents react with alkyl halides in the presence of copper or iron salts to yield coupling products.

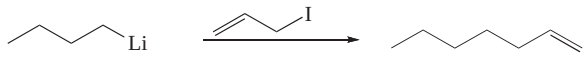


What reactions are possible for organolithium reagents?

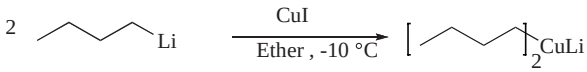
1. Organolithium reagents with acids (e.g., water, alcohols, and amines) to form an alkane.



2. Organolithium reagents react only with very reactive alkyl halides to yield coupling products.



3. Organolithium reagents react with copper salts to form organocuprates.



14.7 BIOLOGICAL RELEVANCE

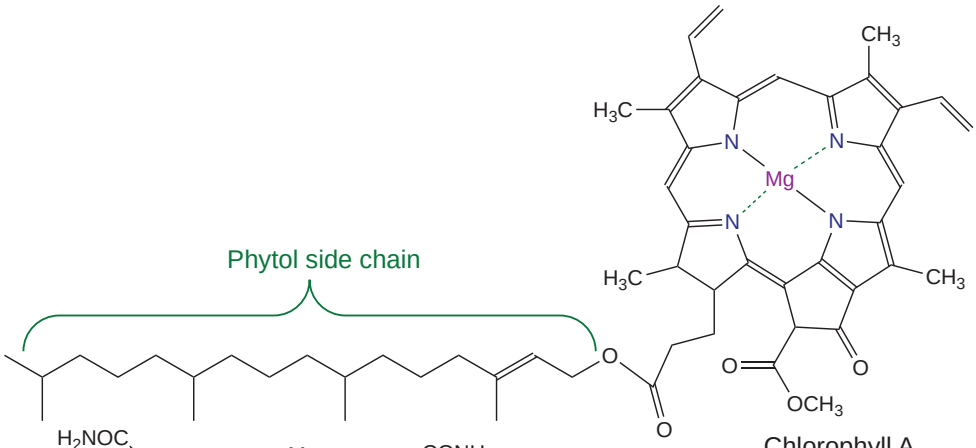
Although it is not an organometallic, lithium metal finds use in medicine. Lithium therapy can "reverse the manic phase of manic depression, and it increases the net re-uptake of certain biogenic amines into nerves, and it is capable of reducing nerve-stimulated release of biogenic amines."[9]

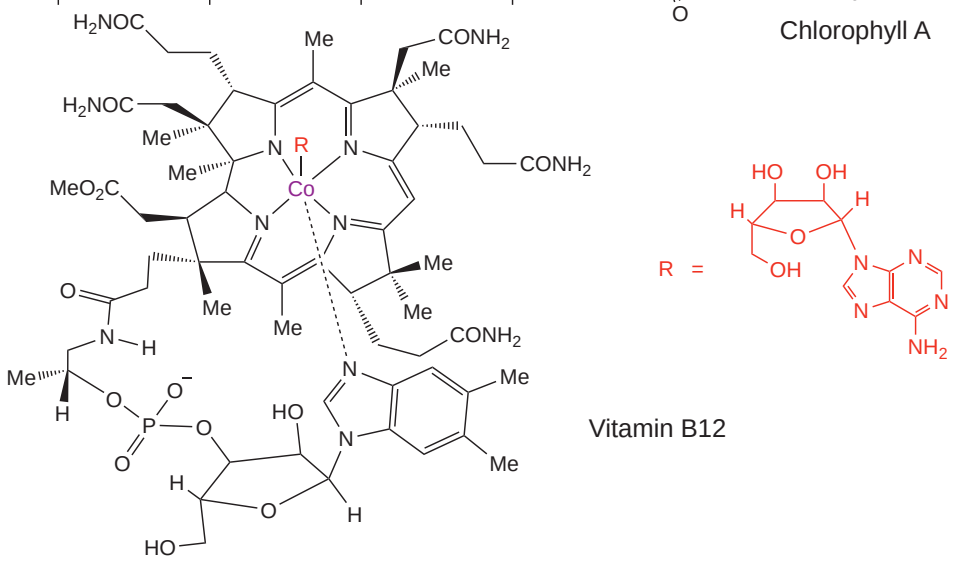
While Grignard reagents, organolithium reagents, and organocuprates may not be found in living systems, metals are essential to biological processes. Enzymes are key to life, and many enzymes require metal ions as cofactors. Tyrosinase is an enzyme that catalyzes the production of melanin and other pigments from tyrosine by oxidation, as in the blackening of a peeled or sliced potato exposed to air. *Cytochrome oxidase* is one of a family of proteins that act as the terminal enzymes of respiratory chains. They require Cu^{2+} or Cu^{+} as a cofactor.[10] Phosphohydrolases are a class of enzymes that cleave phosphoric acid from phosphate

[9] Foye, W.O. (Ed.), *Principles of Medicinal Chemistry* Lea and Febiger, Philadelphia, 1989, p. 296.
[10] Lehninger, A.I., *Biochemistry* Worth Publisher, New York, 1970, p. 149.

ester linkages to give an orthophosphate. Phosphotransferases are a class of enzymes that include the kinases, and catalyze the transfer of phosphorus-containing groups from one compound to another. Both of these enzymes require Mg^{2+} as a cofactor.[10]

Magnesium is important in several biologically important compounds. Magnesium is required with some phosphatases, which are enzymes that remove a phosphate group. Carboxylases are enzymes that catalyze decarboxylation or carboxylation, and some proteolytic enzymes that cleave peptide bonds require magnesium. Chlorophyll A is one of the green pigments found in photosynthetic cell, and it forms a magnesium complex with the porphyrin nitrogen atoms, as shown. Chlorophyll is typically extracted from the leaves of trees and plants. The active form of vitamin B12 is a cobalt complex,[11] and the metal is coordinated to the nitrogen atoms of a porphyrin system.





CORRELATION OF HOMEWORK WITH CONCEPTS

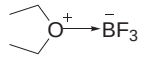
- A Grignard reagent is an organomagnesium compound formed by the reaction of an alkyl, vinyl or aryl halide with magnesium metal in ether solvents: 1, 2, 3, 4, 5, 13, 18.
- Grignard reagents are strong bases: 5, 18, 19.
- Grignard reagents react poorly with alkyl halides unless a transition metal catalyst is present: 6, 18.

[11] Halpern, J. *Pure and Applied Chemistry* 2001, 73, 209–220.

- Organolithium reagents are formed by the reaction of alkyl, aryl, or vinyl halides and Li metal and they react with alkyl halides to yield a new organolithium reagent via metal–halogen exchange:, 7, 8 9, 18, 21.
- Organolithium reagents are strong bases and good nucleophiles: 10, 11, 16, 8, 20.
- Organocuprates can be prepared from organolithium reagents and cuprous halides, and they react with alkyl halides to form a new C—C bond in the product: 12, 17, 18.
- Spectroscopy can be used to determine the structure of a particular molecule (see Chapter 13): 22.

ANSWERS TO IN-CHAPTER QUESTIONS

14.1



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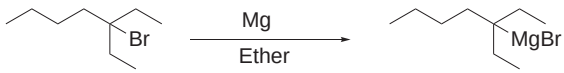

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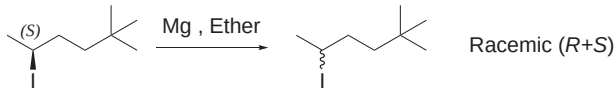

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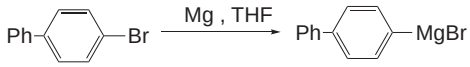


14.5

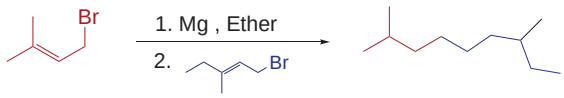
(a) $CH_3CH_2CH_2MgX$ + H-O-H ⟶ $CH_3CH_2CH_2$–H + XMg^+ $^-$O-H

(b) $CH_3CH_2CH_2MgX$ + H-O-CH_3 ⟶ $CH_3CH_2CH_2$–H + XMg^+ $^-$O-CH_3

(c) $CH_3CH_2CH_2MgX$ + H–C≡C–CH_3 ⟶ $CH_3CH_2CH_2$–H + XMg^{+-}:C≡C–CH_3

(d) $CH_3CH_2CH_2MgX$ + H-NMe_2 ⟶ $CH_3CH_2CH_2$–H + XMg^+ $^-NMe_2$

14.6



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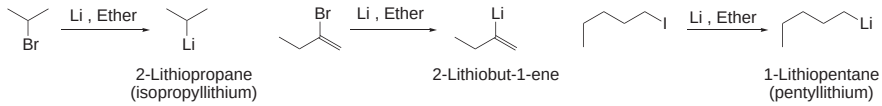
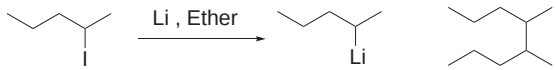


2-Lithiopropane (isopropyllithium) — 2-Lithiobut-1-ene — 1-Lithiopentane (pentyllithium)

14.8



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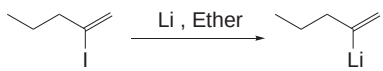

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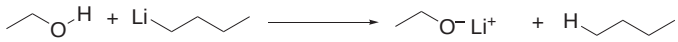

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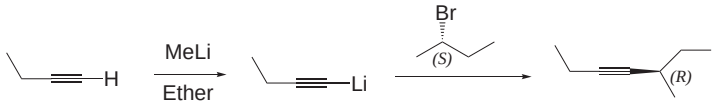

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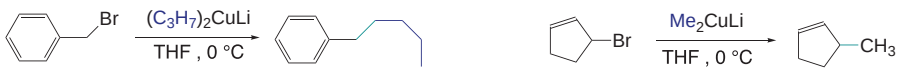


HOMEWORK

13. Draw the product formed when each of the following reacts with magnesium metal in ether or THF:
    (a) 1-iodohexane (b) 2-bromopent-2-ene (c) 4-bromo-2-phenylhexane
    (d) bromobenzene
14. Draw the product formed when each of the following reacts with lithium metal in either ether or THF:
    (a) 1-iodohexane (b) 2-bromopent-2-ene (c) 4-bromo-2-phenylhexane
    (d) bromobenzene

15. Draw the product formed when each of the following reacts with *tert*-butyllithium in a mixture of ether-hexane: (a) 1-iodohexane (b) 2-bromopent-2-ene (c) 4-bromo-2-phenylhexane (d) iodomethane
16. Draw the product formed when each of the following reacts with *n*-butyllithium:
    (a) diethylamine (b) butan-1-amine (c) piperidine
    (d) cyclohexanol (e) 1-butyne (f) dicyclohexylamine
    (g) benzyl bromide (h) CuI (i) *tert*-butyl iodide.
17. Draw the product formed when $LiCuMe_2$ reacts with each of the following in ether at -10 °C:
    (a) 2-bromo-4-methylhexane (b) 3,4-diphenyl-1-iodoheptane
    (c) 2-iodo-2-methylpentane
18. Give the names of the final product, if any, for each of the following reactions:
    (a) 2-iodopentane + 1. Mg/ether 2. Acetylene
    (b) phenylmagnesium bromide + 1. CuBr/THF/-10 °C 2. 2-bromopentane
    (c) 2-bromobut-2-ene + 1. Li/THF 2. CuI/THF/-10 °C 3. iodomethane
    (d) 2-bromobut-2-ene + 1. Mg/THF 2. 1-butyne
    (e) 3-bromocyclopentene + 1. Mg/THF 2. benzyl bromide
    (f) butylmagnesium chloride + water
    (g) 2-methylhexylmagnesium bromide + 1,2-dimethoxyethane
    (h) 1-iodopentane + 1. Li 2. 2-iodo-2-methylpentane
    (i) phenyllithium + 1. CuI/THF/-10 °C 2. 2-bromohexane
    (j) *n*-butyllithium + 1. prop-1-yne 2. dilute aqueous acid
    (k) *n*-butyllithium + *N*-methylpentan-1-amine
    (l) methyllithium + 2,2,4,4-tetramethylhexane.
19. Briefly explain why one should not use ethanol as a solvent to form a Grignard reagent.
20. *n*-Butyllithium (as a hexane solution) can be transferred via syringe without a problem if one is careful. With *tert*-Butyllithium (as a pentane solution) there is almost always a fire on the tip of the syringe. Briefly explain what this indicates about these two organolithium reagents.
21. A bottle of *n*-butyllithium purchased form a commercial vendor is usually packaged in hexane but it is common to find that octane is present. Briefly discuss why octane is found in this commercial product.

Spectroscopy Problems. Do not attempt these until after you have studied Chapter 13.

22. The reaction of 2-bromo-2-methylpropane and Li metal gives product **A**. When **A** reacts with 0.5 molar equivalents of CuI, product **C** is formed, and when **C** reacts with **B**, formed reaction of 3-methylbutan-1-ol and PBr_3 product **D** is formed. Give the structures of **A**, **B**, **C** and **D**. MS: 128 (M, 100%), 129 (M+1, 9.99%), 130 (M+2, 0.36%). IR: 2966-2870, 1478\-1468, 1393-1366 cm^{-1}. ^1H NMR: 1.44 (m, 1H), 1.14 (m, 2H), 1.14 (t, 2H), 0.88 (d, 6H), 0.86 (s, 9H) ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-15.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

15

Oxidation

There is a class of reactions known as *oxidation or reduction reactions* that involve the gain or loss of two electrons. The structural changes in the product of these reaction are often measured by whether hydrogen or oxygen is gained or lost. This chapter will introduce a few oxidation reactions and the typical transformations associated with them. Reduction reactions are discussed in Chapter 17.

To begin this chapter, you should know the following points:

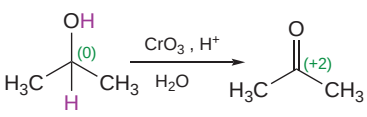
- Nomenclature for hydrocarbons, alcohols, aldehydes, ketones, diols, ethers, and carboxylic acids (Sections 4.3, 4.4, 5.1, 5.2, 5.5, 15.6, and 18.2).
- Chirality and stereochemistry (Sections 9.1 and 9.2).
- Polarized covalent bonds (Section 3.8).
- π-Bonds (Sections 5.1 and 5.2).
- Brønsted-Lowry acids and bases (Sections 2.1–2.6 and 6.1–6.7).
- Lewis bases and acids (Sections 2.7 and 6.8).
- Reactions of alkenes (Chapter 10).
- E2 type reactions (Sections 12.1–12.3 and 12.7).

15.1 DEFINING AN OXIDATION

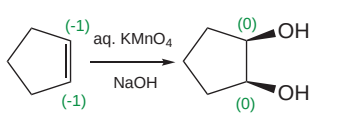
Defining an Oxidation

An oxidation is formally defined as a reaction accompanied by the loss of electrons from an atom or a group. In an oxidation reaction there are structural changes in the product relative to the starting material. These changes usually include either loss of hydrogen atoms or the replacement of a hydrogen atom bonded to carbon with a more electronegative atom, usually a heteroatom. Common heteroatoms include oxygen, halogens, nitrogen, sulfur, and so on, but the most common is probably oxygen. An example of an oxidation is the conversion of an alcohol such as propan-2-ol to a ketone (acetone, propan-2-one). The transformation involves loss of hydrogen atoms from oxygen and from carbon. Another example of an oxidation is the conversion of an alkene such as cyclopentene to a vicinal diol (*trans*-cyclopentane-1,2-diol), which involves the gain of two oxygen atoms. *Oxidation state* is a number assigned to the carbon atoms involved in the transformation. This number is useful for identifying whether electrons are gained or lost during the transformation. Formal rules for determining oxidation state are:

1. The oxidation state of a carbon is taken to be zero.
2. For hydrogen atoms attached to a carbon is given a value of -1 for each hydrogen atom.
3. For heteroatoms attached to a carbon is assigned a value of +1 for each heteroatom.



Propan-2-ol Propan-2-one



Cyclopentene Cyclopentane-1,2-diol

DOI: 10.1201/9781003174929-15

Comparing propan-2-ol with propan-2-one, the oxidation state of C2 changes. In propan-2-ol, C2 is attached to two carbon atoms, one hydrogen atom, and one oxygen so the oxidation state is 0 + 0 -1 + 1 = 0 (zero for each carbon, -1 for the hydrogen, and +1 for the oxygen). In propan-2-one, C2 is bonded to two carbon atoms, with two bonds to oxygen. The oxidation state of C2 in propan-2-one is calculated to be 0 + 0 + 1 + 1 = +2. The oxidation number change is from 0 to +2, so *two electrons are lost*. Remember that electrons are negatively charged particles, so the carbon becomes more positive as electrons are lost. Similarly, the conversion of an alkene such as cyclopentene to a vicinal diol (*trans*-cyclopentane-1,2-diol (Section 15.3) involves the gain of two oxygen atoms. The change is -2 to 0 for the C=C unit and the oxygen-bearing carbons and is also an oxidation.

15.1 Calculate the oxidation number for the conversion of but-1-ene to 2-bromobutane, and categorize this transformation as an oxidation or a reduction.

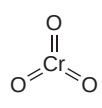
15.2 OXIDATION OF ALCOHOLS

Aldehydes and ketones were introduced in Section 5.6.2. An important method for the preparation of aldehydes and ketones is oxidation of an alcohol. Several reagents are available for this oxidation.

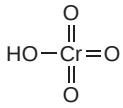
Chromium(VI) Oxidation of Alcohols

15.2.1 CHROMIUM (VI) OXIDATION OF ALCOHOLS

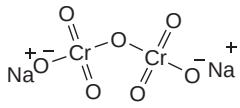
Several common inorganic reagents used for the oxidation of organic compounds contain chromium(VI), a powerful oxidizing agent. Chromium trioxide in the anhydrous form exists as a polymer $[(CrO_3)_n]$ where the "*n*" is an integer indicating the number of repeating CrO_3 units. However, chromium trioxide is usually just written as the monomer CrO_3. Other inorganic reagents that involve Cr(VI) include chromic acid ($HCrO_4$), sodium dichromate ($Na_2Cr_2O_7$), and potassium dichromate ($K_2Cr_2O_7$). When chromium trioxide is dissolved in water, a complex equilibrium is established that includes CrO_3, chromic acid, and dichromic acid ($H_2Cr_2O_7$). When a CrO_3 solution is highly concentrated (only a small amount of water), the equilibrium favors a higher concentration of CrO_3. When the CrO_3 solution is dilute (a large amount of water), the equilibrium favors dichromic acid. All Cr(VI) species are effective for the oxidation of alcohols. Note that chromium (VI) is a *cancer suspect agent*. The handling, the use in chemical reactions, and chemical disposal of these reagents must be carefully monitored.



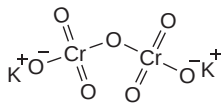
Chromium trioxide



Chromic acid



Sodium dichromate



Potassium dichromate

Chromium(VI) reagents have been used for many years for the oxidation of alcohols. Most Cr(VI) reagents are used in an aqueous acid solution. Since many alcohols are not very soluble in aqueous media, an organic cosolvent is usually added. An important method for the oxidation of organic compounds uses a solution of chromium trioxide in aqueous acetone (propan-2-one), in the presence of H_2SO_4. This mixture is called the *Jones reagent* and the reaction of this mixture with an alcohol is called *Jones oxidation.* It is named after Sir Ewart Ray Herbert Jones (E.R.H Jones; England; 1911–2002). The Jones oxidation of pentan-3-ol affords pentan-3-one in 57% yield.[1] Sodium dichromate and other Cr(VI) reagents can be used for Jones oxidation.

[1] Wiberg, K.B. in Chapter 2 of *Oxidation in Organic Chemistry, Part A*, Wiberg, K.B. (Ed.), John Wiley & Sons, NY, 1965, pp. 146, 147.

In this oxidation, one hydrogen atom has been lost from the oxygen of the alcohol, and another from the carbon atom. The mechanism shown in Figure 15.1 is used to explain the oxidation.

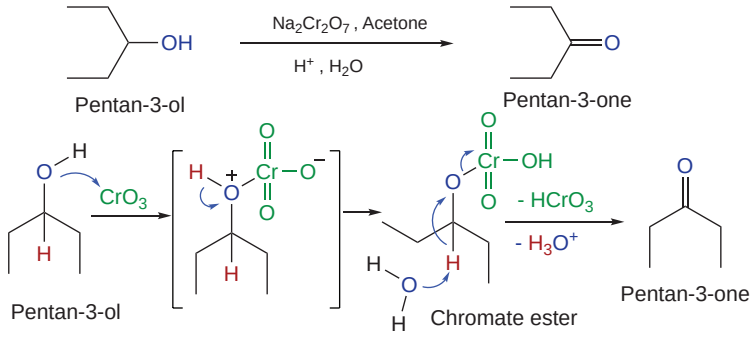
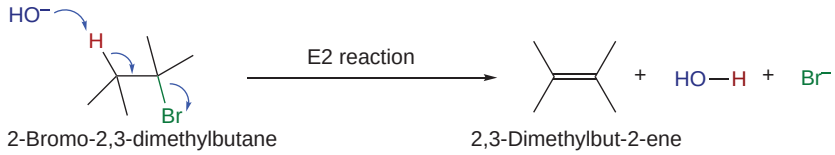
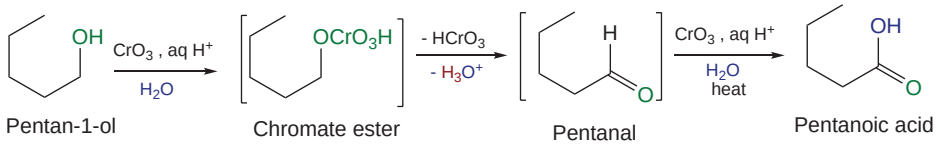


FIGURE 15.1 *Mechanism of chromium trioxide oxidation.*

The other products of this oxidation are the hydronium ion and $HCrO_3$, which is unstable and decomposes. In the initial reaction, the oxygen of pentan-3-ol reacts as a Lewis base to donate two electrons to chromium (a Lewis acid) to form an oxonium salt. Water removes the acidic proton from the oxonium ion via an intermolecular acid-base reaction. Protonation of the negatively charged chromate oxygen leads to an intermediate called a chromate ester. Once formed, the $OCrO_3H$ unit in the chromate ester renders the hydrogen atom on the α-carbon acidic. This α-hydrogen is acidic enough to react with water in an acid-base reaction. Removal of the α-hydrogen leads to formation of a π-bond with loss of the $OCrO_3H$ unit, which is a leaving group. This is an *elimination reaction* to form a carbonyl (C=O). Note the similarity of the mechanism for the Cr(VI) oxidation of an alcohol in Figure 15.1 to the E2 reaction of 2-bromo-2,3-dimethylbutane to yield 2,3-dimethylbut-2-ene. Elimination of the hydrogen atom β- to the leaving group in the E2 reaction is similar to removal of a hydrogen atom β- to the chromate leaving group (CrO_3H).



Jones oxidation is a powerful oxidizing medium for the conversion of alcohols to ketones. In some cases, unwanted decomposition or over-oxidation products are possible. Indeed, oxidation of primary alcohols can lead to over-oxidation to a carboxylic acid and the yields of aldehyde from primary alcohols may be very low. Over-oxidation is not surprising since aldehydes are easily oxidized to carboxylic acids. If a sample of butanal were spilled, for example, it is rapidly oxidized to butanoic acid by air. It is therefore not surprising that formation of an aldehyde in the presence of a powerful oxidant such as Cr(VI) gives rapid oxidation to the carboxylic acid. An example of this overoxidation is shown for the reaction of pentan-1ol where initial formation of a chromate ester leads to pentanal in situ.

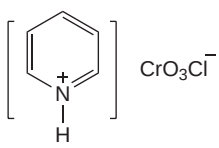


The aldehyde is rapidly oxidized to pentanoic acid. If the reaction mixture is heated, over-oxidation to the carboxylic acid is even more rapid. If cold temperatures and short reaction times are used, reasonable yields of the aldehyde may be obtained. Long reaction times and heat favor formation of the acid.

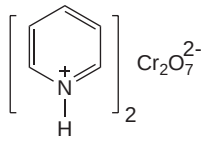
PCC, PDC, and Swern Oxidation

Since over-oxidation of primary alcohols to carboxylic acids is a problem when Cr(VI) reagents are used, the isolation of the aldehyde without overoxidation to the carboxylic acid

is a desirable goal. One solution to this problem is to prepare a Cr(VI) oxidizing agent that is less reactive. Two modified Cr(VI) reagents based on the reaction of CrO_3 and pyridine were developed by Nobel laureate Elias J. Corey (USA) and are widely used for the oxidation of alcohols, especially primary alcohols and allylic alcohols. The first of these reagents is formed by the reaction of chromium trioxide with pyridine in aqueous HCl. This reaction generates a specific compound known as *pyridinium chlorochromate (PCC)* that is isolated and purified. In this aqueous acid solution, CrO_3 forms $HCrO_4$, which reacts with HCl to form $HCrClO_3$. Pyridine (Section 23.1) then reacts as a base with the acidic proton to form PCC. If the reaction conditions are modified to increase the amount of pyridine in a dilute water solution, and the HCl is omitted, the reaction gives *pyridinium dichromate (PDC)*. In dilute solution, CrO_3 is in equilibrium with $H_2Cr_2O_7$, and pyridine reacts with both acidic hydrogen atoms to produce PDC, which is isolated and purified.

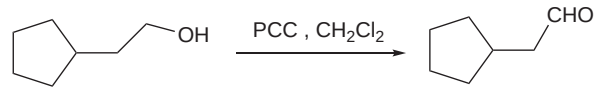


Pyridinium chlorochromate (PCC)



Pyridinium dichromate (PDC)

15.2 Draw the chromate ester and final product of a reaction between 4,4-diethylhexan-2-ol and $K_2Cr_2O_7$ in aqueous acetone.
15.3 Write out the product of a reaction between 3-cyclopentylpropan-1-ol and Jones reagent if the reaction is done at 80°C and a reaction time of 24 h.



2-Cyclopentylethan-1-ol 2-Cyclopentylethanal

4-Propylcyclohexan-1-ol 4-Propylcyclohe xan-1-one

Although PCC and PDC are less reactive than the Jones reagent, alcohols are readily oxidized with either reagent in dichloromethane solvent. These reagents are very effective for converting primary alcohols to the aldehyde and also secondary alcohols to ketones, in good yield and under mild conditions. An example is the reaction of 2-cyclopentylethanol and PCC in dichloromethane to give 2-cyclopentylethanal in 72% yield.[2] In a different experiment, the reaction of 4-propylcyclohexanol and PDC gave 4-propylcyclohexanone in 97% isolated yield.[2] The PCC reagent is more acidic than PDC and sometimes causes deleterious side reactions, but this side-reaction will not be an issue in this book. However, PDC was developed, in part, because of the acidity of PCC.

15.4 Write out the product of the reaction of decan-1-ol with PDC.
15.5 Write out the product when cyclooctanol reacts with PCC.

15.2.2 SWERN OXIDATION

There are other reagents used to oxidize alcohols that do not involve Cr(VI). One is derived from the reaction of dimethyl sulfoxide ($CH_3(S{=}O)CH_3$, DMSO) and oxalyl chloride (Section

[2] Luzzio, F. *Organic Reactions* 1998, 53, 1–74.

18.11). An example is the reaction of butan-2-ol with these reagents at -60 °C to afford butan-2-one in 78% yield along with dimethyl sulfide (MeSMe).[3] The mechanism proposed to explain these observations is shown in Figure 15.2. The oxygen of DMSO attacks one

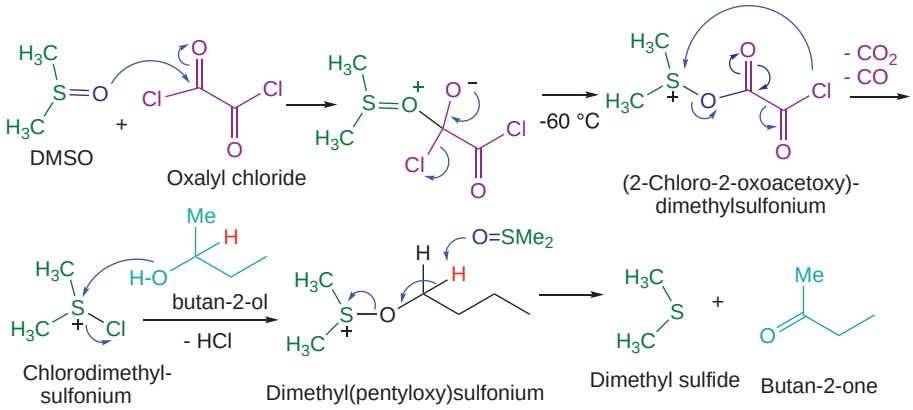


FIGURE 15.2 Swern oxidation of butan-2-ol.

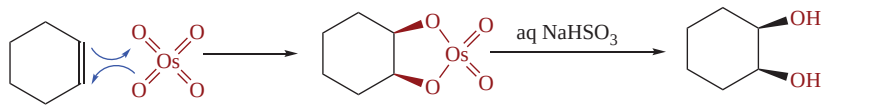
carbonyl carbon of oxalyl chloride in an *acyl substitution reaction to form a tetrahedral intermediate* (Section 18.3). Subsequent loss of chloride ion gives an acyl-sulfonium derivative, (2-chloro-2-oxoacetoxy)dimethylsulfonium. An intramolecular transfer of the chlorine from the acyl carbon to sulfur initiates loss of carbon dioxide (CO_2) and carbon monoxide (CO) to give the chlorodimethylsulfonium salt. This sulfonium salt has an electrophilic sulfur that is attacked by the nucleophilic oxygen of an alcohol (e.g., butan-2-ol). Subsequent loss of a proton gives dimethyl(pentyloxy)sulfonium. This sulfonium salt is related to the chromate ester intermediate discussed in Section 17.2.1 in that a leaving group (Me_2S) is lost as a hydrogen atom (in red) is removed in an acid-base reaction. This particular oxidation of an alcohol to a ketone or aldehyde is called the *Swern oxidation,* named after Daniel Swern (USA; 1916–1982).

15.6 Write out all the products formed by Swern oxidation of 5-methyl-(3*E*)-penten-2-ol.

15.3 DIHYDROXYLATION OF ALKENES

Dihydroxylation with OsO_4

In addition to the reactions of alkenes discussed in Chapter 10, oxidation reactions of alkenes are known. Both potassium permanganate ($KMnO_4$) and osmium tetroxide (OsO_4) react with an alkene to yield a 1,2-diol product where the two OH units have a *cis-* relationship (Section 9.7). Conversion of an alkene to a diol is termed a *dihydroxylation* reaction.



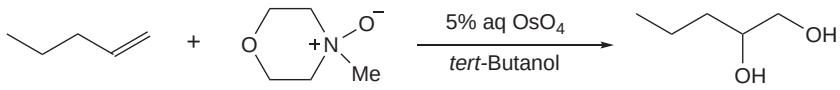
The reaction of cyclohexene with osmium tetroxide gives a five-membered ring product, an *osmate ester*. There is no reactive intermediate, so it is a *concerted* reaction. Concerted means that as the alkene π-bond attacks one oxygen atom of OsO_4, transfer of electrons occurs simultaneously to form the second C—O bond. The osmate ester is formed via *1,3-dipolar addition* (Section 24.4). The cis-relationship of the two OH units in the osmate ester is set during the concerted dipolar addition. Subsequent reaction of the osmate ester

[3] Tidwell, T.T. *Organic Reactions* 1990, 39, 297–572. See pp. 431–557; (b) Tidwell, T.T. *Synthesis* 1990, pp. 857–870.

with aqueous sodium thiosulfite ($NaHSO_3$) affords *cis*-cyclohexane-1,2-diol. Inversion of configuration at carbon is not observed here, so the reaction with thiosulfate must occur at osmium rather than a carbon in order to retain the cis stereochemistry.

Dihydroxylation with $KMnO_4$

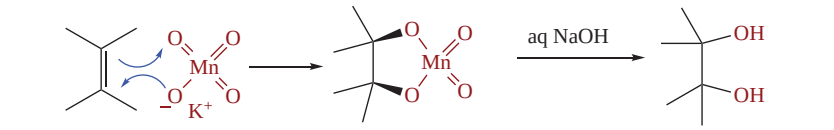
Osmium tetroxide is a rather expensive reagent and using a full molar equivalent is not always practical. If the reaction of an alkene with aqueous OsO_4 is done in the presence of *tert*-butylhydroperoxide ($Me_3C—OOH$) or *N*-methylmorpholine-*N*-oxide (NMO), the reaction is *catalytic in osmium*. Either reagent reacts with the osmate ester in situ to generate the diol and regenerate the OsO_4 reagent. If pent-1-ene reacts with an aqueous solution of OsO_4 and NMO in *tert*-butanol, for example, the final product is pentane-1,2-diol. When NMO is used in reactions with alkenes, treatment of the osmate ester with sodium bisulfite is not needed. Under these conditions, as little as 1% of osmium tetroxide can be used. The osmate ester is formed in situ, reacts with NMO and OsO_4 is regenerated for further reaction with the alkene.



N-Methylmorpholine *N*-oxide

An older dihydroxylation reaction uses dilute aqueous potassium permanganate ($KMnO_4$) and NaOH in a reaction with an alkene to give a cis-1,2-diol. An example is the reaction of 2,3-dimethylbut-2-ene with potassium permanganate. Reaction with the C=C unit proceeds by 1,3-dipolar addition to yield a *manganate ester*. The concerted nature of the $KMnO_4$ reaction with the alkene leads to a *cis-relationship* of the oxygen atoms in the manganate ester. The manganate ester is decomposed in situ by reaction with sodium hydroxide to give *cis*-cyclohexane-1,2-diol. The hydroxide ion attacks the manganese atom of the manganate ester to open the ring and in the presence of water and hydroxide. Further attack at manganese followed by hydrolysis gives a 1,2-diol, in this case 2,3-dimethylbutane-2,3-diol.

The reaction of potassium permanganate to give a diol must be done in a relatively dilute solution (typically 0.1–0.5 M). The temperature must be kept relatively "cold," usually room temperature or lower. If the concentration is too high and the temperature too great, oxidative cleavage (Section 15.4) can occur and a variety of unwanted products are formed. The terms hot and cold, high or low concentration are relative. The actual values of these parameters depend on the particular alkene. In general, however, cold and dilute conditions usually involve temperatures at or below room temperature and concentrations of 0.1 M or less. This concentration is an arbitrary choice but typical.



2,3-Dimethylbut-2-ene — Manganate ester — 2,3-Dimethylbutane-2,3-diol

15.7 Draw the intermediate and final product formed when cycloheptene is treated with $KMnO_4$ in the presence of aqueous NaOH followed by hydrolysis.

For the reaction of either potassium permanganate or osmium tetroxide with cyclohexene, the product is the *cis*-diol, and there is none of the *trans*-diol. Therefore, *dihydroxylation is a diastereospecific reaction*. Of the two diastereomers (cis- or trans-), only the cis- product is formed. Dihydroxylation occurs from either face of the C=C unit, and the reaction gives both enantiomers but only one diastereomer and that diastereomer is racemic. The overall cis- addition of two OH units to the C=C unit of the alkene is easy to see when a cyclic alkene such as with cyclohexene. Dihydroxylation of an acyclic alkene is also diastereospecific.

The diastereospecificity with acyclic alkenes can be examined using the reaction of hex-(2*E*)-ene with OsO_4. The reaction that generates an osmate ester occurs from both faces of

the C=C unit is shown in Figure 15.3. The reaction is concerted, so the *E*-stereochemistry of the two alkyl groups attached to the C=C unit is preserved in the five-membered ring

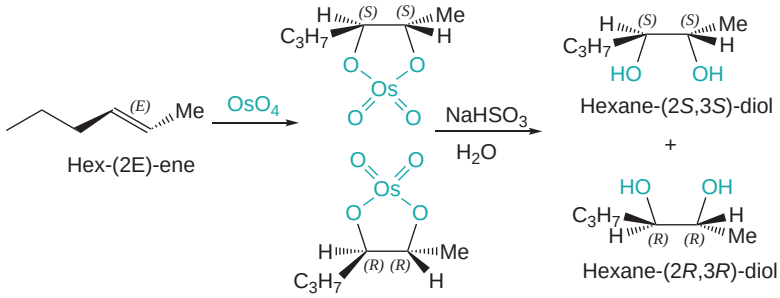


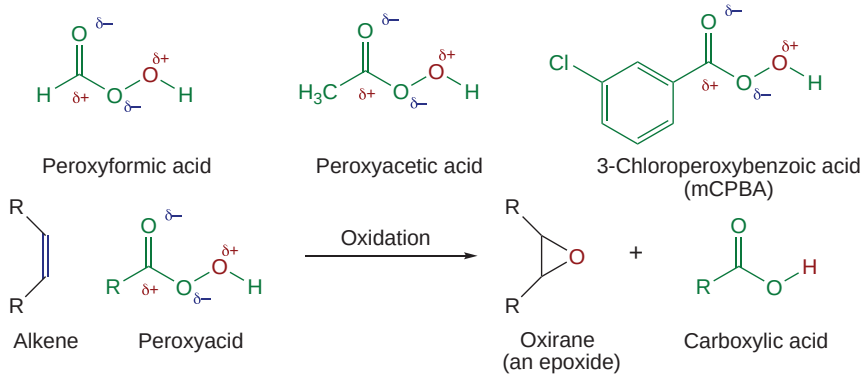
FIGURE 15.3 Diastereospecific dihydroxylation of hex-(2*E*)-ene.

osmate ester. Since there is no facial bias, both the (*S,S*)- and the (*R,R*)- enantiomers of the osmate ester are formed. Reaction with NMO at osmium retains the stereochemistry of all the groups and the diol product is racemic: hexane-(2*S*,3*S*)-diol and hexane-(2*R*,3*R*)-diol. Similarly, a concerted reaction with potassium permanganate gives a manganate ester with no facial bias. Reaction with NaOH gives the racemic (2*S*,3*S*) and (2*R*,3*R*)-diol. The reaction of hex-(2*E*)-ene with OsO_4 or with $KMnO_4$ gives only racemic hexane-(2*R*,3*R*)-diol and hexane-(2*S*,3*S*)-diol. Reaction of hex-(2*Z*)-ene gives only racemic hexane-(2*R*,3*S*)-diol and hexane-(2*S*,3*R*)-diol.

15.8 Draw the product formed by treatment of 3-phenyl-(2*Z*)-pentene with 1. OsO_4 and 2. aq $NaHSO_3$.

15.4 EPOXIDATION OF ALKENES

Epoxidation



Alkenes can be oxidized to a three-membered ring ether known as an oxirane (an epoxide). The three-membered ring is highly strained, analogous to a cyclopropane ring (Section 8.5.2). Due to this ring strain and contrary to most other ethers, epoxides are very reactive (Section 11.6.2). An important method for the epoxidation of alkenes uses peroxide-type reagents that are characterized by a weak oxygen-oxygen bond, –O—O–. Peroxycarboxylic acids, or peroxyacids have the structure shown, RCO_3H. They are named by adding the term *peroxy* to the name of the carboxylic acid parent. The peroxy analog of formic acid is peroxyformic acid, acetic acid is the precursor to peroxyacetic acid, and trifluoroacetic acid is the precursor to peroxytrifluoroacetic acid. *meta*-Chloroperoxybenzoic acid (mCPBA) is a solid peroxyacid derived from *meta*-chlorobenzoic acid (Section 19.2). All peroxyacids have an electrophilic oxygen atom (δ^+) that arises from an induced dipole originating with the

carbonyl oxygen. This electrophilic oxygen atom allows peroxyacids to react with the π-bond of an alkene to give an epoxide and a carboxylic acid. The carboxylic acid product is always the acid "parent" of the peroxyacid (RCO_2H from RCO_3H).

Cyclopentene reacts with peroxyacetic acid to give cyclopentene oxide in 57% yield and acetic acid,[4] as shown in Figure 15.4. Note that the nomenclature used for the epoxide names the alkene precursor (cyclopentene), followed by oxide (the IUPAC name is 6-oxabicyclo[3.1.0]hexane; Section 9.9). There is no intermediate for this reaction. It is concerted so the transition state must involve close to simultaneous formation of all bonds as well as electron reorganization to generate the epoxide and a carboxylic acid product. The transition state

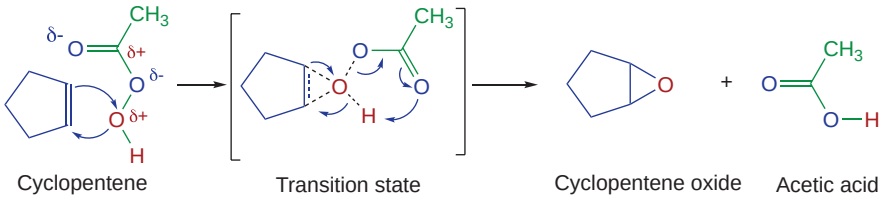
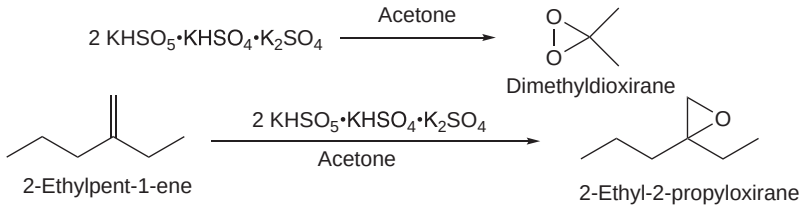


FIGURE 15.4 Epoxidation of cyclopentene.

is shown in Figure 15.4 for the reaction of cyclopentene and peroxyacetic acid. The oxygen atom of the epoxide comes from the OH oxygen in the peroxyacid (labeled δ^+). As mentioned above, the oxygen atom in the peroxyacid is δ^+ because bond polarization extends from the carbonyl unit (C=O). The alkene donates two electrons to the electrophilic oxygen. As the new C—O bond is formed, the O—O bond breaks. Transfer of electrons to the acyl carbon forms a new carbonyl. The electrons in the previous C=O bond are transferred to the proton on the peroxy oxygen to give a carboxylic acid. The initially attacked oxygen reacts with the positive carbon of the former C=C unit as it develops a positive dipole during the reaction. This latter process generates the epoxide product.

15.9 Draw both products formed when 3-ethylhex-3-ene reacts with peroxyacetic acid.

Since an acidic carboxylic acid is formed as a product along with the epoxide, epoxides may undergo ring-opening reactions via an acid-base reaction (Section 11.6.2). Such reactions can generate secondary products that diminish the yield of the epoxide. To circumvent this problem, buffers are added to react with the carboxylic acid byproduct to suppress secondary reactions. Common buffers include the salt of the carboxylic acid produced by the epoxidation. For example, if acetic acid is the product, sodium acetate ($CH_3C_3O^-Na^+$) will be added to buffer the reaction.



There are vast differences in reaction rate among various alkenes. In fact, simple alkenes (e.g., pent-1-ene) are difficult to epoxidize under normal conditions because the reaction is very slow. Indeed, many cannot be epoxidized at all. Alkyl groups are electron donating, and more alkyl substituents on a C=C unit provides greater electron density in the π-bond. A substituted alkene is therefore a stronger Lewis base and more reactive. A tetrasubstituted alkene ($R_2C{=}CR_2$) reacts faster with peroxyacids than a trisubstituted alkene ($R_2C{=}CHR$),

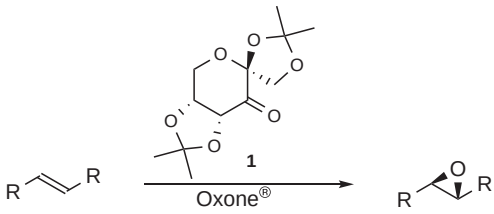
[4] Rickborn, B.; Gerkin, R.M. *Journal of the American Chemical Society* 1971, 93, 1693–1700.

which reacts faster than a disubstituted alkene and that reacts faster than a monosubstituted alkene. There is little or no steric effect in reactions of highly substituted alkenes.

15.10 Draw the transition state and all products of the reaction between 2-methyl-pent-1-ene and peroxytrifluoroacetic acid?

Because of the difficulty in the epoxidation of some alkenes with peroxyacids, alternative reagents have been developed, including *dioxiranes*. Dialkyldioxiranes are formed by the reaction of a ketone with an oxidizing agent such as potassium peroxomonosulfate ($KHSO_5$). Commercially available Oxone® ($2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) is a common source of $KHSO_5$. Oxone® is used in a reaction with a ketone and sodium bicarbonate to oxidize an alkene to an epoxide. The reaction of acetone and $KHSO_5$ gives dimethyldioxirane,[5] for example, and reaction with 2-ethylpent-1-ene affords 2-ethyl-2-propyloxirane. The dialkyldioxirane epoxidation of alkenes generates a racemic epoxide.

Asymmetric Epoxidation



Yian Shi

However, the reaction of Oxone® with a chiral ketone generates a chiral dioxirane and subsequent reaction with an alkene gives a chiral epoxide with good enantioselectivity. When Oxone® is used in conjunction with a chiral ketone such as (-)-**1**[6], a dihydropyran-3-one derivative derived from fructose (Section 25.1), the product is a chiral epoxide. With this reagent, alkenes are epoxidized with good enantioselectivity in what is called *Shi epoxidation*[7] named

[5] (a) Frohn, M.; Wang, Z.-X.; Shi, Y. *Journal of Organic Chemistry* 1998, 63, 6425–6426; (b) Baumstark, A.L.; Harden Jr., D.B. *Journal of Organic Chemistry* 1993, 58, 7615–7625; (c) Baumstark, A.L.; Vasquez, P.C. *Journal of Organic Chemistry* 1988, 53, 3437–3439; (d) Murray, R.W.; Jeyaraman, R. *Journal of Organic Chemistry* 1985, 50, 2847–2853.

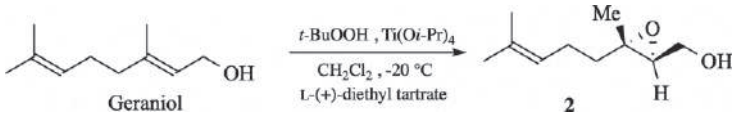
[6] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *Journal of the American Chemical Society* 1997, 119, 11224–11235.

[7] (a) Wong, O.A.; Shi, Y. *Chemical Reviews* 2008, 108, 3958–3987; (b) Shi, Y. *Accounts of Chemical Research* 2004, 37, 488–496.

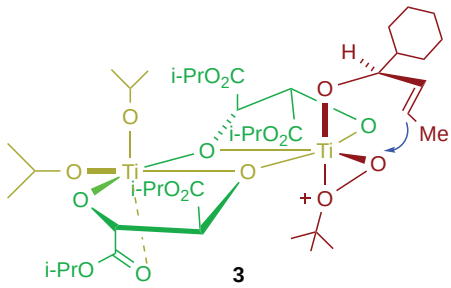
after Yian Shi (China-USA), a Professor of Chemistry at Colorado State University. His research is focused on synthetic organic chemistry. He develops novel methodologies and their application in the synthesis of natural products exhibiting unique chemical complexity and significant biological activity. A recent focus has been the functionalization of alkenes with an emphasis on chemoselectivity, regioselectivity, enantioselectivity, and diastereoselectivity. He developed an efficient asymmetric epoxidation method for a variety of *trans*- and trisubstituted alkenes, electron deficient olefins, *cis*-alkenes and terminal alkenes.

15.11 Draw the product when 2-methylpent-2-ene reacts with acetone and Oxone®.

Other methods are available for the asymmetric epoxidation of alkenes. The C=C unit of allylic alcohols are epoxidized when reacted with *tert*-butyl hydroperoxide (TBHP), catalyzed by tetraisopropoxy titanium (IV) [Ti(O*i*-Pr)$_4$]. The epoxy alcohol product is formed with high enantioselectivity when (+)- or (-)-diethyl tartrate (DET) is added to the reaction medium.[8] Enantioselective indicates that of two enantiomers, one is formed preferentially but both are formed. This asymmetric reaction is known as the *Sharpless Asymmetric Epoxidation*,[9] named after Nobel laureate K. Barry Sharpless (USA) who discovered the reaction. The reaction of geraniol with *tert*-butyl hydroperoxide and Ti(O*i*-Pr)$_4$ in the presence of L-(+)-diethyl tartrate, gave **2** in 77% yield and 95% ee for the (2*S*,3*S*) stereoisomer.[9]



The enantioselectivity of this catalyst system is due to the binding of the peroxide, the hydroxyl unit of the allylic alcohol and two equivalents of the chiral tartrate to titanium to form a species such as **3**, where OR = O*i*-Pr and $CO_2R = CO_2Et$.[10,11] The tartrate will bind to titanium from either from the bottom or the top face depending on the chirality of the tartrate. Tetraisopropoxy titanium first reacts with the tartrate and then with TBHP and an allylic alcohol (C=C–C–OH) to form complex **3**. The peroxide linkage and the allylic alcohol in **3** are bound to the metal and backside attack of the alkene moiety along the axis of the O—O bond will lead to the epoxide to give a single enantiomer. The extent of the enantioselectivity is determined by the extent to which binding of the allylic alcohol and peroxide is limited to a single face. Sharpless provided models **4** and **5** shown in Figure 15.5, to predict the stereochemistry of the epoxide formed in this reaction.



The additives L-(+)-DET or L-(+)-DIPT react with the best selectivity with allylic alcohols of the type represented by generic structure **5**, whereas D-(-)-DET or D-(-)-DIPT are

[8] (a) Katsuki, T.; Sharpless, K.B. *Journal of the American Chemical Society* 1980, 102, 5974–5976; (b) Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *Journal of the American Chemical Society* 1981, 103, 6237–6240.

[9] *The Merck Index, 14th ed.*, Merck & Co., Inc., Whitehouse Station, NJ, 2006, p. ONR-85.

[10] (a) Burns, C.J.; Martin, C.A.; Sharpless, K.B. *Journal of Organic Chemistry* 1989, 54, 2826–2834; (b) Carlier, P.R.; Sharpless, K.B. *Journal of Organic Chemistry* 1989, 54, 4016–4018.

[11] (a) Katsuki, T.; Sharpless, K.B. *Journal of the American Chemical Society* 1980, 102, 5974–5976; (b) See Johnson, R.A.; Sharpless, K.B. *Comprehensive Organic Synthesis Volume 7*, Chapter 3.2, *Asymmetric Epoxidations*, Pergamon Press, Oxford, 1990.

the best choice for **4**. The reaction of (*R*,*E*)-1-cyclohexylbut-2-en-1-ol with L-(+)-DIPT gives a mixture of diastereomers **6** [(*R*)-cyclohexyl((2*R*,3*R*)-3-methyloxiran-2-yl)methanol and **7** (*R*)-cyclohexyl((2*S*,3*S*)-3-methyloxiran-2-yl)methanol. The major product is **7** (38:62).[10,11] Note that the complex **3** from L-(+)-DET or L-(+)-DIPT generates a "pocket" so (*R*,*E*)-1-cyclohexylbut-2-en-1-ol can approach from the face bearing the hydrogen with the least ste-

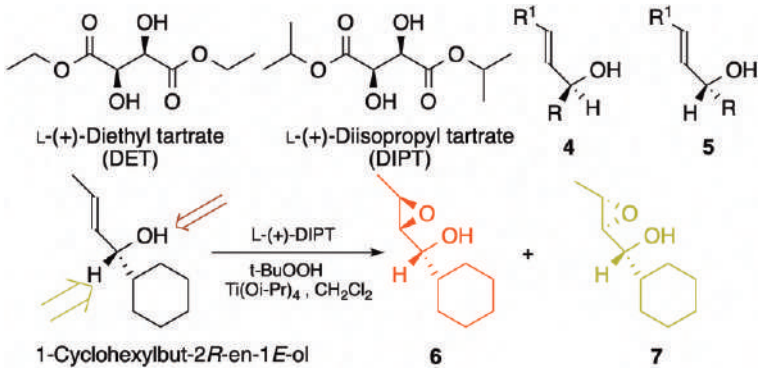
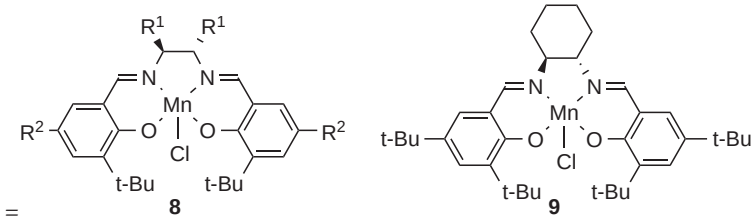


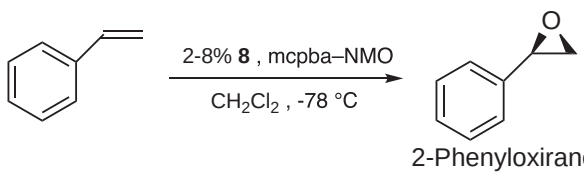
FIGURE 15.5 The model for asymmetric induction of allylic alcohols in the Sharpless asymmetric epoxidation.

ric hindrance. This "matching" of the two stereogenic centers of the reactants is referred to as *consonance.* If the stereogenic centers are mismatched the two reactants cannot easily approach and this is called *dissonance*. The best yields and the best enantioselectivity is achieved when there is consonance between the stereocenters.

The Sharpless asymmetric epoxidation only works with allylic alcohols. Changing the chiral catalyst facilitates the conversion of simple alkenes to the corresponding epoxide with high asymmetric induction.



In independent work, Tsutomu Katsuki (Japan) and Eric Jacobsen (USA) showed that asymmetric epoxidation occurs using manganese–salen catalysts in the presence of *tert*-butylhydroperoxide. Salen is bis(salicylidene)ethylenediamine. In a typical catalyst is **8**, R^1 can be an aryl group or cycloalkyl, bromine, trialkylsilyloxy and other groups. The manganese-salen catalyst **9** is called the *Jacobsen catalyst,* [*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamine]manganese(III)] chloride. Simple alkenes are oxidized with high asymmetric induction (the so-called *Jacobsen-Katsuki reaction*).[12] In a typical transformation, styrene was converted to styrene oxide (2-phenyloxirane) in 89% yield and 86% ee using 2–8 mol% of **8** [R^1 = Ph, R^2 = OSi(*i*-Pr)$_3$], in combination with mCPBA and *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent.[12c]



[12] (a) Hatayama, A.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* 1992, 407–409; (b) Chang, S.; Lee, N.H.; Jacobsen, E.N. *Journal of Organic Chemistry* 1993, 58, 6939–6941; (c) Palucki, M.; McCormick, G.J.; Jacobsen, E.N. *Tetrahedron Letters* 1995, 36, 5457–5460.

15.5 OXIDATIVE CLEAVAGE

Ozonolysis

Ozone (O_3) is another molecule that reacts via a 1,3-dipolar addition reaction with alkenes (Section 22.4), analogous to the permanganate ion and osmium tetroxide in Section 15.3. Ozone is formed by electrical discharge (lightning) in the presence of O_2 in the atmosphere. This process can be mimicked in the laboratory by discharging a spark in an oxygen stream under controlled conditions. Ozone is a resonance-stabilized species, with the four resonance contributors shown in Figure 15.6. Two of the resonance forms have the positive and negative charge at the terminal oxygen atoms ($^{-}$O-O-O^{+}), making them 1,3-dipoles.

A 1,3-dipolar addition reaction of ozone and 2,3-dimethylbut-2-ene gives a five-membered ring product, 4,4,5,5-tetramethyl-1,2,3-trioxolane (Figure 15.6). A trioxolane is a five-membered ring with three oxygen atoms in the ring. Although 1,2,3-trioxolane is formed initially, the observed product *rearranges* to 1,2,4-trioxolane (3,3,5,5-tetramethyl-1,2,4-trioxolane). This rearranged trioxolane is commonly called an *ozonide.* Initial reaction, followed by facile rearrangement leads to cleavage of *both* the σ-bond and the π-bond of the C=C unit in the alkene. The ozonide is usually not isolated and a second chemical step converts the ozonide to the final products. In a second chemical step, hydrogen peroxide (aqueous H_2O_2) is added to decompose the ozonide and give two equivalents of acetone. A symmetrical alkene gives two equivalents of the same carbonyl compound. An unsymmetrical alkene will give two different carbonyl compounds, one from each carbon of the C=C unit. The overall transformation is *oxidative cleavage* of both bonds of the C=C unit by reaction with ozone is called *ozonolysis. Ozonolysis* converts each carbon of the C=C unit to a carbonyl.

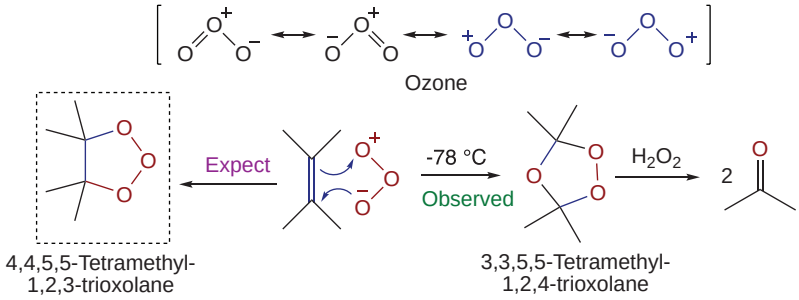


FIGURE 15.6 Ozone and oxidative cleavage of alkenes.

The mechanism of ozonolysis in Figure 15.7 is called the *Criegee mechanism*, named after Rudolf Criegee (Germany; 1902–1975). Experiments have shown that the initially formed trioxolane product is very unstable even at temperatures as low as -78 °C. One of the weak O—O bonds in the trioxolane breaks to yield zwitterion **10**. Once formed, the alkoxide unit in **10** initiates cleavage of the C—C bond to give a carbonyl and the carbonyl oxide structure

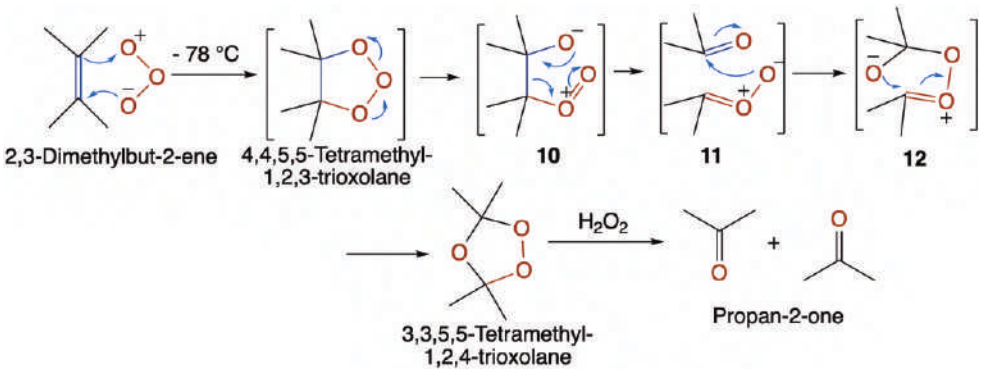
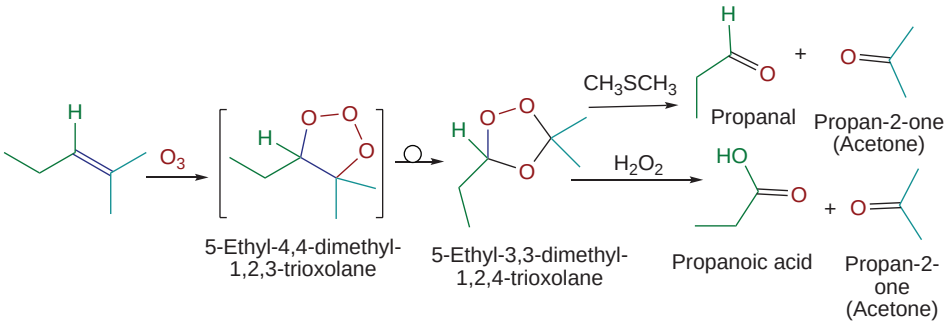


FIGURE 15.7 Mechanism of ozonolysis of 2,3-dimethylbut-2-ene.

shown in **11**. These two separate molecules do not drift apart before the subsequent reaction since dipole-dipole interactions keep them close. The alkoxide unit of one fragment is attracted to and attacks the electropositive carbonyl carbon of the other fragment to yield **12**. Once formed, the alkoxide unit in **12** rapidly reacts with the C=O carbon by the intramolecular reaction shown in Figure 15.7. This acyl addition reaction completes the rearrangement to the ozonide (3,3,5,5-tetramethyl-1,2,4-trioxolane).

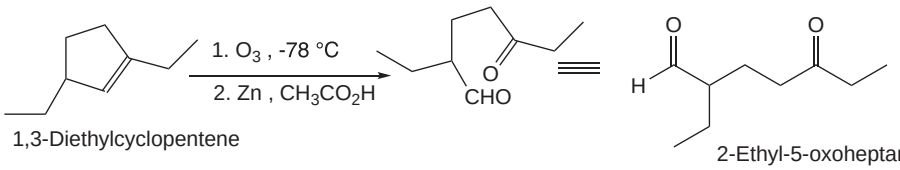
Many alkenes have a hydrogen atom attached to the alkene (C=C—H). This structural feature allows further reaction of the initially formed product after ozonolysis. When 2-methylpent-2-ene reacts with ozone, the initial 1,2,3-trioxolane product is formed, and rearranges to the ozonide. If 5-ethyl-3,3-dimethyl-1,2,4-trioxolane is treated with dimethyl sulfide (CH_3SCH_3) the products are acetone and propanal. The reaction of the ozonide with zinc and acetic acid also gives acetone and an aldehyde. If this ozonide is treated with hydrogen peroxide, the cleavage products are acetone and propanoic acid rather than an aldehyde. As noted for the oxidation of alcohols to aldehydes, simple aldehydes (e.g., propanal) are very susceptible to oxidation when exposed to air. Therefore, formation of propanal in the presence of an oxidizing agent such as H_2O_2 will oxidize the aldehyde to a carboxylic acid. In this reaction, hydrogen peroxide is an oxidizing agent and dimethyl sulfide is a reducing agent (Chapter 17).



Ozonolysis of a cyclic alkene gives oxidative cleavage of the C=C unit, but the two carbonyl fragments are connected so there is only one product. When cycloheptene is treated with ozone and then with zinc and acetic acid or dimethyl sulfide, for example, the product is an α,ω-dialdehyde, heptanedial. If one requires an α,ω-disubstituted molecule, oxidative cleavage of a cyclic alkene with ozone easily generates that product. Another example is 1,3-diethylcyclopentene, which when treated with ozone and then reduction with zinc and acetic acid gives 2-ethyl-5-oxoheptanal.

15.12 Suggest structures for the two carbonyl products obtained by treatment of 3-ethyl-4-methylhept-3-ene with 1. O_3 and 2. H_2O_2.

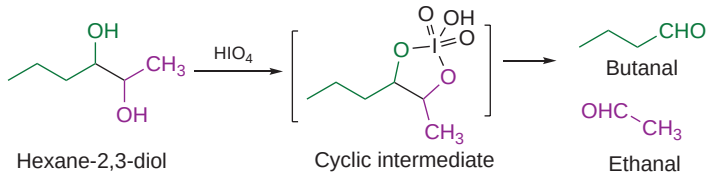
15.13 Draw the product formed when 1-ethyl-1-cyclononene is treated with 1. O_3 and 2. Zn/acetic acid.



Oxidative cleavage of vicinal diols is possible, and the products are aldehydes or ketones. Two common reagents used for this purpose are periodic acid (HIO_4) and lead tetraacetate, LTA [$Pb(OAc)_4$]. When hexane-2,3-diol is treated with HIO_4, a cyclic product is formed (a cyclic periodate). This cyclic intermediate decomposes under the reaction conditions to generate two aldehydes, butanal and ethanal (acetaldehyde). There is little or no overoxidation to

the carboxylic acid. A useful variation of this reaction treats a cyclic diol (e.g., cyclopentane-1,2-diol) with HIO_4 to yield pentanedial, an α,ω-dialdehyde. The reaction of 3,4-dimethylhexane-3,4-diol and HIO_4 gives two ketones. Similarly, 4-ethyloctane-3,4-diol is cleaved to a ketone and an aldehyde.

Oxidative Cleavage of Diols



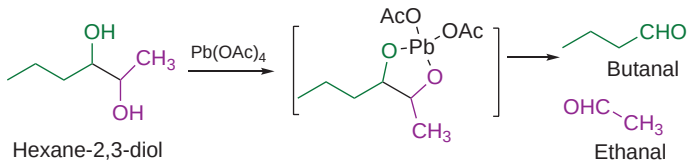
Hexane-2,3-diol Cyclic intermediate

15.14 Write out the reaction that generates hexane-2,3-diol from an appropriate alkene.

15.15 Draw the ketone and aldehyde products of reaction of 4-ethyloctane-3,4-diol and HIO_4.

Lead tetraacetate (abbreviated LTA) reacts with 1,2-diols to give the same kind of oxidative cleavage observed with periodic acid. When hexane-2,3-diol is treated with LTA, the initial cyclic product is a cyclic lead intermediate, which fragments to butanal and ethanal. Both periodic acid and lead tetraacetate are mild and effective reagents for the oxidative cleavage of diols.

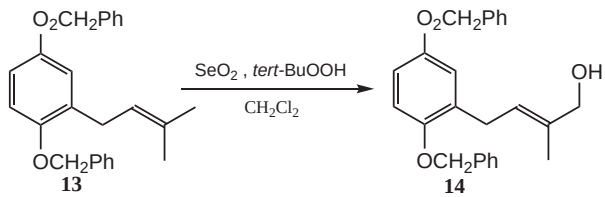
15.16 What is the product when 1-ethylcycloheptene reacts with 1. aq OsO_4 + NMO and 2. LTA?



Hexane-2,3-diol

15.6 C—H OXIDATION

The functionalization of the C—H bond is arguably one of the more difficult transformations in organic chemistry. One method replaces the hydrogen in a C—H bond with a halogen atom by a radical substitution reaction as described in Section 11.7. This exchange reaction is more facile with a tertiary hydrogen than with a secondary hydrogen or a primary hydrogen atom. This difference in reactivity is due to the weakness of the tertiary C—H relative to the secondary or primary C—H.



13 **14**

Organometallic reactions at C—H usually occur at less sterically hindered primary bonds rather than more hindered tertiary bonds. Allylic and benzylic C—H units in a molecule are susceptible to reaction with selenium dioxide (SeO_2) in the presence of *tert*-butylhydroperoxide (Me_3CCOOH) to selectively oxidize allylic or benzylic C—H fragments to the

corresponding allylic alcohol.[13] Benzylic positions react much slower than allylic positions, as seen in the conversion of the allylic site in **13** to alcohol **14**.[14]

M. Christina White

Recent advances in transition metal chemistry have led to reagents that are more general and more selective for C—H oxidation reactions. Professor M. Christina White (USA), at the University of Illinois, Urbana-Champaign developed iron and manganese catalysts that showed for the first time that aliphatic C—H bonds of the same bond type (for example secondary) can be discriminated based on differences in their electronic, steric, and stereoelectronic environments (The *White Rules*; Figure 15.8).[15,16] By altering the ligand framework (PDP to CF_3PDP), the catalysts can be made more sensitive to the steric environment

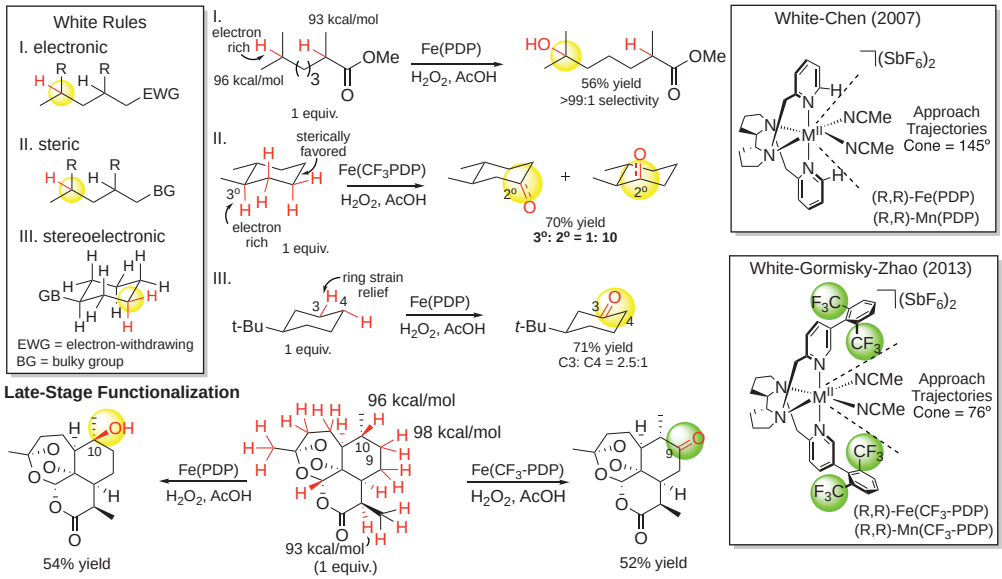


FIGURE 15.8 The White Rules and C—H oxidation with Fe(PDP) or Mn(PDP) and with Fe(CF_3-PDP) or Mn(CF_3-PDP). Courtesy of Professor M. Christina White.

[13] (a) Trachtenberg, E.N. in *Oxidation*, Vol. 1, Augustine, R.L. (Ed.); Marcel-Dekker, NY, 1969, pp 119–187; (b) Waitkins, G.R.; Clark, C.W. *Chemical Reviews* 1945, 36, 235–289.
[14] Tanada, Y.; Mori, K. *European Journal of Organic Chemistry* 2003, 848–854.
[15] Chen, M.S.; White, M.C. *Science*, 2007, 318, 783–787.
[16] Chen, M.S.; White, M.C. *Science*, 2010, 327, 566–571.

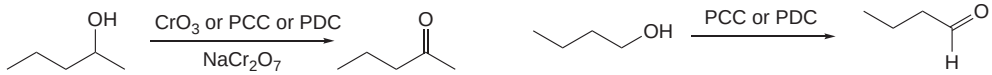
of C—H bonds and alter the site of hydroxylation on the same molecule (see artemisinin in Figure 15.8).[17] Very strong bonds can be functionalized in the presence of much weaker bonds and specific tertiary or methylene C—H bonds in the presence of many others because discrimination is based on elements beyond their bond strengths alone (bond dissociation energy = BDE). Using these catalysts and concepts, chemists can now perform late-stage functionalization on natural products and drugs to alter their chemical and biological properties.[18] For example, the antimalarial drug artemisinin can be selectively hydroxylated at either the C9 tertiary hydrogen or the C10 methylene hydrogens depending on which catalyst is used. By replacing iron with manganese, functional groups that are more susceptible to oxidation can be tolerated (e.g. aromatic rings).[19,20] This enables streamlining the synthesis of drugs and drug metabolites that often have aromatic rings.

15.7 ORGANIZATION OF REACTION TYPES

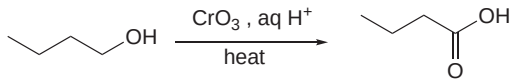
The reaction of alkenes and alkynes can be organized as follows

What reactions are possible for alcohols?

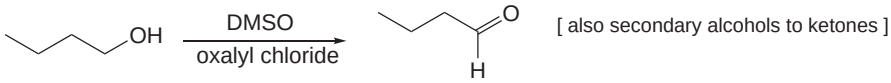
1. Primary and secondary alcohols are oxidized to aldehydes or ketones using Cr(VI) reagents.



2. Primary alcohols are assumed to be oxidized to a carboxylic acid using Jones oxidation.

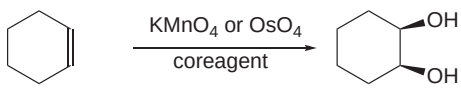


3. Primary alcohols are oxidized to aldehydes and secondary alcohols to ketones by Swern oxidation.

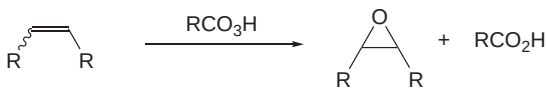


What reactions are possible for alkenes?

1. Alkenes are oxidized to diols with $KMnO_4$ or with OsO_4

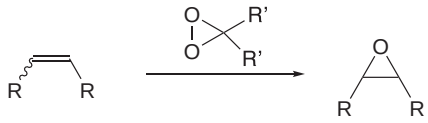


2. Alkenes are oxidized to epoxides with peroxy acids.

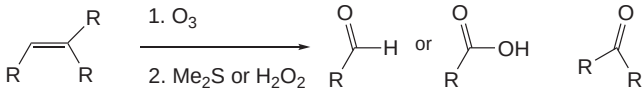


3. Alkenes are oxidized to epoxides with dialkyl oxiranes.

[17] Gormisky, P.E.; White, M.C. *Journal of the American Chemical Society*, 2013, 135, 14052–14055.
[18] White, M.C.; Zhao, J.P. *Journal of the American Chemical Society*, 2018, 140, 13988–14009.
[19] Zhao, J.; Nanjo, T.; de Lucca Jr. E.C.; White, M.C. *Nature Chemistry*, 2019, 11, 213–221.
[20] Chambers, R.K.; Zhao, J.; Delaney, C.P.; White, M.C. *Advanced Synthesis & Catalysis*, 2020, 362(2), 417–423.

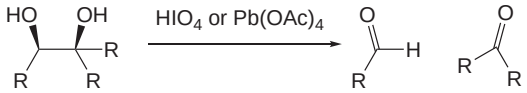


4. Alkenes are oxidatively cleaved to aldehydes, ketones, or acids with ozone, followed by treatment with dimethyl sulfide or hydrogen peroxide.

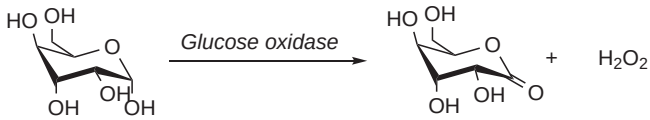


What reactions are possible for diols?

1. Diols are oxidatively cleaved to aldehydes and ketones with periodic acid or with lead tetraacetate



15.8 BIOLOGICAL RELEVANCE



An *oxidase* is an enzyme (Section 24.7) that catalyzes an oxidation-reduction reaction with dioxygen (O_2) as the electron acceptor. An oxidase promotes the transfer of a hydrogen atom from a particular substrate with concomitant reduction of oxygen to water or hydrogen peroxide. The enzyme *glucose oxidase*, also known as *notatin*, is found in *Aspergillus niger* and it is a β-D-glucose specific flavoprotein oxidase that catalyzes the conversion to the lactone.[21] Specifically, the oxidation of glucose gives hydrogen peroxide and D-glucono-δ-lactone.

Dehydrogenase enzymes facilitate the interconversion between alcohols and aldehydes or ketones with concomitant reduction of NAD^+ to NADH (Section 17.7). The oxidizing agent is NAD^+ (nicotinamide adenine dinucleotide) and NADH is the reduced form (nicotinamide adenine dinucleotide). The enzymes are known as *alcohol dehydrogenases*, and in humans they break down alcohols (e.g., ethanol or methanol), which are toxic. In humans, an *alcohol dehydrogenase* is found in the lining of the stomach and in the liver. The dehydrogenation is an oxidation, and the enzyme *alcohol dehydrogenase* catalyzes the oxidation of ethanol to acetaldehyde: $CH_3CH_3OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$

The conversion of ethanol to acetaldehyde allows the consumption of alcoholic beverages, but it probably exists to oxidize naturally occurring alcohols in foods or those produced by bacteria in the digestive tract. The mechanism of this oxidation for the enzyme liver alcohol dehydrogenase is shown in Figure 15.9.[22] In the alcohol complex **17**, where ethanol is bound to the active site of the enzyme. Subsequent hydride transfer from the alkoxide zinc complex to a pyridine ring of NAD^+ (**18**) generates the acetaldehyde zinc complex and the reduced aromatic ring in NADH, **19**. The NAD^+ binds to the active site of the enzyme to induce a conformational change to close the active site. The oxidation of ethanol to acetaldehyde (ethanal) is accompanied by reduction of NAD^+ to NADH, as shown.

[21] Petrović, D.; Frank, D.; Kamerlin, S.C.K.; Hoffmann, K.; Strodel, B. *ACS Catalysis* 2017, 7, 6188–6197.
[22] Eklund, H.; Plapp, B.V.; Samama, J.P.; Branden, C.I. *Journal of Biological Chemistry* 1982, 257, 14349–14358.

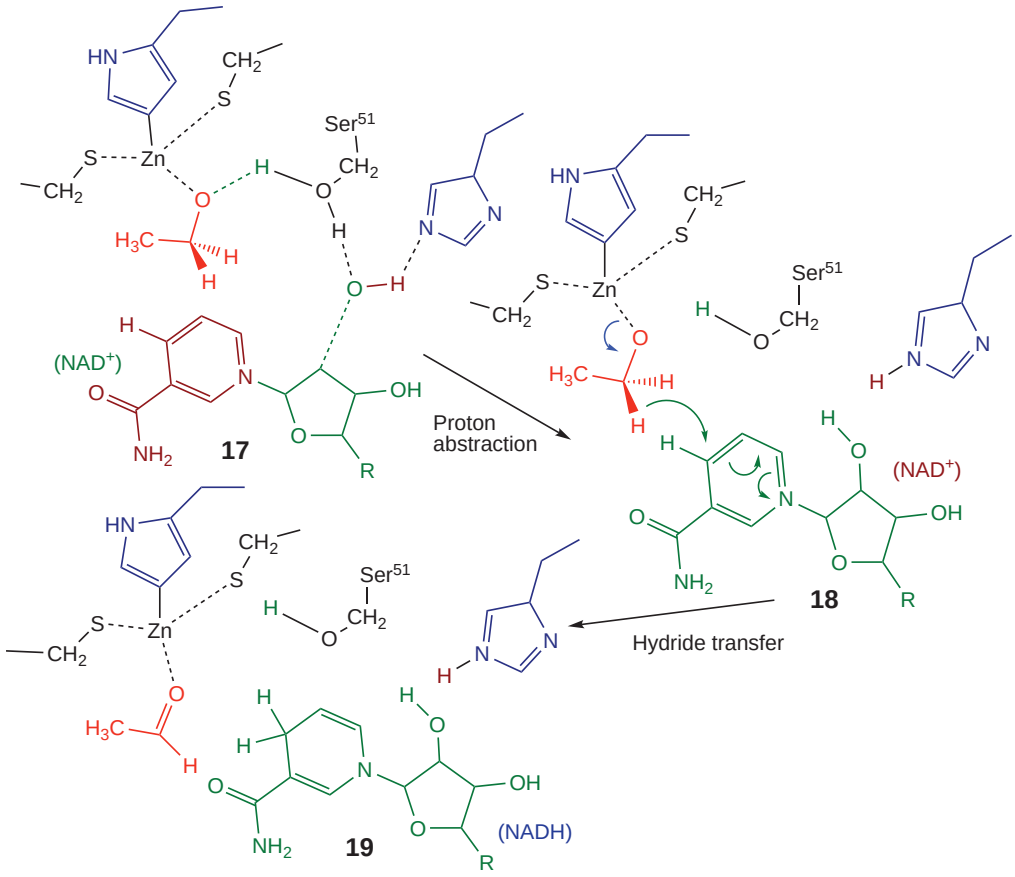


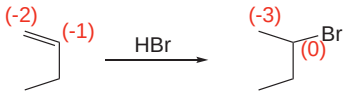
FIGURE 15.9 Mechanism of oxidation for the enzyme *liver alcohol dehydrogenase*. This research was originally published in Eklund, H.; Plapp, B.V.; Samama, J.P.; Branden, C.I. *Journal of Biological Chemistry*, 1982, 257, 14349 © the American Society for Biochemistry and Molecular Biology). This is an open access article distributed under the terms of the Creative Commons CC-license.

CORRELATION OF HOMEWORK WITH CONCEPTS

- Oxidation number is a convenient method to track the gain or loss of electrons in a reaction: 1, 17.
- Chromium (VI) oxidation of an alcohol proceeds by formation of a chromate ester, followed by loss of the α-hydrogen to form the C=O unit. Both PCC and PDC oxidize a secondary alcohol to a ketone, or a primary alcohol to an aldehyde: 2, 3, 4, 5, 18, 19, 23, 29.
- Dimethyl sulfoxide (DMSO) with oxalyl chloride at low temperature oxidizes an alcohol to a ketone or an aldehyde: the Swern oxidation: 6, 19.
- An alkene reacts with osmium tetroxide or potassium permanganate to give a cis-1,2-diol: 7, 8, 23, 29.
- Oxidation of an alkene with a peroxyacid or a dialkyldioxirane leads to an epoxide: 9, 10, 11, 16, 21, 22, 23, 24, 26, 27, 28, 29.
- Oxidative cleavage of an alkene with ozone followed by a reductive workup or an oxidative workup gives ketones and/or aldehydes or carboxylic acids: 12, 13, 20, 23, 25, 29.
- Oxidative cleavage of 1,2-diols with periodic acid or with lead tetraacetate yield aldehydes or ketones: 14, 15, 16, 29.
- Spectroscopy can be used to determine the structure of a particular molecule (see Chapter 13): 30, 31, 32, 33, 34.

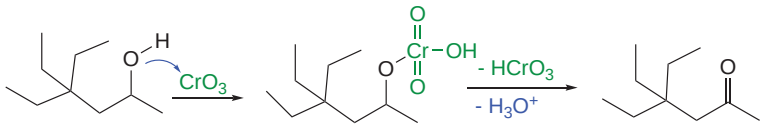
ANSWERS TO IN-CHAPTER QUESTIONS

15.1

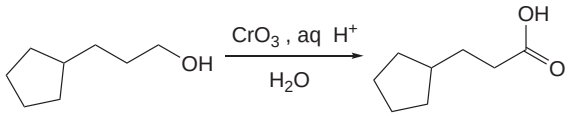


In this reaction, the terminal carbon loses one electron, as does C2. Since there is a net loss of two electrons, this reaction is an oxidation

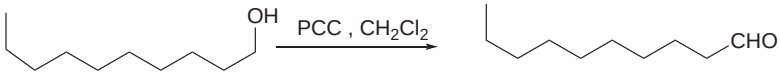
15.2



15.3



15.4



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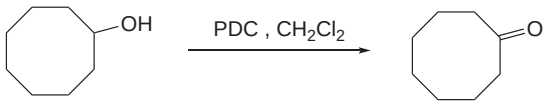

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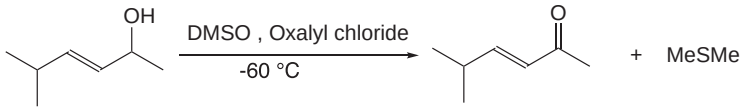

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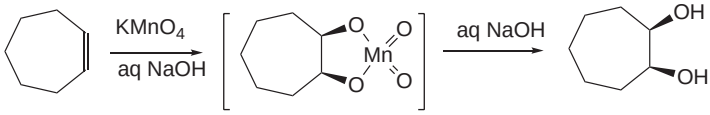

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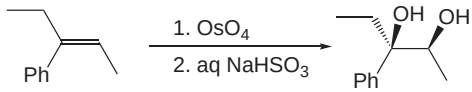

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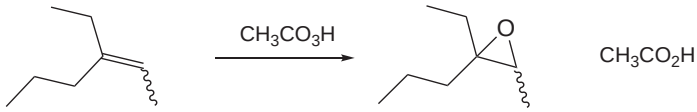

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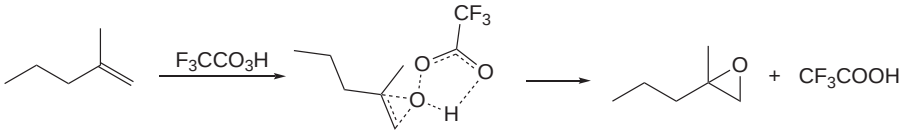

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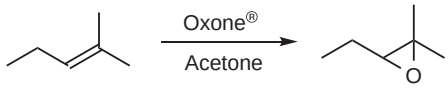

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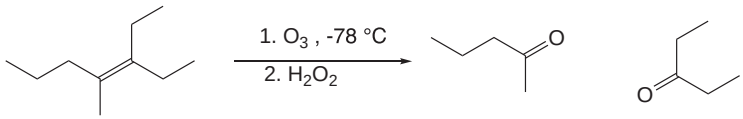

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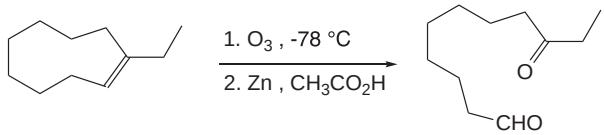

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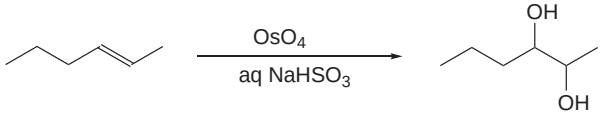

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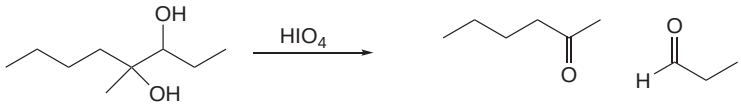

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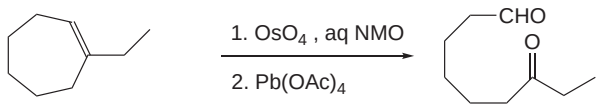
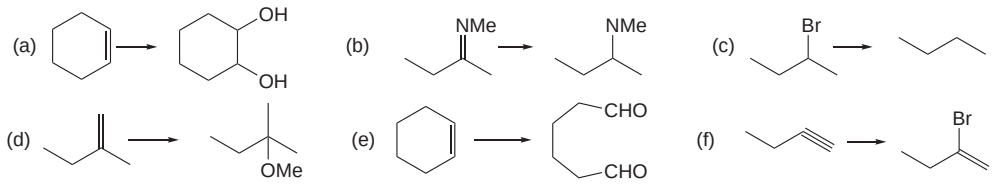
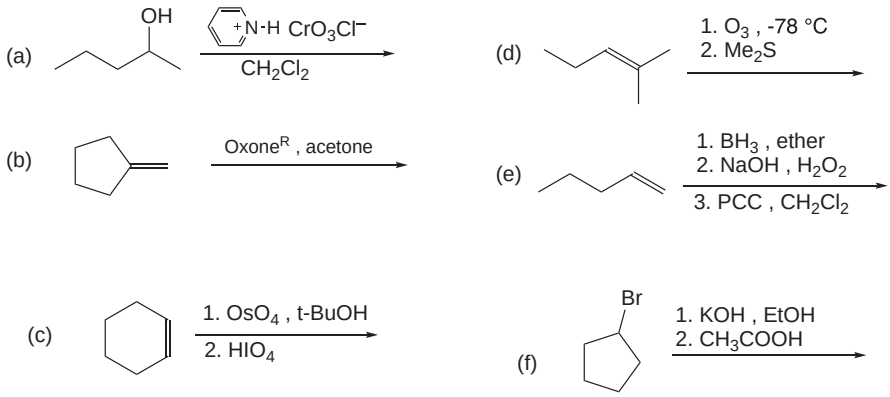


HOMEWORK

17. Categorize each of the following as an oxidation or a reduction using oxidation numbers:

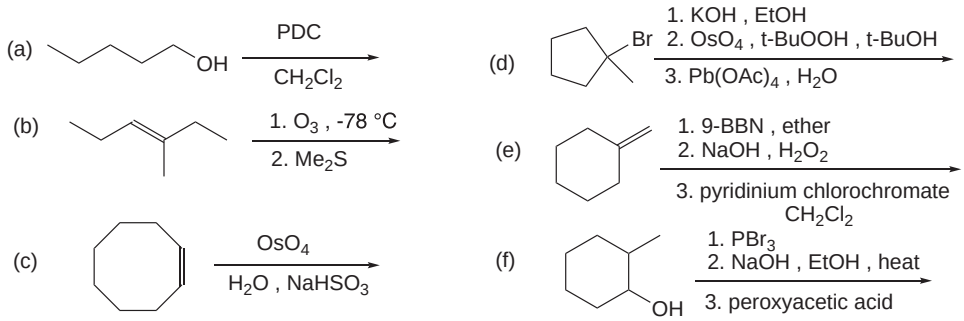


18. Give the major product for each of the following reactions:



19. Suggest a rationale for why Jones' oxidation of 4-methylpentan-2-ol is faster than that of 3,3-dimethylpentan-2-ol.
20. Give the major product for each of the following: (a) 4,4-Diphenylhexan-1-ol + CrO_3 and aq H_2SO_4 in acetone. (b) Cyclohexanemethanol + oxalyl chloride and DMSO at -60 °C. (c) Cycloheptanol + $(COCl)_2$/DMSO/-78 °C
21. What are the products if cycloocta-1,5-diene is treated with ozone, and then with hydrogen peroxide?
22. An alternative method for the preparation of an epoxide reacts a halohydrin (Section 10.5.3) with a base (e.g., sodium hydride). The resulting alkoxide undergoes an intramolecular Williamson ether synthesis. Draw the product expected when 2-bromohexan-1-ol reacts with NaH in THF. Based on the two carbons of the epoxide, is this transformation a net oxidation or a reduction?
23. Why does 3,4-dimethylhex-3-ene react with peroxyacetic acid faster than does hex-3-ene.
24. Peroxytrifluoroacetic acid (CF_3CO_3H) reacts faster than peroxyformic acid (HCO_3H) in an epoxidation reaction with *trans*-but-2-ene. Offer a reason why this is true.
25. Ozonolysis of a tetrasubstituted alkene (e.g., 1,2-dimethylcyclopentene) is faster than ozonolysis of a disubstituted alkene such as cyclopentene. Offer an explanation.
26. Epoxidation of 1-methylcyclopentene followed by treatment with aqueous acid (H^+) leads to a 1,2-diol. Suggest a mechanism for conversion of the epoxide to the diol.
27. Predict the major product formed when 2-methyloct-4*E*-en-3*R*-ol is subjected to reaction with L-(+)-DET, *tert*-BuOOH, Ti(O*i*P*r*)$_4$ in dichloromethane.

28. Draw the structure of the dialkyldioxirane formed when **1** (Section 15.4) reacts with Oxone®.
29. In each case, give the major product of the reaction.



Spectroscopic problems. Do not attempt these problems until you have read and understood Chapter 13.

30. Describe differences in the IR and ^{1}H NMR that will allow you to distinguish 3-phenylpentanal and 3-phenylpentan-2-one.
31. When 4-methylpentan-1-ol is treated with Jones reagent, it is possible to form an aldehyde and/or a carboxylic acid. Describe differences in the IR and ^{1}H NMR that will allow you to distinguish these two products. If both are formed, suggest a simple experimental technique that will separate them.
32. Given the spectral data, provide a structure for $C_9H_{18}O$: IR: 2967-2872, 2713, 1728, 14781469, 1395 cm^{-1}. ^{1}H NMR: 9.74 (s, 1H), 2.631.88 (m, 3H), 1.24-1.16 (m, 2H), 1.02 (d, 3H), 0.92 (s, 9H) ppm.
33. Given the following spectral data, provide a structure for $C_6H_{12}O$: IR: 3045, 2961-2863, 1483-1468, 1432, 1410, 1132, 1070, 955-917, 847-836 cm^{-1}. ^{1}H NMR: 2.9 (m, 1H), 2.73 (m, 1H), 2.45 (m, 1H), 1.53 (m, 2H), 1.45–1.39 (m, 4H), 0.92 (t, 3H) ppm.
34. Given the following spectral data, provide a structure for $C_8H_{16}O_2$: IR: 2960-2673, 1706, 1467-1456, 1417, 1063-943 cm^{-1}. ^{1}H NMR: 11.67 (broad s, 1H; this signal is diminished when washed with D_2O), 2.38 (m, 1H), 1.52-1.35 (m, 8H), 0.92 (broad t, 6H) ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-16.php

16

Reactions of Aldehydes and Ketones

This chapter will discuss two major chemical reactions of aldehydes and ketones. Reaction of nucleophiles with an aldehyde or ketone gives an alkoxide via acyl addition. Subsequent hydrolytic workup gives an alcohol. The carbonyl of aldehydes and ketones reacts as a Brønsted-Lowry base with a suitable acid to generate an oxocarbenium ion intermediate. This reactive intermediate will react with even weak nucleophiles.

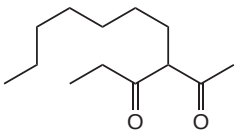
To begin this chapter, you should know the following points:

- Aldehydes and ketones (Sections 5.6.2).
- π-Bonds (Section 5.1–5.3).
- Leaving groups (Section 11.2).
- Carbocations (carbenium ions) (Section 7.2.1).
- Conformations of acyclic and cyclic compounds (Sections 8.1–8.5).
- Mechanisms (Section 7.10).
- Transition states (Section 7.6).
- Alkoxides react with aqueous acid to give an alcohol (Sections 6.4 and 6.7.2).
- Grignard reagents (Sections 14.1 and 14.2).
- Organolithium reagents (Section 14.3).
- Absolute configuration (Section 9.2).
- Diastereomers (Section 9.5).

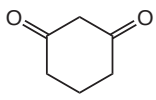
16.1 ALDEHYDES AND KETONES

Aldehydes and Ketones and Nomenclature

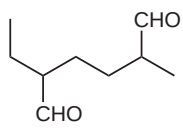
The structure and nomenclature of aldehydes and ketones was introduced in Section 5.9.2. In that section, only molecules that contained a single carbonyl unit were discussed. Many molecules have two ketone units, two aldehyde units, or a ketone and an aldehyde in the same molecule. A molecule with two ketone units is a dione and a molecule with two aldehyde units is a dial. The nomenclature rules require that the longest chain must contain both carbonyl carbons. An example of a diketone is 3-heptylhexane-2,4-dione. In a cyclic diketone, both carbonyl carbons are part of the ring as in cyclohexane-1,3-dione. A dialdehyde is named as a dial, the longest chain must include both carbonyl carbons. The example shown is 2-ethyl-5-methylhexanedial.



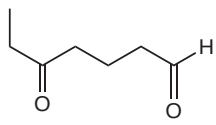
3-Heptylhexane-2,4-dione



Cyclohexane-1,3-dione



2-Ethyl-5-methylhexanedial

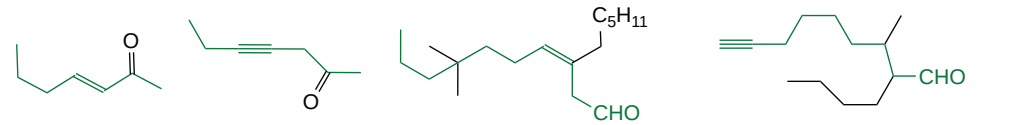


5-Oxoheptanal

Since the longest chain includes both CHO units and they are at each end of the chain, the carbonyl numbers are usually omitted. When there is a ketone and an aldehyde unit in the longest chain, the aldehyde takes priority and *-al* is used as the suffix. The term *oxo* is used to indicate the position of the other carbonyl carbon in that chain. The aldehyde-ketone shown, with a seven-carbon chain that has both a ketone carbonyl and an aldehyde unit is 5-oxoheptanal.

DOI: 10.1201/9781003174929-16

16.1 Draw the structures of 9,9-dichloro-4-cyclopropyl-8-oxodecanal and 2-methylcyclododecane-1,5,-dione.



(*E*)-Hept-3-en-2-one Hept-4-yn-2-one 3-Hexyl-7,7-dimethyldec-(3Z)-enal 2-Butyl-3-methylnon-8-ynal

Many compounds have two or more functional groups and the Cahn-Ingold-Prelog (CIP) selection rules (Section 9.2) are used to assign a priority for nomenclature. Four examples are shown. The C=O unit has a higher priority than the C=C or the C≡C units so the suffix will be -one. The first example is named as an en-one. The two priority groups are on opposite sides of the C=C unit so it is an *E*-double bond. The name is hept-(3*E*)-en-2-one. In the alkyne-ketone, the carbonyl has the higher priority, so it is named hept-4-yn-2-one. The alkene-aldehyde is named 3-hexyl-7,7-dimethyldec-(3*Z*)-enal. The alkyne-aldehyde is named 2-butyl-3-methylnon-8-ynal. The aldehyde unit is drawn using a shorthand version –CHO in both examples.

16.2 Write out the structure of 1-phenyl-(4S)-ethyldodec-(6Z)-en-2-one.
16.3 Draw the structure of deca-1,5-diyn-4-one.

Nucleophilic Acyl Addition

16.2 THE REACTION OF KETONES AND ALDEHYDES WITH STRONG NUCLEOPHILES

Acyl Addition. "C" Nucleophiles

In an S_N2 reaction, a nucleophile Y^- reacts at the electrophilic sp^3 carbon of an alkyl halide such as bromomethane to give the substitution product (Figure 16.1). The carbonyl group (C=O) in ketones and aldehydes is polarized with an *electrophilic* δ^+ carbon and a δ^- oxygen. A nucleophile will react with the δ^+ carbon of the carbonyl to form a new σ-covalent bond with cleavage of the weak π-bond. The two electrons in the π-bond are transferred to the oxygen atom to form an alkoxide anion, as shown in Figure 16.1. This reaction is called *nucleophilic acyl addition*. A nucleophile that gives the alkoxide product in good yield directly after reaction in an irreversible reaction is called a ***strong nucleophile.*** Common strong nucleophiles include carbon nucleophiles such as alkyne anions, Grignard reagents, and organolithium reagents. For example, the alkyne anion of but-1-yne reacts with butan-2-one to give the alkoxide product. Methylmagnesium bromide reacts as a nucleophile with butanal to give the bromomagnesium alkoxide. Similarly, 1-lithiopropane reacts with propanal to give the lithium alkoxide. Although Grignard reagents and organolithium reagents are poor nucleophiles in S_N2 type reactions, they are ***excellent*** nucleophiles with ketones or aldehydes. In all three reactions shown, the product of the reaction with the carbonyl is an alkoxide, so a second chemical reaction is necessary. A hydrolytic workup with aqueous acid converts the alkoxide to 4-methyloct-5-yn-4-ol, pentan-2-ol, or hexan-3-ol respectively. All three acyl addition reactions illustrate one type of reaction with different nucleophiles.

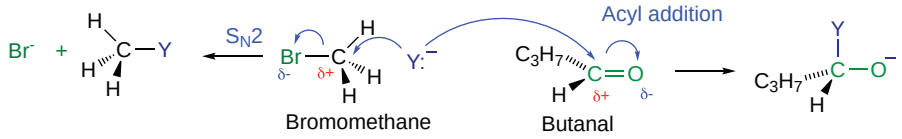
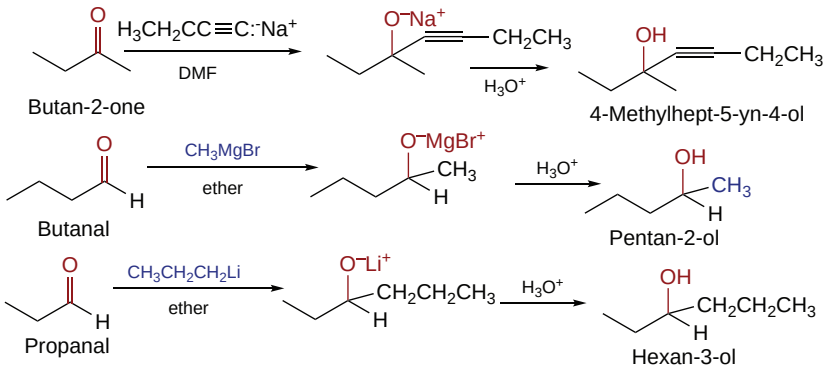
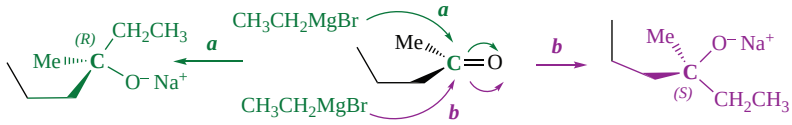


FIGURE 16.1 Aliphatic substitution versus acyl substitution with a generic nucleophile, Y^-.



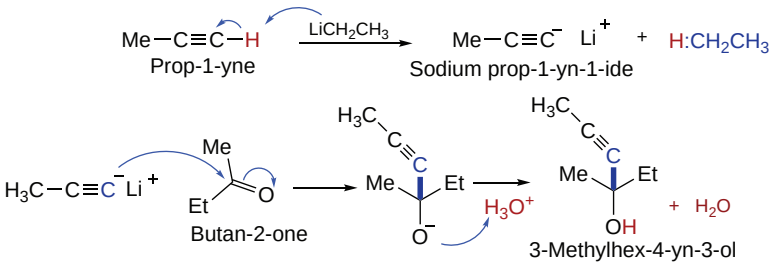
16.4 Draw the products that result when each of the following react with butanal in THF, with no other added reagents or reaction step: (a) KCN, (b) NaOEt, (c) HC≡C:-, and (d) NEt_3.

An aldehyde or ketone starting material such as butan-2-one does not contain a stereogenic carbon. An acyl addition reaction with an unsymmetrical ketone will create a stereogenic center. If a carbon nucleophile such as ethylmagnesium bromide approaches pentan-2-one from the "top" (path *a*), the oxygen is pushed "down" and the (*R*) enantiomer is formed. If the nucleophile approaches from the "bottom" (path *b*) the oxygen is pushed to the "top" and the (*S*) enantiomer is formed. There is nothing to bias approach of the nucleophile from one side or the other of the trigonal planar carbonyl carbon. Both enantiomers are formed in equal amounts, so the product is racemic.



In Section 11.3, the hydrogen atom of a terminal alkyne (e.g., prop-1-yne) was identified as a weak acid. The pK_a of a typical alkyne is ~25. A contributing factor to the acidity of the alkyne hydrogen is the sp-hybridization of the carbon. Terminal alkynes react with a suitable base such as sodium amide or an organolithium reagent to give the alkyne anion. Prop-1-yne reacts with ethyllithium to give lithium prop-1-yn-1-ide. Once formed, this nucleophile reacts with butan-2-one to give the expected alkoxide via acyl addition. Hydrolytic workup affords 3-methylhex-4-yn-3-ol.

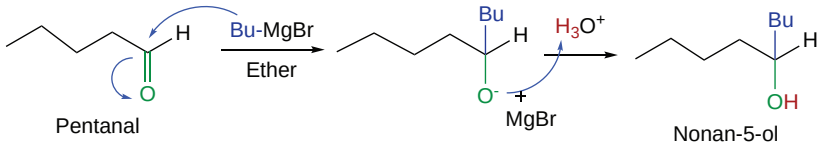
Alkyne Anions



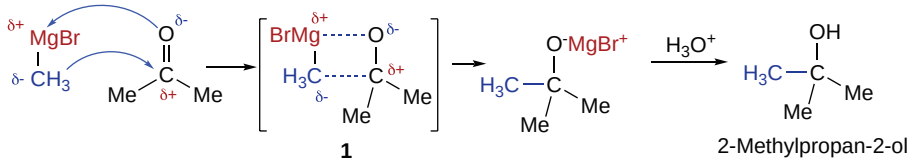
16.5 Draw the reaction sequence and final product(s) resulting from the reaction of 1-phenylethyne with 1. $NaNH_2$ and 2. 1-phenylbutanone and 3. dilute aqueous acid.

Organometallic compounds such as Grignard reagents (Sections 14.1 and 14.2) and organolithium reagents (Section 14.3) have a δ^- carbon. Grignard reagents react with aldehydes or ketones to give an alcohol product in a two-step process known as a *Grignard reaction.* In one example, pentanal reacts with butylmagnesium bromide in diethyl ether to afford an alkoxide product via acyl addition. Subsequent hydrolytic workup gives an 83% yield of

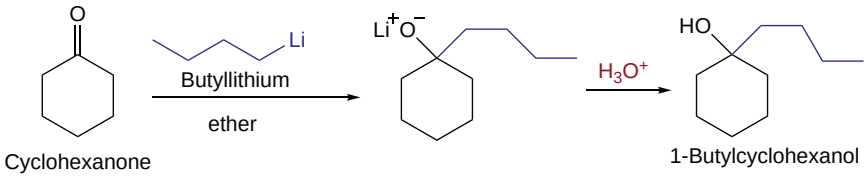
nonan-5-ol.[1] Note that an aldehyde reacts with the Grignard reagent to produce a secondary alcohol whereas ketones react to generate tertiary alcohols. The reaction of cyclohexanone with butylmagnesium bromide, for example, gives 1-butylcyclohexan-1-ol after hydrolytic workup, in 90% yield.[2]



16.6 Write out all reactions necessary to convert 1-iodo-3,3-dimethylpentane to 4-(1-methylethyl)-7,7-dimethyl-3-phenylnonan-4-ol.



Acyl addition reactions of Grignard reagents with aldehydes or ketones give an alkoxide product, but there is no reactive intermediate. Therefore, the transition state must be examined to understand how the reaction works. This reaction proceeds by a *four-center transition* state, **1**, which leads to the alkoxide. After hydrolytic workup in a second step, the product is 2-methylpropan-2-ol. The actual mechanism may involve radical intermediates that ultimately lead to the alkoxide.[3]



As with Grignard reagents, organolithium reagents are strong nucleophiles in reactions with aldehydes and ketones. The reaction of an organolithium reagent (e.g., *n*-butyllithium) with cyclohexanone gave 1-butylcyclohexan-1-ol in 89% yield after an aqueous acid workup.[4]

16.7 Draw the transition state and final product formed when methylmagnesium bromide reacts with cyclobutanone.

16.8 What is the product when butyllithium reacts with cyclobutanone followed by hydrolysis? What is the product when butyllithium reacts with pentan-3-one followed by hydrolysis?

In addition to Grignard reagents and organolithium reagents, other organometallic reagents also react with aldehydes and ketones. Lewis acids are often added to facilitate the reactions with other metal compounds. Tetravalent tin complexes such as allyltin

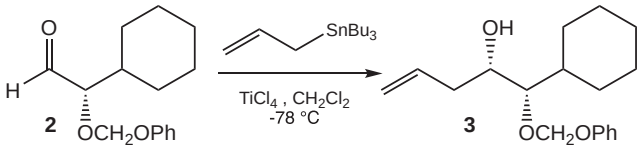
[1] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.40, p. 537.

[2] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.), *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, NY, 1994, Exp. 5.41, p. 538.

[3] Smith, M.B. *March's Advanced Organic Chemistry, 8th ed,* John Wiley & Sons, Inc., Hoboken, NJ, 2020, pp. 1133-1134.

[4] Stowell, J.C. *Carbanions in Organic Synthesis* John Wiley & Sons, NY, 1979, p. 57.

compounds add to aldehydes and ketones in the presence of a Lewis acid.[5] An example is the reaction of chiral aldehyde (**2**) with allyltributyltin and the Lewis acid titanium tetrachloride[6] to give 99% of the (*S,S*)-alcohol (**3**). Different Lewis acids can be used and the stereoselectivity of the reaction depends on the nature of the Lewis acid.



Yoshito Kishi (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Ketones and aldehydes react with a mixture of chromium (II) chloride and lithium aluminum hydride to give an acyl addition product. Lithium aluminum hydride ($LiAlH_4$) is a reducing agent, as will be described in Section 17.3. It reacts with the Cr(II) reagent ($CrCl_3$) to give the active Cr(II) reagent, $CrCl_2$. The reaction of heptanal and 1-bromo-3-methylbut-2-ene with $CrCl_3$ and $LiAlH_4$, for example gave 3,3-dimethyldec-1-en-4-ol in 83% yield with good diastereoselectivity.[7] It was determined that trace amounts of nickel (II) are present in commercially available chromium, and the addition of a catalytic amount of nickel dichloride ($NiCl_2$) to the reaction improved the reliability of what is now known as the *Nozaki-Hiyama-Kishi reaction*.[8] The reaction is named after the work of Tamejiro Hiyama (Japan), Hitoshi Nozaki (Japan), and Yoshito Kishi (Japan-USA). A generic example is the reaction of aldehyde **4** with vinyl iodide **5** to give alcohol **6**. This reaction is one of the many contributions of Yoshito Kishi (Japan-USA), a professor of organic chemistry at Harvard University. Professor Kishi has developed new chemical reactions and published many total syntheses of complex natural products. Apart from his important work in total synthesis and methods development, he also developed a NMR database of various molecules in chiral solvents.[9]

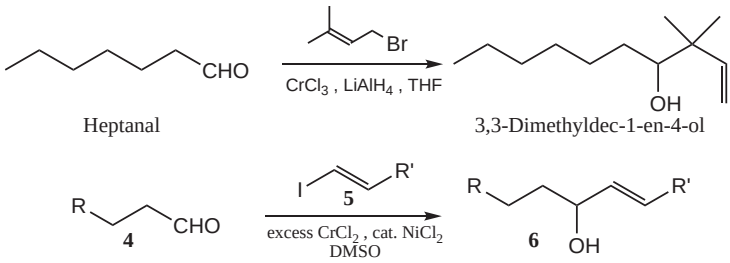
[5] For reactions of this type, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, 1999, pp. 373–378.

[6] Keck, G.E.; Boden, E.P. *Tetrahedron Letters* 1984, 25, 265–268.

[7] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *Journal of the American Chemical Society* 1977, 99, 3179–3181; (b) Cintas, P. *Synthesis* 1992, 248–257.

[8] Jin, H.; Uenishi, J.; Christ, W.J.; Kishi, Y. *Journal of the American Chemical Society* 1986, 108, 5644–5646. Also see Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *Journal of the American Chemical Society* 1986, 108, 6048–6050; Wessohann, L.A.; Scheid, G. *Synthesis* 1999, 1–36 (see pp. 16–18).

[9] (a) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Journal of the American Chemical Society* 2001, 123, 2076–2078; (b) Kobayashi, Y.; Hayashi, N.; Tan, C.-H.; Kishi, Y. *Organic Letters* 2001, 3, 2245–2248; (c) Hayashi, N.; Kobayashi, Y.; Kishi, Y. *Organic Letters* 2001, 3, 2249–2252; (d) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Organic Letters* 2001, 3, 2253–2258.



Cram's Rule

16.3 STEREOSELECTIVITY

As mentioned in Section 16.2, when a nucleophile reacts with an aldehyde or an unsymmetrical ketone, a new stereogenic center can be formed. If the ketone or aldehyde already has a stereogenic center, then a second stereogenic center and a diastereomer is formed by the acyl addition reaction. The newly formed stereogenic center in alcohol product will not be enantiopure, but there is an existing stereogenic center. One diastereomer can be formed in excess relative to the other so the reaction may be diastereoselective. There are models that can be used to predict the major diastereomer. One of the older and more useful models is called the *Cram open chain model (Cram's model)*. If this model applies to a reaction it is said to follow *Cram's rule*.[10] The model is named after Nobel laureate Donald J. Cram (USA; 1919–2001). This model uses a Newman projection such as **7** and assumes a kinetically controlled reaction. A kinetically controlled reaction for asymmetric 1,2-addition to aldehydes and ketones is non-equilibrating and non-catalytic, as shown in Figure 16.2. The

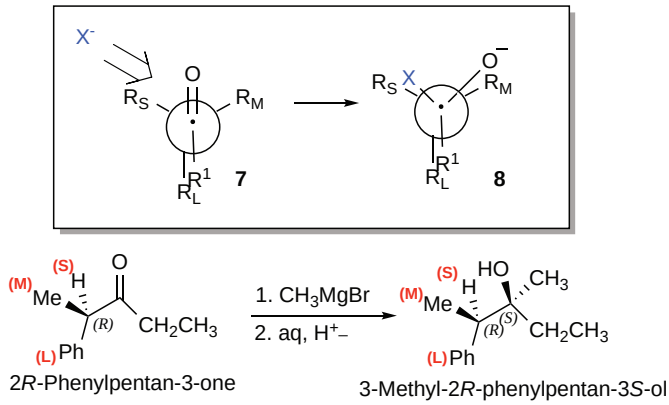


FIGURE 16.2 The Cram model for predicting stereochemistry

three groups in **7** attached to the stereogenic center are labeled R_S (small substituent), R_M (middle-sized substituent), and R_L (large substituent). It is assumed that the Cram model **7** is the predominant rotamer and that it mimics the transition state for reaction. The large substituent (R_L) is assumed to be syn- to the R^1 group attached to the carbonyl. In other words, the R_L substituent and the R^1 group are eclipsed. The nucleophile is delivered from the less sterically hindered face, over the smallest substituent R_S, to give **8** as the major diastereomer. The stereoselectivity of the reaction is determined by the O↔R_S or O↔R_M interaction. As the size difference between R_S and R_M increase, selectivity improves. If R_S and R_M are close in size, this model predicts little or no selectivity. As the size of R^1 increases, the

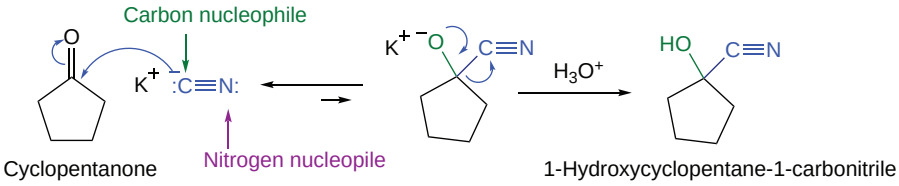
[10] (a) Cram, D.J.; AbdElhafez, F.A. *Journal of the American Chemical Society* 1952, 74, 5828–5835; (b) Cram, D.J.; Kopecky, K.R. *Journal of the American Chemical Society* 1959, 81, 2748–2755; (c) See also Mengel, A. Reiser, O. *Chemical Reviews* 1999, 99, 1191–1224; (c) Eliel, E.L.; Wilen, S.H.; Mander, L.N. *Stereochemistry of Organic Compounds* Wiley, NY, 1994, p 879.

proportion of the anti-product increases. This model also assumes the RL↔R^1 interaction is minimal, which is not entirely correct. Application of Cram's rule is illustrated by the reaction of 2*R*-phenylpentan-3-one and methylmagnesium bromide. This reaction is predicted to give 3-methyl-2*R*-phenylpentan-3*S*-ol as the major product. Note that R_S, R_M and R_L are labeled for convenience.

16.4 THE REACTION OF KETONES AND ALDEHYDES WITH WEAK NUCLEOPHILES

Although strong nucleophiles react with aldehydes and ketone to give an alkoxide via acyl addition, weak nucleophiles react reversibly and give poor yields of an acyl addition product. The cyanide ion was discussed as a good nucleophile in S_N2 reactions in Section 11.3. As noted, cyanide is a *bidentate nucleophile*, but carbon is usually the dominant nucleophile when NaCN or KCN are used. The reaction of cyclopentanone and potassium cyanide gave 1-hydroxycyclopentane-1-carbonitrile, a *cyanohydrin*, in low yield after hydrolytic workup. This reaction is reversible. The cyanide ion is a clearly a moderate nucleophile in reactions with a carbonyl.

Cyanide



An important method to improve the reaction exploits the acid-base chemistry of aldehydes and ketones. In the presence of a Brønsted-Lowry acid the oxygen atom reacts as a base to give a resonance-stabilized intermediate called an *oxocarbenium ion,* as shown in Figure 16.3. The reaction of octan-3-one with H_2SO_4, for example, gives an oxocarbenium ion with two resonance contributors as the conjugate acid. The hydrogen sulfate counterion

Carbonyls React as Bases

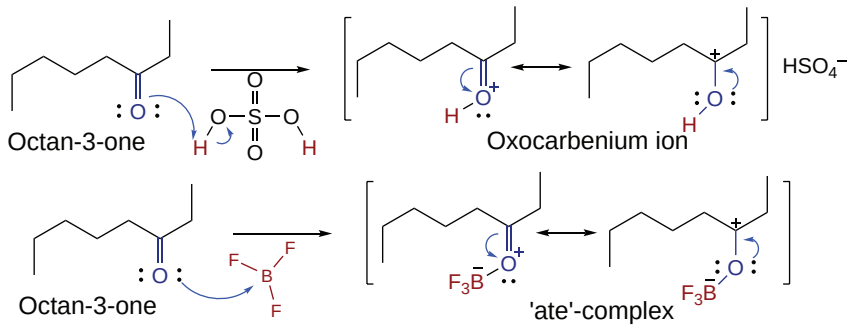


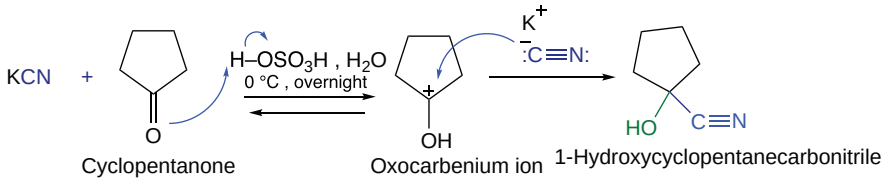
FIGURE 16.3 Acid–base reactions of octan-3-one.

is the conjugate base. It is noted that octan-3-one also reacts with the Lewis acid BF_3 to form an "ate" complex, which is an oxocarbenium ion with the two resonance contributors shown. An oxocarbenium ion carbon is more electrophilic and therefore more reactive than the acyl carbon of an aldehyde or ketone. Indeed, the reaction of a carbonyl compound with an acid to generate an oxocarbenium ion is a general solution to the problem of poor reactivity of weak nucleophiles.

16.9 Draw the oxocarbenium ion formed when butanal reacts with methanesulfonic acid. When pentan-2-one reacts with H_2SO_4.

16.10 Draw the product of the reaction between butan-2-one and KCN, in the presence of an acid catalyst.

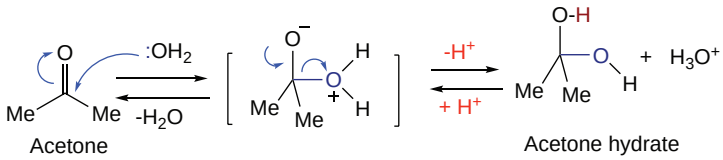
The cyanide ion was shown to be a moderate nucleophile in acyl addition reactions. When cyclopentanone reacts with KCN and H_2SO_4 at 0 °C, 1-hydroxycyclopentanecarbonitrile was formed in 96% yield.[11] It is therefore possible to make a reversible acyl addition reaction with a weak nucleophile usable by exploiting the acid-base reaction of carbonyl using an acid catalyst.



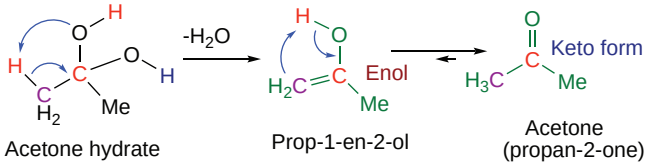
Water and Hydrates

16.4.1 REACTION WITH WATER

Weak nucleophiles react reversibly with an aldehyde or a ketone. For this reason, the acyl addition product is usually formed in poor or very poor yield. The product of an acyl addition reaction with a weak nucleophile usually contains a good leaving group, which makes the reaction reversible. In the reaction of water with ketones or aldehydes the oxygen of water reacts with the acyl carbon to give an intermediate oxonium ion, which is unstable.



Since the $-OH_2^+$ unit is a water molecule bound to carbon, it is an excellent leaving group. The alkoxide unit donates electrons back to the adjacent carbon, which expels the water to regenerate the carbonyl group in acetone. The reaction is therefore reversible, and the equilibrium lies far to the left (*K* is very small). If there is a small concentration of the initially formed oxonium ion, proton transfer to the alkoxide unit may generate acetone hydrate in the aqueous medium. In most cases *hydrates are inherently unstable*.

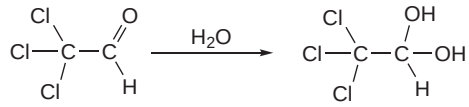


The α carbon (the carbon atom attached to the δ+ carbon bearing both OH groups) is polarized δ- so the attached hydrogen is δ+. This hydrogen atom is slightly acidic and reacts intramolecularly via proton transfer. Subsequent loss of water forms an *enol*, which is formally defined as a molecule with an OH group attached directly to a C=C unit (Sections 10.8.2,4,5). Enols are unstable and they exist in equilibrium with the corresponding carbonyl compound via *keto–enol tautomerism*. When water is mixed with acetone, only acetone and water are isolable, so there appears to be no reaction. In fact, an unstable hydrate product is formed but cannot be isolated. Water is considered to be a weak nucleophile with aldehydes or ketones because no isolable product is formed.

16.11 Draw the mechanism for the hydration reaction of propanal.

[11] Ayerst, G.G.; Scholfield, K. *Journal of the Chemical Society*, 1958, 4097–4104.

Although most hydrates are unstable, they can be isolated in some cases. If the aldehyde or ketone has no hydrogen atoms on the carbon adjacent to the carbon bearing the two OH units, the hydrate is usually stable enough for isolation. An example is trichloroethanal (trichloroacetaldehyde), commonly called *chloral*.



2,2,2-Trichloroacetaldehyde 2,2,2-Trichloroethane-1,1-diol

Chloral reacts with water to form a stable hydrate, 2,2,2-trichloroethane-1,1-diol (otherwise known as *chloral hydrate*). Chloral hydrate is stable because there are no α-hydrogen atoms to lose to form an enol. Chloral hydrate is a white, crystalline solid first prepared in 1832 and it is a depressant used to induce sleep (a sedative). It is more potent when mixed with alcohol.

16.12 Draw the hydrate expected from 2,2,2-triphenylethanal and speculate on its stability.

16.4.2 REACTION WITH ALCOHOLS

Alcohols and Acetals

Alcohols are weak nucleophiles in their reaction with carbonyl compounds, like water. In the absence of an acid catalyst, ethanol may add to butanal to give an oxonium ion. Once formed it contains an ethanol unit [C—O(H)Et$^+$], which is a good leaving group. Therefore, acyl addition reaction is reversible, with the equilibrium lying on the side of the aldehyde or ketone. In the presence of an acid catalyst, alcohols react with aldehydes or ketones to give a stable product known as an *acetal*, with two alkoxy units $R_2C(OR)_2$. The mechanism of this reaction can be deduced by a walkthrough of required steps. The two alkoxy units in the product come from the alcohol but reaction at the acyl carbon must occur in a stepwise manner. Water is a product, and the oxygen of water comes from the carbonyl oxygen, requiring two stepwise protonation reactions. Therefore, the carbonyl reacts with the acid catalyst to give an oxocarbenium ion, allowing one equivalent of the alcohol to react. Loss of a proton from the oxonium ion gives a neutral product that contains an OH unit. Protonation of the OH unit gives the water leaving group and forms an oxocarbenium that allows a reaction with the second equivalent of the alcohol. Loss of a proton gives the acetal.

The Acetal-Alcohol Equilibrium

The complete reversible mechanism for the conversion of butanal to 1,1-diethoxybutane is shown in Figure 16.4. The sequence begins with the reaction of butanal and the acid catalyst to give the resonance-stabilized oxocarbenium ion, **9**. One molecule of ethanol reacts with the positively charged carbon of **9** to give oxonium ion **10**, which is a strong acid. An acid-base reaction of **10** with either butanal or ethanol as a base will give the neutral product,

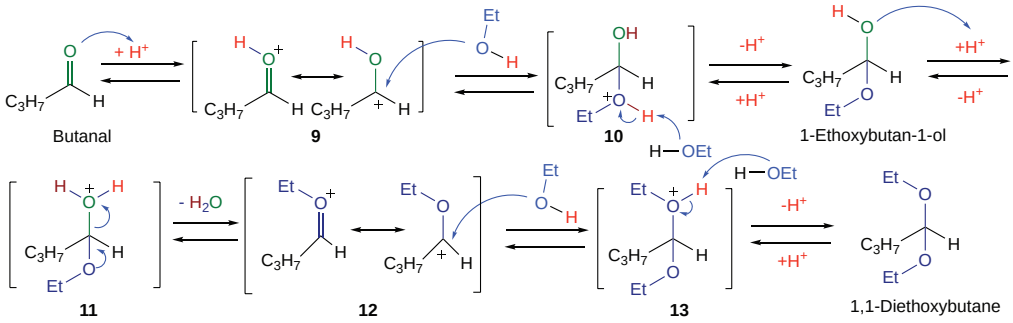


FIGURE 16.4 Mechanism of acetal formation for the reaction of butanal with ethanol.

1-ethoxybutan-1-ol, which is unstable to the reaction conditions. The 1-ethoxybutan-1-ol has an HO—C—OEt unit and it is called a *hemiacetal* (the term "hemi" means half. Remember that all steps in this sequence are reversible, and if the OEt unit in this product is protonated, **9** is regenerated. However, water is a product and the only way to produce water is to protonate the OH unit to yield **11**, which has water as a leaving group. Loss of water yields a new resonance-stabilized oxocarbenium ion **12**. The second molecule of ethanol can now react with the positively charged carbon atom of **12** to give oxonium ion **13**. Loss of a proton in a final acid-base reaction with ethanol gives the acetal product, 1,1-diethoxybutane.

This mechanism of acetal formation in Figure 16.4 is valid for any aldehyde or ketone starting material with virtually any alcohol. This mechanism is the logical step-by-step description of each bond being made or broken and each atom or group being gained or lost, one bond at a time. Only a catalytic amount of acid is required because H^+ is regenerated during the course of the reaction. The catalyst load is typically 1–10%. It is noted that sulfuric acid is a powerful oxidizing acid. For this reason, a sulfonic acid (e.g., methanesulfonic acid, Section 18.12) is commonly used as a catalyst. The sulfonic acids do not cause as many of the problems associated with sulfuric acid. Throughout this book the acid catalyst is often referred to as H^+, but the actual acid is usually sulfuric acid or a sulfonic acid.

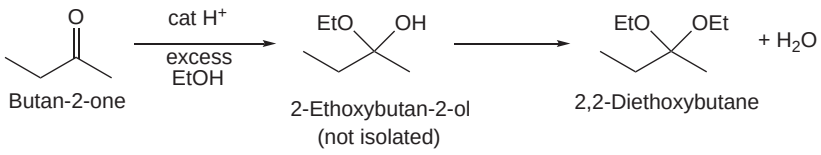
16.13 Write out the complete mechanism for the reaction of cyclopentanecarbaldehyde with methanol in the presence of an acid catalyst.

In the conversion of butanal to 1,1-diethoxybutane in Figure 16.4, every step is reversible. To isolate the acetal product, this equilibrium must be shifted toward the acetal product. Remember *Le Chatelier's principle*, named after Henry Louis Le Chatelier (France-Italy; 1850–1936). "Changes in concentration, temperature, volume or partial pressure in a chemical system at equilibrium will shift the equilibrium to counteract that change." Changing the concentration and temperature or removal of a product from the reaction medium are the most common experimental modifications. Ethanol is one of the reactants in Figure 16.4 and using a large excess as the solvent will shift the equilibrium toward the acetal.

Another way to shift the equilibrium is to remove the water product from the reaction medium. A "drying agent" may be added to the reaction to react with the water. The drying agent should *not* react with the aldehyde, the alcohol or the acid catalyst, however. Common but often inefficient drying agents are sometimes used, including molecular sieves 3Å and 4Å, which are highly porous zeolites that trap water when thermally activated. The less effective magnesium sulfate ($MgSO_4$) or calcium chloride ($CaCl_2$) can be used occasionally. An alternative method for removing water relies on the use of a solvent that forms an *azeotrope* with water. An azeotrope is defined as a constant boiling mixture that often boils at a temperature different from its components. Ethanol and water form an azeotrope containing 89.4% of ethanol that boils at 78.2 °C, lower than the boiling point of ethanol (78.5 °C) or water (100 °C).[12] Therefore, ethanol and water cannot be separated by distillation. A ternary azeotrope of benzene (53.9%), ethanol (22.8%) and water (23.3%) is also known. It is possible to remove water by azeotropic distillation using a specialized piece of equipment called a *Dean-Stark trap*.[13] To put this technique in perspective, a *zeotrope* is defined as a mixture where all components have different boiling points and the components can, in principle be separated by distillation.

[12] *CRC Handbook of Chemistry and Physics*, 94th ed., CRC Press, Inc., Boca Raton, FL, 2013–2014, pp. 6–212 to 6–214.

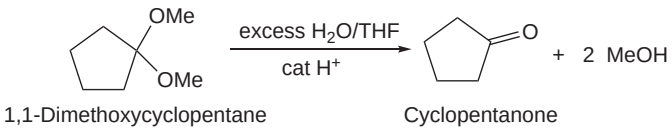
[13] A Dean-Stark trap is a piece of laboratory glassware used to collect water. It is used in combination with a reflux condenser for continuous removal of the water produced during a chemical reaction performed at the reflux temperature of the mixture. The mixture of solvent and water is collected in a trap, overflows and is returned to the reaction flask. The water separates to the bottom of the trap and can be removed so only the solvent is returned.



Ketones also react with alcohols and an acid catalyst. The arcane term for this product is ketal. However, dialkoxy derivatives of both aldehydes and ketones are defined as *acetals*. If butan-2-one reacts with ethanol in the presence of a catalytic amount of an acid catalyst, the isolated product is 2,2-diethoxypropane. The reaction mechanism is the same as that in Figure 16.4 except for the use of the butan-2-one starting material.

16.14 Write out the complete mechanism for the conversion of cyclohexanone to 1,1-dimethoxycyclohexane using methanol and an acid catalyst.

Since the reaction is an equilibrium, it is possible to convert an acetal back to the aldehyde or ketone precursor by heating with excess water and an acid catalyst. This reaction uses a large excess of water to shift the equilibrium back toward the aldehyde or ketone starting material. This transformation is illustrated by the reaction of 1,1-dimethoxycyclopentane with an acid catalyst and a large excess of water, which is often a cosolvent with an aprotic solvent. The product is cyclopentanone along with two molar equivalents of methanol. The mechanism is the exact reverse of acetal or ketal formation, except that an excess of water is the reactant, and the alcohol is the leaving group.



16.15 Write out a mechanism for the conversion of 3,3-diethoxypentane to pentan-3-one using the reverse reactions in Figure 16.4 as a guide.

In preceding sections, aldehydes or ketones were shown to react with *two* molar equivalents of alcohol and therefore two hydroxy units to give an acetal. Diols such as ethane-1,2-diol (called ethylene glycol) have two hydroxyl units that are tethered together by a carbon chain. In other words, each molecule of a diol contains two molar equivalents of an OH unit. When diols react with aldehydes and ketones, the product is a *cyclic* acetal.

The mechanism of the reaction with a diol is the same as that shown in Figure 16.4, but both hydroxyl units come from ethanediol. All steps are reversible. Initial reaction with the carbonyl oxygen of butanal yields oxocarbenium ion **9** in Figure 16.5. Subsequent reaction with one OH of ethane-1,2-diol gives oxonium ion **14**, where the second OH unit of the diol unit is "tethered" by the two carbon chain. Loss of the acidic proton from oxonium ion **14** generates the hemiacetal, 1-(2-hydroxyethoxy)butan-1-ol. Protonation of the OH oxygen yields oxonium ion **15**, which loses water to form oxocarbenium ion **16**. The electrophilic carbon reacts with the second hydroxyl at the end of the ethylene glycol chain to give **17**. It is known that intramolecular reactions usually have lower entropy than intermolecular reactions. The intramolecular reaction of the OH group is therefore faster than the intermolecular reaction of an OH with a separate molecule of ethane-1,2-diol. The lower energy cyclization reaction gives **17** and loss of a proton affords the final product, cyclic acetal 2-propyl-1,3-dioxolane. A five-membered cyclic acetal is a *1,3-dioxolane*, with the ring numbered such that the oxygen atoms are O1 and O3 with a propyl substituent is at C2 (Section 23.5). Ketones react with diols in a manner identical to aldehydes. An example is the reaction of butan-2-one with propane-1,3-diol to form a six-membered ring acetal that contains two oxygen atoms. This product is a *1,3-dioxane*. The oxygen atoms are numbered O1 and O3, with an ethyl and methyl groups at C2. The name is 2-ethyl-2-methyl-1,3-dioxane.

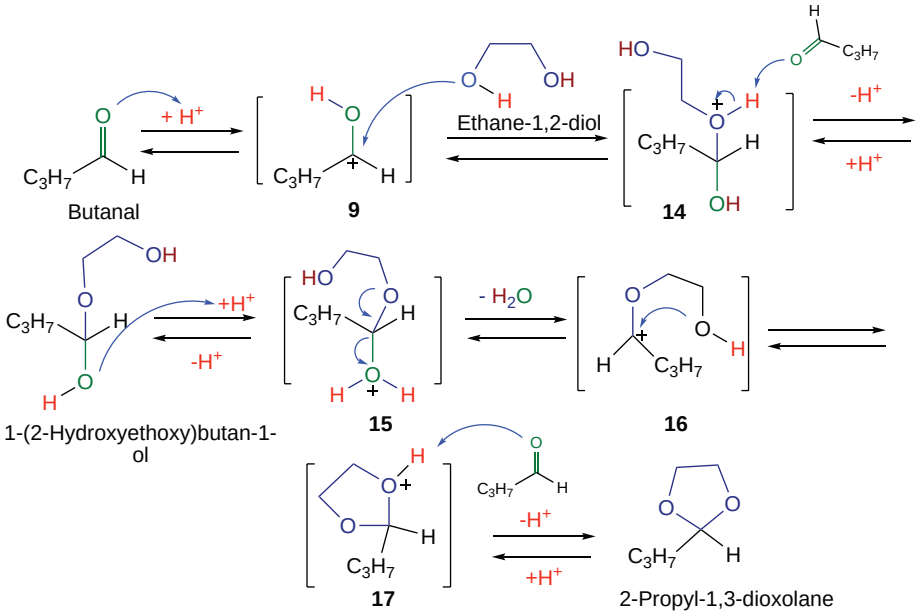
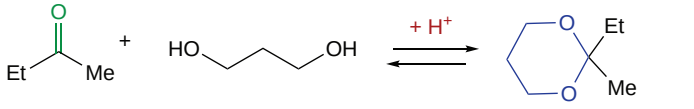


FIGURE 16.5 Mechanism of reaction between butanal and ethane-1,2-diol.

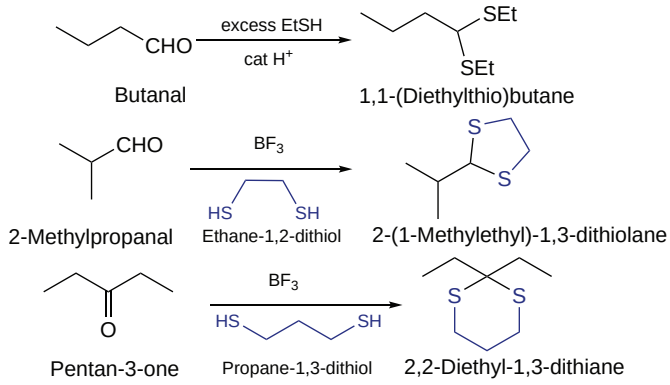
16.16 Write out the complete mechanism for the reaction of butan-2-one and propane-1,3-diol to yield the acetal.



Reactions with Alcohols

Thiols react with aldehydes or ketones in a manner similar to alcohols. If butanal reacts with two equivalents of ethanethiol (CH_3CH_2SH), in the presence of an acid catalyst, the product is 1,1-(diethylthio)butane, a *dithioacetal*. The reaction mechanism is identical to that for the reaction with ethanol (see Figure 16.4) except that CH_3CH_2SH replaces CH_3CH_2OH. The term thio- is used to show the presence of a sulfur atom rather than an oxygen atom. The key intermediate in this latter reaction is a *hemi-thioacetal*. Ketones also react with thiols to form a dithioacetal. An example is the reaction of cyclohexanone with propanethiol to give 1,1-(dipropylthio)cyclohexane. Both 1,2- and 1,3-thiols react with aldehydes and ketones to form cyclic dithioacetals.

Dithioacetals



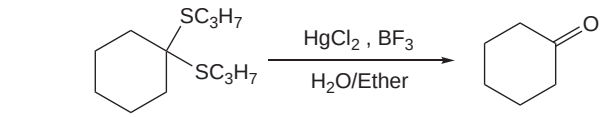
Ethanedithiol derivatives form a five-membered ring that contains two sulfur atoms known as a *1,3-dithiolane*. Propanedithiol derivatives form a six-membered ring with two

sulfur atoms known as a *1,3-dithiane*. The reaction of ethane-1,2-dithiol ($HSCH_2CH_2SH$) and 2-methylpropanal gives 2-(1-methylethyl)-1,3-dithiolane. When pentan-3-one reacts with 1,3-propanedithiol ($HSCH_2CH_2CH_2SH$), the product is 2,2-diethyl-1,3-dithiane. One difference is the use of a Lewis acid (e.g., BF_3) rather than a Brønsted-Lowry acid to initiate the reaction since better yields of product are obtained. Many Lewis acids have a great affinity for sulfur and coordination with a Lewis acid makes the reaction less reversible.

16.17 Write out the complete mechanism for the formation of 2-ethyl-1,3-dithiolane from propanal and ethanedithiol, but use H^+ as a catalyst.

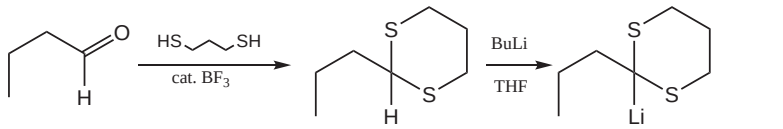
Dithioacetals can be converted back to the aldehyde or ketone under acidic conditions in the presence of an excess of water because every step is reversible, just as with acetals. Aqueous hydrolysis of dithioacetals requires somewhat different conditions when compared to acetals, and water-compatible Lewis acids (e.g., BF_3 or mercuric, Hg^{2+}, salts) are used. The dithioacetal 1,1-(dipropylthio)cyclohexane, for example, is converted back to cyclohexanone when it is treated with $HgCl_2$ (mercuric chloride) and BF_3 (boron trifluoride), in aqueous ether.

Reactions of Thiols

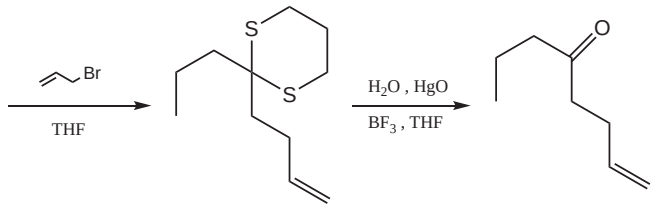


1,1-(Dipropylthio)cyclohexane Cyclohexanone

Dithianes are useful reagents for alkylation reactions. Propane-1,3-dithiol is the usual precursor for the preparation of dithianes by reaction with an aldehyde as described above. The hydrogen atom at C2 is a weak acid due to the polarizing effect of the sulfur. The pK_a of the C2 hydrogen in a 1,3-dithiane is 31–33[14] and a strong base such as butyllithium is required. A typical application is the reaction of butyraldehyde with propane-1,3-dithiol to give 2-propyl-1,3-dithiane.



Butyraldehyde 2-Propyl-1,3-dithiane (2-Propyl-1,3-dithian-2-yl)lithium



2-(But-3-en-1-yl)-2-propyl-1,3-dithiane Oct-7-en-4-one

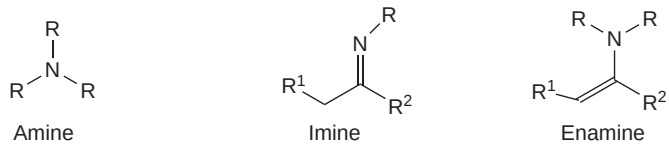
The reaction of the dithiane with butyllithium generates (2-propyl-1,3-dithian-2-yl)lithium. This nucleophile reacts with an alkyl halide (Section 11.2), as illustrated by the S_N2 reaction of allyl bromide to give 2-(but-3-en-1-yl)-2-propyl-1,3-ditiane. Subsequent reaction with a Lewis acid such as mercuric oxide/boron trifluoride in aqueous THF[15] generates oct-7-en-4-one. Therefore, conversion of the aldehyde to the dithiane makes it possible to convert the acyl carbon to a nucleophile, allowing an acyl addition reaction.

[14] (a) Streitwieser, Jr., A.; Caldwell, R.A.; Granger, M.R. *Journal of the American Chemical Society* 1964, 86, 3578–3579; (b) Streitwieser, Jr., A.; Maskornick, M.J.; Ziegler, G.R. *Tetrahedron Letters* 1971, 3927–3930.

[15] (a) Seebach, D.; Corey, E.J. *Journal of Organic Chemistry* 1975, 40, 231–237; (b) Seebach, D. *Synthesis* 1969, 17–36.

16.4.3 REACTION WITH AMINES

Amines were introduced in Section 5.5.3. In addition to their reaction with alkyl halides, amines react with aldehydes and ketones to give important nitrogen containing compounds. Two examples are an *imine* (characterized by a C=N unit) and an *enamine* (characterized by a C=C-N unit).



If a primary amine (e.g., methanamine) reacts with acetone, acyl addition leads to an alkoxide ammonium salt ($^{-}$O–C–$^{+}$NH$_2$CH$_3$). The charged $^{+}$NH$_2$Me unit is a good leaving group, so this reaction is reversible and does not generally give a good yield of a product. As with alcohols, problems due to reversibility are solved by the use of a suitable acid catalyst. The acid-catalyzed reaction of acetone and methylamine is shown in Figure 16.6. The initial reaction generates oxocarbenium ion, **18**, which reacts with the nucleophilic nitrogen atom of

Primary Amines

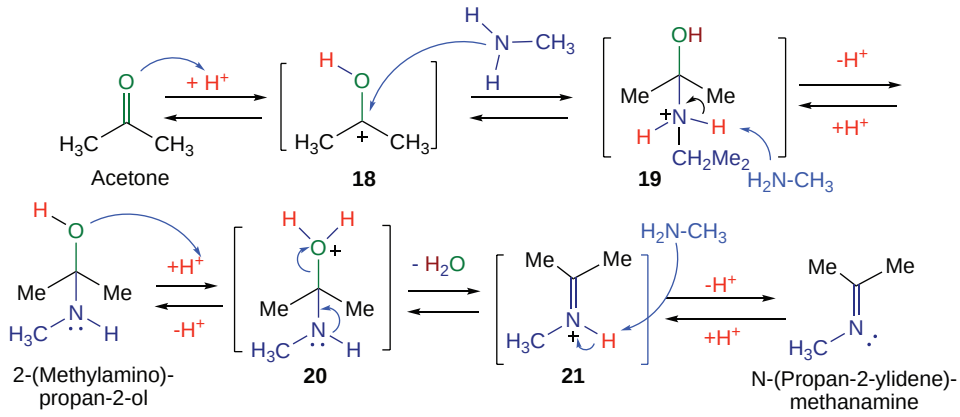
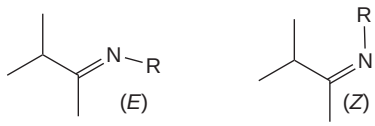


FIGURE 16.6 Mechanism of imine formation in the reaction of propan-2-one and methanamine

the amine to yield the ammonium salt, **19**. An ammonium salt such as **19** is a weak acid that can react with the basic amine. Deprotonation of **19** gives the neutral amino alcohol, 2-(methylamino)propan-2-ol. This *hemiaminal* is unstable to the reaction conditions. Note that a hemiaminal is formally the nitrogen analog of a hemiacetal. Since water is a product of this reaction, the OH unit must be protonated to yield **20**. The electron pair on nitrogen in **20** expels water as a leaving group to form a new π-bond between carbon and nitrogen, a C=N bond in **21**. It is an *iminium salt*. The proton on the nitrogen of the iminium salt is a weak acid so an acid-base reaction with the amine gives a neutral product, the *imine, N*-(propan-2-ylidene)methanamine.

16.18 Give the final product and write out the complete mechanism for the reaction between propanal and butan-1-amine, in the presence of an acid catalyst.



Unsymmetrical ketones or aldehydes form imines that can exist as (*E*) or (*Z*) stereoisomers. In the (*E*)-imine from 3-methylbutan-2-one, the R group on nitrogen and the higher

priority isopropyl group are on opposite sides. In the (*Z*)-imine from 3-methylbutan-2-one, the R group is on the same side as the isopropyl group. In general, imines are formed as a mixture of (*E*)- and (*Z*)-isomers. The mixture favors the (*E*) product because there is less steric hindrance.

16.19 Briefly explain why the reaction of cyclopentanone and triethylamine does not yield an imine.

When a secondary amine (HNR_2) reacts with a ketone, an iminium salt intermediate is also formed. When pentan-3-one reacts with the secondary amine *N*-ethylethan-1-amine (diethylamine, Et_2NH) and an acid catalyst, *N,N*-diethylpent-(2*E*)-en-3-amine was formed in 86% yield along with 14% of *N,N*-diethylpent-(2*Z*)-en-3-amine.[16] Water is also a product of this reaction. The mechanism of the acid-catalyzed reaction of diethylamine with pentan-3-one first generates oxocarbenium ion **22**, as shown in Figure 16.7.

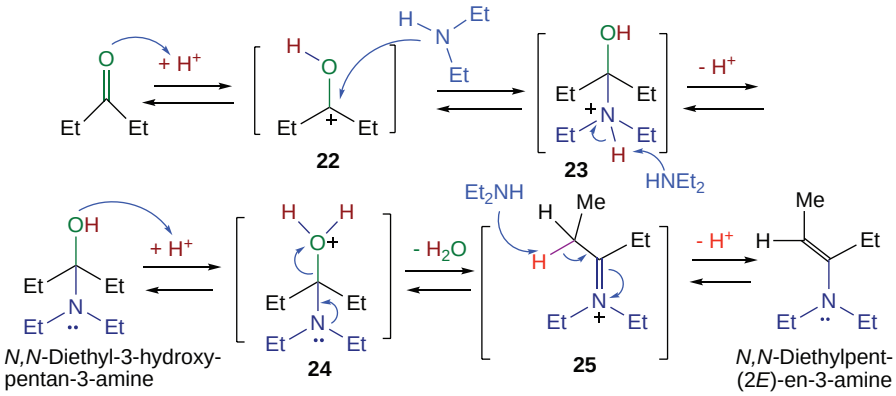
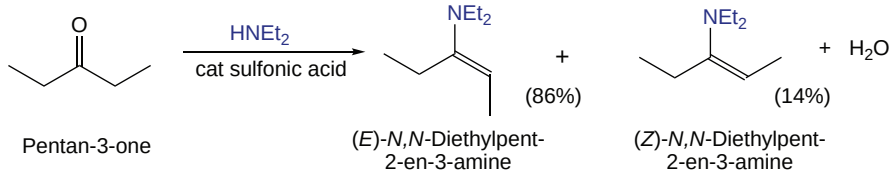


FIGURE 16.7 Mechanism of enamine formation from a ketone and a secondary amine.



This first step is followed by reaction with the nucleophilic amine to give **23**. Loss of a proton from the acidic ammonium salt gives a hemiaminal**,** *N,N*-diethyl-3-hydroxypentan-3-amine. Water is one of the products via protonation of the OH unit to give **24**. Expulsion of water affords iminium salt **25**. Contrary to formation of **21** from the primary amine methanamine, **25** does *not* have a proton on nitrogen. However, there is an acidic hydrogen atom on carbon that can be removed. Bond polarization of the C=C—N unit due to the electronegative nitrogen renders the attached hydrogen atoms slightly acidic. Deprotonation by diethylamine affords the enamine product, *N,N*-diethylpent-2-en-3-amine as a (*E*)- and (*Z*) mixture, although *N,N*-diethylpent-2*E*-en-3-amine is expected as the major product.

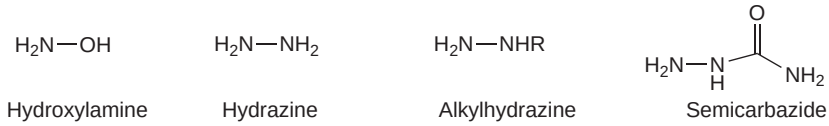
Secondary Amines

16.20 Draw the structure of the product formed when cyclopentanone reacts with diethylamine, in the presence of an acid catalyst.

There are several useful nitrogen-containing molecules that react with ketones or aldehydes as functionalized primary amines: hydroxylamine, hydrazine, alkyl hydrazines and

[16] Cervinka, O. in Chapter 3 of *The Chemistry of Enamines, Part 1*, Rapoport, Z. (Ed.), John Wiley & Sons, Chichester, 1994, p. 223.

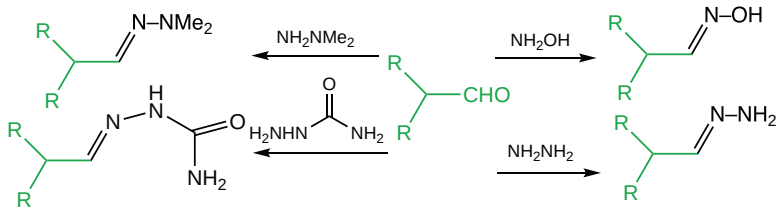
semicarbazide. Hydroxylamine is a functionalized primary amine. It has been used as an antioxidant for fatty acids and soaps (Section 18.13), and as a dehairing agent for hides. Hydrazine is another functionalized primary amine. A commercial product known as Aerozine 50 is a mixture of hydrazine (NH_2NH_2) and dimethylhydrazine (Me_2NNH_2). It was used as a fuel on the Apollo 11 Eagle landing craft. Hydrazine is still used as a propellant on space vehicles and in satellites in order to make course corrections. Semicarbazide is an "amide-substituted" hydrazine that reacts with aldehydes or ketones to yield functionalized imines. All of these compounds have a primary amine unit ($-NH_2$) and each reacts with an aldehyde or ketone as a "functionalized primary amine" to give a "functionalized imine." All react with ketones and aldehydes by the same mechanism shown in Figure 16.6.



The reaction of hydroxylamine with an aldehyde gives an oxime as a mixture of (*Z*)- or (*E*)-isomers. When a ketone or aldehyde reacts with hydrazine, the resulting functionalized imine product is called a *hydrazone*. *N,N*-Dimethylhydrazine also reacts with aldehydes and ketones to form substituted hydrazone derivatives via the NH_2 unit. Another highly specialized hydrazine derivative used for derivatization purposes is semicarbazide, which has a "urea unit" in the molecule. The reaction of semicarbazide with an aldehyde proceeds in an identical manner to give a *semicarbazone*.

Prior to the development of modern spectroscopy, the preparation of well-characterized derivatives based on chemical reactions was used as an identification tool. One such method converted unknown ketones or aldehydes to solid derivatives using the functionalized amines just discussed. The color and melting point of the oxime, hydrazone or semicarbazone derivatives were cross-referenced to a library of known derivatives to help identify the unknown. This derivatization method will not be elaborated further, because it is rarely used today. However, semicarbazone is used as a developing agent in thin-layer chromatography. Some semicarbazones are known to have anti-viral or anti-cancer activity.

Functionalized Primary Amines



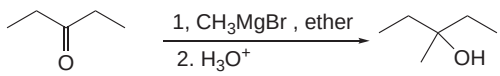
16.21 Draw the structure of the product formed in a reaction between 4,4-diphenylpentanal and hydroxylamine, in the presence of an acid catalyst.

16.5 ORGANIZATION OF REACTION TYPES

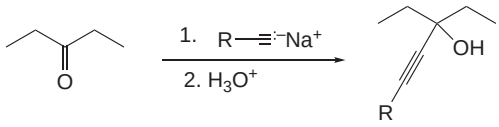
The reaction of aldehydes and ketones can be organized as follows.

What reactions are possible for ketones and aldehydes?

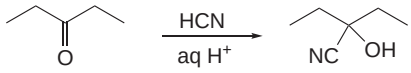
1. Aldehydes and ketones react with Grignard reagents and organolithium reagents to form a new C—C bond and form an alcohol.



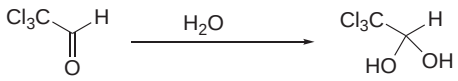
2. Aldehydes and ketones react with alkyne anions to form a new C—C bond and form an alkyne–alcohol.



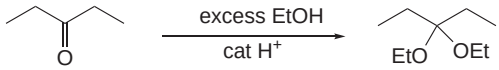
3. Aldehydes and ketones react with NaCN or KCN or HCN/cat H^+ to form a new C—C bond and form a nitrile–alcohol.



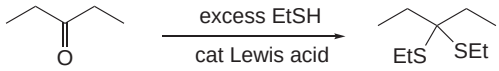
4. Aldehydes and ketones with no α-hydrogen atoms react with water to form hydrates.



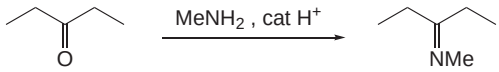
5. Aldehydes and ketones react with alcohols to form acetals or ketals.



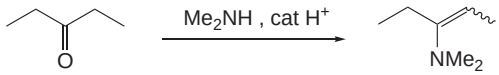
6. Aldehydes and ketones react with thiols to form dithioacetals or dithioketals.



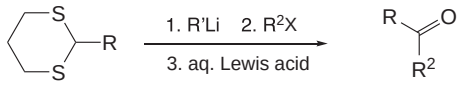
7. Aldehydes and ketones react with primary amines to form imines.



8. Aldehydes and ketones react with secondary amines to form enamines.

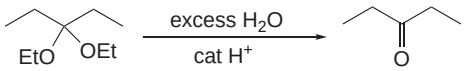


9. Dithianes react with an organolithium and then with an alkyl halide to give a 2-alkyl-dithiane. Hydrolysis with an aqueous Lewis acid give the ketone or aldehyde.

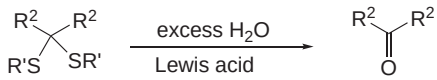


What reactions are possible for acetals?

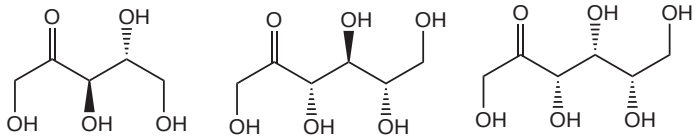
1. Acetals react with aqueous acid to regenerate a ketone or aldehyde



2. Dithioacetals and dithioketals react with an aqueous Lewis acid to generate a ketone or aldehyde



16.6 BIOLOGICAL RELEVANCE



Ribulose Fructose Sorbose

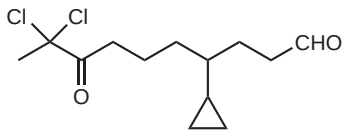
The aldehyde or ketone unit appear in many biologically important systems, including carbohydrates (sugars) such as ribulose, fructose, and sorbose (Sections 25.1 and 25.2). D-Ribulose is an intermediate in the fungal pathway for D-arabitol production. As the 1,5-bis(phosphate) derivative, D-ribulose combines with carbon dioxide at the start of the photosynthetic process in green plants (a CO_2 trap). Fructose is found in many fruits and in honey and is used as a preservative for foodstuffs and as an intravenous nutrient. Fructose is also called *fruit sugar* or *levulose*. Sorbose is about as sweet as common table sugar (sucrose).

CORRELATION OF HOMEWORK WITH CONCEPTS

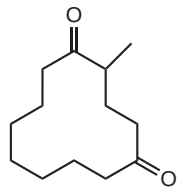
- Nomenclature review for aldehydes and ketones: 1, 2, 3, 25.
- Strong nucleophiles react with aldehydes or ketones by acyl addition to generate alkoxides in a reaction known as acyl addition. A second chemical step converts the alkoxide product to an alcohol via an acid-base reaction: 4, 5, 6, 7, 8, 23, 26, 27.
- The Cram model is used to predict the diastereoselectivity of acyl addition reactions: 31.
- Weak nucleophiles react with aldehyde and ketones via reaction with an acid catalyst to form an oxocarbenium ion: 9, 10, 27, 29.
- Water adds reversibly to aldehydes and ketones to yield an unstable hydrate: 11, 12, 24, 27.
- Alcohols react with aldehydes and ketones with an acid catalyst to yield a transient hemi-acetal or hemi-ketal, which then reacts with more alcohol to give an acetal or a ketal: 13, 14, 15, 16, 24, 28, 29.
- Thiols react with aldehydes or ketones with an acid catalyst to give dithioacetals or dithioketals: 17, 27.
- Primary amines react with aldehydes and ketones to give imines. Secondary amines react to yield enamines: 18, 19, 20, 21, 22, 28, 29.
- Spectroscopy can be used to determine the structure of a molecule (Chapter 13): 32, 33, 34, 35.

ANSWERS TO IN-CHAPTER QUESTIONS

16.1

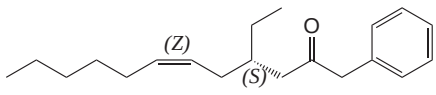


9,9-Dichloro-4-cyclopropyl-8-oxodecanal



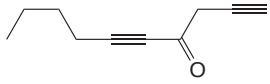
2-Methylcyclododecane-1,5-dione

16.2



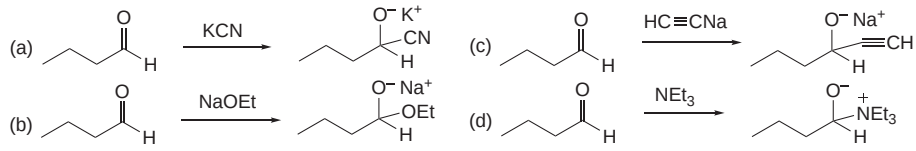
1-Phenyl-(4S)-ethyldodec-(6Z)-en-2-one

16.3

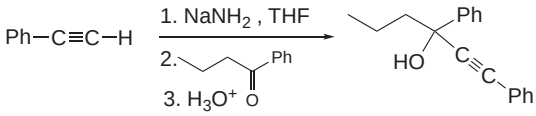


Deca-1,5-diyn-4-one

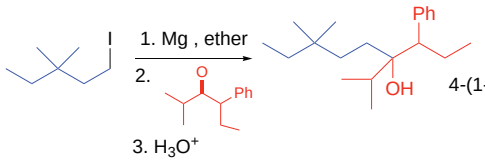
16.4



16.5

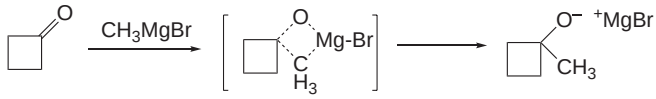


16.6



4-(1-Methylethyl)-7,7-dimethyl-3-phenylnonan-4-ol

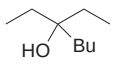
16.7



16.8

From cyclobutanone + BuLi

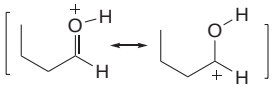
1-Butylcyclobutanol



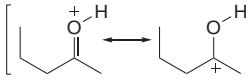
From pentan-3-one + BuLi

3-Ethylheptan-3-ol

16.9

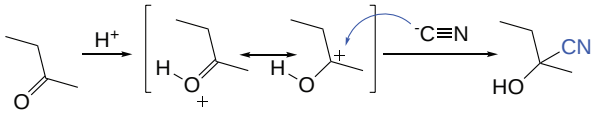


From butanal

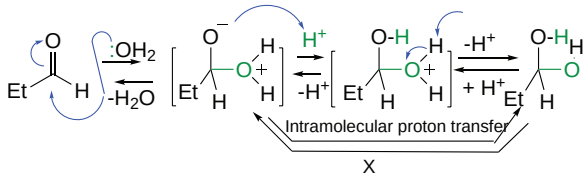


From pentan-2-one

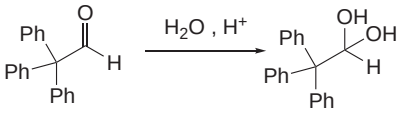
16.10



16.11

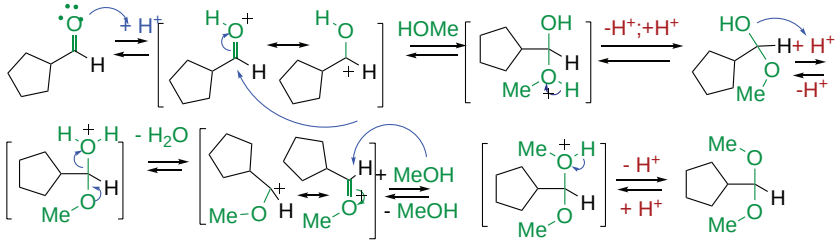


16.12

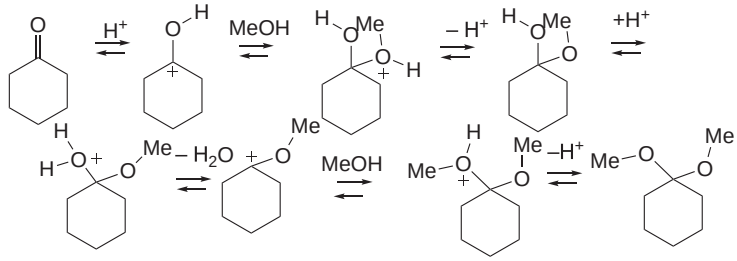


This hydrate should be stable since there is no α-hydrogen, and the phenyl rings should help make the product crystalline.

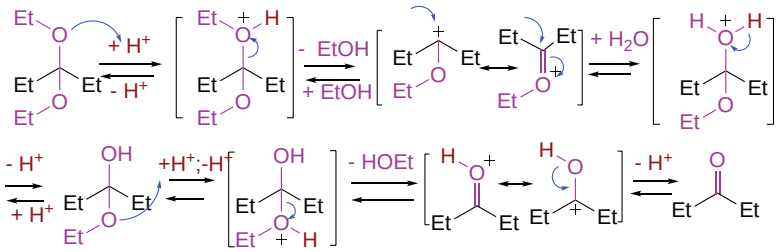
16.13



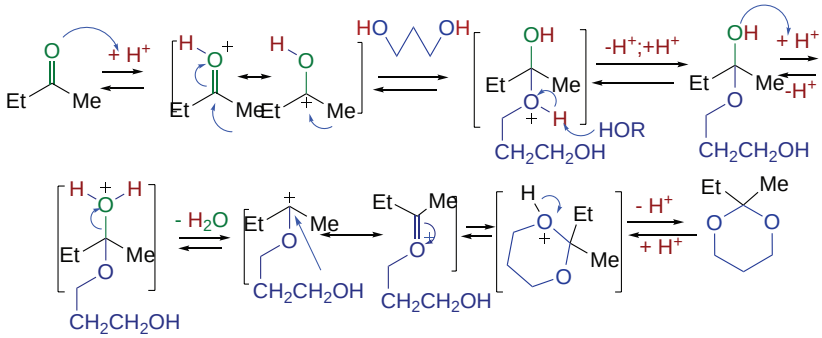
16.14



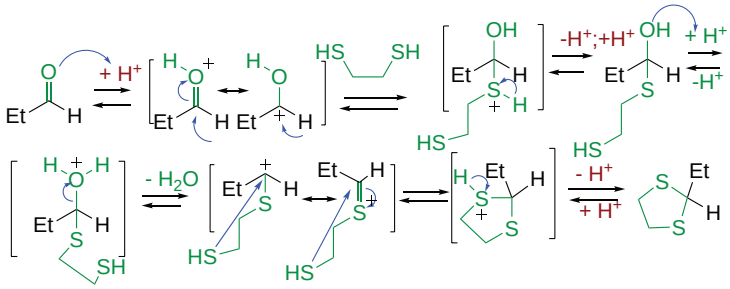
16.15



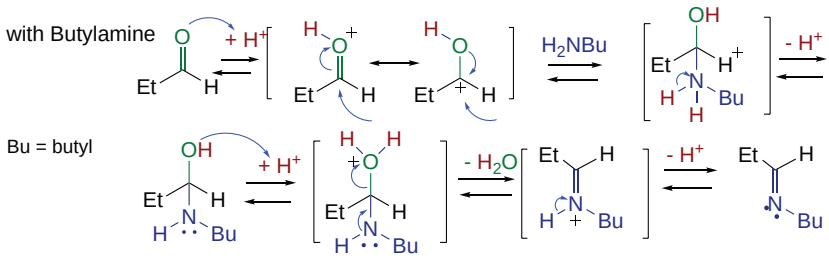
16.16



16.17

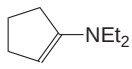


16.18

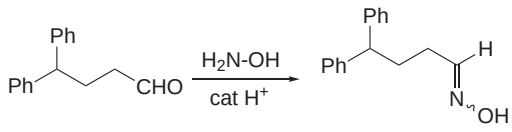


16.19 The key to forming an imine is loss of a proton from the intermediate ammonium and iminium salts. There are no hydrogen atoms attached to nitrogen in a 3° amine, so it is not possible to complete the mechanistic requirements for generating an imine.

16.20



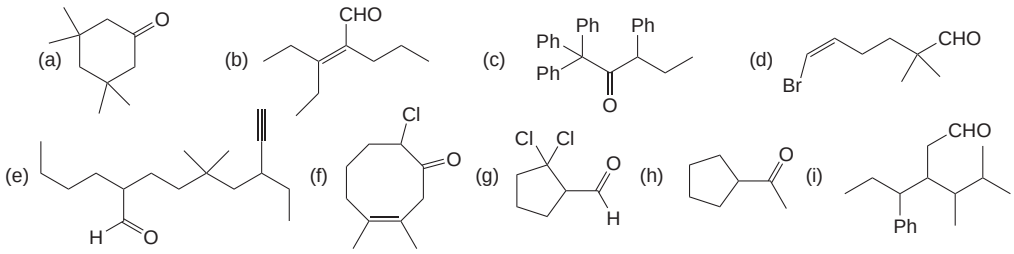
16.21



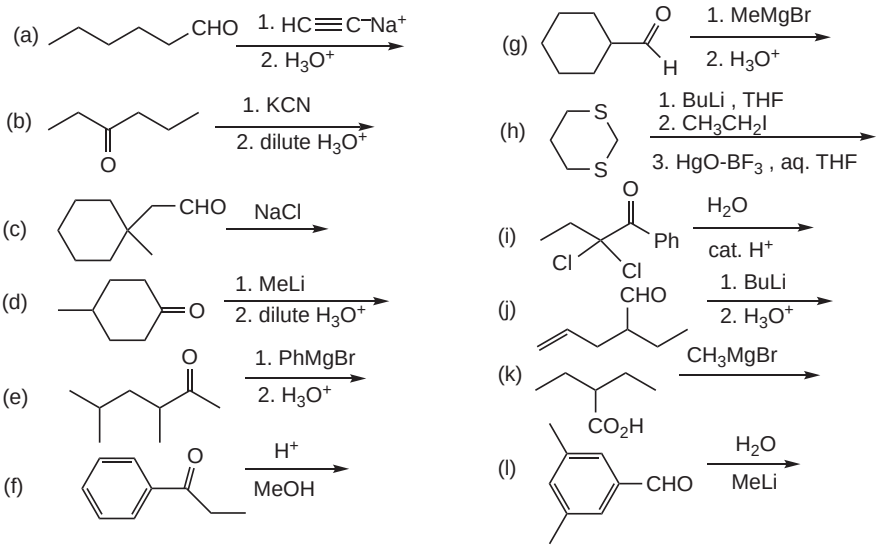
HOMEWORK

22. The reaction of heptan-3-one and butan-1-amine leads to the corresponding imine. Draw it. In order to convert this imine back to heptan-2-one, the imine is heated with aqueous acid. Write out the complete mechanism for conversion of this imine back to heptan-3-one under these conditions.
23. In a few words, describe the fundamental differences and similarities between the C=C unit in an alkene and the C=O unit of a ketone or aldehyde.

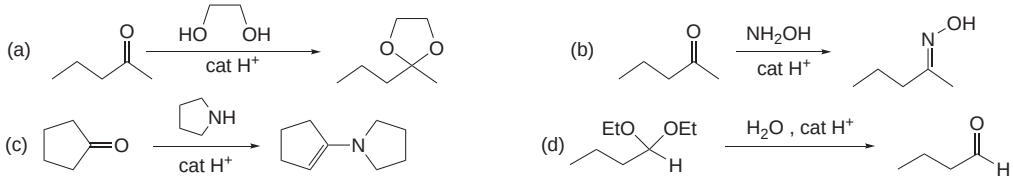
24. Give the complete mechanism for each of the following transformations:
    (a) The reaction of cycloheptanone and methanol to give the ketal (acid catalyzed).
    (b) The reaction of 2-phenylethanal and water to give the hydrate (acid catalyzed).
    (c) The reaction of 2,2-diethoxyhexane to give hexan-2-one and ethanol (acid catalyzed).
    (d) The reaction of pentanal and 1,2-dimethyl-1,2-ethanediol to give the ketal (acid catalyzed).
25. Give the IUPAC names for each of the following:



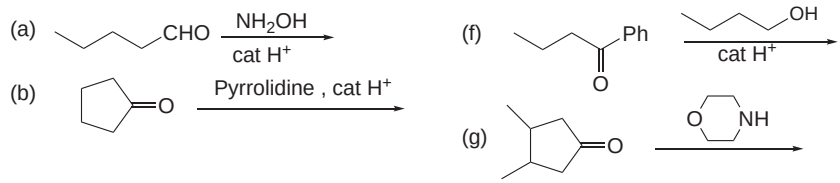
26. Why is 3,3,5,5-tetraethylheptan-4-one less reactive in acyl addition reactions than heptan-4-one?
27. Suggest reasonable products for the following reactions:

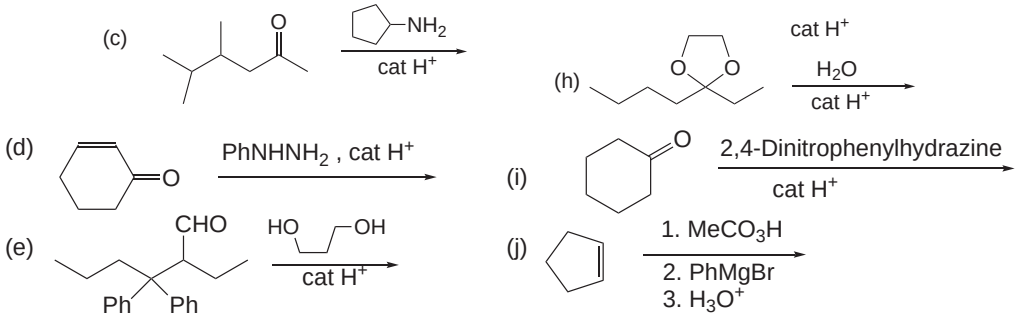


28. Give the complete mechanism for each of the following transformations:

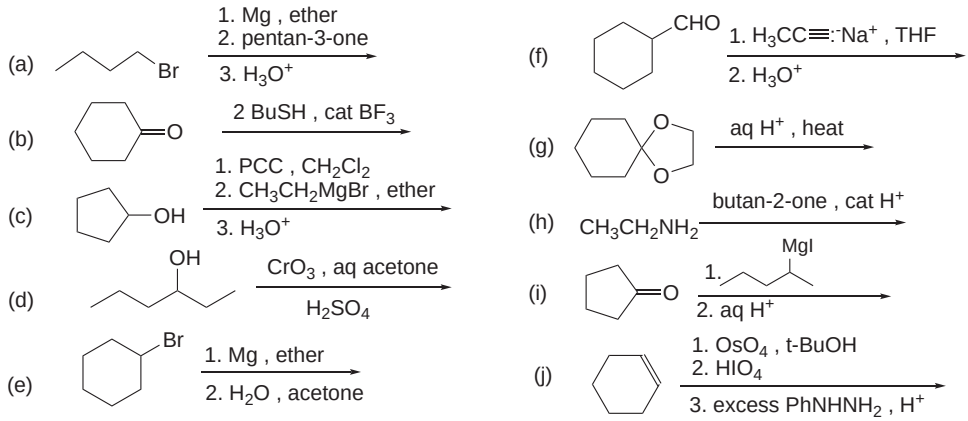


29. Give the product formed from each of the following reactions:

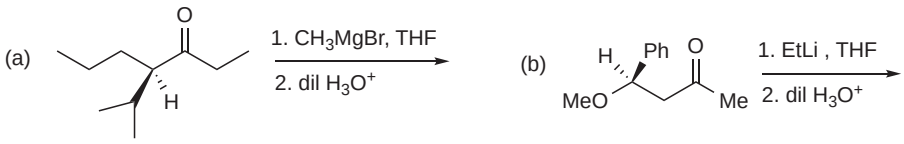




30. Give the major product for each reaction.



31. Predict the correct diastereomeric product using the appropriate Cram model.



Spectroscopy Problems. Do not attempt these problems until you have read and understood Chapter 13.

32. For a formula of $C_6H_{10}O$, and given the following spectral data, provide a structure:

    IR: 3082, 3002–2921, 1718, 1642, 1431–1415, 1363 cm^{-1}. ^1H NMR: 5.79 (m, 1H), 5.02 (m, 1H), 4.97 (m, 1H), 2.52 (t, 2H), 2.34 (m, 2H), 2.15 (s, 3H) ppm.

33. For the formula $C_6H_{15}N$, and given the following spectral data, give the structure.

    IR: IR: 3236 (weak), 2960-2850, 1486, 1016, and 702 cm^{-1}. ^1H NMR: 2.91, (2H, m), 2.0 (broad s, 1H; this peak is diminished when treated with D_2O), and 1.02 (12H, d) ppm.

34. A molecule **A** with the formula C_6H_{12} has the spectra: IR: peaks at 3178, 2960–2839, and a peak at 1643 cm^{-1}; ^1H NMR: 5.77 (m, 1H), 4.97 (m, 1H), 4.96 (m, 1H), 1.94 (m, 2H), 1.63 (m, 1H), 0.90 (d, 6H) ppm. Reaction of **A** with 9-BBN followed by NaOH/H_2O_2 yields **B**, which has the spectra: IR: broad peak at 3325, 2957-2846, and a peak at 1071-1022 cm^{-1}; ^1H NMR: 3.61 (broad t, 2H), 1.94 (broad s, ^1H; this peak is diminished when treated with D_2O), 1.84-1.26 (broad m, 5H), 0.80 (d, 6H) ppm. When **B** is treated with PBr_3, **C** is formed. Subsequent reaction of **C** with magnesium metal

in ether generates **D**, which reacts with butan-2-one to yield **E**. Unknown **E** has the formula $C_{10}H_{22}O$, and the spectra: IR: a broad peak at 3380, 2956-2871, and peaks at 1062-1018 cm^{-1}; ^1H NMR: 1.55 (m, 1H), 1.48 (q, 2H), 1.42 (broad s, 1H; this peak is diminished when treated with D_2O), 1.41(broad t, 2H), 1.32-1.17 (m, 4H), 1.14 (s, 3H), 0.89 (t, 3H), 0.878 (d, 6H) ppm. Show the structures of **A-E**.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-17.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

17

Reduction

The oxidation of one molecule is accompanied by the reduction of another. If an oxidation involves the loss of two electrons, a reduction involves the gain of two electrons. The structural changes in the reduction product are often measured by whether hydrogen is gained or if a heteroatom such as oxygen is lost. This chapter will review important organic reactions that are classified as reductions.

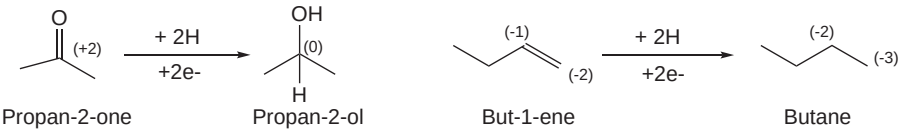
To begin this chapter, you should know the following points:

- Nomenclature for alcohols, aldehydes, ketones, and carboxylic acids (Sections 5.5 and 5.6).
- Bond polarization (Section 3.8).
- Lewis acids and Lewis bases (Sections 2.7 and 6.8).
- Energetics and transition states (Sections 7.4–7.6).
- Rotamers and conformations (Sections 8.1–8.6).
- Chirality, enantiomers, and diastereomers (Sections 9.2–9.6).
- Alkene stereoisomers (Section 9.7).
- Reactivity of alkenes (Sections 10.2–10.7).
- Reactivity of carbonyl compounds (Sections 16.2–16.4).
- Oxidation of an alcohol (Section 15.2).
- Oxidation reactions of alkenes (Sections 15.3–15.5).

17.1 DEFINING A REDUCTION

Defining a Reduction

Just as an oxidation is a reaction in which two electrons are lost, a reduction is defined as a reaction in which two electrons are gained. Structural changes used to monitor a reduction are the gain of hydrogen atoms or loss of an oxygen atom or another heteroatom. Many transformations are categorized as reductions, including the conversion of a ketone to an alcohol, an alkyne to an alkene, or an alkene to an alkane. Oxidation number can be used to track changes in atoms for a putative reduction (Section 15.1). When propan-2-one (acetone) is converted to propan-2-ol, the oxidation number at the carbonyl carbon changes from +2 to 0. Gaining negative electrons makes a carbon less positive, and the product has two more electrons than the starting material. It is a reduction. The conversion of but-1-ene to butane is also a reduction. An oxidation number of -2 is assigned to C1 and -1 is assigned to C2 of the C=C unit. In butane, C1 and C2 have oxidation numbers of -3 and -2, respectively since there are two hydrogen atoms on each carbon. One electron is gained on each carbon for a net gain of two electrons, a reduction.



Propan-2-one Propan-2-ol But-1-ene Butane

DOI: 10.1201/9781003174929-17

Hydride Reducing Agents

17.2 HYDRIDE REDUCING AGENTS

This discussion of reduction begins with the reaction of aldehydes or ketones with so-called hydride reducing agents, *sodium borohydride ($NaBH_4$)* and *lithium aluminum hydride ($LiAlH_4$)*. The BH_4 unit is an "ate" complex of BH_3, a tetrahydridoborate. Similarly, the AlH_4 unit is an "ate" complex of AlH_3, a tetrahydridoaluminate. The respective IUPAC names of these reagents are sodium tetrahydridoborate and lithium tetrahydridoaluminate. Hydrogen is more electronegative than boron, so the B—H bond in sodium borohydride is polarized such that boron is electropositive (δ^+) and hydrogen is electronegative (δ^-). Similarly, the hydrogen atom of the Al—H unit in $LiAlH_4$ is more electronegative than the aluminum, so hydrogen is also electronegative (δ^-).

When sodium borohydride or lithium aluminum hydride react with an aldehyde or ketone, the δ^- hydride is attracted to the δ^+ carbonyl carbon. This acyl addition reaction proceeds by a

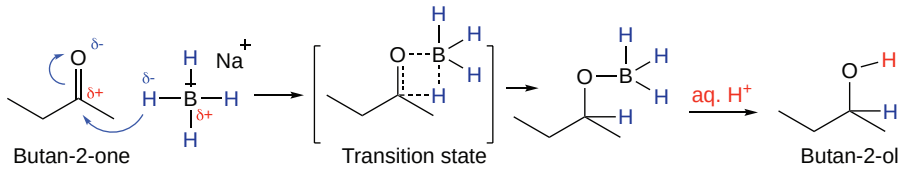


FIGURE 17.1 Reduction of butan-2-one with sodium borohydride.

four-center transition state as shown in Figure 17.1. There is no evidence for a reactive intermediate. Butan-2-one reacts with $NaBH_4$ in CH_3OH to give an alkoxyborate. This alkoxide is converted to butan-2-ol in 87% yield by a hydrolytic workup that uses an aqueous solution of saturated ammonium chloride.[1] Sodium borohydride reduces both ketones and aldehydes and aldehydes usually react faster than ketones.

> 17.1 Draw the transition state and final product when cyclobutanecarbaldehyde is treated with 1. $NaBH_4$ in ethanol and 2. aq ammonium chloride.

Lithium aluminum hydride is a more powerful reducing agent than sodium borohydride, so it easily reduces ketones and aldehydes. The reaction of heptanal with $LiAlH_4$ in diethyl ether, followed by treatment with aqueous acid gave heptan-1-ol in 86% yield,[2] as shown in Figure 17.2. As with sodium borohydride, the reaction proceeds by a four-centered transition

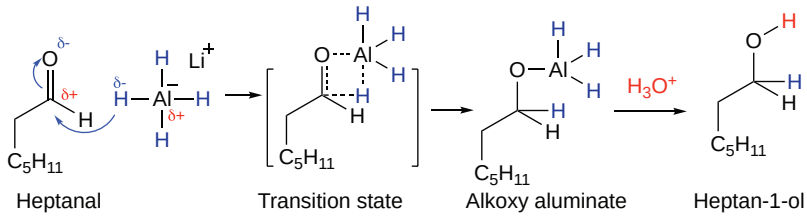


FIGURE 17.2 Lithium aluminum hydride reduction of heptanal.

[1] Hudlický, M. *Reductions in Organic Chemistry,* Ellis Horwood Ltd., American Chemical Society, Washington, DC, 1984, p. 108.

[2] Nystsrom, R.F.; Brown, W.G. *Journal of the American Chemical Society* 1947, 69, 1197–1199.

state to an alkoxyaluminate product. Hydrolytic workup in this reaction requires a stronger acid (H_3O^+), which gives the final product.

The major difference between sodium borohydride and lithium aluminum hydride is the relative strength of each reducing agent. Lithium aluminum hydride reduces most functional groups that contain a heteroatom. This difference in reactivity is most easily seen in the choice of solvent for each reaction. In sodium borohydride reductions, alcohol or water is used as a solvent whereas lithium aluminum hydride reductions require an aprotic solvent such as diethyl ether of THF. Indeed, lithium aluminum hydride reacts *violently* with water or alcohols to release hydrogen gas.

In principle, one molar equivalent of $LiAlH_4$ can reduce four molar equivalents of a ketone or aldehyde As a practical matter, it is not always clear whether the reaction stops after using one or two molar equivalents of the carbonyl compound or uses all four molar equivalents. For this reason, a 1:1 molar equivalency is normally used.

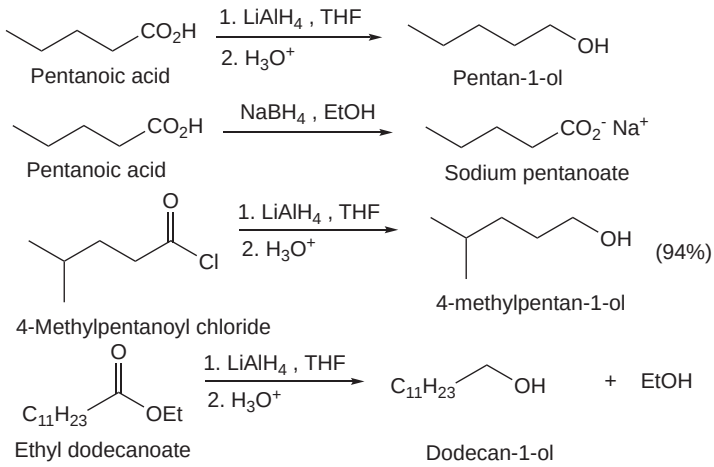
17.2 Draw the transition state and final product when phenylacetaldehyde is treated with 1. $LiAlH_4$ in ether and 2. aq acid.

17.3 HYDRIDE REDUCTION OF OTHER FUNCTIONAL GROUPS

Reduction of Heteroatom Functional Groups

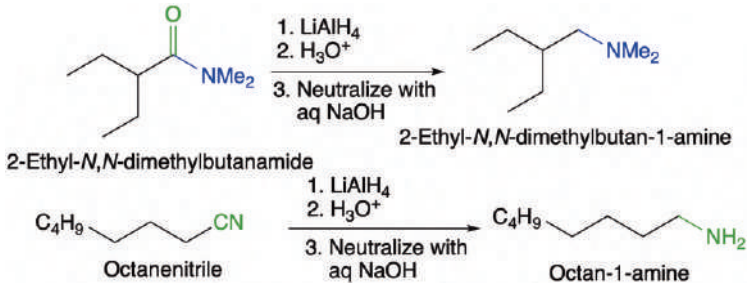
As mentioned, virtually any heteroatom-containing functional group is reduced by lithium aluminum hydride including carboxylic acid derivatives, which will be discussed in Section 18.2. Sodium borohydride is a weaker reducing agent. This difference in reducing strength is clear in the reduction of pentanoic acid to pentan-1-ol with $LiAlH_4$ after hydrolytic workup. Sodium borohydride reacts with pentanoic acid to yield the sodium salt of the acid but does not give reduction to the alcohol. Lithium aluminum hydride reacts with pentanoic acid to give the sodium salt of the acid, which is further reduced in situ to the alcohol.

Acid chlorides, acid anhydrides, and esters are carboxylic acid derivatives (Section 18.2), and all are reduced by $LiAlH_4$ to the corresponding alcohol. In one experiment, 4-methylpentanoyl chloride was reduced to 4-methylpentan-1-ol in 94% yield by $LiAlH_4$.[3] Ethyl dodecanoate is similarly reduced by $LiAlH_4$ to dodecan-1-ol in 94% yield[3] along with ethanol as a second product. This reaction may be a two-step process where initial reduction of the ester generates an aldehyde in situ, which is reduced to the alcohol. Sodium borohydride usually reduces acid chlorides, and it can reduce esters. However, the reduction of esters with $NaBH_4$ is often problematic and many esters are not reduced at all.



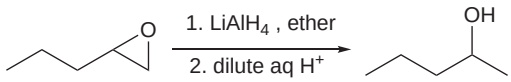
[3] Micovic, V.M.; Mihailovic, M.L.J. *Journal of Organic Chemistry* 1953, 18, 1190–1200.

Sodium borohydride does *not* reduce amides or nitriles. which are also carboxylic acid derivatives. Lithium aluminum hydride reacts with amides, but the product is an amine rather than an alcohol. The reduction of 2-ethyl-*N*,*N*-dimethylbutanamide, for example, gave 2-ethyl-*N*,*N*-dimethylbutan-1-amine in 88% yield after hydrolysis.[3] Although the mechanism will not be discussed here in a formal manner, delivery of hydride to the acyl carbon generates an imine (C=N) type intermediate that is further reduced to the amine. Nitriles (Section 5.9.4) can be considered as carboxylic acid derivatives because hydrolysis of the nitrile leads to the acid (Section 18.13). Reduction of octanenitrile with $LiAlH_4$ gave the amine, octan-1-amine, in 92% isolated yield.[4] In general, $NaBH_4$ does not reduce amides or nitriles.



17.3 Draw the products formed when benzyl cyclopentanecarboxylate (Section 18.2 for the nomenclature) is treated with 1. $LiAlH_4$ and 2. aq acid.
17.4 Draw the product formed when *N*,*N*-dimethylpentanamide (Section 18.2 for the nomenclature) is treated with 1. $LiAlH_4$ in THF and 2. aqueous hydrolysis.

Epoxides react with $LiAlH_4$ to give an alcohol after a hydrolytic workup. The epoxide oxygen coordinates to the aluminum. The hydride is delivered to the less substituted carbon atom by a S_N2-like reaction to give an aluminum alkoxide. 2-Propyloxirane reacts with $LiAlH_4$, for example, and a hydrolytic workup of the alkoxide product gives pentan-2-ol.



17.5 Give the product formed with cyclohexene oxide is reduced with $LiAlH_4$ and the resulting product hydrolyzed with aq acid.

Catalytic Hydrogenation of Alkenes

17.4 CATALYTIC HYDROGENATION

The use of hydrogen gas as a reducing agent has an old history. It can be used to reduce many functional groups including those not reduced by hydride reagents. However, reduction only occurs in the presence of a suitable transition metal catalyst, and it is called *catalytic hydrogenation*. This section examines methods that use hydrogen gas as a reducing agent, the catalysts that are required to facilitate such reactions, and the transformations that are possible.

17.4.1 HYDROGENATION OF ALKENES AND ALKYNES

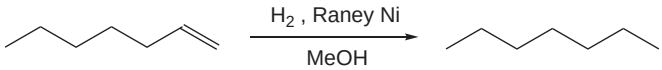
If a practical definition of reduction is addition of hydrogen atoms to a molecule, then hydrogen gas is a logical choice for a reducing agent. If an alkene is mixed with hydrogen gas in

[4] Amundsen, L.H.; Nelson, L.S. *Journal of the American Chemical Society* 1951, 73, 242–244.

the solvent methanol, however, there is no reaction. This result may seem surprising since an alkene quickly reacts with Br—Br as described in Section 10.5. Bromine reacts because the halogens are polarizable. Diatomic hydrogen (H—H) is not polarizable so there is no direct reaction with an alkene. Before any reaction can occur with the π-bond of an alkene, a metal must be added to first break the H—H bond.

Addition of a small amount of a transition metal to a mixture of an alkene and hydrogen gas leads to reduction. There are two major types of catalysts used in hydrogenation. *Heterogeneous catalysts* are insoluble in the reaction medium. A *homogeneous catalyst* is soluble in the reaction medium and will be discussed in Section 17.4.2. This section will focus on heterogeneous catalysis. The nature and amount of the catalyst and the hydrogenation procedure will vary with the functional group that is reduced, the extent of reduction, and the product distribution. The most commonly used heterogeneous catalysts are probably platinum, palladium, nickel. In most cases, < 10 mol% of the catalyst is required per mole of the compound, although some metal catalysts require a higher catalyst loading.

Adding a nickel catalyst to hydrogen gas and hept-1-ene produces an excellent yield of heptane. Only a catalytic amount of the nickel is required. Since there is no reaction until the metal is added, it clearly plays a key role in this reaction.



Hydrogen gas is adsorbed on the surface of the metal catalyst, as are many types of organic molecule. *Active sites* are regions of the catalyst that can accommodate and bind hydrogen atoms and/or organic substrates. As the number of active sites on the metal increases, the rate of hydrogenation increases. The catalyst used in this example is called Raney nickel [abbreviated as Ni(R)], which is a finely divided or powder form of nickel named after Murray Raney (USA; 1885–1966). This catalyst is formed when a nickel-aluminum alloy (Ni-Al) dissolves in aqueous hydroxide.

The mechanism for the catalytic hydrogen of hept-1-ene to heptane is shown in Figure 17.3. For simplicity, the mechanism in Figure 17.3 shows the metal as a sphere to represent the surface of the metal. The catalyst is insoluble in the reaction medium and consists of relatively large particles. The only portion of the metal that is available for chemisorption

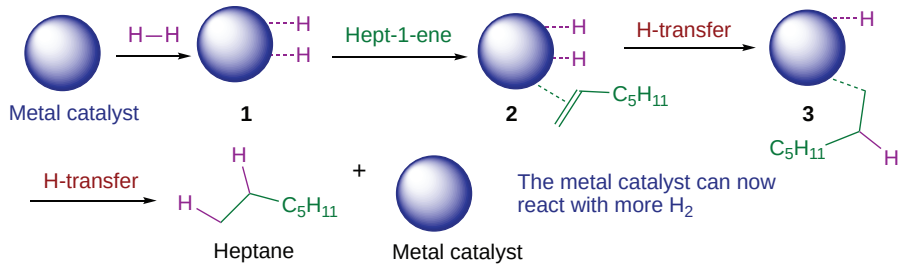
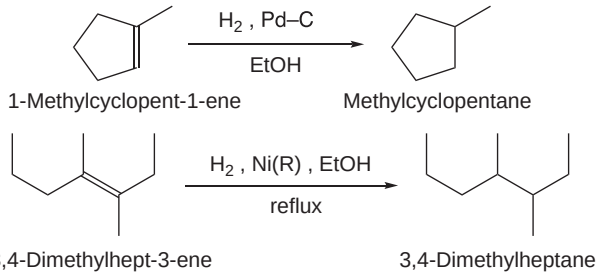


FIGURE 17.3 Heterogeneous catalytic hydrogenation.

of hydrogen gas and the alkene or alkyne is the surface of the particle. The catalyst reacts with diatomic hydrogen to produce highly reactive hydrogen atoms (essentially H•) that are bound to the surface of the metal (complex **1**). Complex **1** reacts with hept-1-ene to form η^2-*complex* **2**, in which the metal is coordinated to the π-bond as well as the hydrogen atoms. A hydrogen atom is transferred to the alkene π-bond to generate bound complex **3** at the surface of the metal with a σ-covalent C—H bond. Transfer of a second atom of hydrogen from the metal to **3** "releases" the product heptane and regenerates a "clean" surface of the catalyst that can react with additional hydrogen gas. Note that the η^2 nomenclature is based on the concept of *hapticity*. Hapticity describes the coordination of a species (known as a *ligand*) to a metal center via an uninterrupted and contiguous series of atoms. The hapticity of a ligand is described with the Greek letter η (eta). The η^2 term describes a two-electron donor ligand that coordinates through two contiguous atoms (like the C=C unit of an alkene).

Catalytic hydrogenation typically uses 5–10% of the metal. As mentioned, hydrogenation occurs on the surface of the metal, so the larger the surface area of the metal, the faster the process. For this reason, finely divided metals are used, not "chunks" of metal. These metals are rather expensive. Therefore, the catalyst is usually mixed with a *solid support*, which is an inert material on which the catalyst is adsorbed or admixed. Mixing a metal powder with a solid support makes the effective surface area of the metal larger. Less metal is used, which moderates the rate of reaction. Carbon black, Kieselgühr (diatomaceous earth and related inert solids), as well as inorganic chemicals (e.g., calcium carbonate, $CaCO_3$), or barium carbonate, $BaCO_3$) are common solid supports. Typical catalysts for reaction with hydrogen are 5% palladium-on-carbon (Pd/C), or 10% platinum-on-calcium carbonate. Note that once the hydrogen covers their surface these catalysts are very reactive. Hydrogen covered catalysts are often *pyrophoric* (spontaneously ignite when exposed to air).



Many alkenes are reduced by catalytic hydrogenation (C=C → HC—CH). The most common metal used for reduction of alkenes is palladium. 1-Methylcyclopentene reacts with hydrogen gas and palladium-on-carbon, for example, to give methylcyclopentane. Catalytic hydrogenation of 3,4-dimethylhept-(3*E*)-ene with a Raney nickel catalyst gives 3,4-dimethylheptane. Highly substituted alkenes are difficult to hydrogenate and may require higher temperatures and a higher catalyst loading.

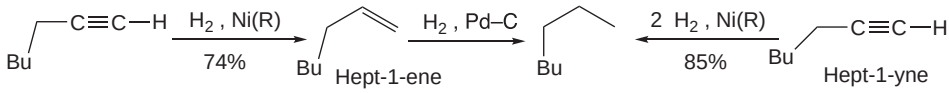
Different catalysts have different reactivity with different functional groups. The following order of reactivity is useful for general applications:

Pt	C=O	>>	C=C	>	(**H**)	> Ar
Pd	C=C	>	(**H**)	>	C=O	> Ar
Ru	C=O	>	C=C	>	Ar	> (**H**)

Hydrogenation of Alkynes

The term (**H**) indicates *hydrogenolysis*. Hydrogenolysis is a catalytic chemical reaction that breaks a chemical bond, usually to a heteroatom in an organic molecule, and replaces the heteroatom with a hydrogen atom. The transformation is C—X ⟶ C—H.

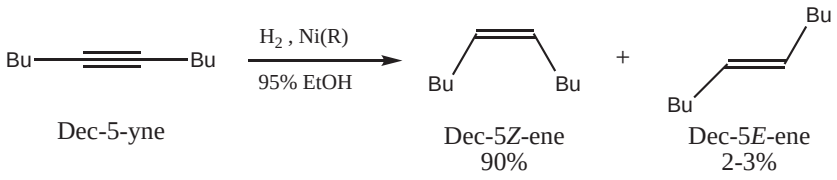
17.6 Draw the product when methylenecyclohexane is treated with hydrogen gas and Pd metal in methanol.



The hydrogenation of alkynes is well known. Alkynes have two π-bonds that may be reduced, and in principle both can react with hydrogen. Therefore, catalytic hydrogenation can lead to either an alkene or an alkane depending on the stoichiometry of the hydrogen gas. If hept-1-yne reacts with only one molar equivalent of hydrogen gas and a Pd-C catalyst, for example, hept-1-ene is the presumed major product. An alkene can also react with hydrogen to give an alkane, however, and alkenes are more reactive than alkynes, so mixtures of products are common. The reaction with an excess of hydrogen gas will convert the alkyne to an alkane. The reaction of hept-1-yne with two equivalents of hydrogen gave heptane in 85% yield.[5]

[5] Campbell, K.N.; O'Connor, M.J. *Journal of the American Chemical Society* 1939, 61, 2897–2900.

The hydrogenation of an internal alkyne presents a further complication. Catalytic hydrogenation of an internal alkyne such as dec-5-yne with one equiv of hydrogen gives both dec-(5*E*)-ene and dec-(5*Z*)-ene. The ratio of isomers changes with the catalyst.

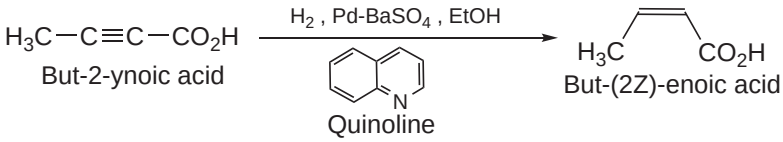


Dec-5-yne | Dec-5*Z*-ene 90% | Dec-5*E*-ene 2-3%

The extent of binding of the alkene to the surface of the metal and the transfer of hydrogen atoms to the π-bond changes with the metal catalyst. When alkene-metal binding is rather strong, as with Ni and Pd catalysts, the (*Z*)-alkene usually predominates. The reaction of dec-5-yne and a Ni(R) catalyst gave dec-(5*Z*)-ene in close to 90% yield, with only about 2–3% of dec-(5*E*)-ene.[6] With a Pt catalyst the binding alkene is not as good and greater amounts of the (*E*)-isomer are formed. If binding of the alkene is weak, there is a significant amount of each isomer in the mixture. Heating, solvent effects, and the structure of the alkene will influence the (*E*)- and (*Z*)-isomer ratio. These factors lead to poor binding of the alkene and poorer selectivity.

17.7 Draw the product of the reaction between 1,2-diphenylethyne and an excess of hydrogen, in the presence of 5% Pd/C in ethanol.

Catalytic hydrogenation can be slowed or even stopped altogether by the addition of organic compounds that diminish the activity of the metal catalyst. Such compounds are called *poisons* because they greatly diminish the reducing power of a hydrogenation catalyst. Catalyst poisons bind to the metal more-or-less irreversibly. The active sites on the surface of the metal are coated, which prevents binding of hydrogen gas, the alkene or the alkyne. Common poisons include metal cations, halides, Hg°, divalent sulfur compounds, carbon monoxide, carbon dioxide, amines, and phosphines. Hydrogenation of molecules containing sulfur, nitrogen or phosphorous units are generally avoided. The organic molecule being reduced or a minor reaction product can poison the catalyst.



But-2-ynoic acid | Quinoline | But-(2Z)-enoic acid

The fact that a "poisoned catalyst" is less reactive may be exploited. A selectively poisoned and "cis-specific" [(*Z*)-specific] catalyst has been developed for alkynes. It was discovered that a mixture of palladium on lead carbonate, in the presence of a lead oxide (PbO) poison gave a catalyst that reproducibly reduced alkynes to (*Z*)-alkenes with only trace amounts of the (*E*)-alkene. This selective catalyst was called the *Lindlar catalyst*, and hydrogenation of alkynes using it has been called *Lindlar hydrogenation or Lindlar reduction*, named for its discoverer, H. Lindlar (Switzerland).[7] Oxidation leads to degradation of the efficiency of the catalyst, which degrades the effectiveness. The Lindlar catalyst has been supplanted by another catalyst system that is easier to prepare and less prone to the oxidation of the lead carbonate and lead oxide constituents. This modified catalyst is formally called the *Rosenmund catalyst*. The new catalyst is composed of palladium on barium sulfate ($BaSO_4$) and it is poisoned with quinoline (Section 23.5). Reduction of alkynes prepares (*Z*)-alkenes

[6] Campbell, K.N.; Eby, L.T. *Journal of the American Chemical Society* 1941, 63, 216–219.
[7] Lindlar, H.; Dubuis, R. *Organic Syntheses, Collected Volume 5* 1973, 880–883.

without significant amounts of the (*E*)-alkene. Hydrogenation of but-2-ynoic acid, for example, afforded but-(2*Z*)-enoic acid in 95% yield.[8]

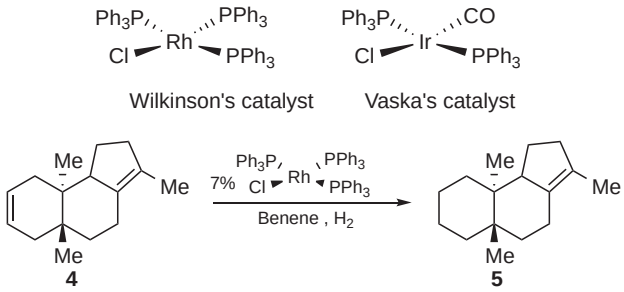
17.8 Draw the major product of a reaction between 3-methyl-1-phenylhex-1-yne and hydrogen gas in the presence of Pd on barium sulfate and quinoline.

Homogenous Hydrogenation

17.4.2 HOMOGENOUS HYDROGENATION

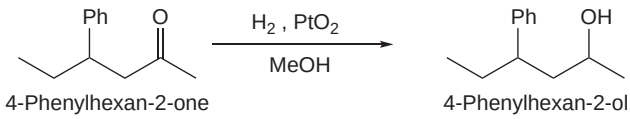
As described in Section 17.4.1, homogenous catalysts are soluble in the reaction medium. There are several interesting differences between homogeneous and heterogeneous catalysis. Heterogeneous catalysts essentially behave as an insoluble matrix, whereas the homogeneous catalyst is soluble in the reaction solvent and functions as a discreet molecule. Depending on the transition metal, these metal compounds typically have three, four, five or six ligands attached in a trigonal, square planar, trigonal bipyramidal or octahedral geometry about the metal. Commonly used ligands include pyridine (Py), cyclooctadiene (cod), tricyclohexylphosphine (PCy_3), triphenylphosphine, bis(phosphine) ligands, and mono and diamines.

A homogeneous catalyst is soluble, so each molecule of catalyst is accessible for reaction with hydrogen gas and the alkene or alkyne substrate. Some of the ligands attached to the metal must be easily displaced by hydrogen or the alkene or alkyne substrate to facilitate the hydrogen atom transfer to the substrate. By contrast, the matrix nature of heterogeneous catalysts often means poor chemoselectivity, bond migration, hydrogenolysis and so on. Homogeneous catalysts are significantly more selective for hydrogenation of alkenes and alkynes, show less reactivity with heteroatom-containing functional groups, and they are less prone to poisoning. Typical homogeneous catalysts include the rhodium complex known as *Wilkinson's catalyst* $(Ph_3P)_3RhCl$[9] and the iridium complex known as *Vaska's catalyst*.[10] An example is the hydrogenation of diene **4** with 7% of Wilkinson's catalyst in benzene to give a 97% yield of **5**.[11]



Hydrogenation of Other Functional Groups

17.4.3 HYDROGENATION OF HETEROATOM FUNCTIONAL GROUPS



[8] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.16, p. 494.

[9] (a) Jardine, F.H., Osborn, J.A.; Wilkinson, G.; Young, G.F. *Chemistry and Industry (London)* 1965, 560–561; (b) Bennett, M.A.; Longstaff, P.A. *Chemistry and Industry (London)* 1965, 846.

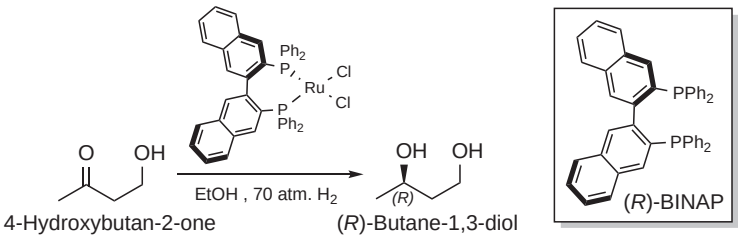
[10] (a) Vaska, L.; DiLuzio, J.W. *Journal of the American Chemical Society*1961, 83, 2784–2785; (b) Vaska, L.; DiLuzio, J.W. *Journal of the American Chemical Society* 1962, 84, 679–680.

[11] Ireland, R.E.; Bey, P.; Cheng, K.-F.; Czarny, R.J.; Moser, J.F.; Trust, R.I. *Journal of Organic Chemistry* 1975, 40, 1000–1007.

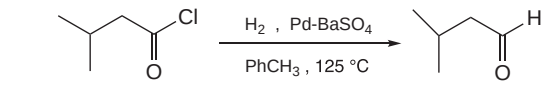
The carbonyl group of an aldehyde or ketone is reduced to an alcohol by either a hydride reagent or by catalytic hydrogenation. As with alkenes, a transition metal catalyst is required to first react with hydrogen gas. A Pt catalyst usually gives the best yields with fewer side reactions but platinum oxide [PtO_2; sometimes called *Adam's catalyst* after Roger Adams (USA; 1889–1971)] is commonly used. The hydrogenation reaction is relatively straightforward and works with most ketones and aldehydes. An example is hydrogenation of 4-phenylhexan-2-one to give 4-phenylhexan-2-ol.

17.9 What is the product formed when 3-methylhexan-2-one reacts with hydrogen gas and Adam's catalyst, in methanol?

There are many homogeneous catalysts with different transition metals. Ruthenium compounds have been developed that are particular effective for the asymmetric hydrogenation of ketones and other functional groups. Nobel laureate Ryōji Noyori (Japan) introduced the *Noyori asymmetric hydrogenation* using methodology a BINAP/Ru catalyst, a *Noyori catalyst*. The Noyori catalysts are effective for the asymmetric reduction of both functionalized and simple ketones.[12] An example is the hydrogenation of 4-hydroxybutan-2-one with using 70 atmospheres of hydrogen gas in ethanol and $RuCl_2$(*R*-BINAP) [dichloro[(*R*)-(-)-,2,2′-bis (diphenylphosphino)-1,1′-binaphthyl]ruthenium (II)] as the catalyst. With this catalyst, (*R*)-butan-1,3-diol was formed in quantitative yield and 98% ee.[12a] Note that BINAP is a ligand, the aromatic compound 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.



Carboxylic acid derivatives are discussed in Sections 18.2,5,6,8. It is possible to reduce acid chlorides using catalytic hydrogenation, but carboxylic acids, esters and amides are very difficult to reduce. Carboxylic acid derivatives will be introduced in Section 18.2. The general order of reactivity of carbonyl functional groups to hydrogenation is: acid chlorides > aldehydes ≈ ketones > anhydrides > esters > carboxylic acids > amides. Acid chlorides are reduced to alcohols via catalytic hydrogenation with an excess of hydrogen gas. However, it is also possible to reduce an acid chloride to an aldehyde with the proper catalyst and control of the number of molar equivalents of hydrogen gas. The *Rosenmund reduction* is a classical reaction in which an acid chloride is reduced with one molar equivalent of hydrogen gas, a Pd-$BaSO_4$ catalyst (in methylbenzene, also known as toluene, at 125 °C). An example is the hydrogenation of 3-methylbutanoyl chloride to afford the 3-methylbutanal in 80% yield.[13]

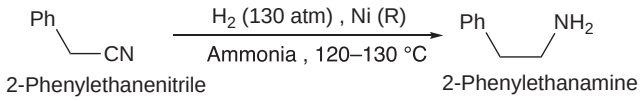


17.10 Draw the product formed when pentanoyl chloride is treated with two molar equivalents of hydrogen gas and a Pd–C catalyst.

[12] (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *Journal of the American Chemical Society* 1988, 110, 629–631. (b) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *Journal of the American Chemical* Society 1980, 102, 7932–7934.

[13] Mosettig, E.; Mozingo, R. *Organic Reactions* 1948, 4, 362–377.

Nitriles are acid derivatives since they can be hydrolyzed to the parent carboxylic acid (Section 18.13). Catalytic hydrogenation of nitriles yields the corresponding amine, and conversion of the C≡N unit to a CH_2NH_2 unit requires two molar equivalents of hydrogen gas. Although the addition of one molar equivalent of hydrogen converts the C≡N unit to an imine (–CH=NH), imines are very difficult to isolate under these conditions. For that reason, an excess of hydrogen is typically used to ensure conversion of the nitrile to the amine. Hydrogenation of the C≡N unit is somewhat difficult, however, and more vigorous reaction conditions (heat or longer reaction times) are usually required. Hydrogenation of 2-phenylethanenitrile at 130 atm of H_2 with a Raney nickel catalyst in ammonia at 120–130 °C gave 2-phenylethanamine in 87% yield.[14]



17.11 Draw the product formed when 3,5-dimethylbenzonitrile is hydrogenated with 2 equivalents of hydrogen and a Ni(R) catalyst.

Dissolving Metal Reductions

17.5 DISSOLVING METAL REDUCTIONS

Group 1 or group 2 alkali metals in liquid ammonia will reduce aldehydes, ketones, alkynes or benzene derivatives. Sodium or potassium, for example, donate electrons to an appropriate functional group. Such reactions are termed *dissolving metal reductions*. A protic solvent is usually added because protonation is slow in ammonia, which is a weak acid. An alcohol is a stronger acid, and the reaction is faster. The reaction of 4-*tert*-butylcyclohexanone with sodium metal in liquid ammonia and *tert*-butanol (2-methylpropan-2-ol), for example, gave 4-*tert*-butylcyclohexanol (4-(1,1-dimethylethyl)cyclohexanone) in 98% yield[15] The mechanism involves transfer of a single electron from sodium metal to the carbonyl unit of the ketone to give a reactive intermediate, a *radical anion* (see Figure 17.4).

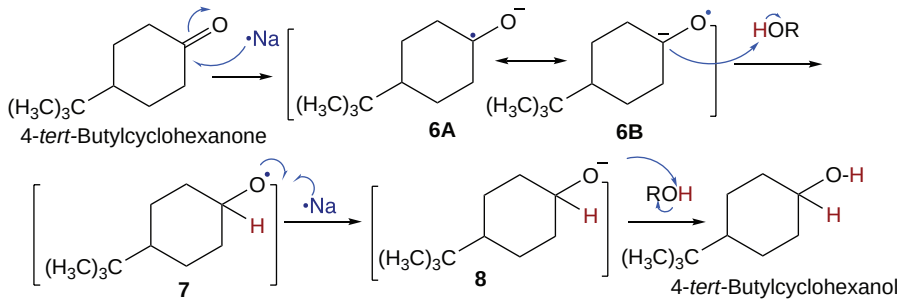


FIGURE 17.4 Mechanism for dissolving metal reduction of 4-(*tert*-butyl)cyclohexanone.

Note the use of the single-headed arrow to indicate the transfer of one electron. A radical anion derived from a carbonyl is known as a *ketyl*, which is a resonance stabilized species, **6A**-**6B**. The ketyl reacts as a carbanion base in an acid-base reaction with either ammonia or the alcohol to give **7**. Radical **7** reacts with another sodium atom via electron transfer to generate alkoxide, **8**. The final step of this mechanism is protonation of the alkoxide unit to give 4-*tert*-butylcyclohexanol. Other alkali metals such as lithium, potassium or calcium can also be used in this reduction.

[14] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, Menlo Park, CA, 1972, p. 18.
[15] House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, Menlo Park, CA, 1972, p. 153; Taken from Huffman, J.W.; Charles, J.T. *Journal of the American Chemical Society* 1968, 90, 6486–6492.

17.12 Draw the ketyl derived from treatment of acetone with Na metal.

While aldehydes and ketones react, unfunctionalized alkenes are usually not reduced under the same conditions. Alkynes, on the other hand, are reduced to alkenes in good yield under dissolving metal conditions, and the experimental evidence shows that the (*E*)-alkene is the major product. In a typical example, oct-4-yne was treated with Na in liquid ammonia to afford oct-(4*E*)-ene in 90% yield. One-electron transfer (single-headed arrow) from the sodium to one π-bond of oct-4-yne leads to radical anion **9**, as shown in Figure 17.5.

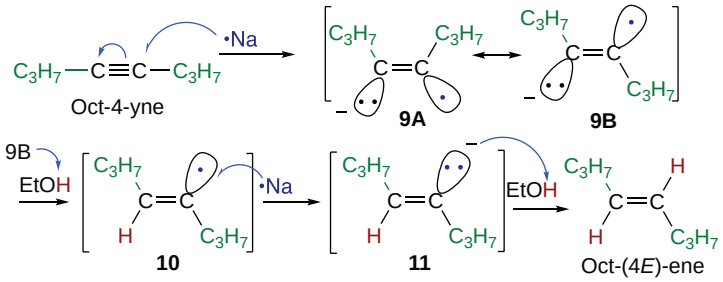


FIGURE 17.5 Mechanism of dissolving metal reduction of oct-4-yne.

One orbital in **9** contains a single electron (a radical) and a second orbital that contains two electrons (an anion). Formation of the observed (*E*)-product is explained by the electronic repulsion between the two orbitals, which is greater in **9A** and lower in **9B**. Therefore, **9B** is the lowest energy and most prevalent species. The preference for **9B** sets the (*E*) stereochemistry found in the alkene product. Reaction of **9B** with ethanol gives vinyl radical, **10**. Transfer of an electron from Na to **10** affords carbanion **11**. Protonation gives the final product, oct-(4*E*)-ene. This method is an interesting counterpoint to the Lindlar reduction discussed in Section 17.4. Lindlar reduction of an alkyne gives a (*Z*)-alkene, but dissolving metal reduction of an alkyne yields an (*E*)-alkene. Dissolving metal reduction of a terminal alkyne such as but-1-yne gives the mono-substituted alkene (but-1-ene).

17.13 Draw the dissolving metal reaction for the conversion of 6-methylhept-3-yne to the (E)-alkene.

Benzene was introduced in Section 5.9. Benzene derivatives along with their characteristic chemical reactions will be discussed in Chapter 19. Benzene and its derivatives can be reduced by dissolving metal reduction to give cyclohexadiene derivatives. When benzene is treated with sodium metal in a mixture of liquid ammonia and ethanol, the product is cyclohexa-1,4-diene, where the C=C units are not directly connected so they are non-conjugated (Section 21.1).

The dissolving metal mechanism for this reaction is shown in Figure 17.6. Initial electron transfer from sodium metal to benzene leads to the radical anion **12**. Resonance delocalization favors resonance contributor **12B** rather than **12A** due to charge separation. Radical anion **12B** reacts with the more acidic ethanol to give radical **13**. A second electron transfer

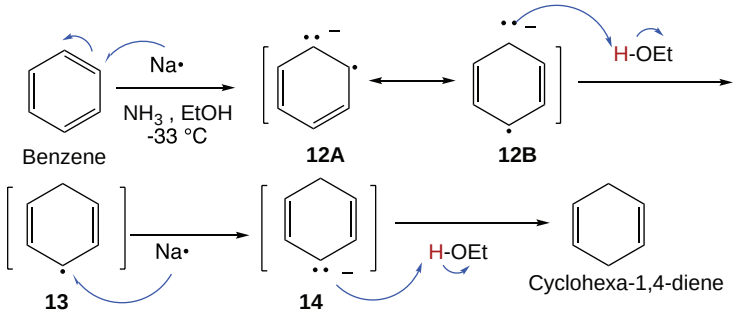


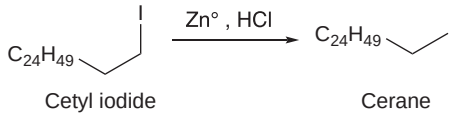
FIGURE 17.6 Birch reduction of benzene.

from sodium metal converts radical **13** to carbanion **14**, which quickly reacts with ethanol to yield the final product cyclohexa-1,4-diene. The nonconjugated diene unit is determined by charge separation in **12B** at the time of the initial electron transfer. This reduction of benzene and its derivatives is commonly known as the *Birch reduction*, after Arthur John Birch (Australia; 1915–1995).

The dissolving metal reductions discussed to this point used protic solvents and alkali metals. If a stronger acid is used as the proton transfer agent, other metals may be used for reductions, including Zn and Sn. Zinc in acetic acid (ethanoic acid, CH_3CO_2H) is commonly used to reduce alkyl halides in a reaction that replaces the halogen atom with a hydrogen atom. The reaction of alkyl halides can be slow with zinc in acetic acid but zinc in HCl is more effective. An example is the reaction of 1-iodohexacosane (cetyl iodide) with Zn/HCl to yield hexacosane (cerane) in 68% yield.[16]

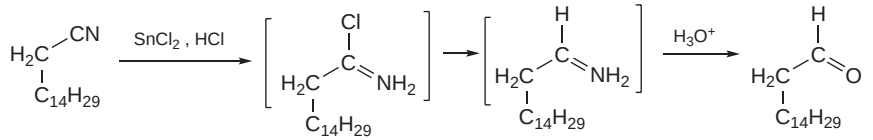
Zn, Sn, Wolff Kishner and Clemmensen Reductions

17.14 Draw the final product of a reaction between 1-bromo-1-phenylpropane and zinc powder, in acetic acid.



Cetyl iodide Cerane

Tin metal in an acid is very effective for the reduction of some functional groups. A mixture of Sn and concentrated HCl will reduce cyclohexanone to cyclohexanol. Stannous chloride ($SnCl_2$) dissolved in a Brønsted-Lowry acid is another useful reducing agent. When hexadecanenitrile was treated with $SnCl_2$ and HCl, the HCl adds to the C≡N unit to yield a chloro-imine, **15** in the initial reaction. Subsequent reduction in situ mediated by $SnCl_2$ in the acidic medium afforded imine **16**. In the aqueous acid solution, the initially formed imine product was converted to an aldehyde, hexadecenal (palmitaldehyde), in quantitative yield.[17] Protonation of the nitrogen to give an iminium salt is followed by addition of water, proton transfer to nitrogen and loss of ammonia. To give an oxocarbenium ion. Loss of a proton gives the aldehyde. Reduction of a nitrile to an aldehyde is called the *Stephen reduction* named after Henry Stephen (England; 1889–1965).



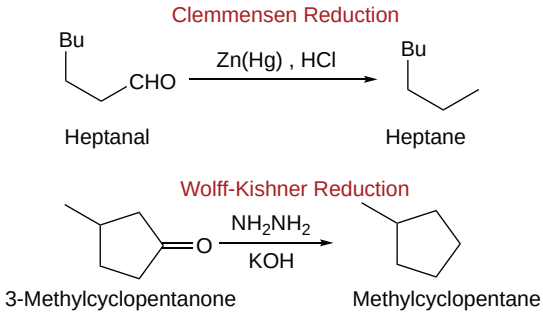
Hexadecanenitrile **15** **16** Hexadecanal

17.15 Write out the reaction of cyclohexanone with Sn/HCl, showing all starting materials and final product.

It is possible to reduce a carbonyl compound to remove the oxygen completely from the molecule. An example is the reaction of heptanal with zinc amalgam (Zn/Hg) in HCl to give heptane as the final product, in 72% yield[18] This reaction is known as *Clemmensen reduction*, named after E. Ch. Clemmensen (Denmark; 1876–1941). The starting material and the product must not react with the concentrated HCl used in the reaction, however. For relatively unfunctionalized molecules it is a very effective method for the complete reduction of ketones to hydrocarbons. Although it is not a dissolving metal reduction, an alternative reductive method treats ketones or aldehydes with hydrazine in aqueous KOH.

Dissolving Metal Reactions

[16] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry* Reinhold, NY, 1961, p. 114.
[17] Stephen, H. *Journal of the Chemical Society* 1925, 127, 1874–1877.
[18] Martin, E.L. *Organic Reactions* 1942, 1, 155–209.

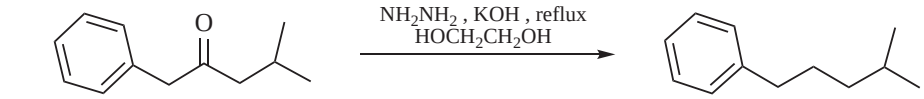


17.16 Draw the product formed when 4,4-diphenylhexan-2-one is treated with zinc amalgam in HCl.

This reaction is the *Wolff-Kishner reduction* [named after Ludwig Wolff (Germany; 1857–1919) and N.M. Kishner (Russia; 1867–1935)]. Wolff-Kishner reduction of heptanal with hydrazine/KOH gave heptane in 54% yield.[19] Reduction of 3-methylcyclopentanone affords methylcyclopentane. The Clemmensen reduction works in acidic media whereas the Wolff-Kishner reduction uses basic media.

Huang-Minlon

Perhaps the most important improvement to Wolff-Kishner reduction is the *Huang-Minlon modification*, in which the substrate and reagents are heated at reflux in diethylene glycol. This modification has been shown to be much more efficient for this transformation.[20] Huang-Minlon (China; 1898–1979) was an organic chemist and pharmaceutical scientist. He is considered to be a pioneer and the founder of the modern pharmaceutical industry in China. The Huang-Minlon modification is the earliest instance of an organic reaction associated with the name of a Chinese chemist. An example is the reduction of the ketone unit in 4-methyl-1-phenylpentan-2-one using this modification to give 2-methyl-5-phenylpentane.



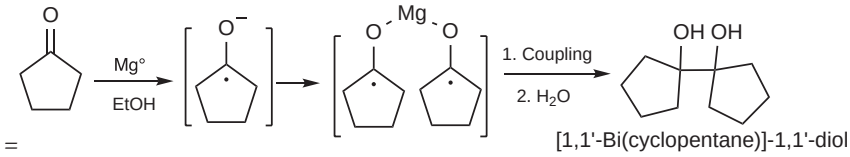
4-Methyl-1-phenylpentan-2-one — 2-Methyl-5-phenylpentane

[19] Todd, D. *Organic Reactions* 1948, 4, 478.

[20] (a) Huang-Minlon. *Journal of the American Chemical Society* 1946, 68, 2487–2488; (b) Huang-Minlon. *Journal of the American Chemical Society* 1949, 71, 3301–3303.

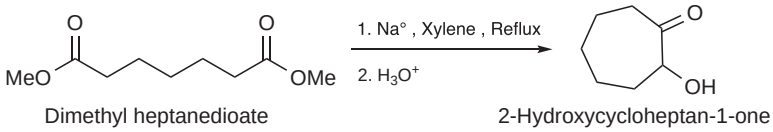
Pinacol Coupling

A classical metal mediated reaction with aldehydes or ketones is the *pinacol reaction* or *pinacol coupling*.[21] The initial reaction with an aldehyde or ketone produces a radical anion via electron transfer. Under these conditions, the dissolving metal reduction does not occur, but intermediate radical anions couple to form 1,2-diols.[22] This method is called *reductive coupling*, and the best conditions use a mixture of magnesium and magnesium iodide ($Mg + MgI_2$). An example is the reaction of cyclopentanone to give [1,1'-bi(cyclopentane)]-1,1'-diol.[21] Initial one-electron transfer to the carbonyl generates the radical anion. Coordination with the magnesium generates the diradical complex shown, which facilitates coupling. Subsequent reaction with water generates the diol.



Acyloin Condensation

A related reaction involves the reaction of esters to prepare α-hydroxy ketones (acyloins). A simple example is the reaction of dimethyl heptanedioate with sodium metal (Na°) in xylene (dimethybenzene) at reflux.[23] The product is 2-hydroxycycloheptan-1-one after a hydrolytic workup. The reaction of an α,ω diester to give an α-hydroxy ketone is called the *acyloin condensation*.[23] A high-speed stirrer is required to generate a fine "sodium sand" to maximize the surface area for effective electron transfer and radical coupling of the ketyl intermediate. Under these conditions, both intermolecular coupling and intramolecular cyclization reactions are possible. The intramolecular cyclization of α,ω diesters to form cyclic acyloins appears to be the most efficient version of this reaction.[24]

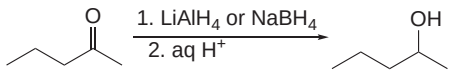


17.6 ORGANIZATION OF REACTION TYPES

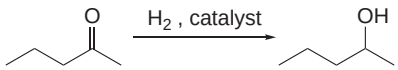
Reduction reactions can be organized as follows.

What reactions are possible for ketones and aldehydes?

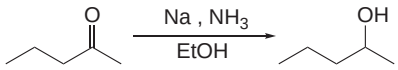
1. Aldehydes and ketones are reduced to alcohols with $NaBH_4$ or $LiAlH_4$.



2. Aldehydes and ketones are reduced to alcohols with hydrogen gas and Pt, or Pd or Ni.

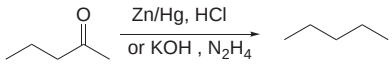


3. Aldehydes and ketones are reduced to alcohols with sodium in liquid ammonia and ethanol.



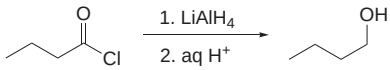
[21] (a) Schreibman, A.A.P. *Tetrahedron Letters* 1970, 4271–4272.
[22] (a) Popp, F.D.; Schultz, H.P. *Chemical Reviews* 1962, *62*, 19–40 (see pp. 27–30); (b) Weber, J.E.; Boggs, A.D. *Journal of Chemical Education* 1952, 29, 363.
[23] (a) McElvain, S.M. *Organic Reactions* 1948, 4, 256–268; (b) Finley, K.T. *Chemical Reviews* 1964, 64, 573–589.
[24] Finley, K.T. *Chemical Reviews*, 1964, 64, 573–589.

4. Aldehydes or ketones are reduced to $-CH_3$ or $-CH_2$- with Zn/Hg and HCl or NH_2NH_2/KOH.

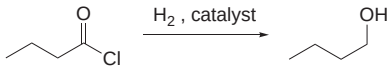


What reactions are possible for acid derivatives?

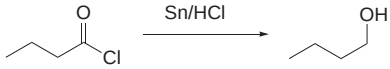
1. Acid chlorides are reduced to alcohols with $LiAlH_4$.



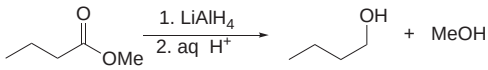
2. Acid chlorides are reduced to alcohols with hydrogen gas and a metal catalyst.



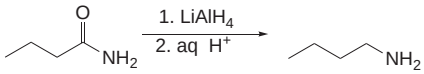
3. Acid chlorides are reduced to alcohols with Sn/HCl.



4. Esters are reduced to alcohols with $LiAlH_4$.

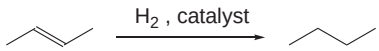


5. Amides are reduced to the amine.



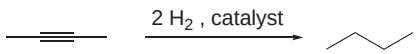
What reactions are possible for alkenes?

1. Alkenes are reduced to alkanes with hydrogen gas and Pd, Ni, or Pt.

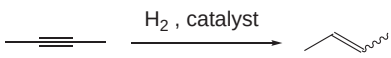


What reactions are possible for alkynes?

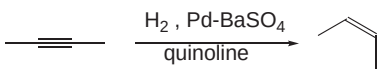
1. Alkynes are reduced to alkanes with an excess of hydrogen gas and Pd, Ni, or Pt.



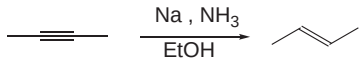
2. Alkynes are reduced to alkenes with an one equivalent of hydrogen gas and Pd, Ni, or Pt.



3. Alkynes are reduced to (*Z*)-alkenes with 1 equiv of hydrogen gas and $Pd/BaSO_4$ and quinoline.

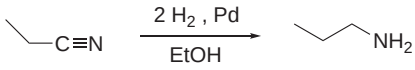


4. Alkynes are reduced to (*E*)-alkenes with Na/NH_3 in ethanol.

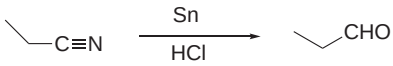


What reactions are possible for nitriles?

1. Nitriles are reduced to the amine with $LiAlH_4$ or via catalytic hydrogenation.

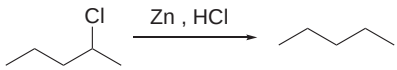


2. Nitriles are reduced to aldehydes with $SnCl_2$ and HCl.



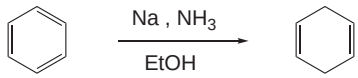
What reactions are possible for alkyl halides?

1. Alkyl halides are reduced to the hydrocarbon by reaction with Zn and HCl.



What reactions are possible for benzene?

1. Benzene is reduced to cyclohexa-1,4-diene with Na/NH_3 in ethanol.



17.7 BIOLOGICAL RELEVANCE

Vegetable oils (olive oil, sunflower oil, etc.) have C=C units as part of long-chain carboxylic acid units, and they are liquids at room temperature. Catalytic hydrogenation of the C=C units leads to an "alkane" backbone, which increases the melting point to make them solid. Hydrogenated oils can be sold directly as "spreads" (e.g., margarine), but they are also used in the food industry in the manufacture of many items (e.g., cakes). The use of hydrogenated oils helps to prolong the shelf-life of the food and maintain flavor stability.

In a study on the impact of enzyme motion on activity, it was discovered that the enzyme *dihydrofolate reductase* catalyzes the conversion of dihydrofolate to tetrahydrofolate. A hydride is transferred from NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) to the imine unit of dihydrofolate to form the products, $NADP^+$ (nicotinamide adenine dinucleotide phosphate) and tetrahydrofolate.[25] As dihydrofolate is reduced, NADPH is oxidized. The conversion of NADPH to $NADP^+$ is also shown in Figure 17.7. This transformation is the reverse of the Birch reduction discussed in Section 17.5.

[25] Hammes-Schiffer, S. *Biochemistry* 2002, 41, 13335–13343.

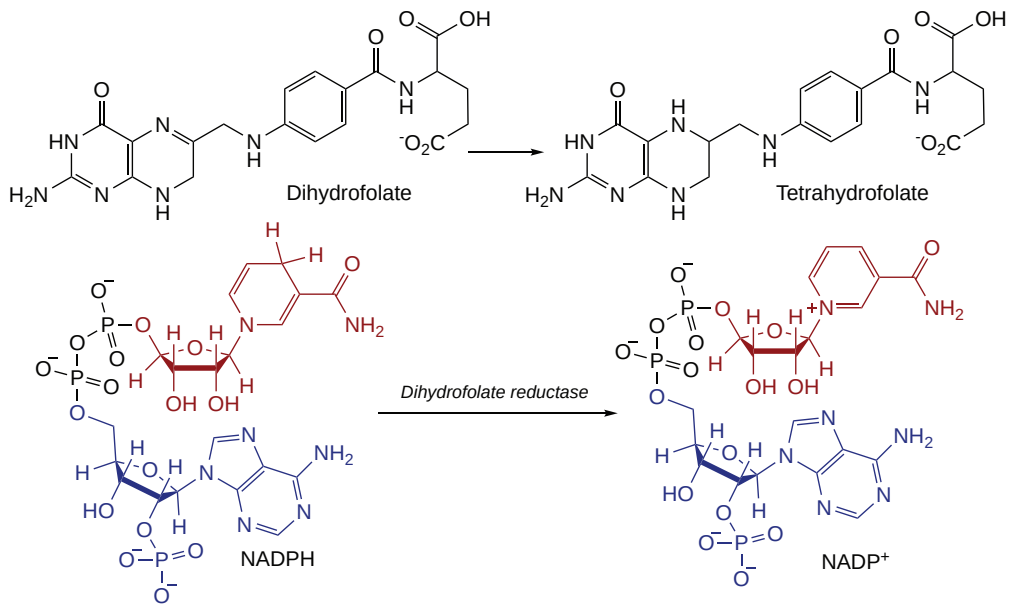


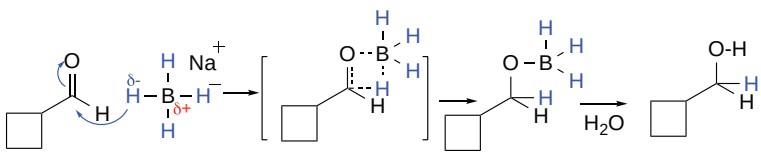
FIGURE 17.7 The enzymatic conversion of dihydrofolate to tetrahydrofolate with *dihydrofolate reductase* in which NADPH is reduced to $NADP^+$. Adapted with permission from Hammes-Schiffer, S. *Biochemistry*, 2002, 41, 13335-13343. Copyright 2002 American Chemical Society.

CORRELATION OF HOMEWORK WITH CONCEPTS

- Both sodium borohydride and lithium aluminum hydride reduce ketones or aldehydes to alkoxides. A hydrolytic workup gives the alcohol. Epoxides are reduced to alcohols. Lithium aluminum hydride is a more powerful reducing agent than sodium borohydride: 1, 2, 5, 17, 18, 19, 20, 21. 22, 24.
- Lithium aluminum hydride will reduce carboxylic acid derivatives to the corresponding alcohol and an amide to an amine. Nitriles are also reduced to an amine: 3, 4, 19.
- In the presence of a transition metal catalyst, hydrogen gas converts an alkene to an alkane, an alkyne to an alkene: 6, 7, 8, 19, 223, 24.
- In the presence of a transition metal catalyst, hydrogen gas reduces a ketone or aldehyde to an alcohol: 9, 24.
- A ketone or aldehyde is reduced to an alcohol by a dissolving metal reaction. Both alkynes and benzene derivatives are reduced under the same conditions: 12, 13, 19, 23.
- Zinc, tin or iron in acid will reduce an aldehyde or ketone to an alcohol. A ketone or aldehyde is reduced to the corresponding hydrocarbon Clemmensen reduction or Wolff-Kishner reduction: 14, 15, 26, 319, 22, 23, 24.
- Spectroscopy can be used to determine the structure of a particular molecule (Chapter 13): 25, 26.

ANSWERS TO IN-CHAPTER QUESTIONS

17.1



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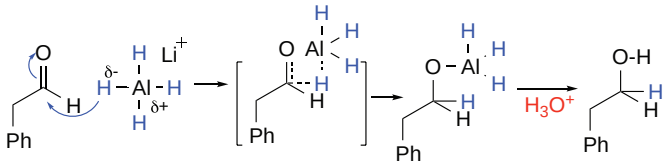

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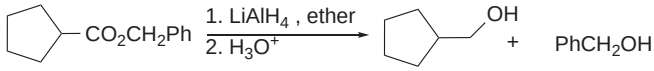

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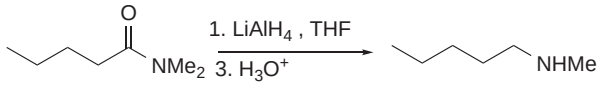
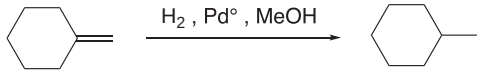


17.5 Cyclohexanol

17.6



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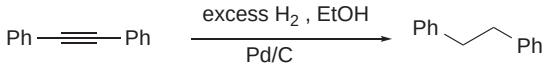

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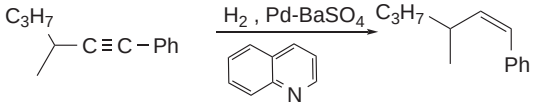
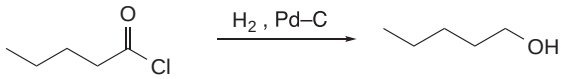


17.9 3-Methylhexan-2-ol

17.10



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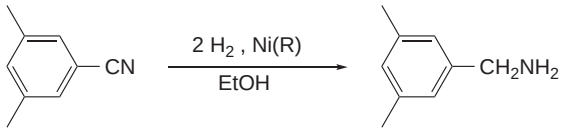

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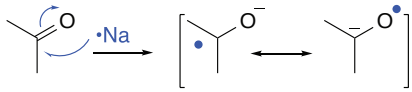

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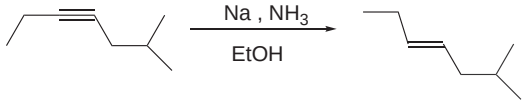

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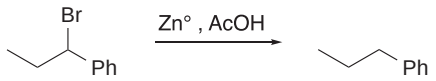

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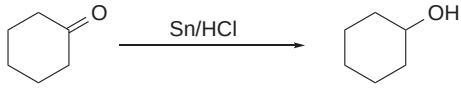
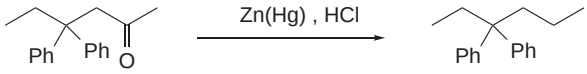
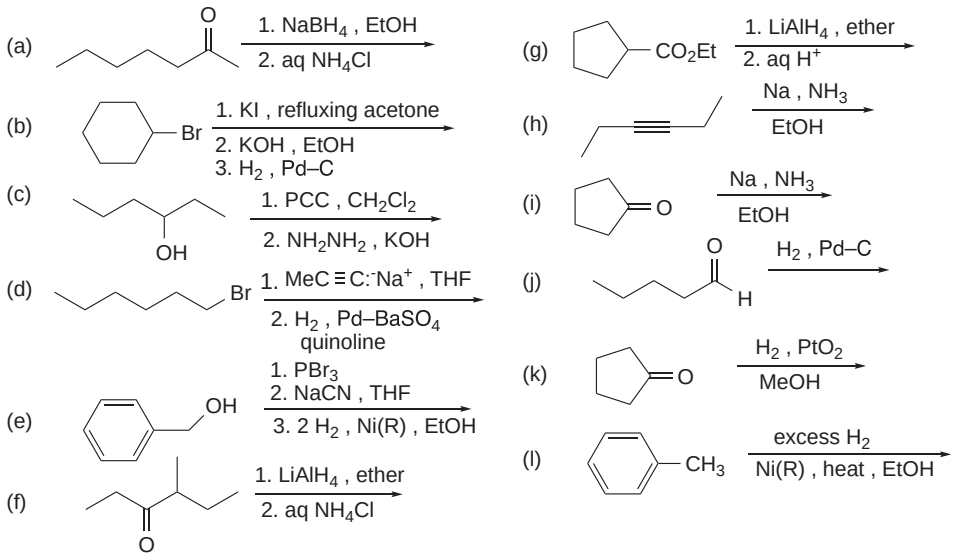


17.16

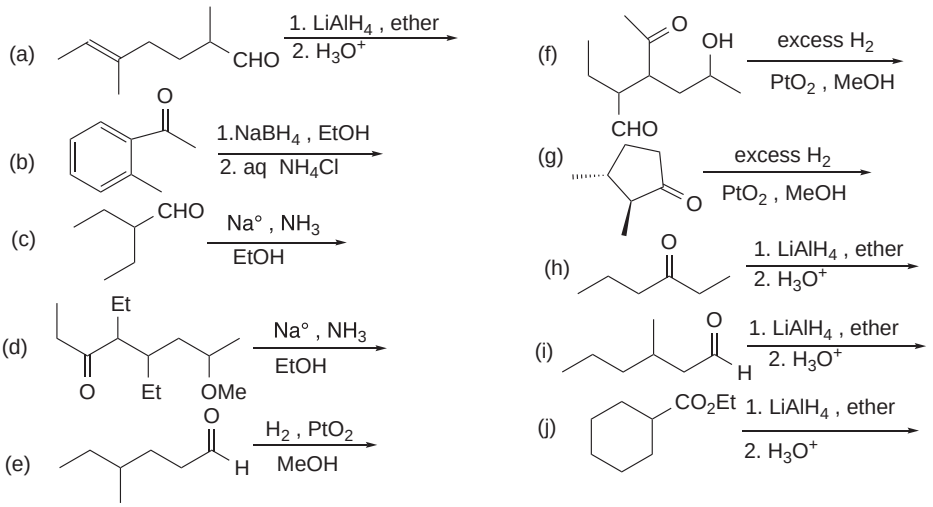


HOMEWORK

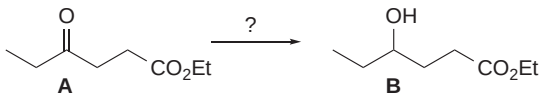
17. Briefly discuss whether you think $LiAlH(OMe)_3$ is stronger or weaker than $LiAlH_4$. Similarly discuss the relative strength of $NaBH_4$ when compared to $NaBHEt_3$.
18. 5-Oxooctanal is treated with 0.25 mol of $NaBH_4$ in ethanol and that product is subjected to aqueous ammonium chloride workup, the major product has only one hydroxyl group. Draw the structure of this product and explain why only one carbonyl group is reduced in preference to the other one.
19. Give the major product for each of the following:



20. What is the major product when 2-butyloxirane is reacted with $LiAlH_4$ and then water?
21. Give the major product for each of the following:



22. Describe an experimental procedure that will allow you to convert A to B.



23. Give the product of each individual step where appropriate, and the final product for each of the following:
    (a) Hex-2-yne + Na, NH_3, EtOH
    (b) Hept-3-yne + H_2, Pd/$BaCO_3$/quinoline
    (c) 4-Phenyl-1-bromopentane + 1. Mg, ether 2. Hot water
24. Give the major product for each of the following reactions:
    (a) 3-Methylhexan-2-ol + 1. PCC 2. $NaBH_4$ 3. aq. NH_4Cl
    (b) (2*R*)-Bromopentane + 1. NaCN, THF 2. $SnCl_2$/HCl

(c) Cyclopentanecarbaldehyde + 1. $NaBH_4$/EtOH 2. hydrolysis
(d) 2-Bromo-2-methylpentane + 1. KOH, EtOH 2. EtOH. H_2, Pd–C

Spectroscopic problems. Do not attempt these problems until Chapter 13 is read and understood.

25. A molecule **A** with the formula C_5H_8: IR: broad peak at 3307, 2968–2843, 2120, 630 cm^{-1}; ^1H NMR: 2.15 (t, 3H), 1.94 (s, 1H), 1.55 (m, 2H), 1.0 (t, 3H) ppm. When **A** is treated with $NaNH_2$ in THF, followed by 1-bromopropane, the product is **B** with the formula C_8H_{14} and IR: 2963–2842, 1464–1435 cm^{-1}; ^1H NMR: 2.12 (broad t, 4H), 1.50 (m, 4H), 0.98 (broad t, 6H) ppm. When **B** reacts with one molar equivalent of H_2/Pd-$BaSO_4$ and quinoline, the product is **C**: IR: 3007, 2959-2874, 1656, 1455–1467, 1404 cm^{-1}; ^1H NMR: 5.37 (m, 2H), 2.00 (m, 4H), 1.36 (m, 4H), 0.91 (broad t, 6H) ppm. Identify **A**, **B** and **C**.
26. Compound **A** (C_5H_{10}): IR: 2979–2884, 1716, 1461 cm^{-1}; ^1H NMR: 2.44 (q, 4H), 1.06 (t, 6H) ppm reacts with $LiAlH_4$ in ether then water, to form **B**: a strong peak in the IR at 3632 cm^{-1}. Reaction of **B** with PBr_3 leads to product **C** ($C_5H_{11}Br$) with no significant peaks in the IR and ^1H NMR: 3.94 (m, 1H), 1.84 (m, 4H), 1.04 (broad t, 6H) ppm. Reaction of **C** with NaCN in DMF gives **D**, for which there is no spectral data. When **D** reacts with $SnCl_2$/HCl the product is **E** ($C_6H_{12}O$): IR: 2967-2879, 2693, 1708, 1462 cm^{-1}; ^1H NMR: 9.6 (s, 1H), 2.12 (m, 1H), 1.67-1.53 (m, 4H), 0.92 (t, 6H) ppm. When **D** reacts with $LiAlH_4$ in THF, followed by hydrolysis, compound **F** is the product, a slightly foul-smelling oil with the formula $C_6H_{15}N$ and the spectra: IR: 3376, 3297, 2962-2864, 1610, 1462, 966-742 cm^{-1}; ^1H NMR: 2.61 (d, 2H), 1.35-1.30 (m, 6H; after treatment with D_2O, this peak is diminished and integrates to only 4H), 1.20 (m, 1H), 0.88 (broad t, 6H) ppm. Identify **A, B, C, D, E,** and **F**.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-18.php

18

Carboxylic Acid Derivatives and Acyl Substitution

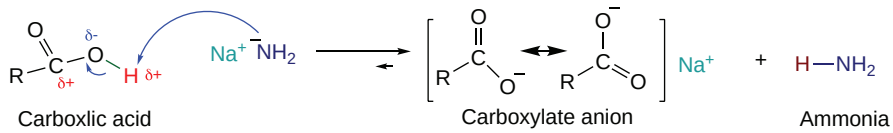
The acyl addition reactions of nucleophiles with aldehydes and ketones are discussed in Chapter 16. Carboxylic acid derivatives also contain a carbonyl unit, but they have a leaving group attached to the acyl carbon that facilitates acyl substitution reactions.

To begin this chapter, you should know the following points:

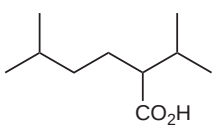
- Nomenclature (Sections 4.3, 5.1, 5.2, 5.3, 5.5, and 5.6).
- The carboxyl functional group (Section 5.6.3).
- The acid-base properties of carboxylic acids (Sections 6.2 and 6.3).
- The CIP rules (Section 9.2).
- The π-bond (Sections 5.1 and 5.2).
- Aldehydes and ketones (Sections 5.6.1,2).
- Acyl addition (Sections 16.1 and 16.2).
- Mechanisms (Section 7.10).
- Intermediates (Sections 7.2, 10.1, and 10.10).
- Lewis acids and bases (Sections 2.7 and 6.8).
- Nucleophiles (Sections 6.9 and 11.1–11.3).
- Leaving groups (Section 11.1).
- The S_N2 reaction (Section 11.2.)
- Grignard reagents and organolithium reagents (Sections 16.2).
- Organocuprates (Section 14.4).
- The mechanism of acetal and ketal formation (Section 16.4.2).
- Oxidation reactions of peroxyacids (Sections 15.4).
- Reagents for the conversion of alcohols to alkyl halides (Section 11.5).

18.1 CARBOXYLIC ACIDS

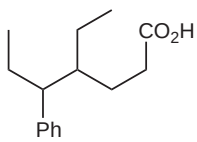
Carboxylic Acids



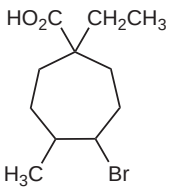
Carboxylic acids were introduced in Section 5.9.3. Carboxylic acids contain a carbonyl that is connected to an OH unit in a COOH unit called the *carboxyl group.* As the name implies, carboxylic acids are good Brønsted-Lowry acids, with pK_a values that typically range from 1–6 (Sections 6.2–6.3). An acid-base reaction of a carboxylic acid with sodium amide is shown, generating the resonance-stabilized carboxylate anion and the conjugate acid, ammonia (Section 6.3).



2-(1–Methylethyl)-5-methylhexanoic acid



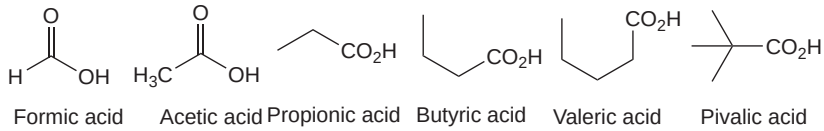
4-Ethyl-5-phenylheptanoic acid



4-Bromo-1-ethyl-5-methylcycloheptane-1-carboxylic acid

DOI: 10.1201/9781003174929-18

The IUPAC nomenclature for carboxylic acids identifies the longest continuous chain for the acid that contains the CO_2H unit. The carboxyl is the locant and it is always C1 so 1- is omitted from the name. The suffix for carboxylic acids is *-oic acid*, and "acid" is separated from the first part of the name. Examples are 2-(1–methylethyl)-5-methylhexanoic acid and 4-ethyl-5-phenylheptanoic acid. Carboxylic acids that have a carboxyl group attached to a ring are named as the cyclic alkane carboxylic acid, as in 4-bromo-1-ethyl-5-methylcycloheptane-1-carboxylic acid. The ring carbon bearing the COOH unit is identified as C1 and the substituents are assigned the lowest number based on the carboxyl. Many simple carboxylic acids are known primarily by their common names. These include formic acid, acetic acid, propionic acid, butyric acid, valeric acid, and pivalic acid.



Formic acid | Acetic acid | Propionic acid | Butyric acid | Valeric acid | Pivalic acid

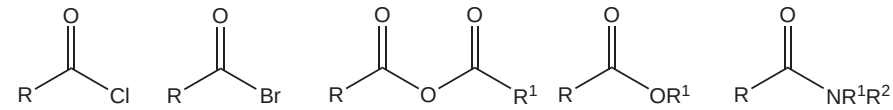
Formic and acetic acids are used for the manufacture of paints, adhesives, and coatings. Vinegar contains acetic acid. Propanoic acid is used as a food preservatives in animal feed and it is used in baked goods and cheese to kill microorganisms that can lead to spoilage. Butyric acid is used in the treatment of disorders of the digestive tract, and it is responsible for the disagreeable odor of rancid butter.

18.1 Write out the structure of 3-bromo-4-ethylnonanoic acid.

Acid chlorides, Anhydrides, Esters, Amides

18.2 CARBOXYLIC ACID DERIVATIVES: STRUCTURE AND NOMENCLATURE

There are four important derivatives of carboxylic acids in which the OH connected to the carbonyl in RCOOH is replaced by a halogen, a carboxyl, an alkoxy or an amino group. When the group is a halogen, the molecule is an *acid halide*, where the OH unit in RCOOH is replaced with Cl, Br or I. When the halogen is chlorine, the molecule is an *acid chlorid*e. When OH is replaced by bromine the molecule is called an *acid bromide*. An *acid anhydride* is formed when the OH group is replaced by a carboxyl unit (O_2CR). As the name suggests, anhydride means without water.

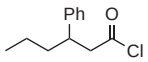
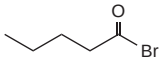
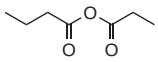
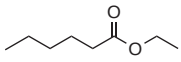
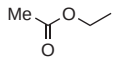
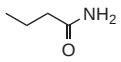
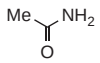
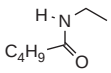
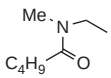
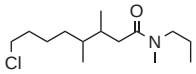


Acid chloride | Acid bromide | Acid anhydride | Ester | Amide

Indeed, anhydrides are two carboxylic acid units joined together with loss of a water molecule. If the OH group in RCOOH is replaced by an OR' group (from an alcohol), it is called an *ester*. Finally, if OH in RCOOH is replaced with an amine group (NH_2, NHR^1, or NR^1R^2), the derivative is called an *amide*. The structure of several acid derivatives and their names are shown in Table 18.1, along with the parent acid.

The nomenclature of each acid derivative is based on the carboxylic acid precursor, the "parent" acid. Acid chlorides are named by taking the carboxylic acid name (R in RCOOH, ending in -oic acid) and replacing the -oic acid term with *oyl chloride*. The first structure in Table 18.1 replaces OH with Cl to give 3-phenylhexanoyl chloride. Acid bromides are less common than acid chlorides, but an example is pentanoyl bromide. Acid anhydrides consist of two carboxylic acid units and the IUPAC rules demand that the two acids are each named and alphabetically, followed by the word anhydride. The anhydride shown in Table 18.1 is derived from butanoic acid and propanoic acid. The name is butanoic propanoic anhydride. It is an *unsymmetrical* anhydride since the two acid components are different. If both acid

TABLE 18.1 Typical Acid Derivatives

Structure	Parent Acid	Name
	3-Phenylhexanoic	3-Phenylhexanoyl chloride
	Pentanoic	Pentanoyl bromide
	Butanoic	Butanic propanoic anhydride
	Ethanoic (acetic)	Ethanoic anhydride (acetic anhydride)
	Hexanoic	Ethyl hexanoate
	Ethanoic (acetic)	Ethyl ethanoate (ethyl acetate)
	Butanoic	Butanamide
	Ethanoic (acetic)	Ethanamide (acetamide)
	Pentanoic	*N*-Ethyl pentanamide
	Pentanoic	N-Ethyl-N-methylpentanamide
	Octanoic	8-chloro-*N*,3,4-trimethyl-*N*-propyloctanamide

components are identical, it is a *symmetrical* anhydride. The example shown is diethanoic anhydride or just ethanoic anhydride. The common name acetic anhydride.

Esters are a combination of a carboxylic acid and an alcohol. The name includes the parent carboxylic acid and the -oic acid is replaced by *-oate*. Therefore, butanoic acid becomes butanoate and hexanoic acid becomes hexanoate. The alcohol portion of the name is listed first and uses the prefix for the number of carbon atoms with the suffix -yl. An ester with a methanol component is a methyl ester and an ester with a propanol component is a propyl ester. Ethyl hexanoate is one example and ethyl ethanoate ($MeCO_2Et$) is another. The common name of ethanoic acid is acetic acid, and the common name of the ethyl ester is ethyl acetate. Note the "shorthand" way of writing ethyl acetate (EtOAc), where Et is ethyl and OAc is the acetate unit O_2CCH_3.

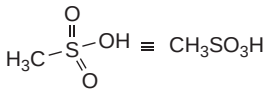
Structurally, *amides* are a combination of an amine and an acid, and the name replaces the -oic acid with the word *amide*. For primary amides an $-NH_2$ group is attached to the carbonyl of the acid. The two examples in Table 18.1 are butanamide and ethanamide. As a derivative of acetic acid, the common name acetamide is used more often than ethanamide. If the amide has a –NHR group, it is a secondary amide. Groups attached to the carboxylic acid chain are numbered as usual, but the group on nitrogen must be identified. The term *N*-alkyl is used to identify an alkyl group attached directly to nitrogen (Section 5.5.3). An example is *N*-ethylpentanamide. When the amide has two alkyl groups attached to nitrogen, a $-NR_2$ group, it a tertiary amide and both alkyl groups on nitrogen are designated by using the "*N*-" protocol. The use of *N*- is analogous to using a number, so each group on nitrogen is given an *N*-. If the two alkyl groups on nitrogen are different, the names of those groups are listed alphabetically using an *N*- with each group. An example is 8-chloro-*N*,3,4-trimethyl-*N*-propyloctanamide.

18.2 Draw the structure of 3-cyclopentylheptanoyl bromide, 3,3,4-trimethylpentanoic 2-phenylheptanoic anhydride, 2-phenylethyl 3,3-dimethylpentanoate and *N*,3-diethyl-*N*-methyl-5-phenylhexanamide.

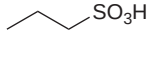
Sulfonic Acids

18.3 SULFONIC ACIDS AND DERIVATIVES

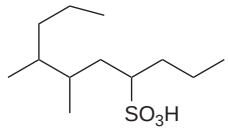
The sulfonic acids are another important class of organic acids with the general structure RSO_3H, where R is any alkyl group. Sulfonic acids are named by identifying the hydrocarbon unit R, with the suffix *sulfonic acid*. The longest continuous chain must contain the SO_3H unit, and that carbon receives the lowest number, which is always 1. Examples include the one-carbon sulfonic acid, methanesulfonic acid. Propanesulfonic acid is the three-carbon sulfonic acid. Substituents are treated in the usual manner.



Methanesulfonic acid

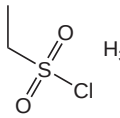


Propanesulfonic acid

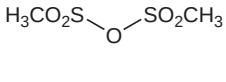


3,4-dimethyl-1-propylheptanesulfonic acid

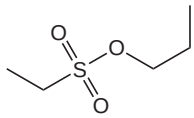
The 7-carbon chain sulfonic acid has a propyl group at C1 and two methyl groups, so it is named 3,4-dimethyl-1-propylheptanesulfonic acid. Sulfonic acids are more acidic than the analogous carboxylic acid due in large part to the resonance stability of the sulfonate anion formed by reaction with a base. The one-carbon sulfonic acid (methanesulfonic acid) can be compared with ethanoic acid (acetic acid), for example. The pK_a of ethanoic acid is 4.76, whereas the pK_a of methanesulfonic acid is -1.9.[1]



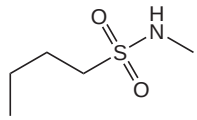
Ethanesulfonyl chloride



Methanesulfonic anhydride



Propyl ethanesulfonate



N-Methybutanesulfonamide

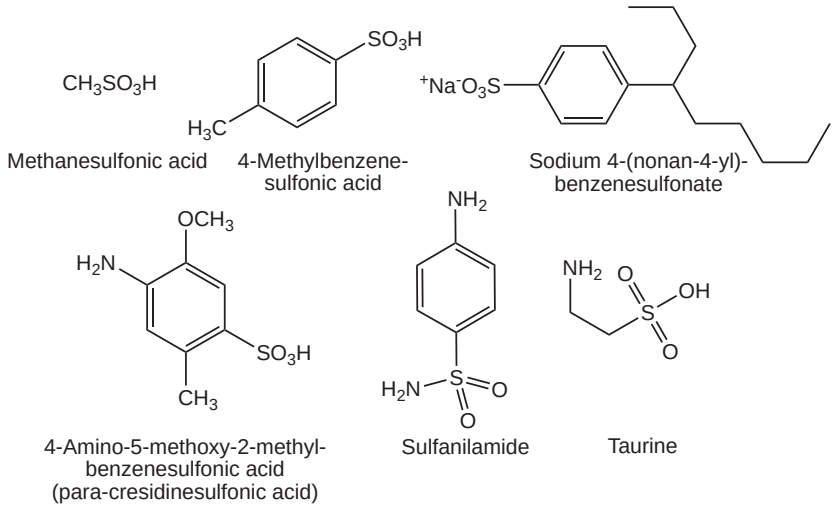
Sulfonic acids form acid halides, anhydrides, esters, and amides. The sulfonic acid derivatives are sulfonyl chlorides (RSO_2Cl), sulfonic anhydrides, sulfonate esters (RSO_2OR^1), and sulfonamides ($RSO_2NR^1_2$). An example of a sulfonyl chloride is ethanesulfonyl chloride. Anhydride derivatives of sulfonic acids are known (RSO_2OSO_2R), such as methanesulfonic anhydride. Sulfonate esters are common, and an example is propyl ethanesulfonate. *N*-Methylbutanesulfonamide is an example of a sulfonamide. Sulfa drugs are sulfonamide derivatives, and they were the first chemical substances used to treat and prevent bacterial infections in humans. They are not used as much because penicillins are more effective antibiotics.

18.3 Write out the reaction that converts methanesulfonic acid to methanesulfonyl chloride.
18.4 Write out the reaction and give the products formed when ethyl propanesulfonate reacts with propan-1-amine.

Sulfonic acid derivatives have a wide variety of uses, although many are derived from aromatic compounds (Chapter 19). Methanesulfonyl chloride (aka, *mesyl chloride*) and 4-methylbenzenesulfonyl chloride (aka, *para*-toluenesulfonyl chloride) are two common sulfonic

[1] Stewart, R. *The Proton: Applications to Organic Chemistry,* Academic Press, Orlando, FL, 1985, p. 17.

acids. 4-Methylbenzenesulfonyl chloride is abbreviated as *tosyl chloride* or TsCl (Section 19.2). A soap is a surfactant usually derived from fatty acids (Section 18.12).



A detergent is a surfactant is usually an alkylbenzene sulfonate but more soluble in hard water than a soap. Surfactants are compounds that lower the surface tension between two liquids, between a gas and a liquid, or between a liquid and a solid. An example of an anionic detergent is sodium 4-(dodecan-5-yl)benzenesulfonate. Sulfonic acid derivatives are important components of dyes, especially washable dyes. The aromatic compound *para*-cresidinesulfonic acid (4-amino-5-methoxy-2-methylbenzenesulfonic acid) is used to make food dyes. A sulfonic acid known as taurine, a common constituent of bile, is found in the lower intestines of humans. Taurine is found in many "energy drinks."

18.4 ACYL SUBSTITUTION AND HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES

Acyl Substitution

There are two fundamental reactions of carboxylic acid derivatives, acyl substitution and the acid-base reaction of the carbonyl oxygen. The acyl addition reactions of aldehyde or ketones with a nucleophile can be contrasted with the acyl substitution reaction with carboxylic acids. Strong nucleophiles (Y) react with aldehydes and ketones via *acyl addition* to give an alkoxide, as shown in Figure 18.1. A hydrolytic workup affords the alcohol product. Acid derivatives react with a nucleophile (Y) to generate an alkoxide intermediate, otherwise known as a *tetrahedral intermediate.* If X is Cl from an acid chloride, the tetrahedral intermediate has a *leaving group* attached to the carbonyl. Expulsion of the leaving group regenerates the C=O unit with formation of a new acid derivative where "Y" has replaced "X."

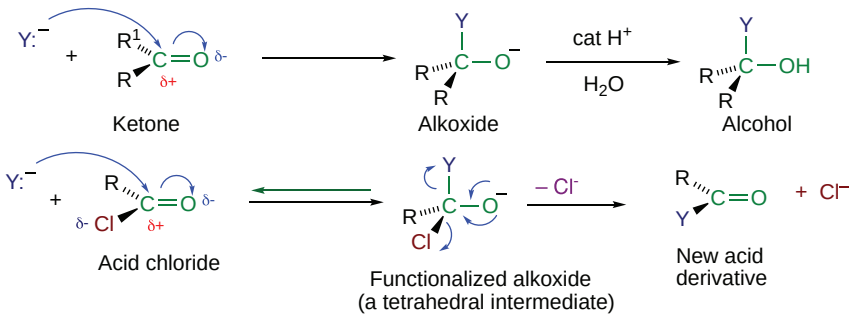


FIGURE 18.1 Acyl addition vs acyl substitution.

This reaction is known as *acyl substitution*. Carboxylic acids undergo facile acid-base reactions and do not undergo acyl substitution reactions with nucleophiles.

The second type of reaction for an acid derivative is an acid-base reaction. The carbonyl of a carboxylic acid derivative reacts with a strong Brønsted-Lowry acid such as sulfuric acid, as shown in Figure 18.2. The product is a functionalized and resonance stabilized oxocarbenium ion: X = Cl for an acid chloride, X = O_2CR for an anhydride, X = OR for an ester, and X = NR_2 for an amide. The initially formed oxocarbenium ion reacts with a nucleophile (Y) to give a tetrahedral intermediate. Loss of the leaving group followed by deprotonation affords the new acid derivative.

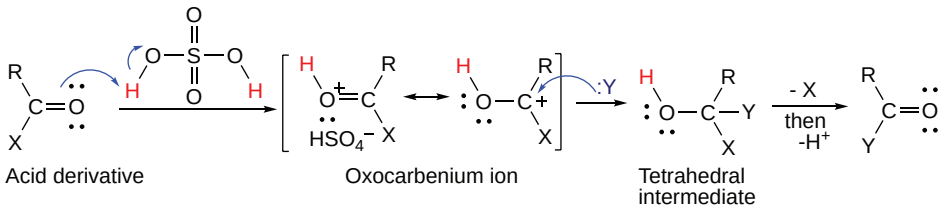


FIGURE 18.2 Formation of an oxocarbenium ion from an acid derivative.

Hydrolysis of Acid Chlorides and Anhydrides

An important example of acyl substitution is the hydrolysis of acid derivatives. Many acid chlorides react directly with water to give the acid. However, most esters or amides do not react directly with water to give a carboxylic acid. If an acid catalyst is added, however, acid derivatives react to give an oxocarbenium ion that easily reacts with water to give a tetrahedral intermediate. Loss of the leaving group generates the "parent" carboxylic acid used to prepare that derivative. The acid-catalyzed conversion of an acid derivative to a carboxylic acid by reaction with water is known as *acid hydrolysis.*

Hydrolysis of Esters

The acid-catalyzed hydrolysis reaction shown for butanoic acid derivatives in Figure 18.3 applies to all the acid derivatives and leads to the carboxylic acid as the product. Initial reaction with the acid catalyst forms oxocarbenium ion **1**. There is no hydroxide in this reaction medium so the only source of the OH unit is water. Reaction with water generates oxonium ion **2**. The acidic proton of oxonium ion **2** is removed by either water or the unreacted butanoyl derivative. The product is tetrahedral intermediate **3**. There are *two* leaving groups in tetrahedral intermediate **3**, OH (from the water nucleophile) and X (from the acid derivative). It is known that the X groups (Cl, O_2CR, OR or NR_2) are superior leaving groups when compared to the poor leaving group OH. The reaction therefore proceeds with loss of "X" to give oxocarbenium ion **4**. Loss of the acidic proton gives butanoic acid as the final product.

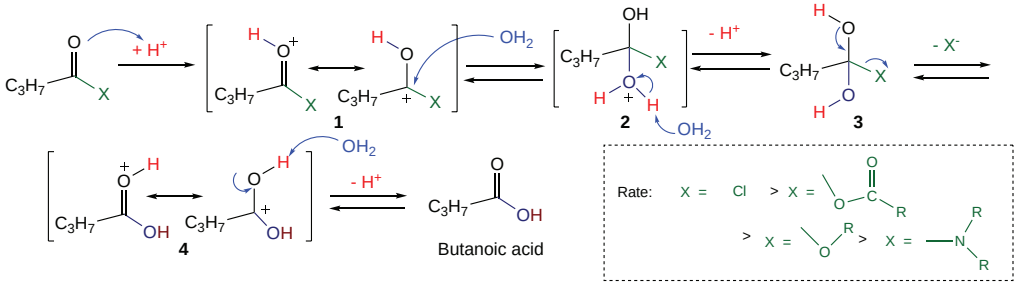


FIGURE 18.3 Acid-catalyzed hydrolysis of a carboxylic acid derivative.

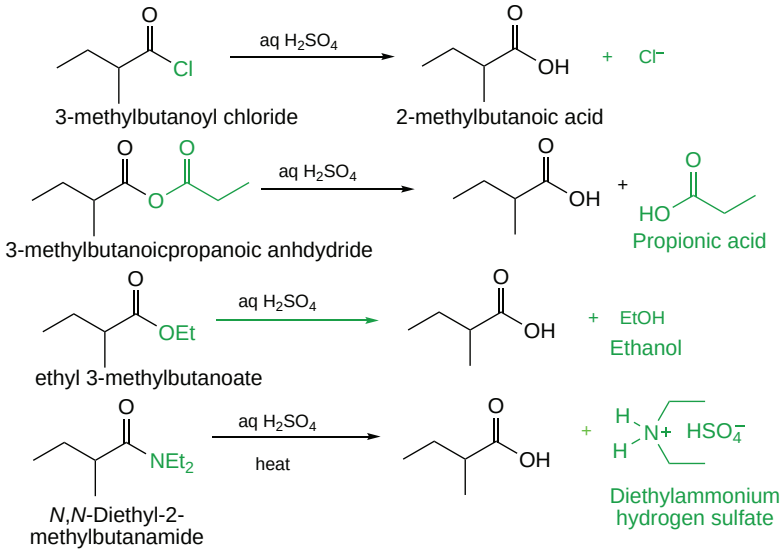
18.5 Write the mechanism for the acid-catalyzed hydrolysis of 2-methylpropanoyl chloride.

The mechanisms for the acid hydrolysis of all acid derivatives are identical except for the leaving group, but their reactivity differs. The reactivity differences can be correlated

with the leaving group ability of the "X" group in the tetrahedral intermediate: X= Cl > $-O_2CR$ > OR > NR_2. The reactivity of acid derivatives is acid chlorides > acid anhydrides > esters > amides. The hydrolysis of acid chlorides leads to loss of chloride ion. Acid chlorides are so reactive that many react with water without the need for an acid catalyst. Hydrolysis of 3-methylbutanoyl chloride give 3-methylbutaoic acid. Acid anhydrides are only slightly less reactive than acid chlorides. The hydrolysis of anhydrides with aqueous acid leads to loss of an acid unit and formation of two acids. Hydrolysis of the unsymmetrical 3-methylbutanoic propanoic anhydride gives 3-methylbutanoic acid and propanoic acid. Acid hydrolysis of the symmetrical dibutanoic anhydride gives to two molar equivalents of butanoic acid. Esters are less reactive than acid chlorides or acid anhydrides. Esters are hydrolyzed with aqueous acid under acidic conditions to form the carboxylic acid with loss of an alcohol leaving group from the tetrahedral intermediate. When ethyl 3-methylbutanoate is treated with an acid-catalyst in water, for example, the products are 3-methylbutanoic acid and ethanol.

It is more difficult to hydrolyze an amide when compared to other acid derivatives so higher temperatures and longer reaction times are required. Amides react under acidic conditions to yield the parent carboxylic acid and an amine for secondary and tertiary amides, or the carboxylic acid and ammonia from a primary amide. A hydrolytic workup of pentanamide with acid gives pentanoic acid and ammonia (NH_3). With the acid conditions, the ammonia is converted to the ammonium ion (NH_4^+). The acid-catalyzed hydrolysis of the tertiary amide *N,N*-diethyl-3-methylbutanamide gives 3-methylbutanoic acid and *N,N*-diethylamine (*N*-ethylethan-1-amine), which is converted to diethylammonium hydrogen sulfate.

Hydrolysis of Amides



18.6 Write out the mechanism for the acid-catalyzed hydrolysis of methyl butanoate.

The hydrolysis of acid derivatives under basic conditions is well known. The reaction with aqueous hydroxide followed by reaction with aqueous acid also gives a carboxylic acid. The basic $^-$OH ion reacts with butanoyl chloride (X= Cl), as shown in Figure 18.4, to give tetrahedral intermediate **5** directly, but "X" is a leaving group. Breaking the C—X bond is more facile than the C—O bond and loss of the "X" leaving group from **5** leads directly to butanoic acid. However, this acid is formed in a solution of hydroxide so butanoic acid reacts to give the carboxylate anion, sodium butanoate. Butanoic acid is generated from the carboxylate anion after a second chemical step, reaction with aqueous acid.

The reaction of anhydrides (X = $-O_2CR$) with aqueous base follows the mechanism shown in Figure 18.4, but there are two acid units in an anhydride and there are two products (the two carboxylic acids). The reaction of dibutanoic anhydride with aqueous NaOH, for example, leads to two molar equivalents of sodium butanoate. Similarly, basic hydrolysis of

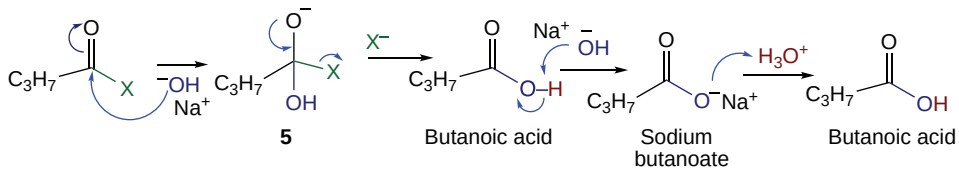


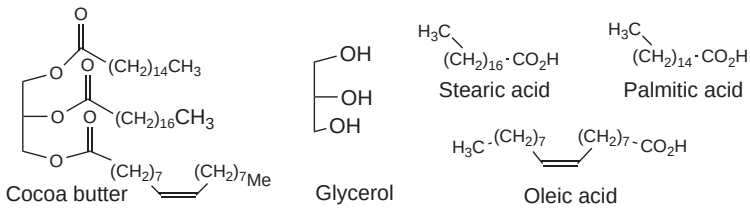
FIGURE 18.4 Base hydrolysis of butanoic acid derivatives.

butanoic propanoic anhydride affords one molar equivalent of sodium propanoate and one molar equivalent of sodium butanoate. In both cases, subsequent reaction with aqueous acid gives the acid(s).

Esters (X = –OR) are hydrolyzed under basic conditions to yield the carboxylate. The leaving group in **5** is the alkoxide (RO^-). The products are the alkoxide and the carboxylic acid. In the basic conditions, the acid is converted to the carboxylate anion. Acid hydrolysis gives the carboxylic acid and the alcohol. For example, heating isopropyl acetate (1-methylethyl ethanoate) in aq NaOH at reflux and then neutralization with aqueous acid gives acetic acid and isopropyl alcohol (propan-2-ol). Amides ($X = -NR_2$) are less reactive so higher reaction temperatures and more concentrated aq NaOH are often required. The reaction of *N*-ethylbutanamide with aqueous hydroxide gives the carboxylate salt of butanoic acid and the amine anion to the ammonium salt of ethylamine, H_3NEt^+.

18.7 Write out all reactants and products formed in the base hydrolysis reactions of butanoic anhydride and also for butanoic ethanoic anhydride.

The base hydrolysis of esters is given a special name because of its place in chemical history. It is known as *saponification*. Saponification means "to make soap" and the term comes from the ancient practice of using wood ashes (rich in potassium hydroxide) to convert animal fat to soap.



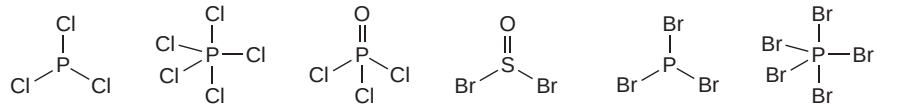
Animal fat as well as vegetable oils are usually a mixture of triglycerides, the triester derivatives of fatty acids (Section 18.12) and glycerol (1,2,3-propanetriol). The salts of these fatty acid are solids, and they are the fundamental constituent of what is known as "soap." Cocoa butter is a triglyceride, 3-(palmitoyloxy)-2-(stearoyloxy)propyl oleate, extracted from cocoa beans. Base hydrolysis gives glycerol along with the sodium salts of the three carboxylic acids, stearic acid, palmitic acid, and oleic acid.

18.8 Draw the structure for the triethyl ester of glycerol.

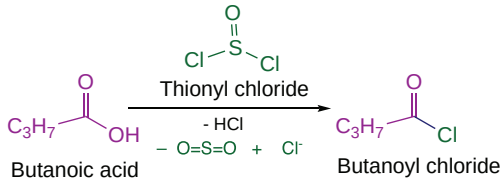
Preparation of Acid Chlorides and Anhydrides

Sulfonyl chlorides such as methanesulfonyl chloride (CH_3SO_2Cl) react similarly to carboxylic acid chlorides and are used to form sulfonate esters and sulfonamides. Hydrolysis of a sulfonyl chloride or the other sulfonic acid derivatives gives the parent sulfonic acid. If butanesulfonyl chloride reacts with aqueous acid or aqueous base, for example, the hydrolysis reaction leads to butanesufonic acid. Likewise, sulfonate esters are hydrolyzed to the sulfonic acid and an alcohol whereas sulfonamide are hydrolyzed to the sulfonic acid and an amine.

18.5 PREPARATION OF ACID CHLORIDES AND ACID ANHYDRIDES

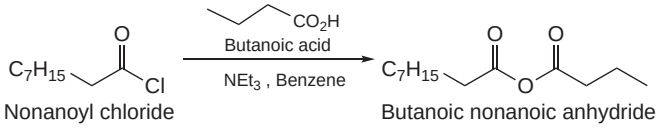


Acid chlorides are prepared from carboxylic acids. There are several inorganic reagents that are used for this transformation, including thionyl chloride ($SOCl_2$). Thionyl chloride was used in Section 11.5.2 for the conversion of alcohols to alkyl chlorides. Butanoic acid reacts with $SOCl_2$ to give butanoyl chloride, sulfur dioxide (SO_2), and HCl.



In many cases, an amine such as triethylamine (NEt_3) is added as a base to the reaction to "trap" the HCl, forming triethylammonium hydrochloride ($Et_3NH^+Cl^-$). Formation of the ammonium salt drives the reaction toward the acid chloride. Other chlorinating reagents are shown, including phosphorus trichloride (PCl_3), phosphorus pentachloride (PCl_5), and phosphorus oxychloride ($POCl_3$).

18.9 Draw the structures for all products generated by the reaction of cyclohexanecarboxylic acid and thionyl chloride, in the presence of triethylamine.



Anhydrides, as the name suggests, are the product of two carboxylic acid units that couple together with loss of water. However, simply heating two carboxylic acids usually gives a poor yield of the anhydride. Acid-catalysis gives a better yield, but a "statistical mixture" of products is possible when different acids are coupled. If propanoic acid is treated with butanoic acid, for example, a 1:2:1 mixture of dipropanoic anhydride, butanoic propanoic anhydride and dibutanoic anhydride is formed. An acid chloride is especially useful for the preparation of unsymmetrical anhydrides. If nonanoyl chloride and butanoic acid react in the presence of triethylamine as the base, butanoic heptanoic anhydride is formed. Butanoic nonanoic anhydride can also be prepared by the reaction of butanoyl chloride with hexanoic acid.

18.10 Draw the two starting materials that will produce pentanoic 2-methylpropanoic anhydride when they react, and not give a statistical mixture.

Preparation of Esters

Sulfonic acids are readily converted to the sulfonyl chloride by reaction with thionyl chloride. The reaction a thionyl chloride with butane-1-sulfonic acid gives butane-1-sulfonyl chloride. This reaction is general for many sulfonic acids, including methanesulfonic acid ($MeSO_3H$), which is converted to methanesulfonyl chloride ($MeSO_2Cl$). Thionyl bromide ($SOBr_2$) converts sulfonic acids to the corresponding sulfonyl bromide. Sulfonyl chlorides are good reaction partners with alcohols to give sulfonate esters or with amines to give sulfonamides.

18.6 PREPARATION OF ESTERS

Esters have two structural components, a carboxylic acid, and an alcohol. Simply mixing a carboxylic acid and an alcohol in the absence of an acid catalyst generally gives a poor yield or no yield of an ester, however. Esters can be prepared by the reaction of a carboxylic acid and an alcohol in the presence of an acid catalyst. Acetic acid reacts with butanol in the presence of an acid catalyst to afford butyl acetate. This reaction is reversible, so a large molar excess of the alcohol is used to shift the equilibrium toward the ester (Le Chatelier's principle). The mechanism of acid-catalyzed ester formation is shown in Figure 18.5. The reaction of acetic acid and butanol is formally the reverse of the ester hydrolysis mechanism shown in Figure 18.3. Initial reaction with the acid catalyst generates oxocarbenium ion **6**, which reacts with butanol to give oxonium ion **7**. Loss of a proton gives tetrahedral intermediate **8**. Protonation of a hydroxyl unit gives oxonium ion **9** and loss of water generates oxocarbenium ion **10**. Loss of a proton gives the ester, butyl ethanoate (butyl acetate). Note that if butyl acetate is treated with an acid catalyst and water as the solvent rather than butan-1-ol, the reverse of the mechanism shown will convert the ester back to acetic acid and butan-1-ol.

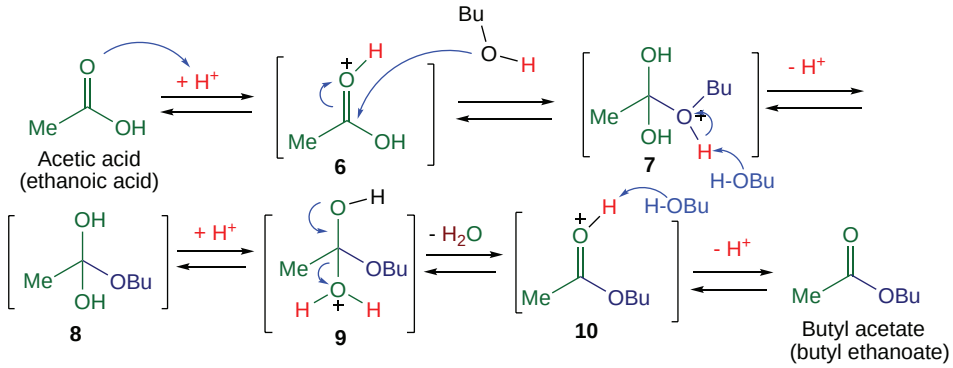
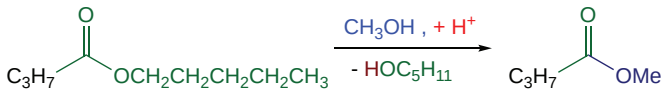
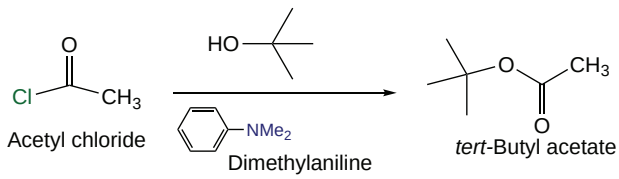


FIGURE 18.5 Acid-catalyzed esterification of acetic acid.

An acid-catalyzed esterification can be used to change the alcohol portion of an ester. In other words, replacing one OR group in a ester with a new alkoxy group (OR') gives a different ester in a reaction known as *transesterification*. The technique is commonly used to prepare methyl or ethyl esters from a different ester since those alcohols have relatively low boiling points and can be used as a solvent. If pentyl butanoate is heated with a large excess of methanol with an acid catalyst, for example, the product is methyl butanoate and pentan-1-ol. This reaction is driven toward the methyl ester because a large excess of methanol is used as the solvent, in accord with Le Chatelier's principle. Note that if this reaction is done with a large excess of ethanol the product is the ethyl ester.



18.11 Draw the structure of the product that results when methyl pentanoate and isopropyl alcohol react in the presence of an acid-catalyst.

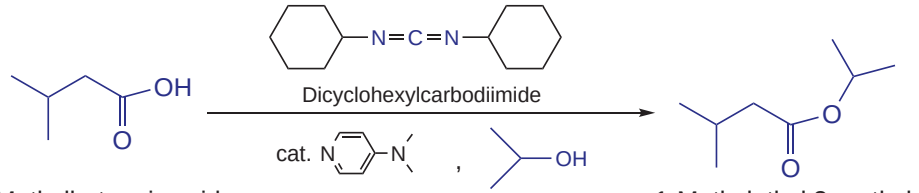


The reaction of an acid chloride with an alcohol will give an ester. The reaction of 2-methylpropan-2-ol (*tert*-butyl alcohol) with acetyl chloride in the presence of the amine

base dimethylaniline gave a 62% yield of 1,1-dimethylethyl ethanoate (*tert*-butyl acetate).[2] The added amine reacts with the acidic HCl as it is formed to remove it from the reaction medium. Alcohols are nearly as reactive with acid anhydrides as with acid chlorides in acyl substitution reactions. This procedure is most useful when symmetrical anhydrides such as acetic anhydride are used. Heating acetic anhydride and 2-methylbutan-2-ol, for example, yields 2-methylbutan-2-yl acetate, along with acetic acid.

18.12 Draw two starting materials that can react to produce 1-methylethyl 3-phenylpentanoate as the final product.

Esters can be formed using a diimide reagent with an alcohol and a carboxylic acid. A diimide has a N=C=N structure and a *carbodiimide* is R–N=C=N–R. Carbodiimides such as dicyclohexylcarbodiimide function as "dehydration agents" to facilitate acyl substitution reactions with carboxylic acids. The reaction of 3-methylbutanoic acid with *tert*-butanol, dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-(dimethylamin-1-yl)-pyridine (DMAP) gave 1-methylethyl 3-methylbutanoate in 65% yield.[3] One molar equivalent of dicyclohexyl urea is also isolated. This type of "DCC coupling" of an acid and an alcohol is very attractive because it occurs *under neutral conditions*. In other words, no strong acid or base is present)



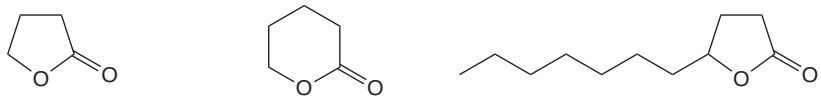
3-Methylbutanoic acid | 4-(Dimethylamino-1-yl)-pyridine (DMAP) | Propan-2-ol | 1-Methylethyl 3-methylbutanoate

18.13 Draw the product formed when 3,3-diphenylpentanoic acid reacts with 3,3-dimethylbutan-1-ol in the presence of DCC.

The DCC esterification reaction is explained by the mechanism shown in Figure 18.6. If DCC is mixed with 3-methylbutanoic acid, the acidic hydrogen of the OH unit reacts with the nitrogen of the carbodiimide to form iminium salt **11** and the carboxylate anion 3-methylbutanoate. Due to bond polarization, the central carbon of the iminium unit in **11** is even more electrophilic than in DCC. Attack by the weakly nucleophilic oxygen of the carboxylate ion gives **12**. The DMAP reacts with **12** to form an acylammonium salt, which is more reactive with the alcohol and facilitates the conversion of **12** to **13**. This step is very important since the reaction of alcohols with **12** can be very slow. Reaction of acyl carbon of **12** with the alcohol yields tetrahedral intermediate **13**. Proton transfer from the oxonium unit in **13** to the imine nitrogen leads to loss of dicyclohexyl urea. The urea derivative is a good leaving group and a very stable molecule. The product is 1-methylethyl 3-methylbutanoate. The DCC unit "activates" the acyl carbon of a carboxylic acid to attack by an alcohol.

Lactones

All esters discussed so far are acyclic molecules, but there are cyclic esters where both the acyl carbon and the oxygen are constituent members of a ring. Cyclic esters are called *lactones.* The IUPAC names of the lactones shown are based on a parent cyclic ether, dihydrofuran-2(3*H*)-one and tetrahydro-2*H*-pyran-2-one, respectively.



Dihydrofuran-2(3H)-one | Tetrahydro-2*H*-pyran-2-one | 5-Heptyldihydrofuran-2(3H)-one

The common names for the five-membered ring lactone is γ-butyrolactone and the six-membered ring lactone is δ-valerolactone. These names are taken from the common names for

[2] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.148, p. 704.
[3] Hassner, A.; Alexanian, V. *Tetrahedron Letters* 1978, 4475–4478.

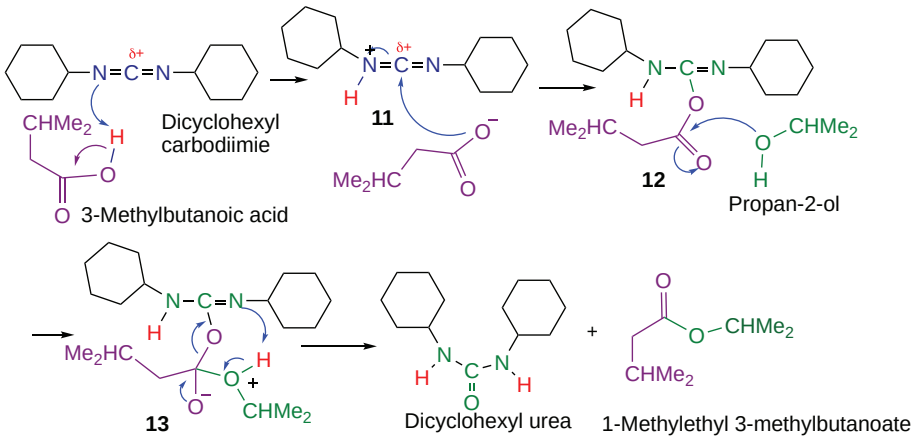
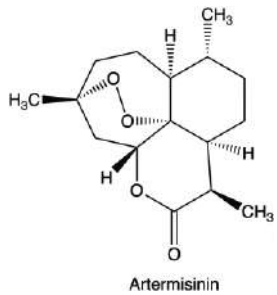


FIGURE 18.6 Mechanism of DCC coupling of a carboxylic acid and an alcohol.

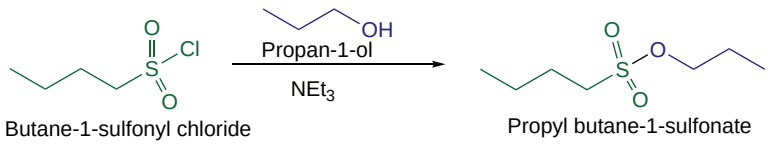
the four-carbon acid (butyric acid) and the five-carbon acid (valeric acid). The third example is 5-heptyl-γ-butyrolactone or 5-heptyldihydrofuran-2(*3H*)-one. Hydrolysis of the ester unit in lactones generates a hydroxy acid. Hydrolysis of valerolactone, for example, yields 5-hydroxypentanoic acid. In the case of five-membered ring lactones, the lactone tends to be more stable than the hydroxy-acid, so this equilibrium favors the lactone, although there is a mixture.

Nobel laureate Tu Youyou (China) is a pharmaceutical chemist and malariologist. Using Chinese medical texts from the Zhou, Qing, and Han Dynasties she found a traditional cure for malaria, and her research led to extraction of *artemisinin*. She also discovered dihydroartemisinin, and both are used to treat malaria, including highly drug-resistant strains. Artemisinins are derived from extracts of sweet wormwood (Artemisia annua). These discoveries have saved millions of lives in South China, Southeast Asia, Africa, and South America. The WHO has recommended artemisinin combination therapy as the first line of defense against malaria. Combination therapies combine artemisinin or its derivatives with some other antimalarial drug. Artemisinin and its derivatives are all sesquiterpene lactones that contain an unusual peroxide bridge. This endoperoxide 1,2,4-trioxolne ring is responsible for their antimalarial properties.



18.14 Draw the structure of the lactone that would yield 3,5,5-triethyl-7-hydroxyheptanoic acid after hydrolysis.

Sulfonate esters are prepared from sulfonic acids by the reaction of a sulfonic acid and an alcohol under acidic conditions or between a sulfonyl chloride and an alcohol. Methanesulfonic acid reacts with methanol under acid-catalyzed conditions to yield methyl methanesulfonate ($CH_3SO_3CH_3$).



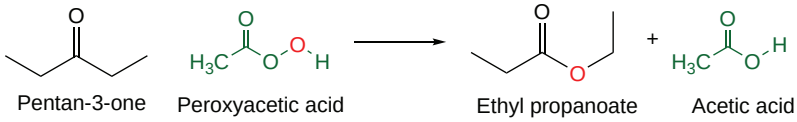
The mechanism of this reaction is remarkably similar to that for the reaction of a carboxylic acid and an alcohol in the presence of an acid-catalyst (Figure 18.5). As with carboxylic esters, every step is reversible, and water must be removed, or an excess of the alcohol must be used. As mentioned previously, sulfonyl chlorides react with alcohols to generate sulfonate esters. The reaction of butane-1-sulfonyl chloride and propan-1-ol in the presence of an amine base, for example, gives propyl butane-1-sulfonate. When sulfonate esters react with aqueous acid or aqueous hydroxide, the parent sulfonic acid is regenerated, in this case butane-1-sulfonic acid. Acid or base hydrolysis of ethyl propane-2-sulfonate yields propane-2-sulfonic acid as the product.

18.15 Draw the mechanism for the acid catalyzed reaction that converts propane-2-sulfonic acid to ethyl propane-2-sulfonate.
18.16 Draw the product of the reaction between benzenesulfonic acid and (1) $SOCl_2$ and (2) cyclopentanol

18.7 BAEYER-VILLIGER OXIDATION

Baeyer-Villiger Oxidation

Peroxyacids were used for the oxidation of an alkene to an epoxide in Section 15.4. Peroxyacids also react with ketones to form esters in what is known as the *Baeyer-Villiger reaction*, named after Johann Friedrich Wilhelm Adolf von Baeyer (Germany; 1835–1917) and Victor Villiger (Switzerland; 1868–1934). Pentan-3-one and peroxyacetic acid, for example, gave two products, ethyl propanoate and acetic acid.



The mechanism for the Baeyer-Villiger reaction is shown in Figure 18.7. Pentan-3-one reacts with the acid catalyst to form oxonium ion **14**. The peroxyacid reacts as a nucleophile via acyl addition to yield **15**, which loses a proton to give the hemiacetal-type intermediate **16**. Protonation of the oxygen atom closest to the carbonyl yields **17**. A skeletal rearrangement with migration of an ethyl group from carbon to oxygen generates oxocarbenium ion

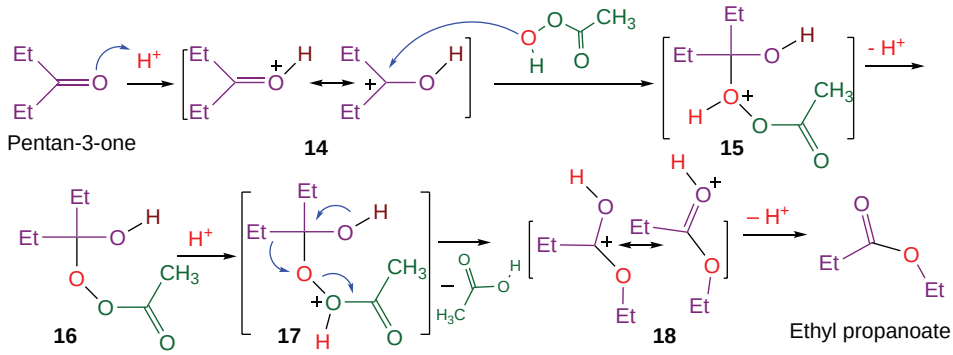
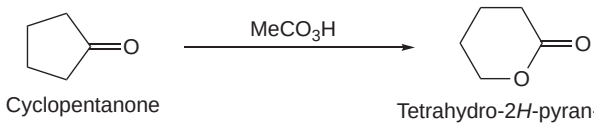


FIGURE 18.7 Mechanism of the Baeyer–Villiger reaction.

18 with loss of acetic acid. Loss of a proton from **18** yields the ester product, ethyl propanoate.

Pentan-3-one is a symmetrical ketone so migration of either group attached to the carbonyl yields the same ester as a product. Rearrangement also occurs in the Bayer-Villiger reaction of unsymmetrical ketones. There are two different groups attached to the carbonyl, however, so migration of each group can potentially give two different esters. An example is the reaction of 2-methylpentan-3-one and peroxyacetic acid to generate an oxocarbenium ion with an attached ethyl and an isopropyl. If the ethyl group migrates the product is

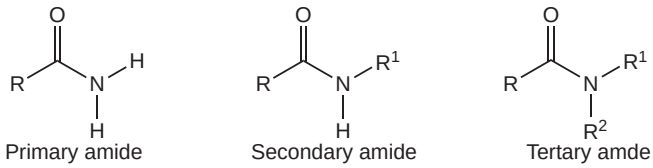
ethyl 2-methylpropanoate, whereas if the isopropyl group migrates the product is 1-methylethyl propanoate. The major product of this reaction is 1-methylethyl propanoate, so the 1-methylethyl group migrates in preference to the primary alkyl group. The preference for group migration is consistent with the ability of each carbon to support a positive charge. In other words, the group that can best form a carbocation migrates. Therefore, a tertiary carbon migrates faster than a secondary, which migrates faster than a primary. The order of migration for groups in unsymmetrical ketones is: *tert*-alkyl > cyclohexyl ≈ 2° alkyl ≈ benzyl ≈ phenyl > vinylic > 1° alkyl > methyl. Cyclic ketones undergo Baeyer-Villiger reaction to yield the corresponding lactone. Following the same mechanism and migration of one of the ring carbons, cyclopentanone with reacts peroxyacetic acid to give valerolactone (tetrahydro-2*H*-pyran-2-one).



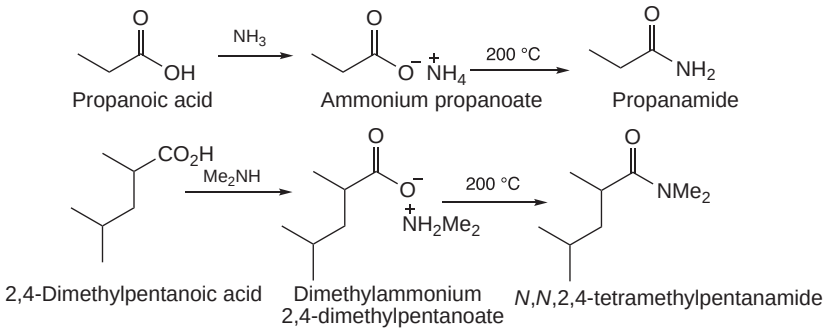
18.17 What is the product formed when 2,4-dimethylpentan-3-one reacts with peroxyformic acid?
18.18 What is the product formed when 2,2-dimethylhexan-3-one reacts with peroxyacetic acid?

Preparation of Amides

18.8 PREPARATION OF AMIDES



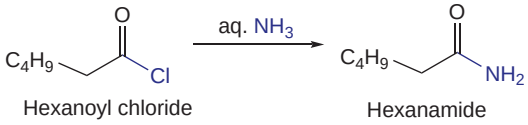
Amides have both a carboxylic acid component and an amine component. There are three structural types of amide, primary amides, secondary amides, and tertiary amides. Primary amides are prepared by the reaction of an acid derivative with ammonia. Secondary amides and tertiary amides are prepared by the reaction of an acid derivative with a primary amine or a secondary amine, respectively.



Ammonia and amines are bases and they react with a carboxylic acid to form an ammonium carboxylate. Therefore, mixing an amine or ammonia with an acid at normal temperatures does not give an amide but rather a carboxylate anion and an ammonium salt. The ammonium salt can be converted to an amide by heating to a high temperature to drive off water (dehydration). Heating ammonium propanoate to 180–220 °C gives propanamide

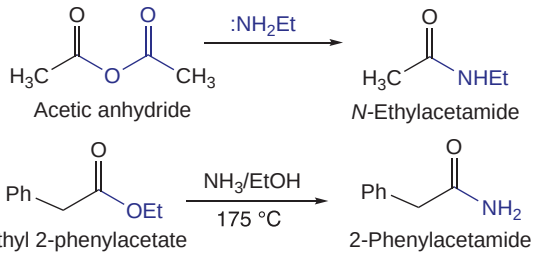
and similar heating of dimethylammonium 2,4-dimethylpentanoate yields *N*,*N*,2,4-tetramethylpentanamide. Tertiary amines also react with carboxylic acids to form an ammonium salt but heating does *not* lead to an amide since water cannot be lost.

18.19 Write out the starting materials and give the reaction conditions necessary to prepare *N*-propylpentanamide.



Hexanoyl chloride Hexanamide

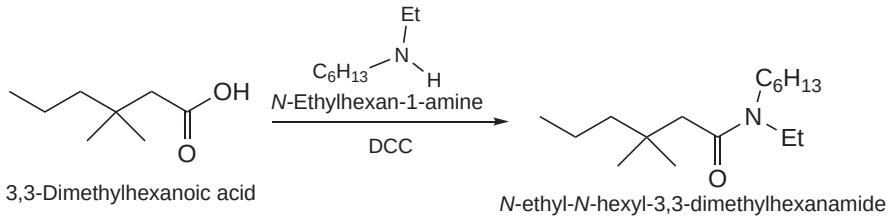
An alternative route to amides reacts ammonia or an amine with acid chlorides, acid anhydrides or with esters. A typical experiment reacted hexanoyl chloride with concentrated ammonia solution at 0 °C, to give 63% of hexanamide.[4] The reaction of an amine, NHR_2 or NH_2R, with an acid chloride will give the tertiary or secondary amide, respectively. The reaction of an amine with an anhydride or an ester gives similar results. The reaction of acetic anhydride and ethylamine, for example, affords *N*-ethyl ethanamide (*N*-acetylethanamine). Ethyl phenylacetate reacted with ammonia in ethanol, at 175 °C, to yield phenylacetamide in 75% yield.[5] There is a clear trend in reactivity, and acid chlorides are slightly more reactive than anhydrides, and both are more reactive than the esters. Note that it is not possible to convert an amide to an ester, an anhydride, or an acid chloride by acyl substitution since in the requisite tetrahedral intermediate –Cl, $-O_2CR$ or –OR are better leaving groups that $-NR_2$.



Acetic anhydride *N*-Ethylacetamide

Ethyl 2-phenylacetate 2-Phenylacetamide

18.20 Write out the reaction in which butanoyl chloride reacts with aqueous ammonia.



3,3-Dimethylhexanoic acid *N*-ethyl-*N*-hexyl-3,3-dimethylhexanamide

Just as esters are formed from carboxylic acids and alcohols in the presence of dicyclohexylcarbodiimide (DCC, Figure 18.6), so amides are formed from amines (or ammonia) and carboxylic acids. An example is the reaction of 3,3-dimethylhexanoic acid with *N*-ethylhexan-1-amine to yield *N*-ethyl-*N*-hexyl-3,3-dimethylhexanamide. Note that one

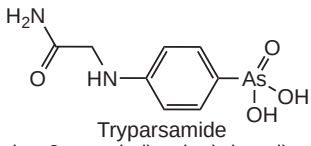
[4] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.154, p. 709.
[5] Fischer, E.; Dilthey, A. *Chemische Berichte* 1902, 35, 844–856 (see p. 856).

reactant is an amine, and the use of the DMAP catalyst used in the esterification reaction is not necessary. Amide bond formation via DCC coupling is important for the synthesis of peptides (Section 24.5).

18.21 Suggest a mechanism for the DCC coupling of butanoic acid and N,N-dimethylamine.

Louise Pearce (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

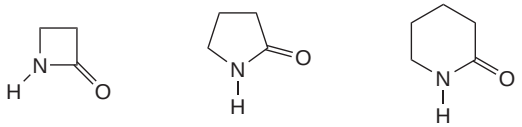
Amides have myriad uses, including the incorporation of amides in pharmacologically important drugs. Louise Pearce (USA; 1885–1959) was a pathologist at the Rockefeller Institute who helped develop a treatment for African sleeping sickness (trypanosomiasis). This fatal disease has devastated areas of Africa, killing two-thirds of the population of the Uganda protectorate between 1900 and 1906 alone. She helped develop the amide-containing drug tryparsamide. Tryparsamide proved successful in combating the fatal trypanosomiasis, curing 80% of cases. This remained the standard treatment for the disease until the 1960s. She also studied the role of viruses in spreading cancer.



Tryparsamide
(4-((2-Amino-2-oxoethyl)amino)phenyl)arsonic acid

Just as there are cyclic esters, there are cyclic amides called *lactams*. Lactams have both a carbonyl carbon and a nitrogen atom in a ring. The IUPAC name for a four-membered ring containing nitrogen is azetidine. β-Propiolactam is formally named azetidin-2-one, but these four-membered ring lactams are commonly called β-lactams. The five-membered ring lactam is known as γ-butyrolactam and the six-membered ring lactam is δ-valerolactam (from butyric acid and valeric acid, respectively). The IUPAC names for γ-butyrolactam and δ-valerolactam are derived from the heterocycles pyrrole (five-membered ring) and pyridine (six-membered ring): 2-oxotetrahydropyrrole and 2-oxohexahydropyridine, respectively (Section 23.7). Heating a lactam with aqueous acid or aqueous base leads to hydrolysis of the amide bond, ring opening and formation of the parent amino acid.

Lactams and Imides

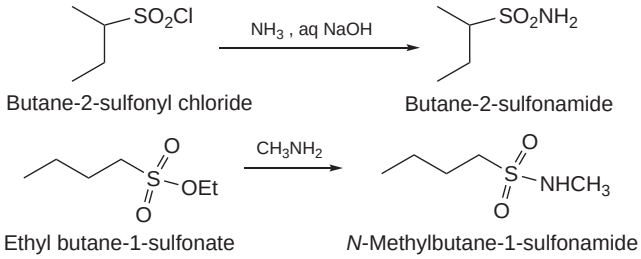


β-Propiolactam γ-Butyrolactam δ-Valerolactam

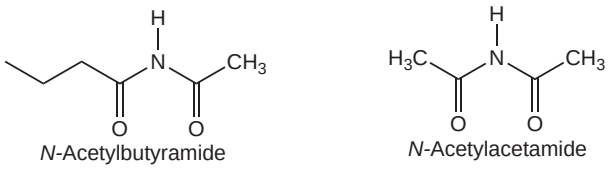
18.22 Give the structure of the product formed when valerolactam is hydrolyzed with aqueous acid.

Sulfonamides are the sulfonic acid analogs of carboxylic acid amides. As mentioned previously, they are formed by reaction of sulfonyl chlorides or sulfonate esters with amines or ammonia. Butane-2-sulfonyl chloride reacts with ammonia, for example, to give butane-2-sulfonamide. When hydroxide is added to the reaction in water, as shown for the conversion of butane-2-sulfonyl chloride to butane-2-sulfonamide, this reaction is known as the *Schotten-Baumann reaction*. This reaction is named after Carl Schotten (Germany; 1853–1910) and Eugen Baumann (Germany; 1846–1896). Amines react with sulfonyl chlorides or sulfonate esters to give *N*-substituted sulfonamides. Ethyl butane-1-sulfonate reacts with methylamine, for example, to give *N*-methylbutane-1-sulfonamide. When a sulfonamide reacts with aqueous acid or aqueous hydroxide, the amine (or ammonia) is "released" along with the parent sulfonic acid. Butanesulfonamide reacts with aqueous hydroxide (followed by an acid neutralization step) to yield butanesulfonic acid and ammonia.

Sulfonic Acid Derivatives



Imides are a specialized class of compounds related to amides in that there are two acyl groups attached to nitrogen, as in *N*-acetylbutyramide and *N*-acetylacetamide. The name for such molecules is based on the longest chain amide derivative of the carboxylic acid parent. In the case of *N*-acetylbutyramide, there are two acyl portions, butanoic acid and ethanoic acid (acetic acid). The name is *N*-acetylbutanamide, or *N*-ethanoylbutanoic acid amide (*N*-ethanoylbutanamide). In cases where the imide is symmetrical (both acyl groups are identical), the name can be simplified. The imide *N*-acetylacetamide is also known as diacetamide (diethanamide).

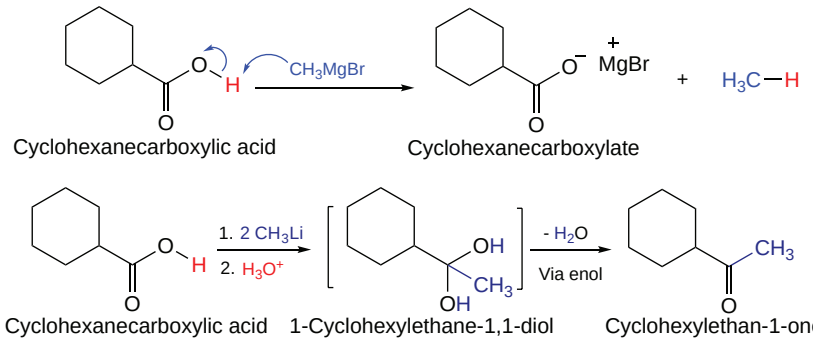


18.23 Draw the structure of *N*-(3-methylbutanoyl) 4,4-diphenylpentanamide.

18.9 CARBOXYLIC ACID DERIVATIVES REACT WITH CARBON NUCLEOPHILES

Grignard Reagents and Organolithium Reagents

The primary reaction of a carboxylic acid is an acid-base reaction, which is much faster than any reaction with a nucleophile at the carbonyl carbon. Both Grignard reagents and organolithium reagents (Sections 14.1–3) are strong bases and they react with carboxylic acids to give a carboxylate salt. The organolithium reagent is much more reactive than the Grignard reagent.



The reaction of two equivalents of methyllithium with cyclohexanecarboxylic acid gives 1-cyclohexylethanone in 83% yield.[6] After the initial acid-base reaction to form the carboxylate anion, methyllithium reacts further to give a dialkoxy product. Subsequent reaction with aqueous acid affords a hydrate (1-cyclohexylethane-1,1-diol). Hydrates are inherently unstable, spontaneously lose water to form an enol (Section 10.8), which tautomerizes to 1-cyclohexylethan-1-one. Methylmagnesium bromide reacts with cyclohexanecarboxylic acid to give cyclohexanecarboxylate as the product, and there is no further reaction.

18.24 Draw out the reaction between butanoic acid and methylmagnesium bromide.
18.25 Draw the reactions necessary to prepare 2,5-dimethylhexan-3-one from the appropriate carboxylic acid.

Grignard reagents react with carboxylic acid derivatives via acyl substitution. An example is shown in Figure 18.8, where butylmagnesium bromide (BuMgBr, where Bu = C_4H_9) reacts with methyl pentanoate to generate tetrahedral intermediate **19**. Methoxide is the leaving group in this reaction, and nonan-5-one is formed initially via acyl substitution. After one

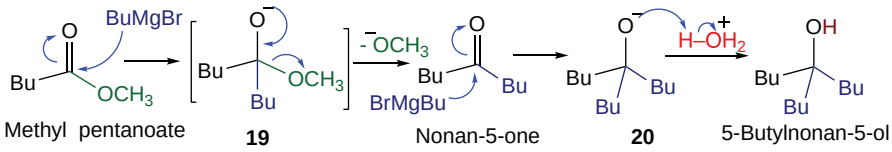
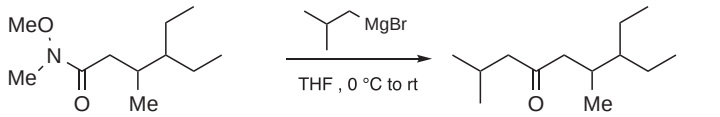


FIGURE 18.8 The reaction of methyl octanoate with butylmagnesium bromide.

half life, however, the ketone product, the Grignard reagent and unreacted ester are all present. It is known that Grignard reagents react with ketones faster than with esters in most cases so butylmagnesium bromide and nonan-5-one react to give alkoxide **20**. Hydrolytic workup affords the tertiary alcohol, 5-butylnonan-5-ol. This reaction will therefore give a mixture of the alcohol and the ketone, usually favoring the alcohol. If an excess of Grignard reagent is used, the product is the alcohol. The reaction of ethyl butanoate and two molar equivalents of methylmagnesium iodide gave an 88% yield of 2-methylpentan-2-ol.[7] Grignard reagents react with acid chlorides or acid anhydrides to give the ketone product. Many acid chlorides and acid anhydrides are more reactive than the ketone product, so the ketone is often the major product. However, mixtures of the ketone and the alcohol products are common. Organolithium reagents are more reactive than Grignard reagents in reactions with aldehydes and ketones and with acid derivatives. In reactions with an acid chloride, acid anhydride, or an ester it is even more difficult to isolate a ketone product and the alcohol is usually the major product.

[6] Jorgenson, M.J. *Organic Reactions* 1970, 18, 1–97 (see. p. 47).
[7] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.42, p. 540.



4-Ethyl-*N*-methoxy-*N*,3-dimethylhexanamide

7-Ethyl-2,6-dimethylnonan-4-one

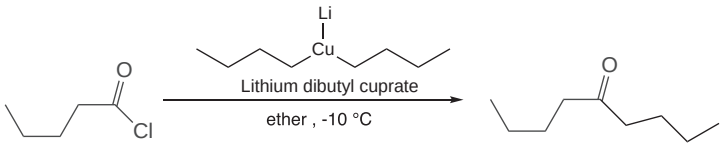
Primary and secondary amides react with Grignard reagents and with organolithium reagents via an acid-base reaction that deprotonates the nitrogen. A tertiary amide has no hydrogen atoms on the nitrogen of course but gives a poor yield of a ketone product unless an excess of the Grignard reagent is used. Vigorous reaction conditions are often required. An exception is the reaction of a Grignard reagent with a highly reactive amide unit. An example is a *Weinreb amide*, where the activated amide unit –CONMe(OMe) is an excellent leaving group and the reaction stops at the ketone. An example is the reaction of 4-ethyl-*N*-methoxy-*N*,3-dimethylhexanamide with 2-methylpropane-1-magneium bromide, which gave 7-ethyl-2,6-dimethylnonane-4-one. The amide reagent is named after Steven M. Weinreb (USA) who first used it for the synthesis of ketones.

18.26 Draw the product expected when ethyl 3-phenylbutanoate reacts with ethylmagnesium bromide, followed by hydrolysis.

18.27 Draw the product of a reaction between methyl propanoate and 2.5 equiv of phenyllithium, followed by hydrolysis.

Organocuprates were shown to react with alkyl halides in Section 14.4.1, and they also react with acid chlorides. Lithium dialkyl cuprates (e.g., lithium dibutylcuprate) are prepared from organolithium reagents and Cu(I) compounds (e.g., cuprous iodide). The reaction of two molar equivalents of *n*-butyllithium and CuI affords lithium dibutylcuprate (Bu_2CuLi). Organocuprates react with acid chlorides to form a ketone as the major product. The ketone does not react further. When lithium dibutyl cuprate reacts with 4-methylpentanoyl chloride the product is the ketone, 2-methylnonan-5-one.

18.28 What is the product formed by first heating hexan-1-ol with Jones reagent (see Section 15.2.1), and then reaction with thionyl chloride, followed by reaction with lithium dimethylcuprate?



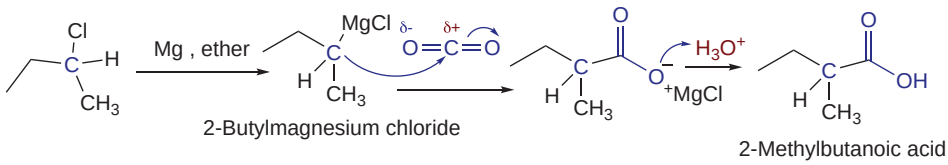
Pentanoyl chloride

Nonan-5-one

Nitriles and Organocuprates

Other molecules have an electrophilic carbonyl or a reactive electrophilic atom, including carbon dioxide and nitriles. The structure of carbon dioxide is O=C=O, which has a carbonyl unit. An ether solution of 2-butylmagnesium chloride is prepared and added to crushed dry ice (CO_2). This slurry is poured onto crushed ice containing concentrated HCl to give 2-methylbutanoic acid in 79% yield.[8] This reaction is reasonably general, although the yields of the reaction vary considerably. Organolithium reagents also react with CO_2, analogous to Grignard reagents, and the product is also the carboxylic acid. The yields also vary from quite good to poor.

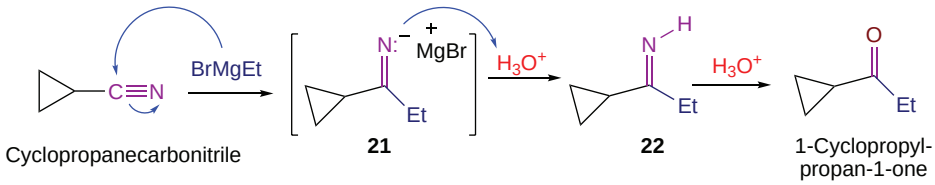
[8] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.129, p. 674.



18.29 Describe all reactions necessary to make 2-(1-methylethyl)-3-phenylpent-2-enoic acid from an appropriate vinyl bromide.

A nitrile has the cyano functional group, C≡N, as described in Section 5.9.4. The nucleophilic carbon of ethylmagnesium bromide reacts with the electrophilic nitrile carbon of cyclopropanecarbonitrile to give an iminium salt, **21**.[9] A hydrolytic workup of **21** gives the conjugate acid, imine **22**. Under these aqueous acid conditions, the imine is difficult to isolate. Protonation of **22** gives an iminium salt, which undergoes reaction with water to give 1-cyclopropylpropan-1-one in 68% yield. Organolithium reagents also react with nitriles to yield the imine. If butyllithium reacts with cyclopropanecarbonitrile, the product is butyl cyclopropyl ketone after a hydrolytic workup.

Nitriles



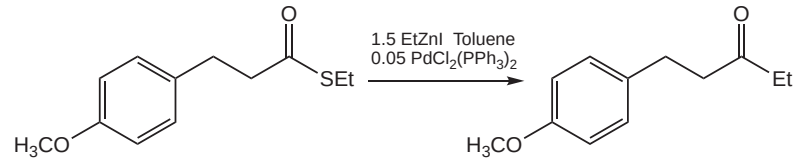
18.30 Write out the mechanism described in words for the conversion of imine **22** to cyclpopylpropan-1-one in aqueous acid.

Tohru Fukuyama (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Other organometallic reagents react with acid derivatives. The *Fukuyama coupling*[10] is the palladium-catalyzed coupling reaction in which a thioester reacts with an organozinc compound. The reaction is essentially an acyl substitution reaction that gives a ketone product. The reaction proceeds with high chemoselectivity for the thioester rather than the ketone formed as a product. An example is the reaction of *S*-ethyl 3-(4-methoxyphenyl)propanethioate with ethylzinc iodide, catalyzed by $PdCl_2(PPh_3)_2$ to give 1-(4- methoxyphenyl)

[9] Hrubiec, R.T.; Smith, M.B. *Journal of Organic Chemistry* 1984, 49, 431–435.
[10] Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Letters* 1998, 39, 3189–3192.

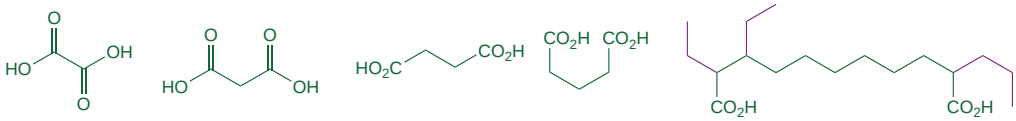
pentan-3-one in 91% yield.[10] This reaction was discovered at the University of Tokyo by Professor Tohru Fukuyama (Japan). He is an organic chemist who has made major contributions to the synthesis of natural products with interesting biological activity, including vinblastine, lysergic acid, tetrodotoxin, kainic acid, lemonomycin, naphthyridinomycin, and the mitomycins. Professor Fukuyama's work also includes the investigation of new synthetic methodologies and the synthesis of amines using nitrobenzenesulfonyl groups, indole synthesis by radical cyclization of ortho-alkenylphenylisocyanides or ortho-alkenythioanilides, and the transformation of thiol esters to aldehydes or ketones.



S-Ethyl 3-(4-methoxyphenyl)propanethioate — 1-(4-Methoxyphenyl)pentan-3-one

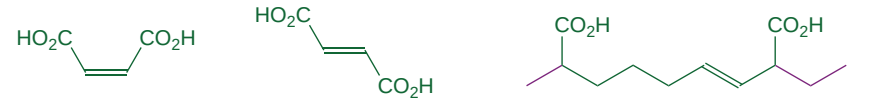
18.10 DICARBOXYLIC ACIDS AND DERIVATIVES

Dicarboxylic Acids



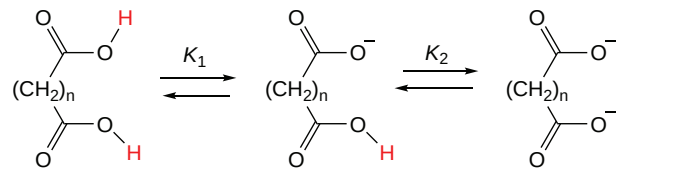
Ethanedioic acid (oxalic acid) | Propanedioic acid (malonic acid) | Butanedioic acid (succinic acid) | Pentanedioic acid (glutaric acid) | 2,3-Diethyl-10-propylundecanedioic acid

Dicarboxylic acids are molecules with two carboxyl groups in the same molecule. The presence of two acid units lead to some interesting reactions. The IUPAC suffix for a dicarboxylic acid is *dioic acid* and the C_1-C_{10} dioic acids are ethanedioic acid, propanedioic acid, butanedioic acid, pentanedioic acid, hexanedioic acid, heptanedioic acid, octanedioic acid, nonanedioic acid and decanedioic acid. The IUPAC nomenclature requires that the longest chain contain both carboxyl groups. Since the longest chain must contain both COOH units on terminal carbon atoms, the numbers are unnecessary. The common names of the C2-C5 dioic acids are also provided, so oxalic acid is ethanedioic acid. Malonic acid is propanedioic acid, succinic acid is butanedioic acid, and glutaric acid is pentanedioic acid. Using the IUPAC nomenclature, the 11-carbon example contains both carboxyl units, and the substituents are given the lowest sequence of numbers, so the name is 2,3-diethyl-10-propylundecanedioic acid. When the dicarboxylic acid has an alkene backbone, it is an enoic acid. Three examples are shown but there are two but-2-enedioc acids, the (2*E*)- and (2*Z*)-stereoisomers.



But-(2*Z*)-enedioic acid (maleic acid) | But-(2*E*)-enedioic acid (fumaric acid) | 2-Ethyl-8-methylnon-(3*E*)-enedioic acid

These two isomers also have common names. Maleic acid is but-(2*Z*)-enedioic acid and fumaric acid is but-(2*E*)-enedioic acid. The third example is 2-ethyl-8-methylnon-(3*E*)-enedioic acid using the IUPAC system.



Dicarboxylic acid — Monocarboxylate anion — Carboxylate dianion

Dicarboxylic Acid Derivatives

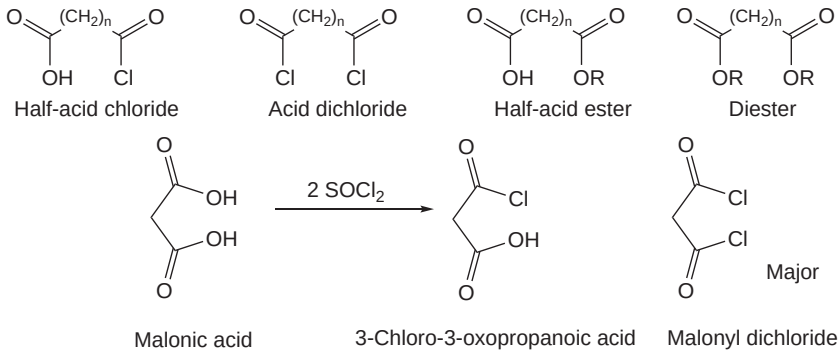
There are two acidic hydrogen atoms in a dicarboxylic acid and two Brønsted-Lowry acid-base reactions. Therefore, there are two equilibrium constants (K_1 and K_2), one for each acid-base reaction, and two pK values, pK_1 and pK_2. The pK values for several dicarboxylic acids are shown in Table 18.2.[11] This table also contains the pK values of the mono-carboxylic acid that is the closest structural relative of the dicarboxylic acid. The common names of these dioic

TABLE 18.2 The pK Values for Common Dicarboxylic Acids

Structure	pK_1	pK_2	Common Name	pK of RCO_2H
$HO_2C–CO_2H$	1.25	3.81	Oxalic acid	3.75 R = H
$HO_2C–CH_2–CO_2H$	2.85	5.7	Malonic acid	4.76 R = CH_3
$HO_2C-(CH_2)_2–CO_2H$	4.21	5.64	Succinic acid	4.87 R = Et
$HO_2C-(CH_2)_3–CO_2H$	4.32	5.42	Glutaric acid	4.83 R = C_3H_7
$HO_2C-(CH_2)_4–CO_2H$	4.41	5.41	Adipic acid	4.83 R = C_4H_9
$HO_2C-(CH_2)_5–CO_2H$	4.71	5.58	Pimelic acid	4.85 R = C_5H_{11}
$HO_2C-(CH_2)_6–CO_2H$	4.52	5.40	Suberic acid	4.89 R = C_6H_{13}
$HO_2C-(CH_2)_7–CO_2H$	4.53	5.33	Azelaic acid	4.89 R = C_7H_{15}
$HO_2C-(CH_2)_8–CO_2H$	4.59	5.59	Sebacic acid	4.96 R = C_8H_{17}

acid are also shown in Table 18.2. Oxalic acid is more acidic than formic acid (pK_1) due to the presence of a proximal electron withdrawing acyl group that influences the acidity of that proton. The dicarboxylic acids are more acidic than the corresponding monocarboxylic acids because of the enhanced inductive effects possible when the second carboxyl unit is present. In all cases, the first pK is for loss of the more acidic proton to form a mono-carboxylate anion. As the electron-withdrawing carboxyl "moves further away" from the first one (malonic to succinic to glutamic to adipic, etc.) pK_1 increases and it is a weaker acid. Table 18.2 clearly shows that the second pK value of the dicarboxylic acids is rather close to the "parent" mono-carboxylic acid. The value of pK_2 reflects loss of the second proton to yield the dianion.

Both acid chlorides and esters are possible for dicarboxylic acids. Derivatives with only one chlorine (a half-acid chloride) or two chlorine atoms (an acid dichloride) are possible. Similarly, a half-acid ester can be formed or a diester.

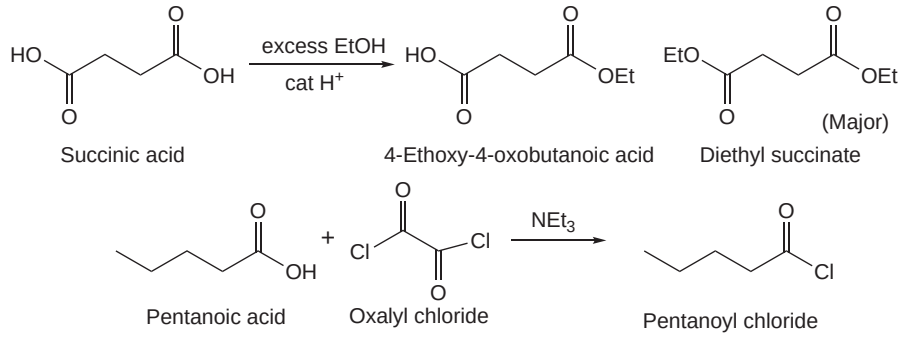


In reactions of dicarboxylic acids with thionyl chloride, it can be difficult to generate *only* a half-acid chloride such as malonyl monochloride (3-chloro-3-oxopropanoic acid). Indeed, the acid dichloride (malonyl dichloride) is usually formed as the major product of this reaction. Diesterification of a dicarboxylic acid is accomplished using an excess of an alcohol. The acid-catalyzed reaction of succinic acid and an excess of ethanol yields the diester (diethyl succinate) rather than the mono-ester (monoethyl succinate; 4-ethoxy-4-oxobutanoic acid). Acid dichlorides react with alcohols to form diesters, so the reaction of malonyl dichloride with ethanol gives diethyl malonate.

Oxalyl chloride is an efficient and mild method for converting acids to acid chlorides. It reacts with a carboxylic acid (e.g., pentanoic acid) in the presence of an amine base (e.g., triethylamine) to convert the acid to an acid chloride (in this case pentanoyl chloride). It is

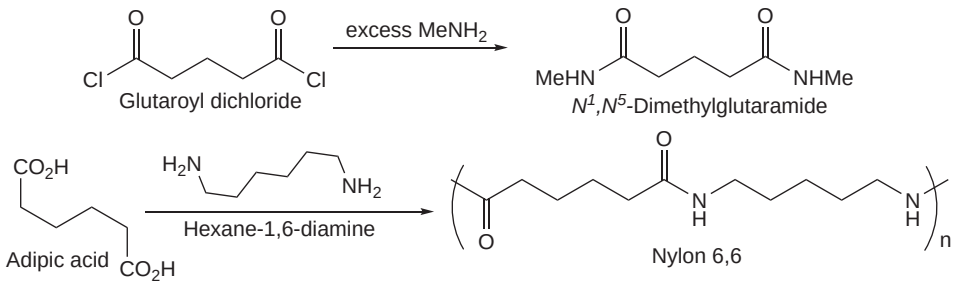
[11] *CRC Handbook of Chemistry*, 94th ed., CRC Press, Inc., Boca Raton, FL, 2013–2014, pp. 5–94 to 5–103.

used with acids that are sensitive to acids or bases, or when the acid chloride product is too reactive in the presence of acids or bases.



18.31 Draw the product of the reaction between 3,3-diphenylbutanoic acid and oxalyl chloride.

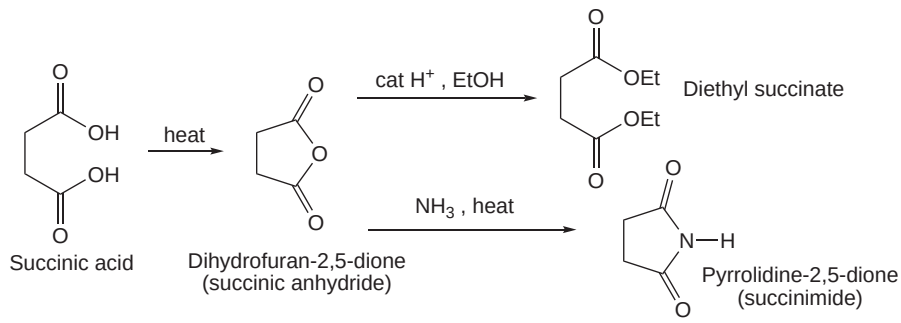
Acid dihalides react with amines to afford diamides. Glutaryl dichloride reacts with 2 equivalents of methanamine to yield N^1,N^5-dimethylglutaramide. The formal IUPAC name is 1,5-(*N*-methyl)pentanedioic acid diamide. Polyamides are an important class of acid derivatives, commonly prepared from dicarboxylic acids or acid dichlorides.



Polymers were introduced in Section 10.11. Nylon 6-6 is a polyamide, prepared by the polymerization of adipic acid and hexamethylenediamine (hexane-1,6-diamine) and it is used in carpet fibers, clothing, airbags, and hoses.

18.32 Draw the product from the reaction of the acid dichloride of adipic acid and an excess of propan-1-amine.

Since a dicarboxylic acid has two COOH units, it is possible to couple those units intramolecularly to form a *cyclic* anhydride. A common cyclic anhydride is formed by heating succinic acid. Loss of a molecule of water leads to formation of dihydrofuran-2,5-dione, which is more commonly called *succinic anhydride*. Acid hydrolysis of succinic anhydride regenerates the dicarboxylic acid, succinic acid**.** Reaction of succinic anhydride with ethanol and an acid-catalyst leads to diethyl succinate.

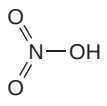


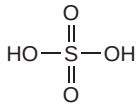
Imides are described in Section 18.10, and they are formed by the coupling of an acid unit with an amide unit. Cyclic imides are formed from dicarboxylic acid derivatives. If a cyclic anhydride such as succinic anhydride is heated with ammonia, the cyclic imide (pyrrolidine-2,5-dione) more commonly known as succinimide is formed. The succinimide derivatives *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) are halogenating agents. *N*-Chlorosuccinimide (NCS) is used as a chlorinating reagent (converts a molecule to a chloride) and is particularly useful in radical chlorination reactions. Similarly, NBS is used as a brominating reagent (converts a molecule to a bromide) via radical bromination reactions of alkanes using NCS and NBS as discussed in Section 11.7.

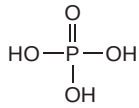
18.33 Draw all of the reactions necessary to convert 2,3-dimethylsuccinic acid first to the anhydride and then to the dimethyl ester of the diacid.
18.34 Write all of the reactions necessary to convert pentanedioic acid first to the acid dichloride and then to the *N*-ethyl imide.

18.11 NITRATE ESTERS, SULFATE ESTERS, AND PHOSPHATE ESTERS

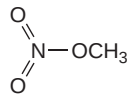
Discussions of acid derivatives in preceding sections and chapters focused on carboxylic acids and sulfonic acids. Notably missing are derivatives of the mineral acids nitric, sulfuric, and phosphoric acid. This section offers a brief introduction into some of the organic chemistry of these mineral acids.

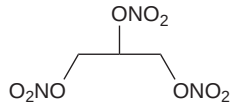

Nitric acid

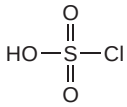

Sulfuric acid

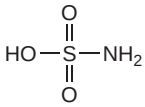

Phosphoric acid

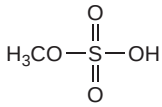
The structures of the mineral acids suggest that replacing one or more OH units will lead to acid derivatives. Esters are possible for all three mineral acids. Nitric acid yields a nitrate ester, methyl nitrate. but nitrate esters are often unstable. The trinitrate ester of glycerol (propane-1,2,3-triyl trinitrate) is the well-known explosive, nitroglycerin, discovered by Alfred Nobel (Sweden; 1833–1896).

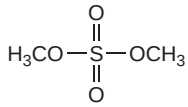

Methyl nitrate


Propane-1,2,3-triyl trinitrate (nitroglycerine)


Sulfurochloridic acid (Chlorosulfonic acid)


Sulfamic acid


Methyl hydrogen sulfate

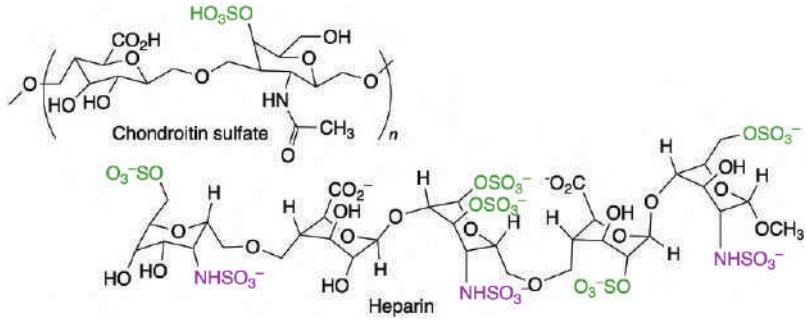

Dimethyl sulfate

Nitroglycerin and related nitrate esters are important compounds that relax vascular smooth muscle, which leads to vasodilatation. They are used to treat episodes of angina (chest pain) in people who have coronary artery disease (narrowing of the blood vessels that supply blood to the heart).[12] A vasodilator relaxes the muscle wall of blood vessels that leads to widening of those vessels. Amide derivatives $O_3N—NR_2$ are known as nitramides.

[12] Katzung, B.G.; Chatterjee, K. in *Basic and Clinical Pharmacology* (Katzung, B.G., Ed.), Appleton and Lange, Norwalk, CT, 1989, p. 1017.

Acid derivatives of sulfuric acids are more complicated because there are two acidic protons, and two OH units. If one OH unit is replaced with Cl, the acid chloride equivalent is sulfurochloridic acid. However, this compound is more commonly known as chlorosulfonic acid, and the chemistry is related more to the sulfonic acids found in Section 18.3. The amide derivative is known as sulfamic acid, which is used in the manufacture of some sweetening agents, and it finds use in some pharmaceutical preparations. The ester derivatives of sulfuric acid include the monoesters and diesters, represented by methyl hydrogen sulfate and dimethyl sulfate. Dimethyl sulfate is an alkylating agent that reacts with alcohols to give ethers. Organic sulfates are used in some chemical transformations, and they are found in pharmaceutical preparations. Some sulfates are important biological compounds. Chondritin sulfate, for example, is a biopolymer and an important structural component of cartilage. It has been used as a dietary supplement for the treatment of osteoarthritis. Heparin has sulfate units and sulfamic acid units. It is used as an injectable anticoagulant that is effective for the prevention of deep vein thromboses and pulmonary emboli.[13]

18.35 Give the product formed when dimethyl sulfate reacts with butan-2-ol.

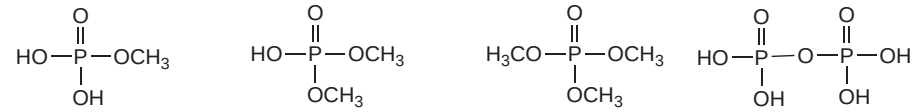


There are many important derivatives of phosphoric acid. An example of an acid chloride derivative is $ClPO(OH)_2$, chlorophosphoric acid. Phosphoramic acid, $H_2N—PO(OH)_3$ is an amide derivative. The chemistry of phosphate esters is rich and varied and they are important in biological systems (Sections 25.5,6). A *nucleoside* is a ribose derivative with an attached nucleobase (Section 25.5). The phosphate ester of a nucleoside is called a *nucleotide*. Nucleotides are structural components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

Three ester derivatives of phosphoric acid are possible, a monoester, a diester, and a triester. Using the methyl esters as examples, the monoester is methyl dihydrogen phosphate, the diester is dimethyl hydrogen phosphate, and the triester is trimethyl phosphate. There are also derivatives of pyrophosphoric acid (diphosphoric acid), which may have various ester derivatives by replacing any or all of the OH units. In principle, the preparation of phosphate esters or other acid derivatives should be similar to the chemistry of carboxylic acids and sulfonic acids, but it is more complex because several derivatives are possible. There are synthetic routes that are specific for phosphorus compounds. For example, the reaction of phosphoric acid and an alcohol may give the ester, but the reaction is slow, and this is not a good preparative method. An alternative is the reaction of phosphorous pentoxide with an excess of an alcohol to yield a mixture of phosphate esters. The reaction of ethanol and P_4O_{10} (the dimeric form of phosphorus pentoxide) yields a mixture of ethyl dihydrogen phosphate and diethyl hydrogen phosphate.

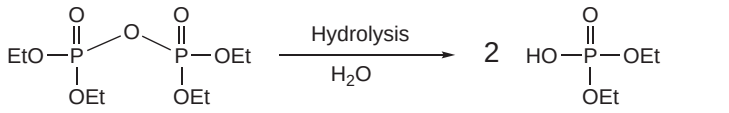
[13] (a) Agnelli, G.; Piovella, F.; Buoncristiani, P.; Severi, P.; Pini, M.; D'Angelo, A.; Beltrametti, C.; Damiani, M.; Andrioli, G.C.; Pugliese, R.; Iorio, A.; Brambilla, G. *New England Journal of Medicine* 1998, 339, 80–85; (b) Bergqvist, D.; Agnelli, G.; Cohen, A.T.; Eldor, A.; Nilsson, P.E.; Le Moigne-Amrani, A.; Dietrich-Neto, F. *New England Journal of Medicine* 2002, 346, 975–980.

18.36 Give the structure of the dibenzyl ester of phosphoric acid.



Methyl dihydrogen phosphate | Dimethyl hydrogen phosphate | Trimethyl phosphate | Diphosphoric acid

Hydrolysis of a phosphate ester may yield the parent phosphoric acid, but it is also possible to observe "partial hydrolysis." The hydrolysis of pyrophosphate esters such as tetraethyl diphosphate gives the phosphate ester diethyl hydrogen phosphate.

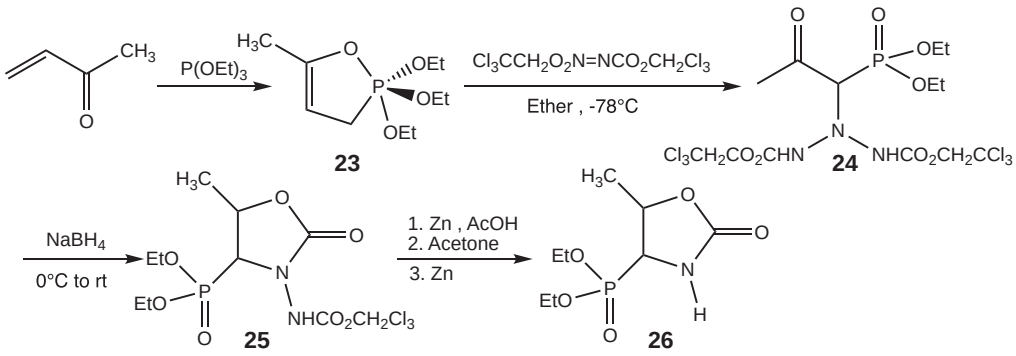


Tetraethyl diphosphate → 2 Diethyl hydrogen phosphate

Cynthia K. McClure (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Cynthia K. McClure (USA; 1953–2014) was a professor of chemistry at Montana State University who began her career at the University of Delaware. Her work focused on the development of new reactions and the synthesis of natural products. In part, she studied phosphonate and oxaphospholene analogs that could be used for a synthesis of sphingomyelin and ceramide-1-phosphate using pentacovalent organophospholene methodology.[14] Initial reaction of methyl vinyl ketone with triethylphosphate gave oxaphospholene **23** in 69% yield.[14b] The reaction of **23** with 2,2'-bis(2,2,2-trichloroethyl) azodicarboxylate gave **24** in about 90% yield. Reduction with sodium borohydride gave **25** in 93% yield, and this was converted to **26** in about 83%.[14a] Derivatives of **26** were postulated as precursors to sphingomyelin and ceramide phosphonate derivatives (Section 18.13).

[14] (a) McClure, C.K.; Mishra, P.K.; Grote, C.W. *Journal of Organic Chemistry* 1997, 62, 2437–2441; (b) McClure, C.K.; Jung, K.Y. *Journal of Organic Chemistry* 1991, 56, 2, 867–871.

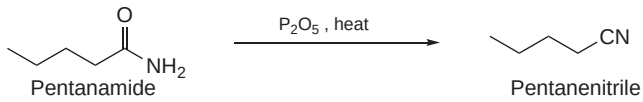


18.37 Give the products formed when ethanol reacts with P_4O_{10}.

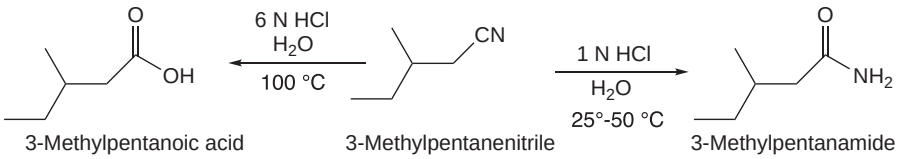
18.12 NITRILES ARE CARBOXYLIC ACID DERIVATIVES

Reactions of Acid Derivatives

Nitriles are formed by an S_N2 reaction of an alkyl halide with NaCN or KCN (see Section 11.3). Nitriles can be classified as acid derivatives because (1) nitriles are formed by dehydration reactions of primary amides and (2) acid hydrolysis of nitriles leads to either an amide or a carboxylic acid. The dehydration reaction is specific for primary amides.



Phosphorus pentoxide has the structure P_2O_5, and heating a primary amide (e.g., pentanamide) leads to pentanenitrile by loss of water (O from the carbonyl and hydrogen atoms from the nitrogen). The P_2O_5 acts as a drying agent to facilitate the dehydration of a primary amide. The yields of this reaction are often quite poor.



Strongly acidic conditions are required to convert a nitrile to a carboxylic acid because hydrolysis first gives an amide, which is resistant to hydrolysis. When 3-methylpentanenitrile is treated with HCl and then with water, at ambient temperatures or with mild heating, the product is the amide, 3-methylpentanamide. Prolonged heating in 6 N HCl is usually required to hydrolyze the nitrile to the corresponding acid, 3-methylpentanoic acid. This constitutes a two-step procedure to prepare acids from a nitrile. Combined with the S_N2 reaction, formation of a nitrile followed by hydrolysis allows the conversion of an alkyl halide to a carboxylic acid.

18.38 Give the product formed when pent-1-ene is treated with 1. HBr, 2. NaCN in DMF, and 3. 6N HCl.

18.13 FATTY ACIDS AND LIPIDS

Fatty Acids and Lipids

Lipid is a general term for a group of molecules that that are hydrophobic. Lipids are insoluble in water but soluble in organic solvents. In biochemistry a lipid is a macro-biomolecule that

is soluble in nonpolar solvents. Lipids have many functions, including the storage of energy, signaling and they are structural components of cell membranes. There are eight categories of lipids: the fatty acids, glycerolipids, glycerophospholipids, sphingolipids, saccaharolipids, polyketides, sterol lipids, and prenol lipids. Fatty acids are a sub-class of lipids, and their derivatives are important in their own right. Fatty acids are common components of complex lipids that include many natural oils, waxes, etc.

Fatty acids are long chain carboxylic acids. Common naturally occurring fatty acids include myristic acid (tetradecanoic acid) found in nutmeg and palmitic acid (hexadecanoic acid) found in butter, cheese, meat and in palm oil. Stearic acid (octadecanoic acid), a waxy solid, is a component of animal and vegetable fats and it used in cosmetics. It is also a dietary supplement, and it is used to make candles. Arachidic acid (eicosanoic acid) is found in peanut oil as well as in fish oil. The carboxylic acid end is polar, associated with water solubility, and is labeled the delta (Δ) end of the fatty acid. The methyl end is associated with being nonpolar, more soluble in oils, and is labeled the omega (Ω) end.

There are many unsaturated fatty acids, and they are characterized by having an alkene unit, diene or polyene unit in the long carbon chain rather than an "alkane" chain, as shown in Figure 18.9. Most naturally occurring unsaturated fatty acids are of the *cis* configura-

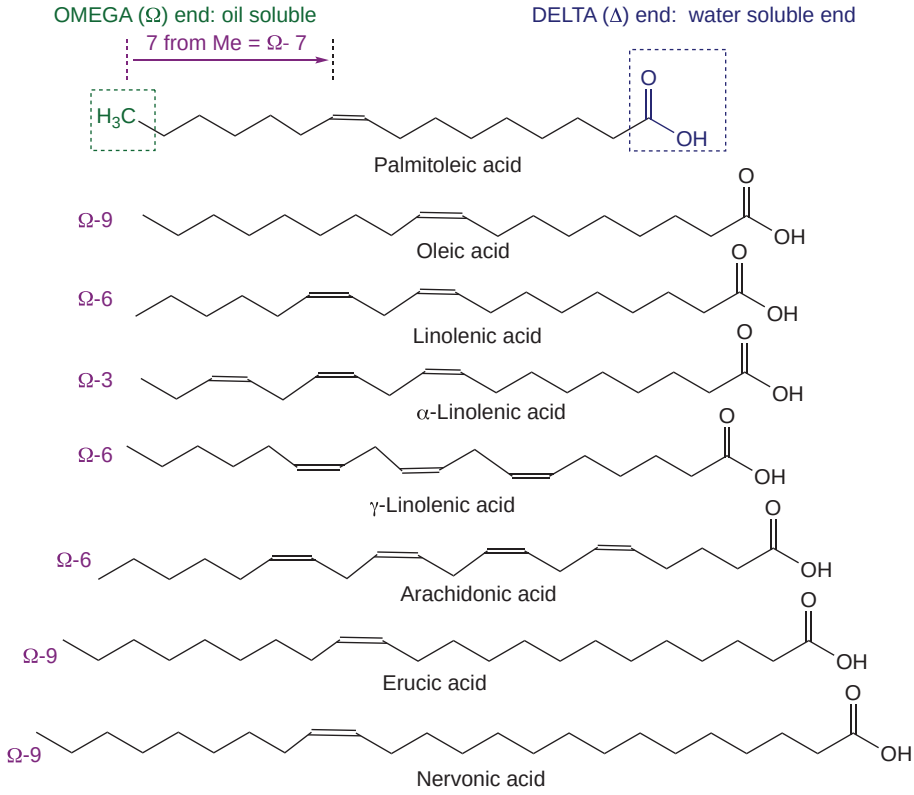


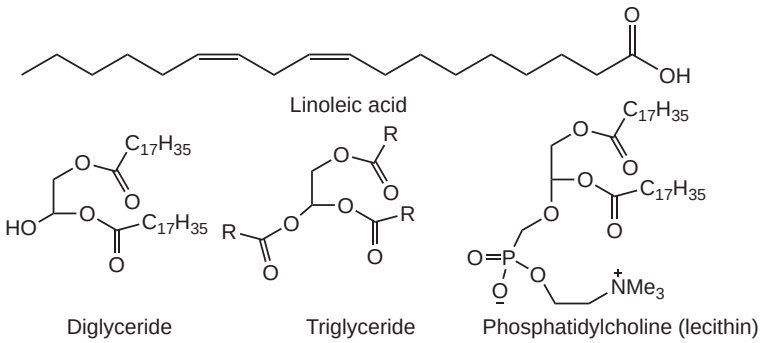
FIGURE 18.9 Unsaturated fatty acids.

tion, although the *trans* form does exist in some natural and partially hydrogenated fats and oils. Common unsaturated fatty acids are palmitoleic acid (C_{16}), oleic acid (C_{18}), linolenic acid (C_{18}), α-linolenic acid (C_{18}) and γ-linolenic acid (C_{18}). Linolenic acid is the most abundant fatty-acyl chains of plant *thylakoid membranes*, and they make these membranes highly *fluid* despite environmental low-temperatures. Other examples include arachidonic acid (C_{20}), erucic acid (C_{22}; found in mustard seed), and nervonic acid (C_{24}; important for the biosynthesis of nerve cell myelin).

The site of C=C units relative to the terminal methyl group (the Ω end) is used in unsaturated fatty acids. Because the closest double-bond to the methyl group in oleic acid is nine carbon atoms away from the methyl, oleic acid is called an omega-9 (Ω-9)

fatty acid. In α-linolenic acid, the double bond closest to the methyl group is only three carbons away so it is an omega-3 (Ω-3) fatty acid. Omega-3 fatty acids are known to lower triglycerides and blood pressure. Omega-9 fatty acids reduce the risk of cardiovascular disease and stroke. They may help eliminate plaque build-up in arteries by increasing high-density lipoproteins (HDL or good cholesterol) and lowering low-density lipoproteins (LDL or bad cholesterol).

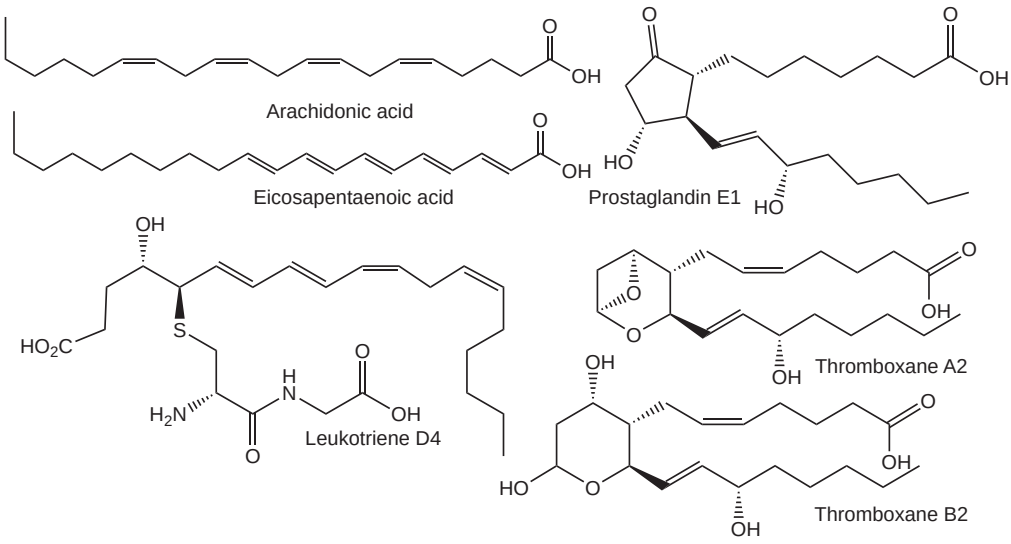
The essential fatty acids are unsaturated fatty acids that cannot be made in the body, but are required for normal, healthy functioning of the body. These fatty acids must be obtained from foods (e.g., nuts, sunflower oil or other vegetable oils, and oil-rich fish). Wild salmon, for example, are rich in Ω-3 fatty acids. A deficiency of these essential fatty acids may result in hyperactivity, reduced growth, or in extreme cases, death. There are two families of essential fatty acids, the Ω-3 and Ω-6 fatty acids. Linoleic acid is an essential fatty acid used by the body to produce arachidonic acid, which is physiologically significant because it is the precursor for prostaglandins. Note that Ω-9 fatty acids are not classified as essential fatty acids because they can be created by the human body from unsaturated fat (see below) and are therefore not essential in the diet.



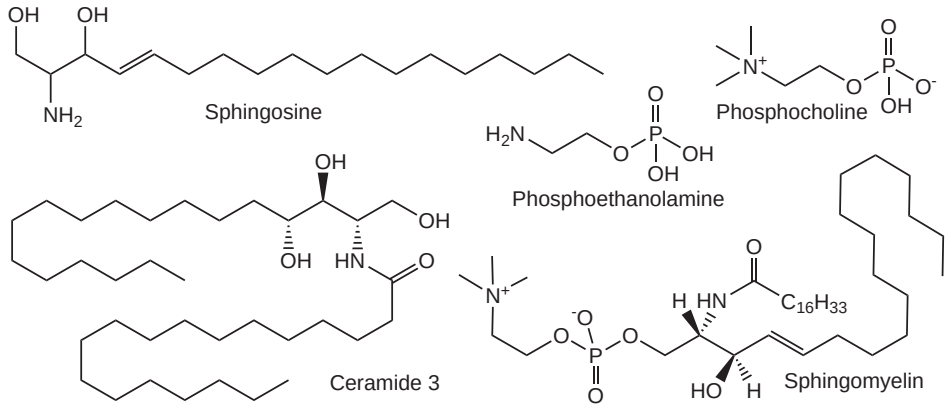
Fatty acids are usually found as esters of 1,2,3-propanetriol (glycerol) known as diglycerides or triglycerides, with the hydroxyl groups esterified with a fatty acid, typically different fatty acids. Glycerolipids are therefore mono-, di-, and tri-substituted glycerols, for example the diglycerides and triglycerides (see saponification in Section 18.4). Triglycerides store energy and comprise the bulk of storage fat in animal tissues. *Fats* are fatty acid esters that are solid or semi-solid at room temperature. Fats are one of the three main macronutrient groups in the human diet, along with carbohydrates and proteins. Fats are the main components of common food products such as milk, butter, and cooking oils. Unsaturated fats are lipids that have one or more C=C groups, are usually liquid or semi-liquid at room temperature and so are called *oils*. The hydrolysis of the ester bonds of triglycerides and the release of glycerol and fatty acids are the initial steps in metabolizing fat. Triglycerides are present in the blood to enable the bidirectional transference of adipose fat and blood glucose from the liver, and they are a major component of human skin oils.

Most natural fats and oils are mixed triglycerides, in which the fatty acid constituents are different, but many triglycerides have three identical fatty acids, with three stearic acid units. Naturally occurring triglycerides are usually composed of fatty acids with 16, 18, and 20 carbons. The fats obtained from the food we eat is the usual source of the triglycerides found in our blood plasma, and an excess of triglycerides in blood plasma is called hypertriglyceridemia. An elevated level of triglycerides is linked to the occurrence of coronary artery disease.

An important diglyceride is phosphatidic acid, which has stearic acid ester units (stearates). It is the parent compound for glycerol-based phospholipids. One is phosphatidylcholine (also known as lecithin), which contains the trimethylammonium ethanolamine unit. Lecithin is used as an emulsifier, to keep cocoa and cocoa butter in a candy bar from separating, for example. It is produced by the liver and is a building block of cell membranes. Lecithin is found in the protective sheaths surrounding brain cells.



The eicosanoids are an important class of lipids that are derived primarily from arachidonic acid and eicosapentaenoic acid, that include prostaglandins, leukotrienes, and thromboxanes. Eicosanoids are signaling molecules that inhibit inflammation, allergy, fever, contribute to the perception of pain, regulating cell growth, control blood pressure among other things. Prostaglandins such as prostaglandin E_1 are important group of physiologically active eicosanoids with diverse hormone-like effects in animals. Every prostaglandin contains 20 carbon atoms and a 5-carbon ring. Prostaglandins activate inflammatory response, the production of pain, and also fever. They are implicated in other biological functions. Leukotrienes such as leukotriene D_4 are eicosanoid inflammatory mediators that use lipid signaling to regulate immune response. Leukotriene D_4 triggers contractions in smooth muscles that line bronchioles and their overproduction is a major cause of inflammation in asthma. Thromboxane A2 and thromboxane B2 are eicosanoid lipids that are distinguished by the presence of a 6-membered ether containing ring. Thromboxane is named for its role in blood clot formation. Thromboxane A2 is one of the compounds that stimulate constriction and clotting of platelets.



Glycerophospholipids, or phospholipids are common in nature and the main component of the lipid bilayer of cells. Phospholipids are also important in metabolism and cell signaling. Glycerophospholipids are subdivided based on the nature of the polar headgroup at the *sn*-3 position of the glycerol backbone in eukaryotes and eubacteria or the *sn*-1 position in the case of archaebacteria. Sphingolipids are a family of compounds that include ceramides, phosphosphingolipids, and glycosphingolipids. The major sphingoid base of mammals is commonly referred to as sphingosine and ceramides are *N*-acyl-sphingoid bases. The fatty acid components are typically saturated or mono-unsaturated with chain lengths from 16 to

26 carbon atoms. Sphingosine is 2-amino-4-trans-octadecene-1,3-diol is the primary part of sphingolipids, a class of cell membrane lipids such as sphingomyelin.

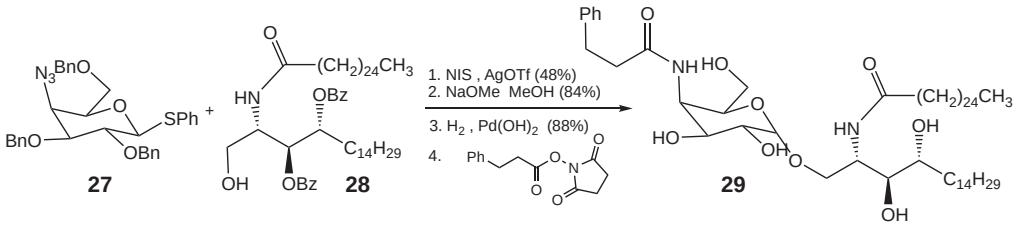
Ceramides such as *ceramide 3* [*N*-((2*S*,3*S*,4*R*)-1,3,4-trihydroxyoctadecan-2-yl)stearamide] are found in high concentrations within the cell membrane of eukaryotic cells. Ceramides can participate in the regulation of cell differentiation, proliferation and programmed cell death. Sphingomyelin [(2*S*,3*R*,*E*)-2-heptadecanamido-3-hydroxyoctadec-4-en-1-yl (2-(trimethylammonio)ethyl) phosphate] is a type of sphingolipid that contains phosphocholine and ceramide found the animal cell membranes, especially the myelin sheath that surrounds some nerve cell axons. Sphingomyelins with a phosphoethanolamine head group can also be classified as phosphosphingolipids. The major phosphosphingolipids of mammals are sphinogomyelins whereas insects contain mainly ceramide phosphoethanolamines and fungi have phytoceramide phosphoinositols and mannose-containing headgroups.

Amy R. Howell (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

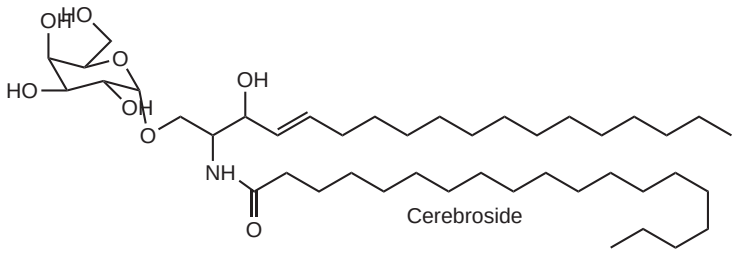
Professor Amy R. Howell (USA), an organic chemist at the University of Connecticut, does research to develop new synthetic methodology. Professor Howell has completed several syntheses that exploit the chemistry of 2-alkylidene oxetanes (Section 23.7), oxopirohexanes and dioxaspirohexanes. She has developed metal mediated approaches to the rapid assembly of diverse β-lactones as tools for proteomic profiling. Recent work has focused on modification of α-galactosylceramides to activate invariant natural killer T (iNKT) cells by stimulating strong immune responses and potent anti-tumor immunity. The prototypical iNKT cell antigen is KRN7000, an α-galactosylceramide[15] derived from structure-activity relationship studies around glycolipids isolated from a marine sponge. Professor Howell has synthesized modified linked C4-saccharide modifications of KRN7000.[16] This work showed that these modifications provided improved stimulation of human invariant NKT cells and anti-tumor immunity in a humanized mouse model. In the example shown, the galactose derivative **27** (Section 25.1) reacted with the ceramide derivative **28** in the presence of N-iodosuccinimide (NIS) and silver triflate (silver trifluoromethanesulfonate). The benzoate esters were saponified to give the diol. Catalytic hydrogenation cleaved the O—C bond of the OBn groups to give $PhCH_3$ and liberate the hydroxyl units on the sugar unit. Hydrogenation also reduced the azide moiety to the amine, allowing amide formation by reaction with benzenepropanoic acid succinimide ester. The final product was **29**. Note that Bn is benzyl ($-CH_2Ph$) and Bz is benzoyl ($-O_2CPh$).

[15] (a) Wu, T.-N.; Lin, K.-H.; Wu, Y.-T.; Huang, J.-R.; Hung, J.-T.; Wu, J.-C.; Chen, C.-Y.; Chu, K.-C.; Lin, N.-H.; Yu, A.L.; Wong, C.-H. *ACS Chemical Biology* 2016, 11, 3431–3441; (b) Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science* 1997, 278, 1626–1629.

[16] Saavedra-Avila, N.A.; Keshipeddy, S.; Guberman-Pfeffer, M.J.; Pérez-Gallegos, A.; Saini, N.K.; Schäfer, C.; Carreño, L.J.; Gascón, J.A.; Porcelli, S.A.; Howell, A.R. *ACS Chemical Biology* 2020, 15, 3176–3186.



The glycosphingolipids are a diverse family of molecules composed of one or more sugar residues linked via a glycosidic bond to the sphingoid base and examples are the cerebrosides and the gangliosides. The structure of *cerebroside* is shown, which has a galactose unit attached. Gangliosides have a similar structure except that an oligosaccharide is attached to the ceramide core (oligosaccharides are introduced in Section 25.2).



Sterols (Section 5.4) are steroids in which one of the hydrogen atoms is substituted with a hydroxyl group at position 3 in the carbon chain. Sterols include cholesterol and its derivatives, are an important component of membrane lipids, along with the glycerophospholipids and sphingomyelins. Other examples of sterols are the bile acids. In mammals, bile acids are oxidized derivatives of cholesterol, and they are synthesized in the liver. The predominant sterol in fungal cell membranes is ergosterol. Steroids were discussed in Section 5.4. Prenol lipids are synthesized from the five-carbon-unit precursors isopentyl diphosphate and dimethylallyl diphosphate.

Saccharolipids are compounds that have fatty acid residues linked directly to a sugar backbone. Saccharolipid structures are compatible with membrane bilayers. The most common saccharolipids are probably the acylated glucosamine precursors of the Lipid A component, which are disaccharides of glucosamine, of the lipopolysaccharides in Gram-negative bacteria. Typical lipid A molecules are disaccharides of glucosamine, which are derivatized with as many as seven fatty-acyl chains.

Polyketides are a large group of secondary metabolites which either contain alternating carbonyl groups and methylene groups. Polyketides comprise many secondary metabolites and natural products from animal, plant, bacterial, fungal, and marine sources, and have great structural diversity. Many polyketides are cyclic molecules, and many are anti-microbial, anti-parasitic and anti-cancer.

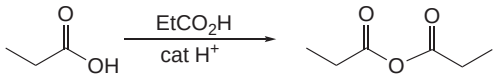
18.14 ORGANIZATION OF REACTION TYPES

The reaction of carboxylic acids and derivatives can be organized as follows:

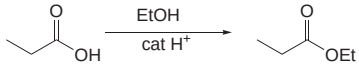
What reactions are possible for carboxylic acids?

1. Carboxylic acids react with thionyl chloride and other chlorinating agents to yield an acid chloride

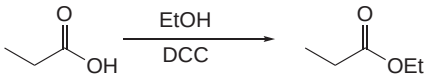
2. Carboxylic acids react with other carboxylic acids to yield an acid anhydride.



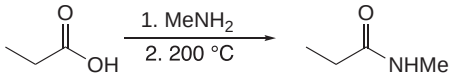
3. Carboxylic acids react with alcohols to yield an ester.



4. Carboxylic acids react with alcohols with DCC to yield an ester.

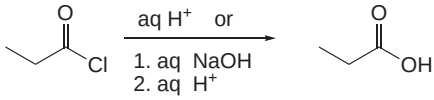


5. Carboxylic acids react with amines or ammonia to yield an ammonium salt, which can be heated to yield an amide.

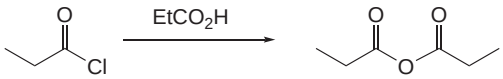


What reactions are possible for acid chlorides?

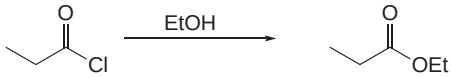
1. Acid chlorides react with aqueous acid or base to yield a carboxylic acid.



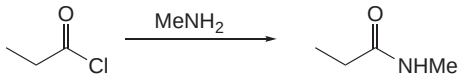
2. Acid chlorides react with carboxylic acids to yield an acid anhydride.



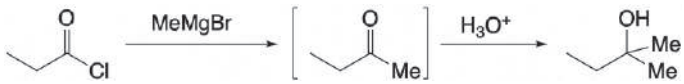
3. Acid chlorides react with alcohols to yield an ester.



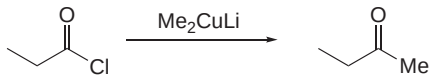
4. Acid chlorides react with amines or ammonia to yield an amide.



5. Acid chlorides react with Grignard reagents or organolithium reagents to yield ketones or alcohols.

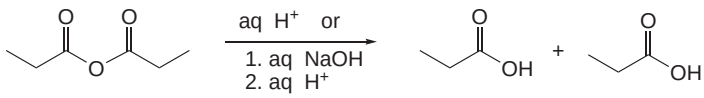


6. Acid chlorides react with organocuprates to yield ketones.

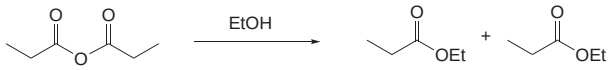


What reactions are possible for acid anhydrides?

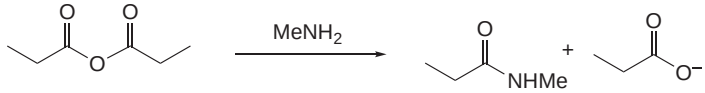
1. Acid anhydrides react with aqueous acid or base to yield two carboxylic acids.



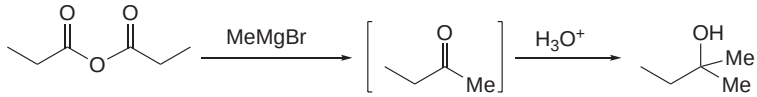
2. Acid anhydrides react with alcohols to yield an ester.



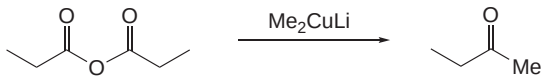
3. Acid anhydrides react with amines or ammonia to yield an amide.



4. Acid anhydrides react with Grignard reagents or organolithium reagents to yield ketones or alcohols.

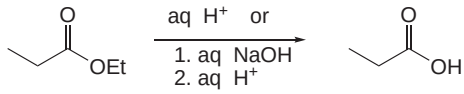


5. Acid anhydrides react with organocuprates to yield ketones.

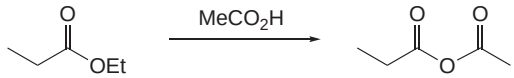


What reactions are possible for esters?

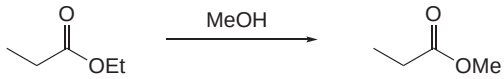
1. Esters react with aqueous acid or base to yield a carboxylic acid and an alcohol.



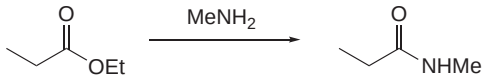
2. Esters react with carboxylic acids to yield an acid anhydride.



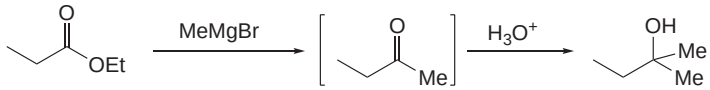
3. Esters react with alcohols to yield a new ester.



4. Esters react with amines or ammonia to yield an amide.

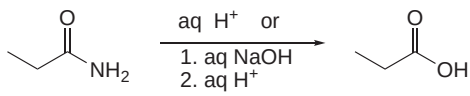


5. Esters react with Grignard reagents or organolithium reagents to yield ketones or alcohols.

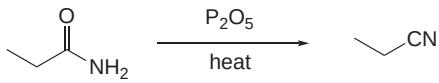


What reactions are possible for amides?

1. Amides react with aqueous acid or base to yield a carboxylic acid and an amine.

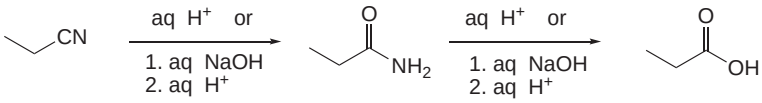


2. Amides (primary) react with P_2O_5 to yield a nitrile.

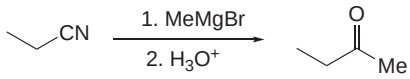


What reactions are possible for nitriles?

1. Nitriles react with aqueous acid or base to yield a carboxylic acid or an amide.

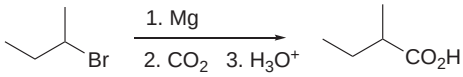


2. Nitriles react with Grignard reagents or organolithium reagents to yield an imine, which is hydrolyzed to a ketone.

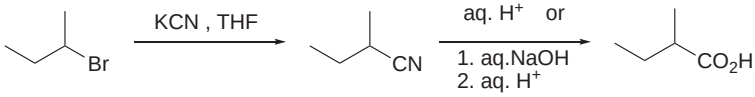


What reactions are possible for alkyl halides?

1. Alkyl halides react with Mg or Li and then CO_2 to yield a carboxylic acid.

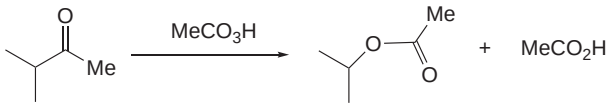


2. Alkyl halides react with KCN or NaCN to yield a nitrile, which can be hydrolyzed to an amide or a carboxylic acid.



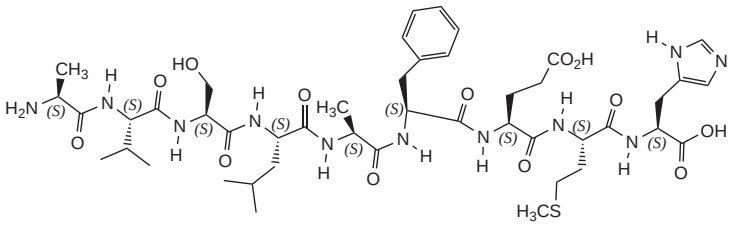
What reactions are possible for ketones?

1. Ketones react with peroxyacids to yield esters.



18.15 BIOLOGICAL RELEVANCE

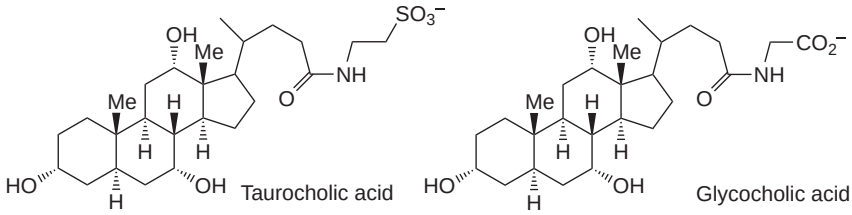
Carboxylic acid derivatives are ubiquitous. Proteins are characterized by so-called peptide bonds, but they are amide bonds. A simple example is the nonapeptide (nine amino acid residues) shown. This nonapeptide is composed (reading from left to right) of alani ne–valine–serine–leucine–alanine–phenylalanine–glutamic acid–methionine–histidine (Section 24.4).



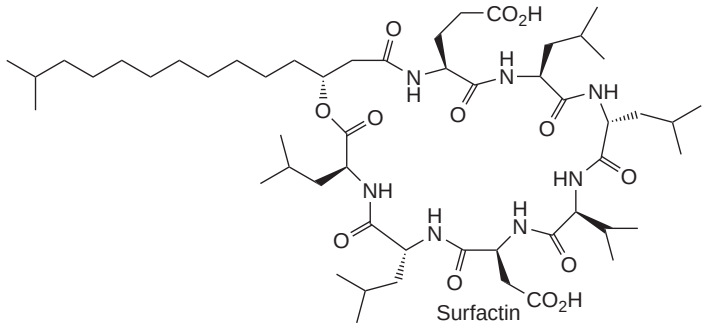
alanine-valine-serine-leucine-alanine-phenylalanine-glutamic acid-methionine-histidine

One of the principal pancreatic lipases is known as steapsin. A lipase is an enzyme that catalyzes the hydrolysis of fats. Lipases are a subclass of the esterases. Cleavage occurs at the C1 and C3 positions and the hydrolysis depends on bile salts (bile salts are carboxylic acid salts linked to a steroid), which act as detergents to emulsify the triglycerides and facilitate

the ester cleavage reaction. The long-chain fatty acid products are converted to micelles via interaction with the bile salts, and carried to the surface of epithelial cells, where they react with glycerol to form new triglycerides. Bile salts are commonly amide derivatives of steroids. Two bile acids are taurocholic acid and glycocholic acid.



Many natural peptides are produced by bacteria via non-ribosomal peptide synthesis. *Bacillus subtilis* produces the heptapeptide surfactin, which has antibiotic and antifungal activity.[17] Non-ribosomal peptide synthesis means that the peptide is not produced by the transfer-RNA-messenger-RNA (tRNA-mRNA) mechanism described in Section 25.6.



Each amino acid found in surfactin is directly selected for incorporation into the growing peptide chain by one of the domains of the enzyme *surfactin synthetase*, shown with the pendant SH groups in Figure 18.10.[17] Substrate activation occurs after binding the amino acid, and the enzyme catalyzes the formation of an aminoacyl adenylate intermediate using Mg^{2+}-ATP and release of a cofactor. Subsequently, the amino acid—O—AMP oxoester is converted into a thioester by a nucleophilic attack of the free thiol-bound cofactor of an adjacent PCP domain. Note that PCP is an abbreviation for a *peptidyl carrier protein*. This reaction is effectively an acyl substitution. Note that ATP is adenosine triphosphate and AMP is adenosine monophosphate (Section 25.6).

In Figure 18.10, the binding domains attach two amino acids in **30** by an acyl substitution reaction in which the thiol unit attacks the acyl carbon, and each coupling proceeds by the appropriate tetrahedral intermediate shown as **31**. Loss of the O—AMP leaving group leads to **32A**, redrawn as **32B** to show that the nucleophilic amine unit of one amino acid residue attacks the acyl unit of the other in an acyl substitution reaction to yield another tetrahedral intermediate (**33**). The leaving group is the thiol-bound unit and formation of the bound dipeptide in **34**. The organism will produce the heptapeptide using similar coupling reactions, and then complete the biosynthesis of surfactin. This sequence shows that organisms can produce peptides by alternative mechanisms to ribosomal peptide synthesis.

[17] Sieber, S.A.; Marahiel, M.A. *Chemical Reviews* 2005, 105, 715–738.

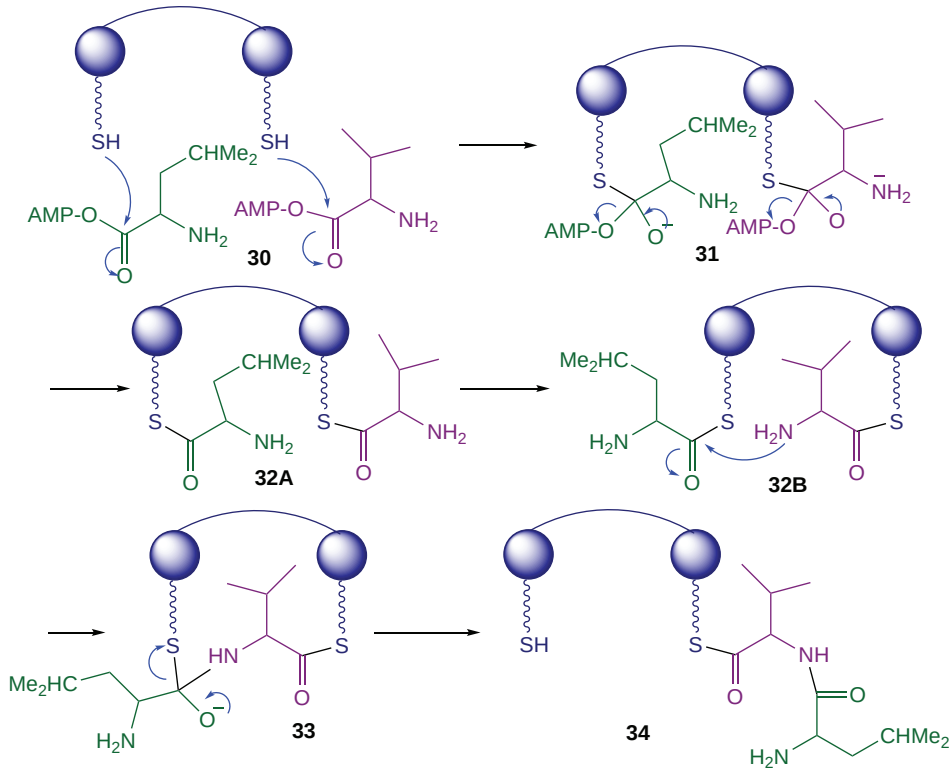


FIGURE 18.10 Biosynthesis of surfactin. (Reprinted with permission from Sieber, S.A.; Marahiel, M.A. *Chem. Rev.*, 2005, 105, 715. Copyright 2005 American Chemical Society).

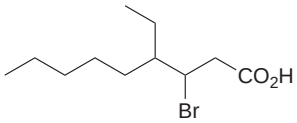
CORRELATION OF HOMEWORK WITH CONCEPTS

- Carboxylic acids are acids: 1, 38, 42.
- Many acid derivatives can be generated by "replacing" the OH unit of a carboxylic acid (COOH) with another atom or group; —Cl, —Br, —O_2CR, —OR, —NR_2. Common acid derivatives are acid chloride, acid anhydrides, esters, and amides: 2, 36, 37.
- Sulfonic acids can be converted to sulfonic acid chlorides, sulfonate esters, and sulfonamides, similar to reactions of carboxylic acids: 3, 4, 15, 16, 51, 53.
- Acid or base hydrolysis of acid chlorides, acid anhydrides, esters, or amides regenerates the "parent" carboxylic acid: 35, 6, 7, 22, 41, 46, 47, 51, 52.
- Acid chlorides are prepared by reaction of a carboxylic acid with a halogenating agent. Acid anhydrides can be prepared by reaction of an acid chloride with a carboxylic acid or by the dehydration of two carboxylic acids that leads to coupling: 10, 41, 44.
- Esters can be prepared by the reaction of an acid chloride or anhydride with an alcohol, as well as by direct reaction of an acid and an alcohol, with an acid-catalyst, or by using a dehydrating agent (e.g., DCC). Lactones are cyclic esters: 8, 12, 13, 14, 42, 44, 45, 46, 48, 50, 51.
- Transesterification converts one ester to another: 11.
- Peroxy acids react with ketones to yield esters in the Baeyer–Villiger reaction: 17, 18, 39, 51.
- Amines react with carboxylic acids to yield ammonium salts. Heating these salts to ~ 200 °C will usually yield the amide. Amides can be prepared by the reaction of an acid chloride, acid anhydride, or an ester with ammonia or an amine. Acids and amines can be coupled in the presence of a dehydrating agent (e.g. DCC). Cyclic amides are known as lactams: 9, 19, 20, 21, 23, 41, 43, 44, 51.

- Imides are formed by the reaction of amides with other acid derivatives. Cyclic anhydrides and cyclic imides can be prepared from dicarboxylic acids or acid dichlorides: 23.
- Acid derivatives react with Grignard reagents and organolithium reagents to yield ketones, but this initial product reacts with a second equivalent of Grignard reagent or organolithium reagent to yield a tertiary alcohol. Organolithium reagents react with copper(I) salts to yield lithium dialkyl cuprates, which react with acid chlorides to yield ketones: 24, 25, 26, 27, 29, 40, 48, 49, 51.
- Grignard reagents and organolithium reagents react with carbon dioxide: 49.
- Grignard reagents and organolithium reagents react with nitriles to yield imine anions, and aqueous acid hydrolysis usually convert the imine anion to a ketone as the final product: 30, 48, 49.
- Dicarboxylic acid derivatives generate mon- and diacid derivatives: 31, 32, 33, 34, 46, 49.
- Primary amides are dehydrated to nitriles and nitriles are hydrolyzed to carboxylic acids: 35, 38, 44.
- Spectroscopy can be used to determine the structure of a particular molecule (see Chapter 13): 54, 55, 56, 57, 58, 59, 60.

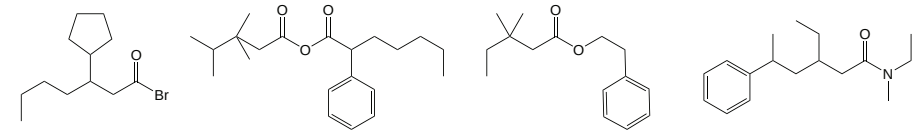
ANSWERS TO IN-CHAPTER QUESTIONS

18.1



3-Bromo-4-ethylnonanoic acid

18.2



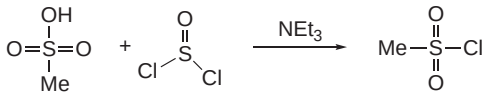
3-Cyclopentylheptanoyl bromide

3,3,4-Trimethylpentanoic 2-phenylheptanoic anhydride

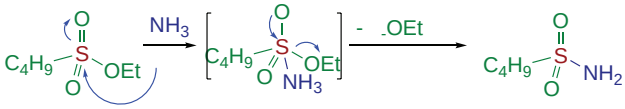
2-Phenylethyl 3,3-dimethylpentanoate

N,3-Diethyl-*N*-methyl-5-phenylhexanamide

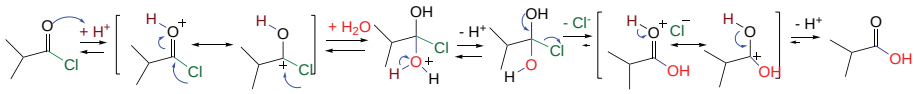
18.3



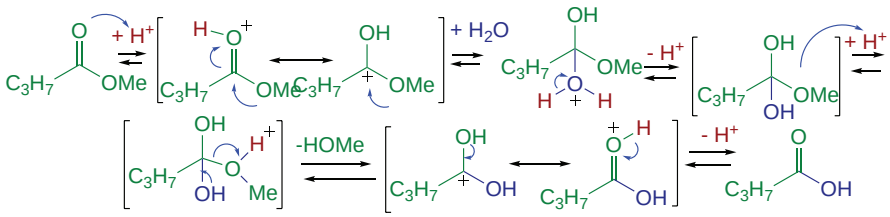
18.4



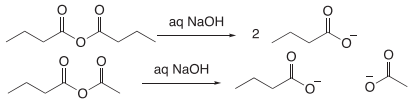
18.5



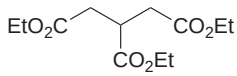
18.6



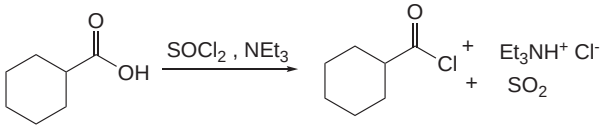
18.7



18.8



18.9



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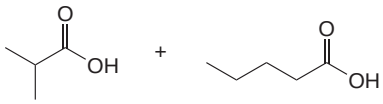

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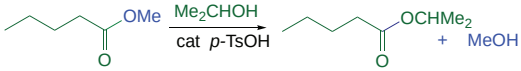

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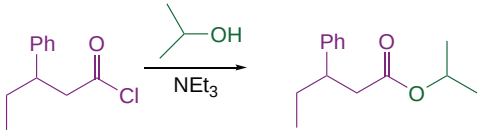

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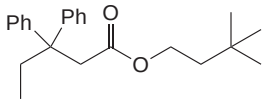

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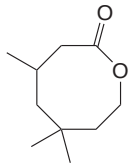

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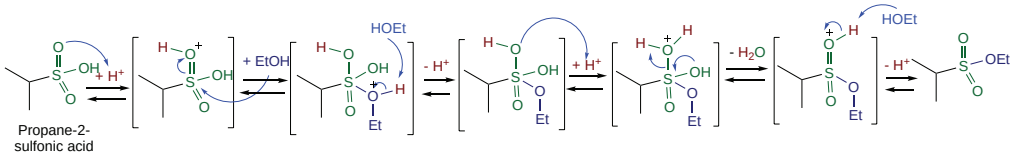
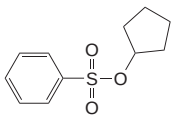


Propane-2-sulfonic acid

18.16



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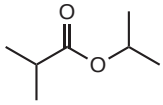

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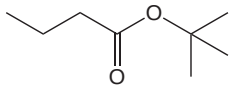
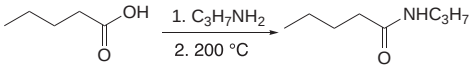


tert-Butyl butyrate

18.19



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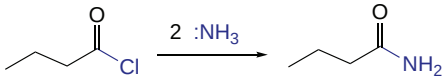

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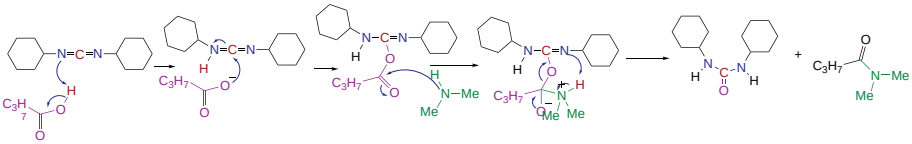

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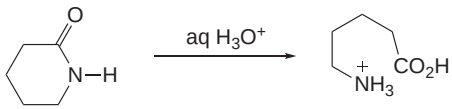

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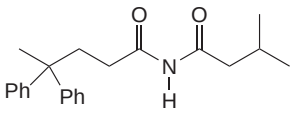
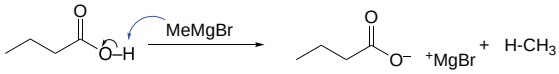


N-(3-Methylbutanoyl)-4,4-diphenylpentanamide

18.24



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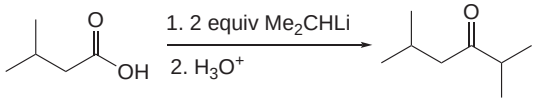

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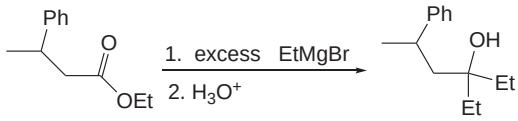

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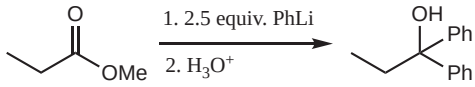

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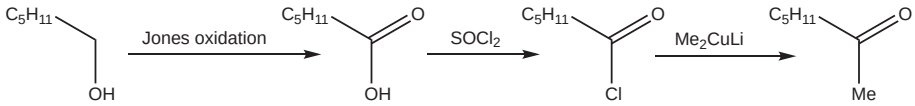

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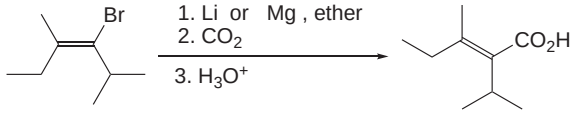

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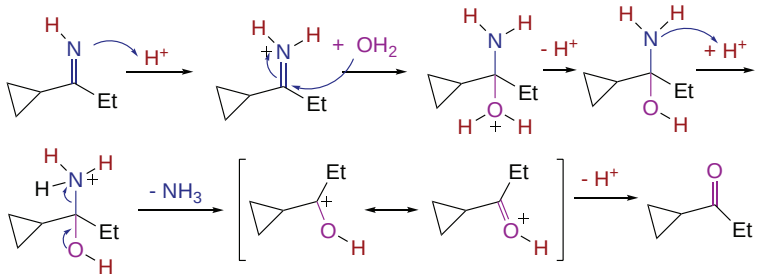

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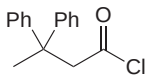

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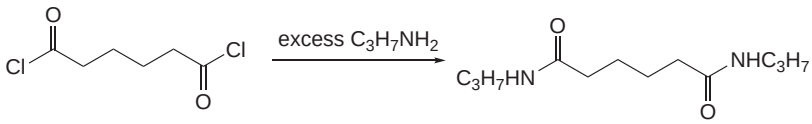

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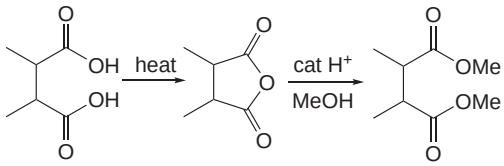

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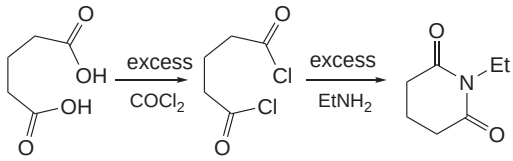

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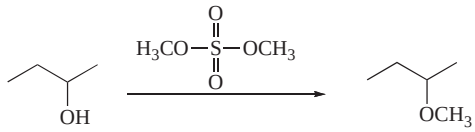

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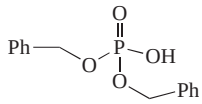

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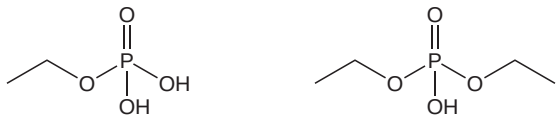

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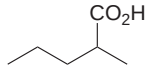
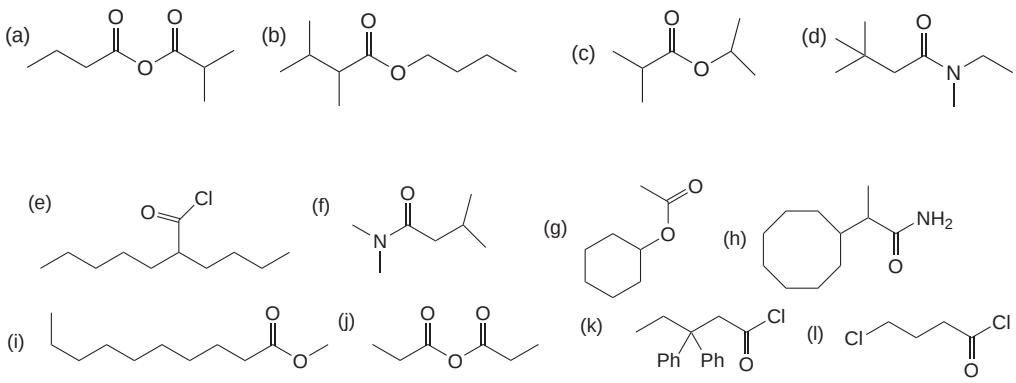
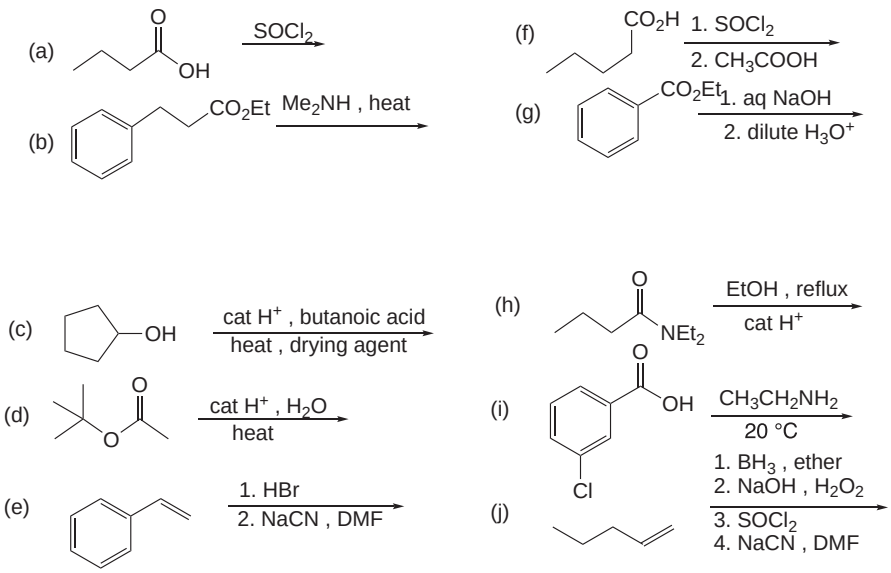


HOMEWORK

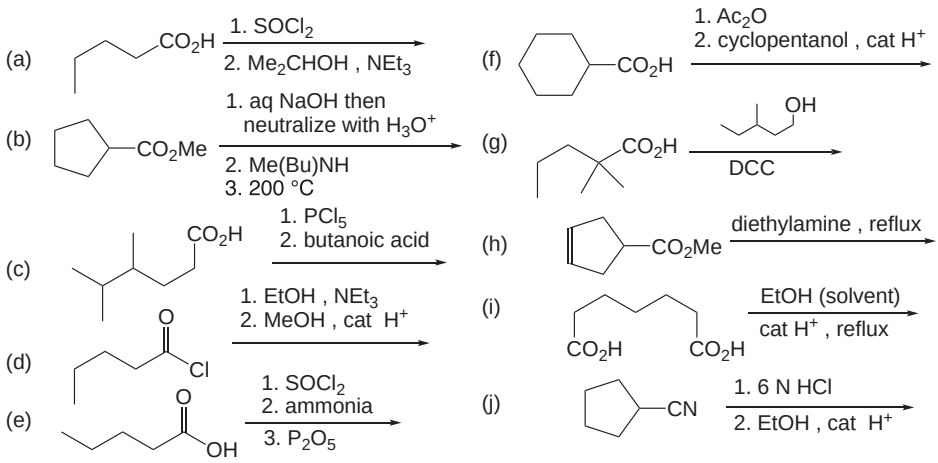
39. Give the correct IUPAC name for each of the following:



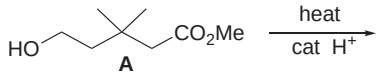
40. Draw the structure for each of the following:
    (a) *N,N*-Diphenylhexanamide (b) Cyclobutyl 3,3-dimethylhexanoate
    (c) Dipentanoic anhydride (d) Hexadec-(5*Z*)-enoyl chloride
    (e) Ethyl oct-4-ynoate (f) *N*-Chlorobutanamide
    (g) Butyl butanoate
    (h) *N*-Cyclopropyl-4,4-diphenyldodecanamide
    (i) 4-Phenyl-3-cyclohexenyl pentanoate
41. Draw the structure for each of the following:
    (a) 2,2-Diethylcyclobutane-1-carboxylic acid (b) 16-Phenylhexadecanoic acid
    (c) 1-Butyl-1,4-butanedioic acid
    (d) 4-Bromo-3-cyclopropyl-2-hydroxyhexanoic acid
    (e) 3,3-Diethyloctanenitrile.
42. In the Bayer-Villiger reaction of nonan-4-one to butyl pentanoate with trifluoroperoxyacetic acid, a large excess of sodium acetate is sometimes added as a buffer. Explain why this is necessary.
43. Draw the product formed when 2-bromopent-1-ene is treated with (a) Mg , THF (b) 3-phenylbutanoyl chloride at -78 °C.
44. Give the major product for each of the following:



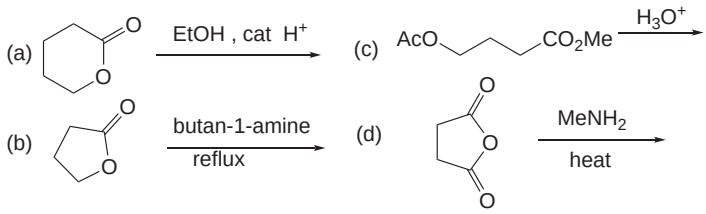
45. After hexanoic acid was converted to ethyl ethanoate, in ethanol solvent, the ethanol was removed, and the product was washed with aqueous sodium bicarbonate. What is the purpose of this last step?
46. If an ester is treated with an amine, the product is an amide. If an amide is heated at reflux with ethanol, no ester is obtained. Why not?
47. Give the major product for each of the following reactions.



48. A new molecule is produced when **A** is heated in the presence of an acid-catalyst. Give the structure of that product and propose a mechanism for its formation.



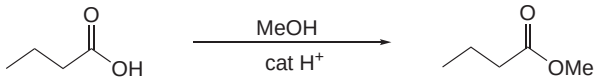
49. Give the major product for each of the following reactions:



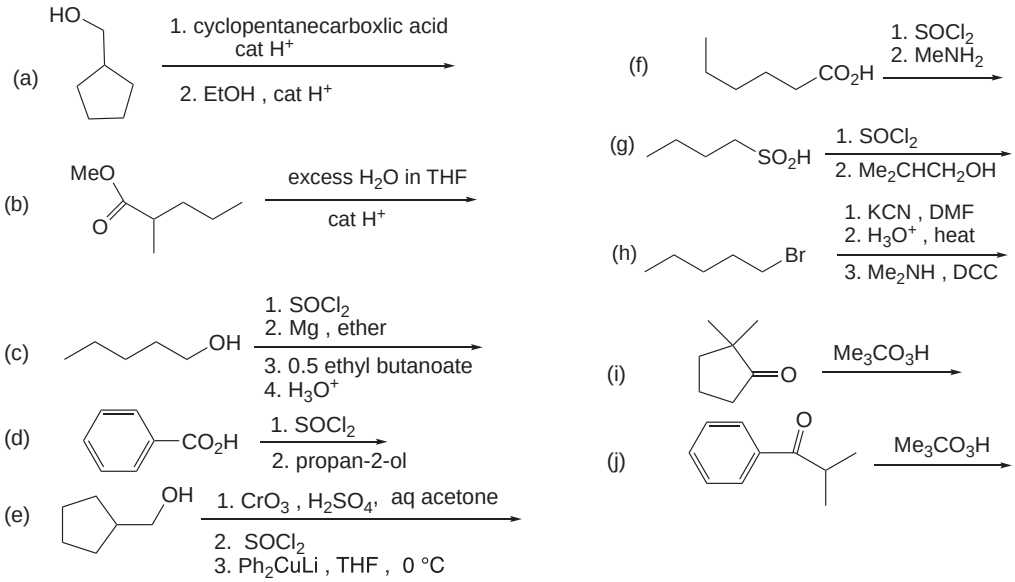
50. The C—N bond length for a typical amine is 1.47 Å, (147 pm) but for a typical amide it is 1.32 Å (132pm). Suggest a reason for this difference.
51. Draw the final product, if any, of the following reactions:
    (a) 1-Bromobutane + 1. Mg/ether 2. ethyl butanoate (0.5 equivalents)/ether 3. hydrolysis.
    (b) Pentanoic acid + 1. oxalyl chloride 2. Li enolate of acetophenone/THF 3. hydrolysis.
    (c) 3,3-Diphenylpentanoic acid + 1. $SOCl_2$ 2. EtOH 3. excess MeLi/ether 4. hydrolysis.
    (d) 1-Butyne + 1. MeLi/THF 2. propylpentanoate 3. hydrolysis.
    (e) *n*-Butyllithium + 1. 0.5 CuI 2. 0.5 butanoyl chloride
    (f) Butanoic anhydride + 1. excess phenylmagnesium bromide 2. hydrolysis
52. Draw the final product, if any, of each of the following reactions:
    (a) 2-Bromopentane + 1. Mg/ether 2. CO_2 3. hydrolysis
    (b) 2-Bromopentane + 1. Mg/ether 2. butanenitrile 3. H_3O^+.
    (c) 2-Bromopentane + 1. Mg/ether 2. 1-butyne 3. mild hydrolysis.
    (d) *n*-butyllithium + 1. cyclopentanecarboxylic acid 2. hydrolysis.

(e) Butylmagnesium chloride + 1. cyclopentanecarboxylic acid 2. hydrolysis.
(f) Phenyllithium + 1. CO_2 2. hydrolysis 3. PCl_5 4. diethylamine
(g) Pentanenitrile + 1. ethylmagnesium bromide 2. H_3O^+ 3. CH_3MgBr 4. hydrolysis
(h) Pentanenitrile + 1. 6 N HCl/reflux 2. $SOCl_2$ 3. $(CH_3)_2CuLi$ 4. *n*-butyllithium 5. hydrolysis
(i) Ethyl butanoate + 1. acid hydrolysis 2. 2 equivalents of propyllithium 3. hydrolysis
(j) Cyclopentylmagnesium bromide + 1. CO_2 2. hydrolysis 3. DCC/EtOH 4. Li enolate of acetone
(k) Hexan-1-ol + 1. Jones regent, heat 2. $SOCl_2$ 3. NH_3 4. P_2O_5.

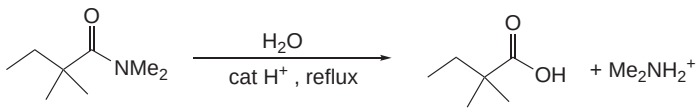
53. Give the complete mechanism for the following transformation:



54. Give the major product for each of the following:



55. Give the complete mechanism for the following transformation:



56. Draw the products that result from the reaction of methanesulfonyl chloride with
(a) Ethanol (b) Diethylamine (c) Cyclohexanol (d) Aqueous acid

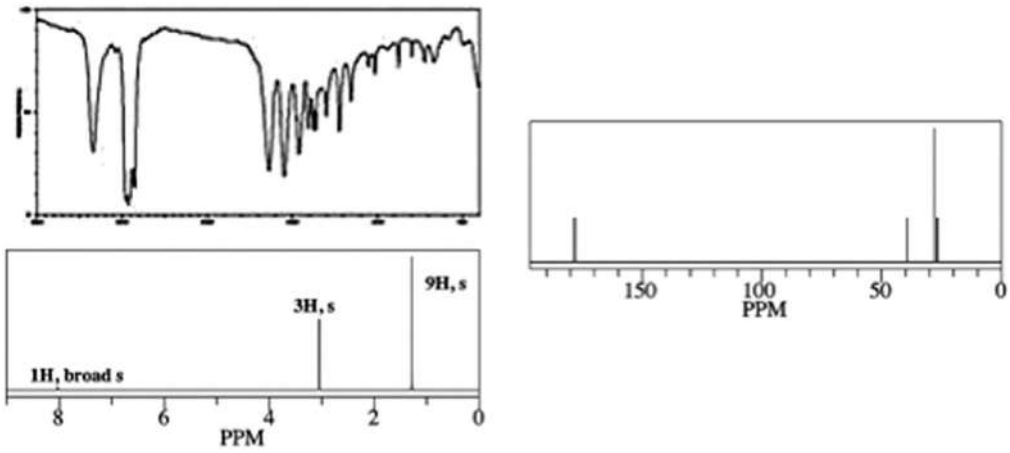
Spectroscopy Problems. Do not attempt until you have read and understood Chapter 13.

Spectroscopy of Acid Derivatives

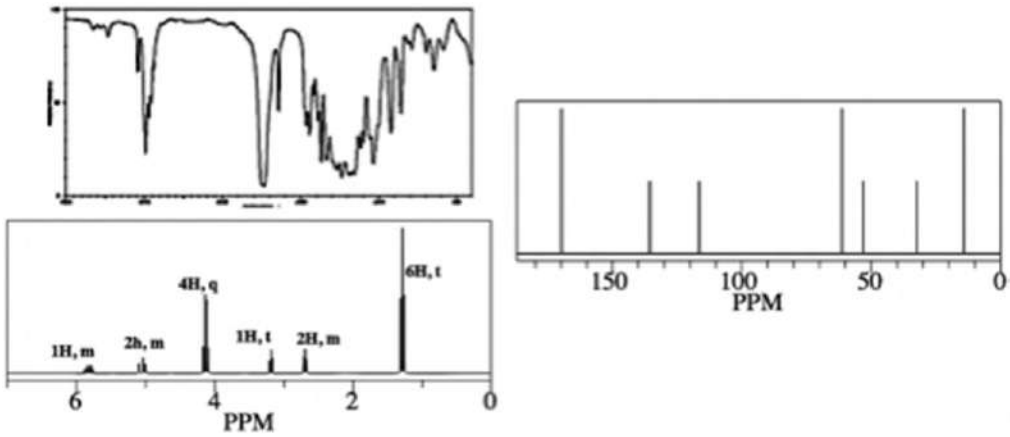
57. Given the following spectral data, give a structure:
IR: 3300-2920, 1708, 1483, and 1201 cm^{-1}. ^1H NMR: 11.0 (1H, broad s) and 1.23 (9H, s) ppm ^{13}C NMR: 179.0, 40.9 and 27.1 ppm.

58. For a formula of $C_8H_{14}O_3$, and given the following spectral data, provide a structure:
IR: 2980–2861, 1813, 1747, 1471, 1389, 1169–965 cm^{-1}. ^1H NMR: 2.66 (m, 2H), 1.24 (d, 12H) ppm.

59. You have two bottles containing a liquid and you know one is hexanoic acid and the other is ethyl butanoate but the labels have fallen off. The power is out so you have no access to IR or ^{1}H NMR instruments. Devise an unambiguous chemical test that will allow each unknown to be identified.
60. Give the structure: M=115, 100%. M+1=116, 7.04%. M+2=117, 0.42%.



61. When butanenitrile reacts with methyllithium, a ketone is formed after hydrolysis of the iminium salt product. What would you look for in the IR spectrum to confirm that the nitrile has reacted completely? What would you look for in the IR to confirm that a ketone has been formed?
62. For a molecule with the formula $C_{10}H_{16}O_4$, determine the structure given the following spectral data:



63. For a molecule with the formula C_5H_9ClO, determine the structure given the following spectral data:
IR: 2966–2877, 1802, 1469, 1403, 1134, 1010, 986 $cm^{-1.}$
^{1}H NMR: 2.76 (d, 2H), 2.22 (m, 1H), 1.0 (d, 6H) ppm.

The video clips for this chapter are available at:
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The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

19

Aromatic Compounds and Benzene Derivatives

Benzene was identified as a special type of hydrocarbon in Section 5.9. Benzene and derivatives are aromatic hydrocarbons with one ring or several rings fused together. The aromatic character of benzene and derivatives have special stability, which imparts a unique chemical profile.

To begin this chapter, you should know the following points:

- Resonance and resonance-stability (Sections 2.6 and 6.3.1).
- Nomenclature and structure of alkenes, alkyl halides, alcohols, amines, aldehydes, and ketones (Sections 5.1, 5.2 5.85, and 5.6).
- Carboxylic acids and carboxylic acid derivatives (Chapter 18).
- The structure and nature of π-bonds (Section 5.1).
- Reactivity of alkenes (Sections 10.1–10.6).
- E2 elimination reactions of alkyl halides (Sections 12.1–12.3).
- E1 elimination reactions (Section 12.4).
- The CIP rules (Section 9.2).
- Electron-releasing and withdrawing substituents (Sections 3.8, 6.3.2).
- Brønsted-Lowry acid-base reactions of alkenes (Sections 10.5–10.7).
- Carbocation stability (Sections 7.2.1, 10.1 and 10.3).
- Leaving groups (Sections 11.1–11.3 and 18.4).
- Lewis acids and Lewis bases (Sections 2.7 and 6.8).
- Rate of reaction (Section 7.11).
- Reduction of functional groups (Sections 17.2–17.5).

19.1 BENZENE AND AROMATICITY

Structure of Benzene

Benzene is a liquid first isolated from an oily condensate deposited from compressed illuminating gas by Michael Faraday (England; 1791–1867) in 1825. Benzene is a hydrocarbon and the parent of a large class of compounds known as aromatic hydrocarbons. In 1834, Eilhard Mitscherlich (Germany; 1794–1863) established the formula to be C_6H_6 and named the material benzin. Justus Liebig (Germany; 1803–1873) changed the name to benzol. In 1837, August Laurent (France; 1807–1853) proposed the name pheno (*Greek*; I bear light) since it was isolated from illuminating gas. The name was not adopted, but has given rise to the term *phenyl* for a benzene ring used as a substituent C_6H_5 (Section 5.9).

The structure of benzene was introduced in Section 5.9 and is shown again in Figure 19.1. If the C—C and C=C bonds were localized, as in cyclohexatriene, the bond length should alternate long-short around the ring. This arrangement is not observed, and all six carbon-carbon bonds have a measured bond distance of 1.397 Å (139.7 pm). The bond length of benzene therefore lies in between that for a C—C bond (1.536 Å, 153.6 pm) and a C=C bond (1.34 Å, 134 pm). This molecule is benzene not cyclohexatriene. The p-orbitals in benzene are contiguous (one p-orbital on every carbon of the ring) and all are parallel. The bonding in benzene is consistent with delocalization and resonance-stabilization.

Each carbon in benzene is sp^2 hybridized so each has a trigonal planar geometry, and the molecule is planar. This is clearly seen in the ball-and-stick model. Each carbon atom has a

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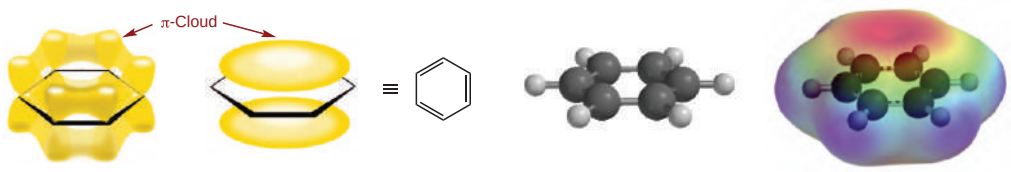
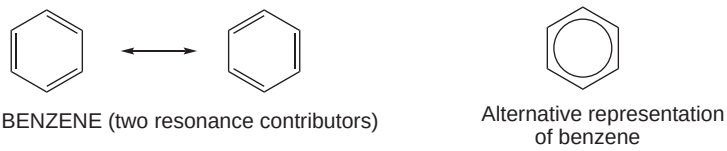


FIGURE 19.1 Structure and delocalization of electron density in benzene.

p-orbital that is perpendicular to the plane of the carbon and hydrogen atoms. There is one π-electron associated with each of six p-orbitals so there are six π-electrons. The p-orbitals are contiguous (one p-orbital on every carbon of the ring) and all are parallel. There is delocalization of the π-cloud of electrons above and below the plane of the atoms due to resonance. The electron density map in Figure 19.1 shows a red area in the center of the ring to indicate high electron density, consistent with the π-cloud.

The delocalized bonding in benzene is not properly described by a structure that shows localized single and double bonds. Two structures are needed to properly represent benzene, with a double-headed arrow to show they are resonance contributors. *Together* they represent the resonance delocalization of the π-electrons in benzene. Each of the two resonance contributors is known as *a Kekulé structure*, named after August Kekulé (Germany; 1829–1896). Benzene is sometimes drawn as a single six-membered ring with a circle in it, but it is more common for one of the Kekulé structures to be used to represent benzene.



There is a story associated with Kekulé and his proposed structure for benzene. He is said to have had a dream about an *Ouroboros*, which is a mythical serpent that devours itself as it simultaneously regenerates. The Ouroboros or a related mythical creature probably originated in ancient Egypt, but it is also associated with alchemy. Whether or not Kekulé used this dream as an inspiration for the cyclic structure of benzene is debated to this day (Figure 19.2).

Structurally, benzene is resonance-stabilized with six π-electrons are confined to a ring so every carbon atom in that ring is sp^2 hybridized with no intervening sp^3 atom, and six contiguous and continuous p-orbitals. Compounds with these properties are said to be *aromatic* and aromaticity gives special stability to benzene and other aromatic compounds. An important rule has been developed to predict aromaticity called *Hückel's rule,* named after Erich Armand Arthur Hückel (Germany; 1896–1980). As the value on *n* changes in the series 0, 1, 2, 3, 4, and so on, a new series of numbers is generated. Hückel's rule states that for a hydrocarbon to be aromatic the number of π-electrons must be equal to one of the numbers in the $4n+2$ series. For $n = 0, 1, 2, 3, 4, 5, 6, \ldots$ the $4n+2$ series = 2, 6, 10, 14, 18, 22, 26, … Benzene has six π-electrons confined to a planar ring, which is in the $4n+2$ series. It is resonance stabilized, aromatic, particularly stable and therefore less reactive than alkenes or alkynes in chemical reactions.

Hückel's rule

Hückel's rule states that for planar, monocyclic hydrocarbons containing completely conjugated sp^2 hybridized atoms, the presence of $(4n+2)$ π-electrons leads to aromaticity (*n* is an integer in the series 0, 1, 2, 3, etc.).

The special stability of benzene is easily shown by simple chemical reactions. The π-bond of an alkene or a diene reacts as a Brønsted-Lowry base with an acid HX (HCl, HBr, HI, etc.) as discussed in Section 10.2. Since benzene is aromatic and more stable it is a *poor* electron donor (a weaker base). A comparison of the relative reactivity of HBr with cyclohexene, cyclohexadiene or benzene is shown in Figure 19.3. The reaction with cyclohexene

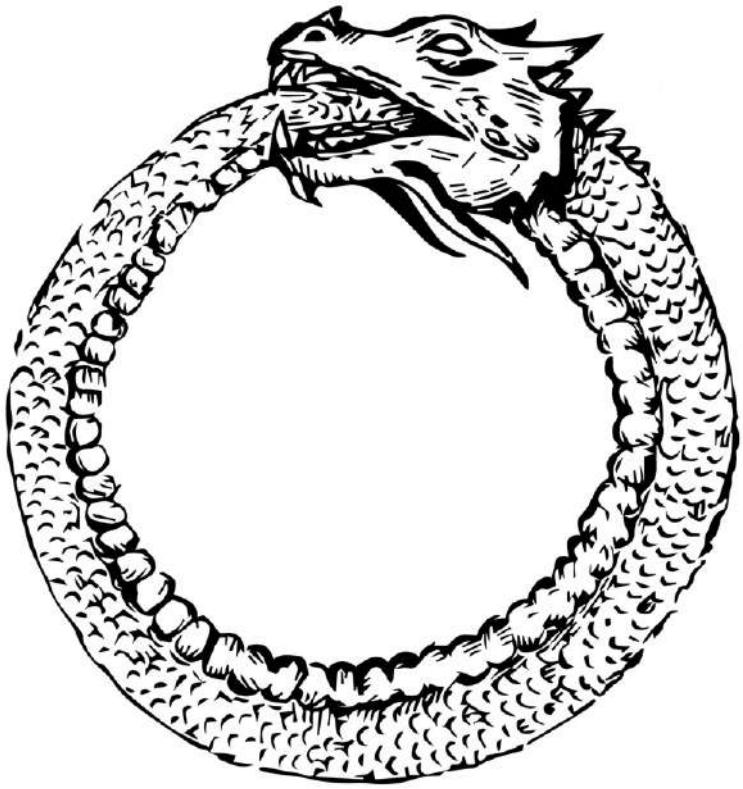


FIGURE 19.2 Ouroboros. A mythical creature probably originated in ancient Egypt, but it is also associated with alchemy. Royalty-free stock vector ID: 1093389248.

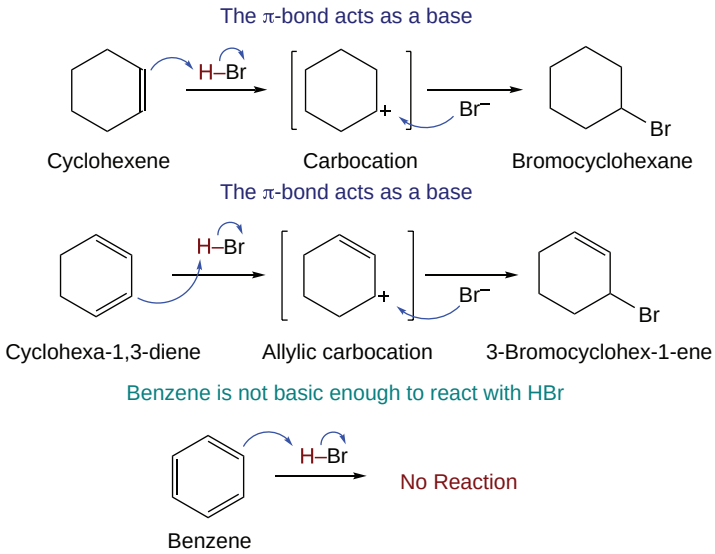


FIGURE 19.3 Comparative reactivity of HBr with cyclohexene, cyclohexadiene and benzene.

and with cyclohexadiene is rapid to give a carbocation, which leads to bromocyclohexane or 3-bromocyclohex-1-ene, respectively. Benzene does *not* react with HBr, even with heating, so it is clearly a weaker base. The observation that benzene does not react is a good indication that the six π-electrons are held tightly by the molecule due to aromaticity and are unavailable for donation.

19.1 Why is cyclohexadiene is much more reactive than cyclohexene in reaction with HBr?

19.2 SUBSTITUTED BENZENE DERIVATIVES

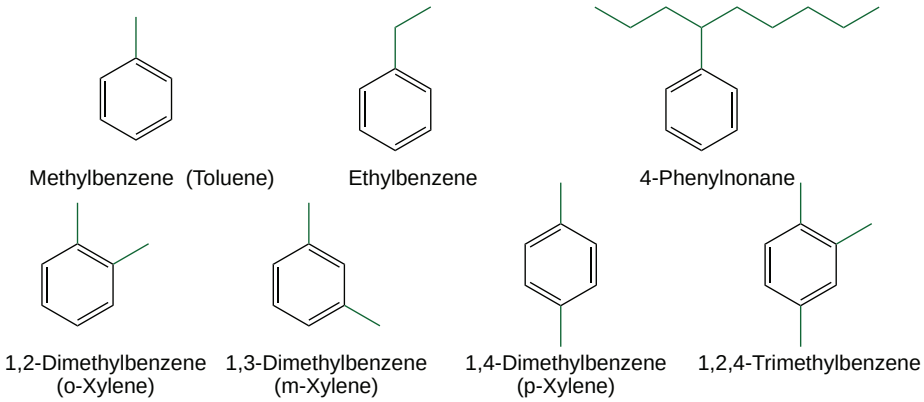
Nomenclature of Arenes

Benzene is the parent of a large class of compounds known as aromatic hydrocarbons. The structure and chemical reactivity of aromatic hydrocarbons are unique. Therefore, they are given a unique set of names in the IUPAC system.

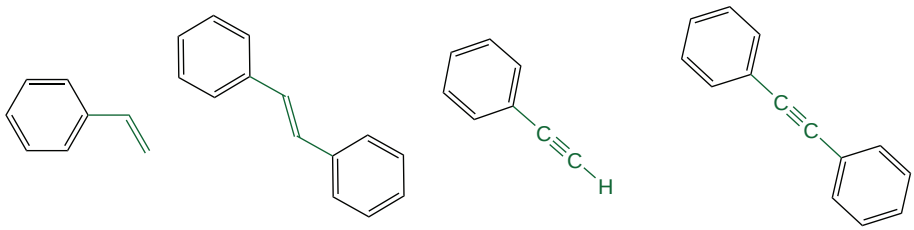
19.2.1 ALKYL SUBSTITUENTS (ARENES)

In benzene derivatives one or more hydrogen atoms have been replaced with alkyl groups, heteroatom substituents, or functional groups. When a hydrogen atom on the benzene ring is replaced with an alkyl group (methyl, ethyl, etc.), the resulting molecule is an alkyl benzene, but these compounds are known as an *arene*. For an arene with a carbon chain of six carbons or less, the molecule is named as an alkylbenzene (methylbenzene, ethylbenzene butylbenzene, etc.). Methylbenzene is a common paint solvent, and it has the common name *toluene*. If a benzene ring is attached to an alkane carbon chain of more than six carbon atoms, the benzene ring is treated as a substituent with the name *phenyl*. An example is 4-phenylnonane.

Dimethylbenzene is an arene with two substituents on the ring and has the common name *xylene*. There are three isomeric derivatives, 1,2-dimethylbenzene, 1,3-dimethylbenzene, and 1,4-dimethylbenzene. An arcane common name system is used for benzene derivatives with two substituents. Two substituents with a 1,2-relationship are said to be *ortho*. Those with a 1,3-relationship are said to be *meta*. Those with a 1,4-relationship are said to be *para*. Therefore, 1,2-dimethylbenzene is *ortho*-xylene (*o*-xylene), 1,3-dimethylbenzene is *meta*-xylene (*m*-xylene), and 1,4-dimethylbenzene is *para* xylene (*p*-xylene). Note that the terms ortho-, meta-, and para- can be used in a comparative sense. A methyl and an ethyl in a molecule may have an ortho relationship to each other or to another group, for example. The IUPAC names should not be mixed with these common names. The xylenes are constituents of gasoline and airplane fuel, commercial inks, rubber, adhesives as well as paint thinners and varnishes. Many arenes have three or more substituents. There are several trimethylbenzenes, including 1,2,4-trimethylbenzene where the ring is numbered to yield the lowest combination of numbers (1,2,4 rather than 1,2,5, or 1,3,6).



19.2 Draw the structure of *o*-diethylbenzene and of *m*-diisopropylbenzene.
19.3 Draw the structures of (a) 2,3-dimethylethylbenzene, (b) 3,4,5-triethylisopropylbenzene, and (c) 3-ethyl-4-methyl-(1,1-dimethylethyl)benzene.

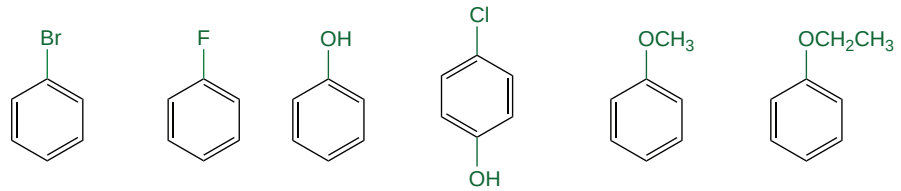


Ethenylbenzene (Styrene) | (E)-1,2-Diphenylethene (trans-Stilbene) | Ethynylbenzene (Phenylacetylene) | 1,2-Diphenylethyne (Tolane)

Alkene and alkyne groups may be attached to a benzene ring. The name identifies the functional group followed by the term "benzene." Examples are ethenylbenzene or ethynylbenzene. Ethenylbenzene has a common of *styrene* and 1,2-diphenylethene is *stilbene*, which has *cis*- and *trans*-isomers. The hydrocarbon shown with two benzene rings attached to an alkyne unit is simply known as 1,2-diphenylethyne or diphenylacetylene, although it has the common name of *tolane*. Styrene is a commercially used monomer to make the polymer poly(styrene), which is in rubber, plastics, insulation materials, fiberglass, automobile parts, and food containers (Section 10.11).

19.2.2 FUNCTIONAL GROUPS ON THE BENZENE RING

Nomenclature of Functionalized Benzene Derivatives

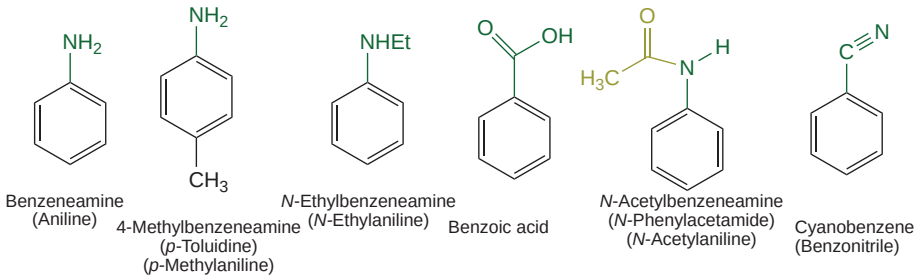


Bromobenzene | Fluorobenzene | Benzeneol (Phenol) | 4-Chlorobenzeneol (4-Chlorophenol) | Methoxybenzene (Anisole) | Ethoxybenzene (Phenetole)

Many different heteroatoms or functional groups may be attached to a benzene ring, each with a unique name for that family of compounds. The molecule with an OH unit on a benzene ring is named *benzenol* using the IUPAC system but the common name is *phenol*. In the past, phenol was called *carbolic acid* and in the late 19th century it may have been the first surgical antiseptic. Benzene derivatives that have a single OH group are named as substituted *benzenols* but they are commonly named as substituted phenols. For ether derivatives the OR unit is treated as an alkoxy substituent (methoxybenzene, ethoxybenzene, etc.). The common name for methoxybenzene is *anisole* and ethoxybenzene is *phenetole*.

19.4 Give the structures for 3,5-dimethylbenzenol, 2-nitrobenzenol, and 3,4,5-trichlorobenzenol.
19.5 Draw the structure of 2,6-diiodophenol, 1,2-dimethoxybenzene, and *p*-iodoanisole.

When an amine group is on the benzene ring (e.g., -NH_2), the nomenclature is similar to that used for amines in Section 5.5.3. The molecule with a single NH_2 unit is named *benzeneamine* but the common name is *aniline*. A substituent on the benzene ring is indicated by a number relative to the amine group, but a substituent on the nitrogen is indicated by *N*-, as in *N*-ethylbenzeneamine ($PhNHCH_2CH_3$). Benzoic acid is the parent structure of acid derivatives that have a benzene ring such as esters (*benzoates*), acid chlorides (*benzoyl chlorides*), and amides (*benzamides*). The amide of benzoic acid is *N*-acetylbenzeneamine, but this compound has other names: *N*-acetylaniline or *N*-phenylacetamide. The common name is *acetanilide*. The nitrile derivatives is *cyanobenzene*, but the common name is *benzonitrile*.



Benzeneamine (Aniline)

4-Methylbenzeneamine (*p*-Toluidine) (*p*-Methylaniline)

N-Ethylbenzeneamine (*N*-Ethylaniline)

Benzoic acid

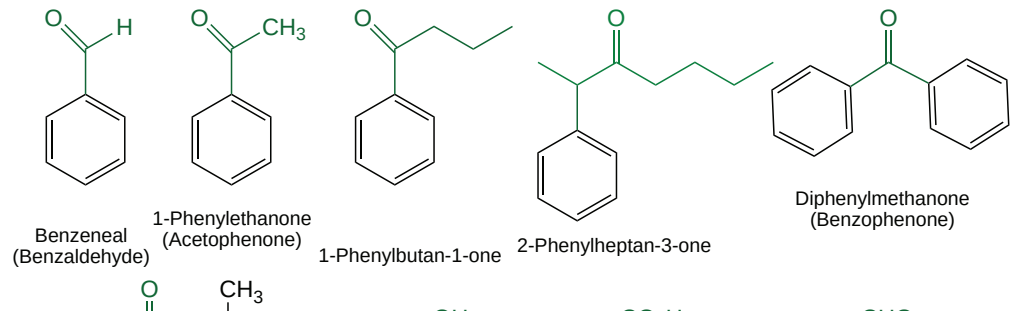
N-Acetylbenzeneamine (*N*-Phenylacetamide) (*N*-Acetylaniline)

Cyanobenzene (Benzonitrile)

19.6 Draw the structure of 3,5-dichloroaniline, *N*-ethyl-*N*-methylaniline, and 4-methyl-*N*-propanoylaniline.

19.7 Draw the structure of (a) 3-bromobenzoic acid, (b) benzyl 4-ethylbenzoate, (c) *N*,3,5-trimethylbenzamide, and (d) 2,6-dichlorobenzonitrile.

An aldehyde or a ketone unit may be attached to a benzene ring. The compound with CHO directly attached to the benzene ring is named *benzenal* with the common name *benzaldehyde*. In a ketone, the benzene ring is a substituent when attached to the carbonyl carbon is C1. An example is 1-phenylethanone, which has the common name *acetophenone*. When the benzene ring is attached to another carbon in the longest chain, it is a substituent identified as phenyl. When two phenyl rings are attached to a carbonyl the name is diphenylmethanone, but the common name is *benzophenone*. When both benzene rings of benzophenone are substituted, the name becomes a bit more complicated. An example is (4-bromo-2-methylphenyl)(2,3-dimethylphenyl)methanone, using the IUPAC nomenclature. An older and more simple method for nomenclature is based on the benzophenone nomenclature. It identifies the substituent in one ring by numbering 1,2,3, and so on,. Substituents in the other ring are numbered with a "prime," (1', 2', 3', etc.). Using this system, (4-bromo-2-methylphenyl)(2,3-dimethylphenyl)methanone is 4'-bromo-2,2',3-trimethylbenzophenone.



Benzeneal (Benzaldehyde)

1-Phenylethanone (Acetophenone)

1-Phenylbutan-1-one

2-Phenylheptan-3-one

Diphenylmethanone (Benzophenone)

(4-Bromo-2-methylphenyl)(2,3-dimethylphenyl)methanone

1,2-Benzenediol (Catechol)

1,2-Benzenedioic acid (Phthalic acid)

1,2-Benzenedial (Phthalaldehyde)

More than one functional group may be attached to a benzene ring. When a benzene ring contains two hydroxyl groups the ortho dihydroxy derivative is named *1,2-benzenediol*, but its common name is *catechol*. The meta compound is *1,3-benzenediol (resorcinol)* and the para compound is *1,4-benzenediol (hydroquinone*). There are also three compounds that have two carboxyl groups, the dicarboxylic acids. *1,2-Benzenedioc acid (phthalic acid)* is shown, and it has two carboxyl groups with an ortho relationship. In *1,3-benzenedioc acid (isophthalic acid)*, the carboxyl groups are meta, and in *1,4-benzenedioc acid (terephthalic acid)* the carboxyl groups have a para relationship The dialdehyde compounds are

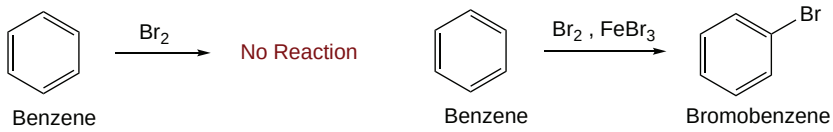
1,2-benzenedial (*phthaladehyde*; also phthalic dicarbaldehyde), *1,3-benzenedial (isophthaldehyde;* also isophthalic dicarbaldehyde), and *1,4-benzenedial (terephthalaldehyde*; also terephthalic dicarbaldehyde).

19.8 Draw the structure of (a) 5-ethyl-1,3-benzenediol, (b) 4,5-dichlorophthalic acid, and (c) 2-ethyl-3-methylterephthaldehyde.

19.3 ELECTROPHILIC AROMATIC SUBSTITUTION

Electrophilic Aromatic Substitution

As shown in Figure 19.3, benzene does not react with HCl or HBr. Likewise, benzene does *not* react with bromine. However, if benzene and bromine are mixed together in the presence of ferric bromide ($FeBr_3$), bromobenzene is formed in good yield, along with HBr. Benzene does not react with ferric bromide without bromine being present, so there must be a reaction between bromine and the Lewis acid. Indeed, diatomic bromine reacts with ferric bromide to give an "ate" complex, $Br^+ FeBr_4^-$.



Halogenation, Nitration and Sulfonation

Although benzene is a weak electron donor with HBr or Br_2, it is good enough electron donor to react with the cation Br^+ in the "ate" complex $Br^+FeBr_4^-$. In the conversion of benzene to bromobenzene a bromine atom has replaced one H on the benzene ring, so this reaction is a *substitution (S).* Experiments have shown that the reaction proceeds by a *cation intermediate*, so it is an *electrophilic (E)* reaction. It clearly involves an *aromatic* species such as benzene, so it is given the symbol *Ar* for aryl. This type of reaction is an *electrophilic aromatic substitution,* and it is labeled S_EAr. Many Lewis acids other than ferric bromide can be used in S_EAr reactions, including aluminum bromide ($AlBr_3$), aluminum chloride ($AlCl_3$), boron trifluoride (BF_3), or ferric oxide (Fe_2O_3).

19.3.1 AROMATIC SUBSTITUTION: HALOGENATION, NITRATION, AND SULFONATION

The reaction of benzene and bromine in the presence of aluminum chloride affords bromobenzene is *a S_EAr reaction*. As shown in Figure 19.4 benzene donates two electrons to the Br^+ of the "ate" complex to form a new C—Br bond. Formation of this bond disrupts the aromatic

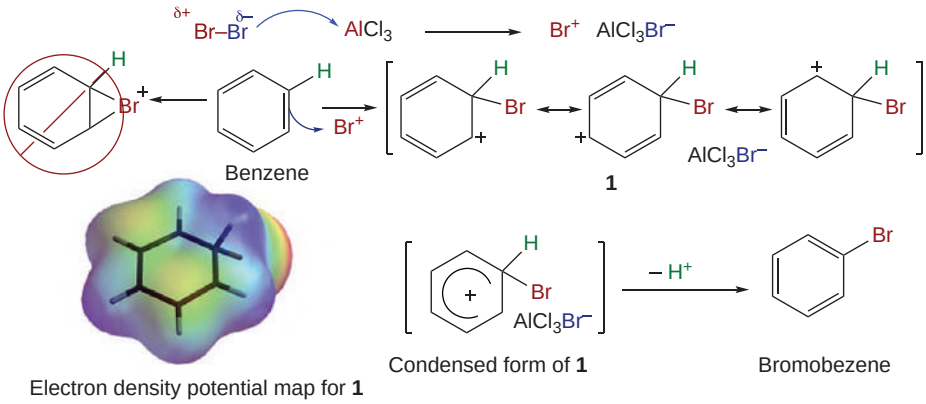


FIGURE 19.4 Mechanism of electrophilic aromatic substitution with benzene and bromine.

system of benzene to form the resonance-stabilized carbocation intermediate **1**. This intermediate has been called a *Wheland intermediate*, named after George Willard Wheland (USA; 1907–1976). Such intermediates have also been called *Meisenheimer adducts* named after Jakob Meisenheimer (German; 1876–1934), and even σ-adducts. The modern term, which will be used exclusively in this book, is an *arenium ion*. It is important to state that the arenium ion is resonance-stabilized, but it is *not* aromatic. There are three resonance contributors for **1** and the positive charge is delocalized on C2, C4 and C6 relative to the bromine-bearing carbon. The electron density potential map of **1** shows blue areas over carbons C2, C4, and C6 relative to the sp^3 hybridized C1 that bears the halogen. The *blue* color indicates less electron density that correlates with the positive charges in the arenium ion. Once arenium ion **1** is formed, a proton is lost from the carbon bearing the bromine to generate a new C=C unit. Loss of this proton regenerates the aromatic benzene ring to yield bromobenzene. The energetic driving force for losing this proton is regeneration of the aromatic ring. Conversion of an arenium ion to a benzene derivative is formally an E1 reaction, an acid-base reaction.

Electrophilic aromatic substitution is not limited to bromination. If it is possible to form a cationic species X^+ in the presence of benzene, a S_EAr reaction can occur. The reaction of chlorine and benzene, in the presence of $AlCl_3$, generates Cl^+ and subsequent reaction with benzene yields chlorobenzene. Both Br^+ and Cl^+ are obviously electrophilic, but nitrogen,

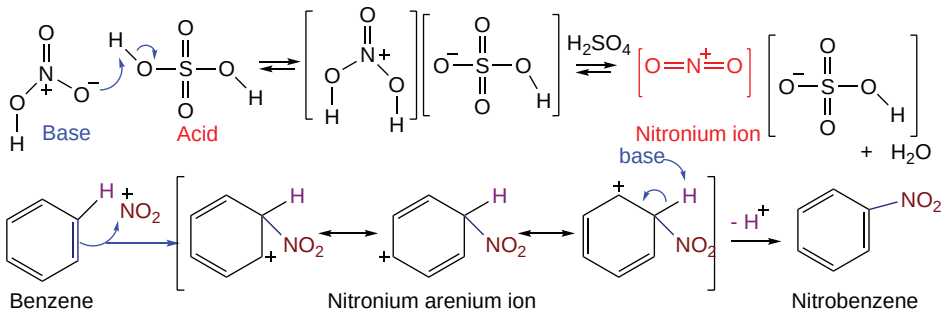
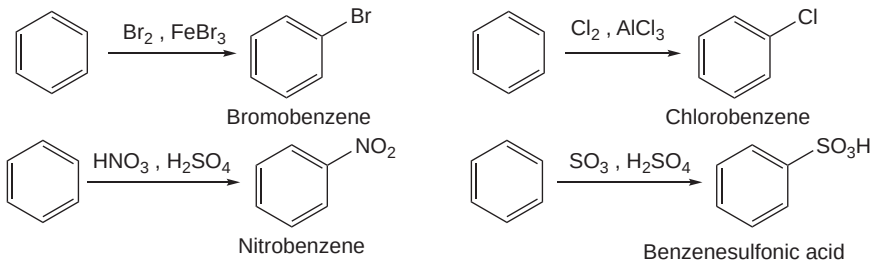


FIGURE 19.5 Formation of the nitronium ion and nitration of benzene.

sulfur, and carbon electrophiles are known in this reaction. A nitrogen electrophile is the nitronium ion, $X = NO_2^+$, formed when nitric acid is mixed with sulfuric acid. In this reaction the nitric acid functions as a base as shown in Figure 19.5. This acid-base reaction generates the nitronium ion (NO_2^+) with a hydrogen sulfate counterion. Loss of water from the protonated nitric acid yields the nitronium ion. Once the nitronium ion is generated, benzene reacts to yield an arenium ion and an E1 reaction followed by loss of a proton gives nitrobenzene.

19.9 Draw the product formed when Cl_2 reacts with $AlCl_3$. Draw the complete reaction between benzene, diatomic chlorine and aluminum chloride, showing the arenium ion intermediate and the structure of the product.



Both sulfuric acid and sulfur trioxide (SO_3) are sulfur electrophiles in the S_EAr reaction. The sulfonation of benzene by reaction with concentrated sulfuric acid involves the reaction

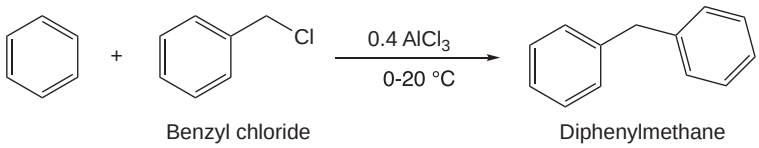
of benzene with the electrophilic sulfur atom. Formation of a sulfonium arenium ion intermediate, is followed by loss of a molecule of water and loss of a proton via the E1 reaction to give benzenesulfonic acid. Fuming sulfuric acid is simply concentrated sulfuric acid saturated with sulfur trioxide (SO_3), and it reacts faster to yield benzenesulfonic acid with fewer problems. The SO_3 is more electrophilic than the sulfur atom in sulfuric acid so it reacts faster with benzene. The halogenation, nitration, and sulfonation reactions presented in this section are the fundamental S_EAr reactions most commonly associated with benzene.

19.10 Suggest a mechanism for the conversion of benzene to benzenesulfonic acid with SO_3.

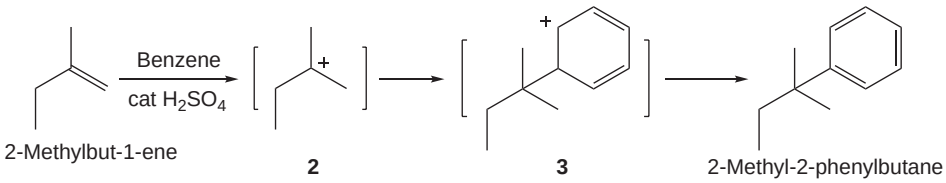
19.3.2 FRIEDEL–CRAFTS ALKYLATION

Friedel–Crafts Alkylation

Carbocations react with nucleophiles, as described for S_N1 reactions (Section 11.4.1). In S_EAr reaction benzene reacts as an electron donor with X^+ to give an arenium ion intermediate. The X^+ can be a carbocation, and formation of the arenium ion leads to an alkylbenzene. An example is the reaction of benzyl chloride with $AlCl_3$ to generate the benzyl carbocation as an "ate" complex, $PhCH_2^+AlCl_4^-$. Reaction with benzene gives the expected arenium ion and loss of a proton gives diphenylmethane in 59% yield.[1] This reaction is generically called the *Friedel–Crafts reaction*, named after the work of Charles Friedel (France; 1832–1899), and James M. Crafts (USA; 1839–1917).



Carbocations are produced by several different reactions. A carbocation generated by any reaction will react in the Friedel-Crats alkylation reaction. Alkenes give carbocation intermediates by reaction with an acid. 2-Methylbut-1-ene reacts with benzene in the presence of a sulfuric acid catalyst to give a tertiary carbocation **2**, for example. Subsequent reaction with benzene leads to resonance stabilized arenium ion **3**, and the S_EAr product 2-methyl-2-phenylbutane.

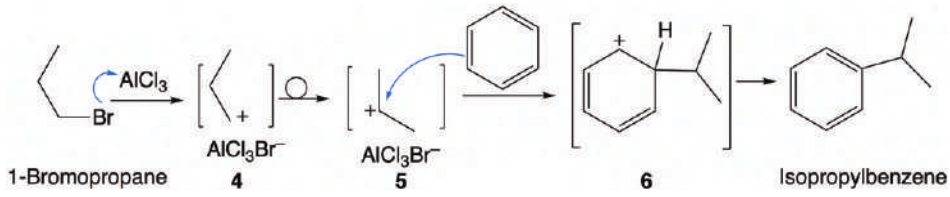


19.11 Draw all intermediates and the final product formed when 1-methylcyclopentene reacts with benzene in the presence of a sulfuric acid catalyst.

If a tertiary carbocation is the intermediate, the reaction is relatively straightforward. If a primary or secondary carbocation is formed, however, rearrangement to a more stable cation (Section 10.3) will occur *before* the reaction with benzene to give an arenium ion. When 1-bromopropane reacts with aluminum chloride ($AlCl_3$) in the presence of benzene, the initial reaction gives primary carbocation (**4**). However, the isolated product is isopropylbenzene, *not n*-propylbenzene. A facile 1,2-hydride shift of the initially formed **4** gives the more stable secondary cation **5**. Reaction with benzene gives arenium ion **6** and loss of a proton by

[1] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry*, Reinhold Pub., NY, 1961, p. 650.

the E1 reaction yields the final product. In all cases, rearrangement to a more stable carbocation occurs before the reaction with benzene.



19.12 Draw the product of a reaction of benzene with 3-chloro-3-ethylpentane and $AlCl_3$; of benzene with 1-bromo-2-methylpropane and $AlBr_3$.

Friedel–Crafts Acylation

19.3.3 FRIEDEL–CRAFTS ACYLATION

Another type of Friedel–Crafts reaction involves reaction of benzene with an acid chloride. If benzene and butanoyl chloride are heated *without* the $AlCl_3$, there is no reaction. When benzene reacted with butanoyl chloride in the presence of $AlCl_3$, the isolated product was a ketone; butyrophenone (1-phenylbutan-1-one) in 51% yield.[2] This observation shows that there is a reaction between $AlCl_3$ and the acid chloride prior to reaction with benzene. The chlorine atom in butanoyl chloride reacts with the aluminum atom of $AlCl_3$ to form a new type of carbocation known as an *acylium ion* **7** as shown in Figure 19.6. An acylium ion is a positively charged, resonance-stabilized cation with two resonance contributors. An acylium ion is sufficiently stable that it *does not rearrange*, but it readily reacts with benzene. Indeed, benzene reacts with acylium ion **7** via a S_EAr reaction to give arenium ion **8**. Loss of a proton from **8** gives the ketone product, 1-phenylbutan-1-one. This reaction is called *Friedel–Crafts acylation.*

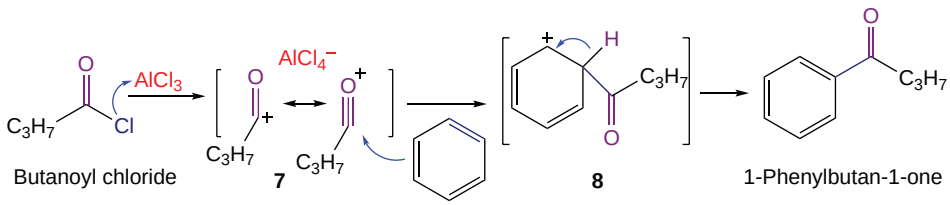


FIGURE 19.6 Friedel–Crafts acylation of benzene with butanoyl chloride.

19.13 Draw the acylium ion formed by the reaction of aluminum chloride with acetyl chloride; with benzoyl chloride.

19.4 DISUBSTITUTED BENZENE DERIVATIVES

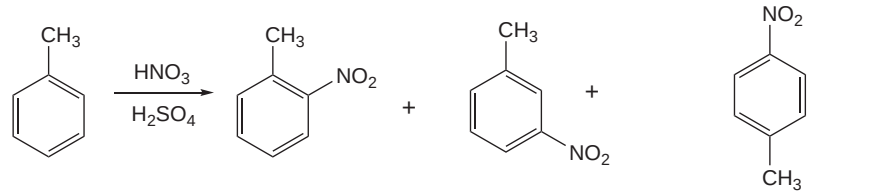
Formation of monosubstituted benzene derivatives is rather straightforward by the S_EAr mechanism. For the S_EAr reaction of a monosubstituted benzene derivative (e.g., toluene, anisole, or nitrobenzene) different isomers are possible, so there is a regioselectivity issue. The second group can be at C2, C3, or C4 relative to the substituent on the benzene ring.

[2] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994. Exp. 6.121, pp. 1008–1009.

19.4.1 REGIOSELECTIVITY

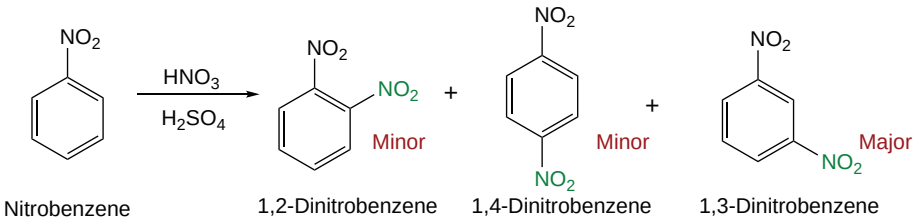
Regioselectivity

When a monosubstituted benzene derivative (e.g., toluene) is subjected to an S_EAr reaction, there are three possible isomeric products. When toluene reacted with HNO_3/H_2SO_4 2-nitrotoluene was isolated in 43% yield, 3-nitrotoluene in 4%, and 4-nitrotoluene in 53%.[3] In addition, the rate of reaction of toluene is about 25 times *faster* than the similar reaction with benzene. Clearly, the reaction is regioselective since 2- and 4-nitrotoluene are the major products to the near exclusion of 3-nitrotoluene. Remember that regioselectivity is any process that favors bond formation at one particular atom over other possible atoms. Each product arises from a unique arenium ion intermediate. The arenium ion intermediates leading to the ortho and para products are formed faster than the arenium ion intermediate for the meta product. Those intermediates must be more stable and have a lower activation energy.



This selectivity for *ortho-para* products does *not* extend to S_EAr reactions for all monosubstituted derivatives. The S_EAr reaction of nitrobenzene with a mixture of nitric and sulfuric acid gives 1,3-dinitrobenzene as the major product, with only trace amounts of 1,2- and 1,4-dinitrobenzene. Further, the rate of the nitration reaction for nitrobenzene is much slower than the rate of nitration for benzene. If the relative rate for the nitration of benzene is 1, the rate of nitration for nitrobenzene is about 6 $x10^{-8}$.

Predicting Regioselectivity



The differences in the S_EAr reactions just described is attributed to the nature of the substituent attached to the benzene ring. A generic benzene derivative in Figure 19.7 is used to explain the regioselectivity and reactivity of substituted benzene derivatives in S_EAr reactions. This analysis requires a reference point, which is the *ipso carbon (•).* The ipso carbon bears the substituent, X. Whether the X group is electron releasing or electron withdrawing, there are only three possible arenium ion intermediates for the substitution of a monosubstituted benzene derivative. Using the S_EAr reaction with Br^+ as an example, substitution must occur at the ortho, the para, or the meta carbon to form **9**, **10** or **11**.

In one resonance contributor for arenium ions **9** and **10**, the positive charge resides on the carbon attached to the X group (the ipso carbon). If X is an electron-releasing alkyl group (e.g., methyl), the positive charge is stabilized since opposite charges attract. There is no resonance contributor for **11** with the charge on the ipso carbon, so the *activation energy* to form **9** and **10** is lower than the activation energy to form **11**. Therefore, **9** and **10** will form faster than **11**. Arenium ions **9** and **10** have the same number of resonance contributors and

[3] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry* Reinhold Pub., NY, 1961, p. 635.

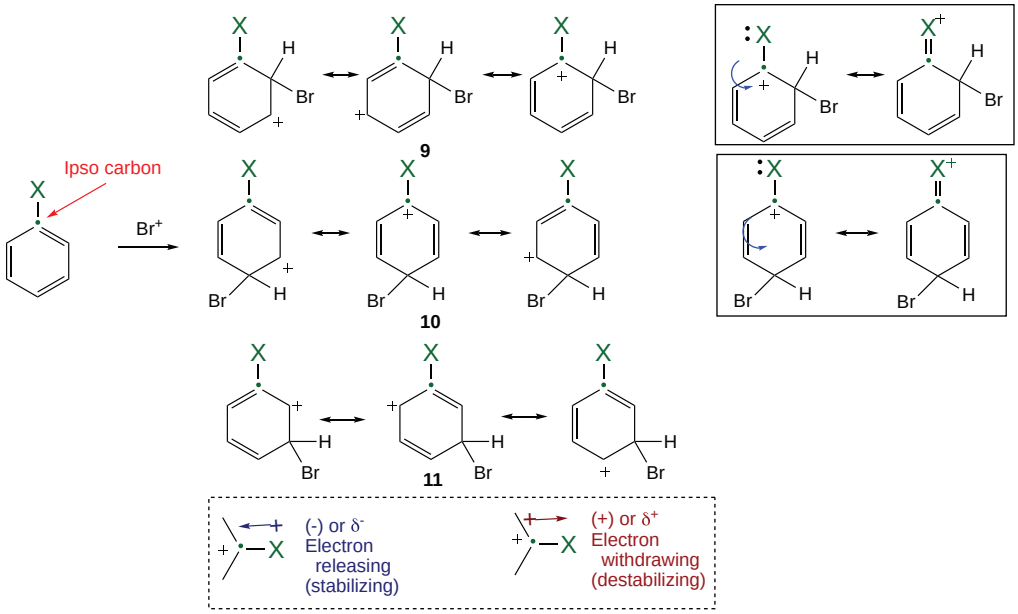


FIGURE 19.7 Arenium ion intermediates for electrophilic aromatic substitutions for ortho, meta, and para substitution.

should be about equal in energy. Therefore, the ortho and para products should be formed in roughly equal amounts in the absence of other mitigating factors.

Substituents with unshared electrons (O, N, halogen) on the ipso carbon are better electron-releasing groups than a methyl group. If the heteroatom has unshared electrons, as shown in the boxed structures in Figure 19.7, then a *fourth resonance contributor* is possible for arenium ions **9** and **10**. This extra delocalization provides greater stability and increases the preference for the ortho and para arenium ion over attack at the meta position. A benzene derivative with these heteroatom substituents will react faster than toluene.

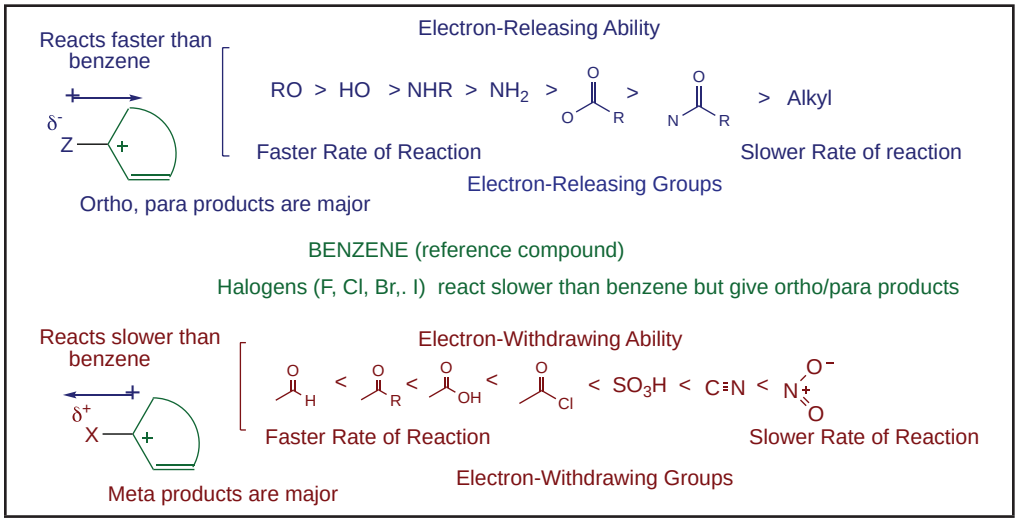
If the X group in Figure 19.7 is electron-withdrawing, then reaction at the ortho or para position places a positive charge on the ipso carbon of a resonance contributor in **9** or **10**. In **9** and **10** there is also a formal charge of +1 on the nitrogen of the nitro group, so X = nitro destabilizes the arenium ion. The repulsive interaction of two like charges will destabilize both **9** and **10**. If the arenium ion less stable, it is more difficult to form because it has a higher activation barrier. In other words, if arenium ions **9** and **10** have an electron-withdrawing group on the ipso carbon, formation of the ortho and para arenium ion is more difficult. Formation of **11** is less destabilized since meta attack does not generates a resonance contributor with a positive charge on the ipso carbon. Formation of **11** is therefore faster than formation of **9** or **10**.

Several groups are categorized as electron releasing or electron withdrawing in Table 19.1. All electron-releasing groups have a δ^- atom or a negative charge attached to the ipso carbon except for alkyl groups. However, alkyl group are electron releasing relative to C^+ of the arenium ion. Since there is an attractive interaction with C^+ of the arenium ion when attack occurs at the ortho and para positions the E_{act} to generate those intermediates is lower. The ortho and para arenium ions form faster than the meta arenium ion. These substituents are labeled as *activators and ortho-para directors.* Activating means that a S_EAr reaction is faster than the corresponding reaction with benzene.

Activating and Deactivating Groups

All electron-withdrawing groups have a positive charge (as in nitro) or a δ^+ atom on the ipso carbon. Like charges repel and destabilize the arenium ion when there is attack at the ortho and para positions, leading to a higher E_{act}. The reaction is *slower* for at the ortho and para positions and the meta product is the major product. These substituents are labeled *deactivators (slower) and meta directors.* Deactivating means that the rate of a S_EAr reaction is slower than the reaction with benzene itself.

TABLE 19.1 Electronic Characteristics of Groups in Electrophilic Aromatic Substitution



19.4.2 ACTIVATING AND DEACTIVATING SUBSTITUENTS

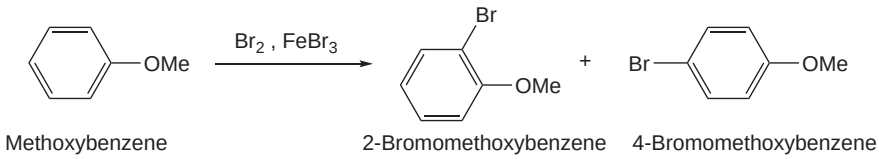
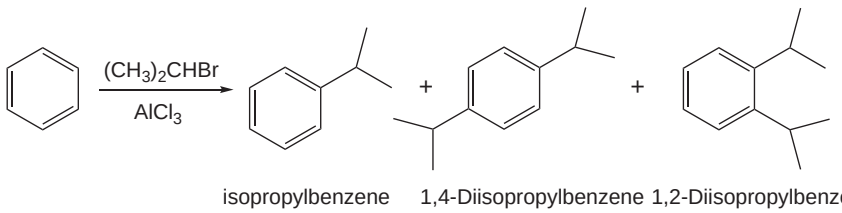


Figure 19.7 illustrates electrophilic substitution using a generic benzene derivative. How does this mechanistic analysis apply to specific molecules? The reaction of anisole (methoxybenzene) with bromine/ferric bromide. Methoxy is an activating group, so the reaction gives 2-bromomethoxybenzene and 4-bromomethoxybenzene as major products. In the absence of additional information, it is reasonable to assume that the ortho and para products are formed as a 1:1 mixture.

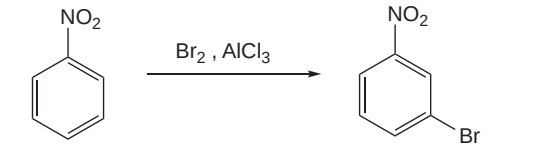


Friedel–Crafts alkylation generates a monosubstituted arene, but overalkylation is a problem. When benzene reacts with 2-bromopropane and $AlCl_3$, isopropylbenzene was formed as expected along with two different disubstituted products, 1,4-diisopropylbenzene plus 1,2-diisopropylbenzene. The latter two products are the major products if an excess of 2-bromopropane is used. Overalkylation is explained by recognizing that alkyl groups are electron-releasing. After one half-life for the reaction, 50% of benzene and 50% of 2-bromopropane will remain, but there is also 50% of isopropylbenzene. Isopropylbenzene reacts faster than benzene because the isopropyl group is electron releasing (activating). Isopropylbenzene competes with benzene for reaction with 2-bromopropane to give the diisopropylbenzene products.

19.14 Draw the reaction and major product(s) for the reaction of toluene with nitric acid and sulfuric acid.

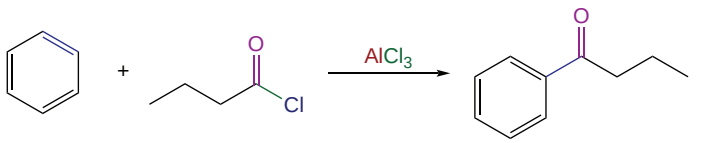
19.15 Draw all resonance forms for the reaction of phenol with Br^+ (from bromine and $AlBr_3$) at the ortho, meta, and the para position.

If a benzene derivative has an electron withdrawing nitro substituent, the electron density of the benzene ring is diminished. Therefore, the benzene ring is a weaker electron doner and reacts slower in S_EAr reactions. Once nitrobenzene reacts with Br^+ an arenium ion is formed. If reaction occurs at the ortho and para position, one resonance contributor places a positive charge on the ipso carbon. Those arenium anions are destabilized, higher in energy and harder to form. For attack at the meta position the positive charge of the arenium ion is never of the ipso carbon and it is less destabilized than the ortho- or para-arenium ions. The major product is 3-bromonitrobenzene. No dibromonitrobenzene product is formed since 3-bromonitrobenzene is less reactive than the nitrobenzene starting material.



Nitrobenzene 3-Bromonitrobenzene

In Section 19.3.3, the Friedel–Crafts acylation of benzene with butanoyl chloride gave 1-phenylbutan-1-one as the only product. The 1-phenylbutan-1-one product has a carbonyl unit attached to the benzene ring. The acyl carbon has a δ^+ dipole, so C=O is an electron-withdrawing group. The ketone product reacts slower than the benzene starting material so 1-phenylbutan-1-one will not compete for reaction with the acylium ion. In other words, there is no diacylation. Note that benzene rings with powerful electron withdrawing substituents such as nitro, do *not* give Friedel–Crafts reactions. It is usually a good assumption that benzene rings bearing an electron-withdrawing group give no reaction in Friedel–Crafts reactions.

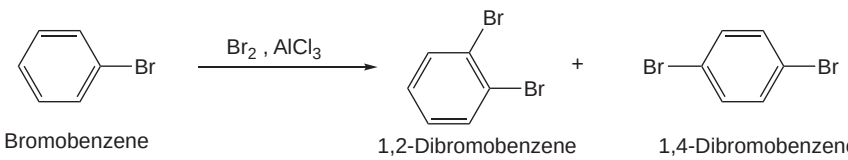


Butanoyl chloride 1-Phenylbutan-1-one

S_EAr Reactions of Halobenzenes

19.16 Draw all resonance forms for the reaction of acetophenone with Cl^+ for attack at C3, and then draw the structure of the final product.

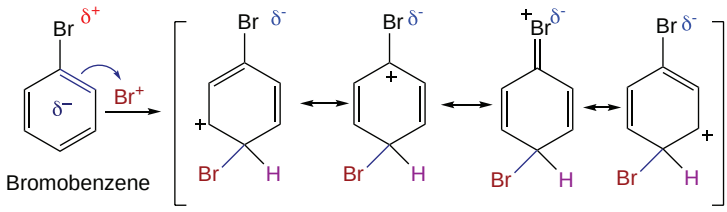
19.4.3 HALOGEN SUBSTITUENTS



Bromobenzene 1,2-Dibromobenzene 1,4-Dibromobenzene

One additional type of substituent in the S_EAr reaction must be considered. When halobenzenes such as bromobenzene react with bromine and $AlCl_3$, the reaction proceeds *slower* than the bromination of benzene. However, the major products are 1,2- and 1,4-dibromobenzene, the ortho and para products. The fact that bromobenzene reacts more slowly shows that the halogen is a deactivating substituent. All of the halogens are *deactivating*,

but they are *ortho-para directors*. The halogens are *polarizable.* If the bromine or any other halogen is polarized δ^+, electron density is donated from the benzene ring to the bromine atom so the bromine is electron-withdrawing. If the benzene ring is less able to donate electrons, bromobenzene reacts as a weaker Lewis base relative to benzene. The rate of reaction for electrophilic substitution is slower and it is deactivated. For reaction at the ortho and para positions, the positive charge resides on the ipso carbon in one resonance contributor (Figure 19.7). Since it is polarizable, the bromine atom is polarized δ^- in those arenium ion intermediates. The ortho and para arenium ions are therefore stabilized, which leads to ortho and para products.

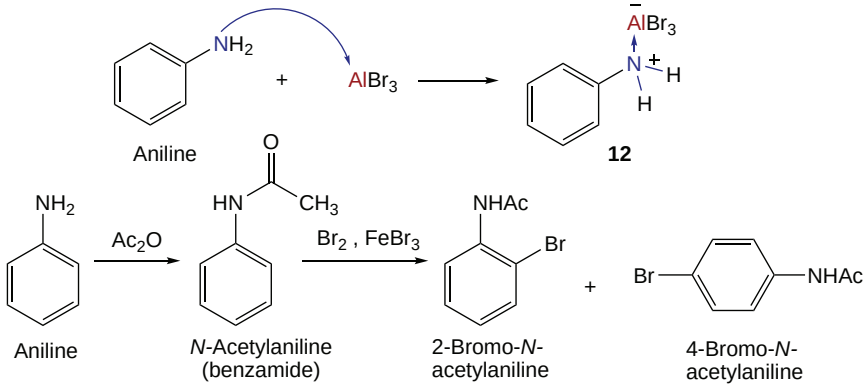


19.17 Draw the products formed when bromobenzene reacts with HNO_3/H_2SO_4.

19.4.4 ANILINE AND ANILINE DERIVATIVES

S_EAr Reactions of Aniline

The amine group ($-NH_2$) of aniline (benzeneamine) is an electron-releasing and activating group. However, the amine group is also a Lewis base that reacts with a Lewis acid catalyst. When aniline is mixed with $Br_2/AlBr_3$, the amine unit reacts with $AlBr_3$ to generate **12**, an "ate" complex, so it cannot react with Br_2 to form Br^+. The positive charge on nitrogen in **12** makes that group electron-withdrawing, which deactivates the benzene ring. Indeed, S_EAr reactions do *not* occur with aromatic amines in the presence of a Lewis acid.



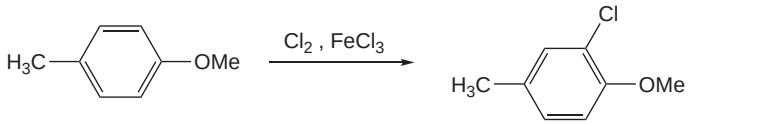
There is a solution to this problem. The reaction of aniline with acetic anhydride or acetyl chloride gives the amide, *N*-acetylaniline (benzamide). Note the use of the NHAc abbreviation for NH-acetyl. The acyl carbon has a δ^+ dipole so it is electron withdrawing relative to the attached nitrogen. This inductive effect makes the nitrogen less electron rich and much less basic. The NHAc unit is electron-releasing, activating and ortho-para directing. A normal electrophilic aromatic substitution reaction occurs, and the acetyl group *protects* the nitrogen from reaction with the Lewis acid. The reaction of *N*-acetylaniline and bromine with $FeBr_3$ affords 2-bromo-*N*-acetylaniline and 4-bromo-*N*-acetylaniline. The acetyl group is removed by acid or base hydrolysis to regenerate the amine (Section 18.4).

19.18 Draw the arenium ion and all resonance contributors for reaction of *N*-acetylaniline and Br^+ at the para position.

S_EAr Reactions of Disubstituted Benzenes

19.5 POLYSUBSTITUTED BENZENE DERIVATIVES

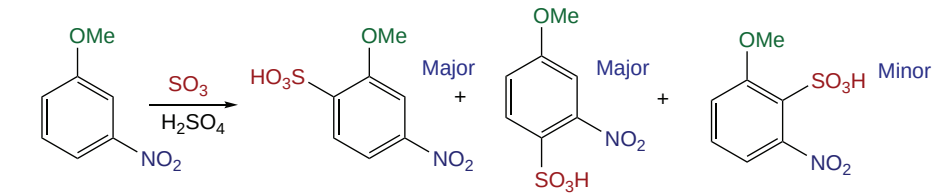
If the benzene derivative in a S_EAr reaction has two substituents on the benzene ring, a S_EAr reaction places a third group on the ring. Different trisubstituted derivatives are possible, depending on the presence of two electron-releasing substituents, two electron-withdrawing substituents, or one electron-releasing and one electron-withdrawing group. When a molecule has two activating substituents (electron-releasing groups), as with 4-methylanisole, both are ortho-para directing. In this example, the para position is blocked, and the question becomes which ortho position will react with Cl^+ from the Cl_2/$FeCl_3$, ortho to OMe or ortho to methyl. Since OMe is a very strong activator and methyl is a weak activator, the rate of reaction at the position ortho to OMe is much greater. Therefore, the substitution reaction of methoxybenzene with chlorine and aluminum chloride yields 2-chloro-4-methylmethoxybenzene as the major product. In general, the stronger activating group will direct the reaction at a faster rate, which leads to the major product.



4-Methylmethoxybenzene — 2-Chloro-4-methylmethoxybenzene

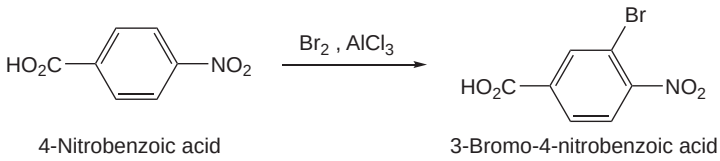
19.19 Draw both products of the chlorination reaction of 2-methylanisole and draw all the resonance forms for the intermediate that leads to the product with the Cl para to OMe.

Determining the product is particularly easy when the benzene ring contains one electron-releasing group and one electron-withdrawing group, as in 3-nitromethoxybenzene (3-nitroanisole). The OMe unit is a powerful activating group whereas nitro is a powerful deactivating group. The difference in rate of reaction for these two groups may be $> 10^{10}$, so reaction of 3-nitromethoxybenzene with fuming sulfuric acid (sulfuric acid + SO_3) leads to substitution ortho and para to the OMe group as the products. Note that 2-methoxy-6-nitrobenzenesulfonic acid is formed in a much lower percentage than the other two products. In reactions where the product must be incorporated between two groups, the yield is usually much lower due to increased steric hindrance.



3-Nitromethoxybenzene — 2-Methoxy-4-nitrobenzenesulfonic acid — 4-Methoxy-2-nitrobenzenesulfonic acid — 2-Methoxy-6-nitrobenzenesulfonic acid

The reaction of a starting material in which the benzene ring contains two electron-withdrawing (deactivating) substituents has two problems. The first is that the ring may be so deactivated that the reaction is too slow to take place at all, so there may be no reaction. If it is *assumed* that a slow reaction does indeed occur, the idea of a most "activated" site is not appropriate, but the *less deactivated* site must be determined. Substitution meta to the less deactivated group will be faster than substitution meta to the more deactivated group. In 4-nitrobenzoic acid, the nitro group is a more powerful deactivating group than the COOH unit, and substitution will occur meta to the *least* deactivating group (COOH). Therefore, the reaction of 4-nitrobenzoic acid with Br_2 and $AlCl_3$ will give 3-bromo-4-nitrobenzoic acid.



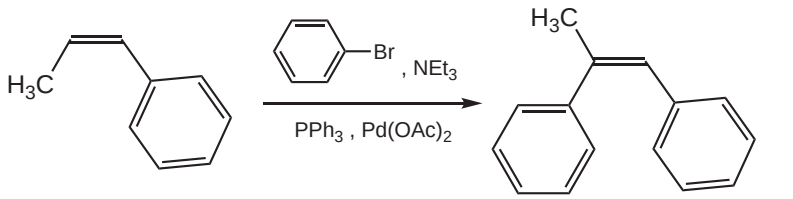
4-Nitrobenzoic acid 3-Bromo-4-nitrobenzoic acid

19.20 Draw the product of a reaction between 3-chloronitrobenzene and bromine in the presence of aluminum bromide.

19.6 AROMATIC COUPLING REACTIONS

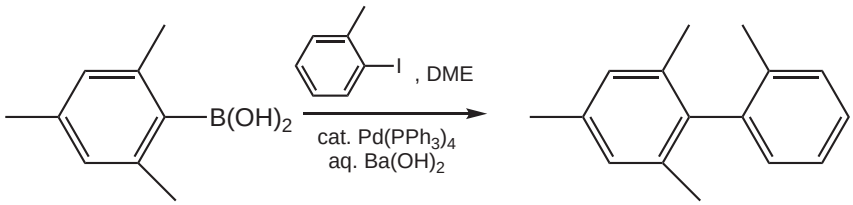
Aromatic Coupling Reactions

In addition to Friedel–Crafts reactions, there are transition-metal catalyzed coupling reactions that form alkenyl and alkynyl substituted aromatic derivatives. Aryl-substituted alkenes can be prepared by the Pd-catalyzed coupling of alkenes and aryl halides in a transformation known as the *Heck reaction* or the *Mizoroki-Heck reaction*, named after Nobel laureate Richard F. Heck (USA; 1931–2015) and Tsutomu Mizoroki (Japan).[4] The Heck reaction usually involves the coupling of aryl halides or vinyl halides with alkenes. An example is the reaction of *Z*-1-phenylprop-1-ene with bromobenzene in presence of triethylamine and a mixture of PPh_3 and $Pd(OAc)_2$, which forms $Pd(Ph_3)_4$ in situ.[5] The coupling reaction gave *Z*-1,2-dipheylprop-1-ene in 79% yield.[4a] The reaction works best with aryl iodides, but conditions are available that give good yields with aryl bromides and aryl chlorides. Aryldiazonium salts have also been used.



Z-1-Phenylprop-1-ene *Z*-1,2-diphenylprop-1-ene

Another palladium catalyzed coupling reaction reacted arylboronic acids [$ArB(OH)_2$] with aryl halides to give the biaryl in what is called *Suzuki coupling* (or *Suzuki-Miyaura coupling*).[6] This reaction is named after the work of Norio Miyaura (Japan) and Akira Suzuki (Japan). The intramolecular reaction is well known. Different conditions (including additives and solvent) for the reaction have been reported, often focusing on the catalyst or the ligand.



Mesitylboronic acid 2,2',4,6-Tetramethyl-1,1'-biphenyl

[4] (a) Heck, R.F. *Accounts of Chemical Research* 1979, 12, 146–151; (b) Mizoroki, T.; Mori, K.; Ozaki, A *Bulletin of the Chemical Society of Japan* 1972, 44, 581 (c) Littke, A.F.; Fu, G.C. *Angewandte Chemie International Edition* 2002, 41, 4176–4211.

[5] (a) Amatore, C.; Jutland, A. *Accounts of Chemical Research* 2000, 33, 314–321; (b) Dieck, H.A.; Heck, R.F. *Journal of the American Chemical Society* 1974, 96, 1133–1136.

[6] Miyaura, N.; Suzuki, A. *Chemical Reviews* 1995, 95, 2457–2483; Kündig, E.P.; Jia, Y.; Katayev, D.; Nakanishi, M. *Pure and Applied Chemistry* 2012, 84, 1741–1748.

An example is the reaction of mesitylboronic acid and 2-iodomethylbenzene to give the biaryl compound 2,2',4,6-tetramethyl-1,1'-biphenyl in 80% yield using a $Pd(PPh_3)_4$ catalyst with aqueous barium hydroxide in dimethoxyethane (DME).[7] Note that mesityl is 2,4,6-trimethylphenyl and the arylboronic acid is prepared by the reaction of mesitylmagnesium bromide with trimethylborate [$B(OCH_3)_3$] followed by hydrolysis with water.[8] Aryl substituted alkenes and dienes can also be prepared from the palladium catalyzed reaction of arylboronic acids and vinyl halides.[9]

Mustafa M. El-Abadelah

Mustafa M. El-Abadelah (Jordan) is Emeritus Professor of organic chemistry at the University of Jordan. His research has focused on the preparation of heterocycles and their derivatives, such as condensed tri-and tetracyclic fluoroquinolones and thienopyridones, hetero-ring opening, expansion and contraction reactions. Professor El-Abadelah has done significant research on amidrazone derivatives, which exhibit anti-microbial, antitubercular, insecticidal, anti-thrombotic, anticancer properties and they are anti-corticotrophin-releasing factors.[10] Amidrazones are a class of chemical compounds formally derived from carboxylic acids that can exist in two tautomeric forms, hydrazide imides ($RC(=NH)NHNH_2$) and amide hydrazones ($RC(NH_2)=NNH_2$). A recent study prepared compounds that were evaluated in vitro for their antimicrobial properties against bacterial and fungal strains. 7-(3,5-Dimethyl-4-methoxyphenyl)-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**14**) was prepared by a Suzuki-Miyaura reaction from 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate, **13**.[11] A series of quinolones were prepared but **14** was the most active with minimum inhibitory concentrations (MIC values) ranging from 0.00007 μg/mL to 0.015 μg/mL. All of the quinolones prepared showed antibacterial activity higher than the activity of ciprofloxacin, both towards Gram positive Bacillus subtilis and Staphylococcus aureus, and Gram negative Haemophilus influenzae strains. Quinolone **14** may be a lead compound worthy of further structural optimization and development as potential antibacterial agent.

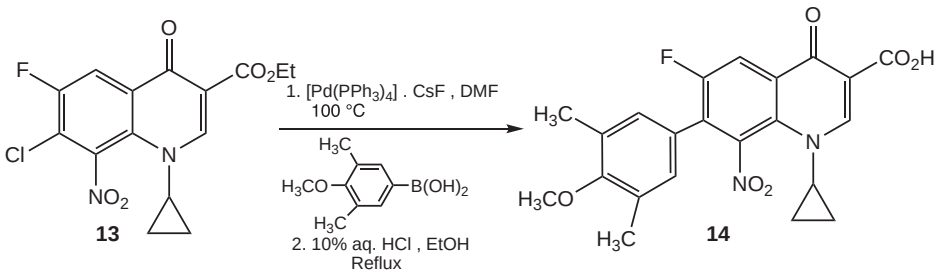
[7] Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* 1992, 207–210.

[8] Hawkins, R.T.; Lennarz, W.J.; Snyder, H.R. *Journal of the American Chemical Society* 1960, 80, 3053–3059.

[9] Miyaura, N.; Suzuki, A. *Organic Syntheses Collective Volume 8* 1993, 532–536.

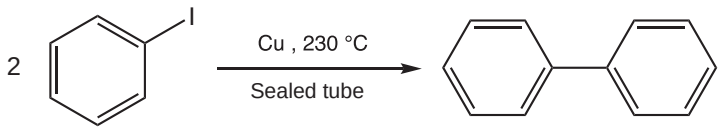
[10] See Almansour, S.M.; Zahra, J.A.; Sabri, S.S.; El-Abadelah, M.M.; Zihlif, M.A.; Taha, M.O. *Letters in Drug Design & Discovery*,2018, 15, 1268–1275.

[11] (a) Al-Trawneh, S.A.; El-Abadelah, M.M.; Al-Abadleh, M.M.; Zani, F.; Incerti, M.; Vicini, P. *European Journal of Medicinal Chemistry* ***2014****, 86, 364-367*; (b) Al-Trawneh, S.A.; Zahra, J.A.; Kamal, M.R.; El-Abadelah, M.M.; Zani, F.; Incerti, M.; Cavazzoni, A.; Alfieri, R.R.; Petronini, P.G.; Vicini, P. *Bioorganic & Medicinal Chemistry* ***2010****, 18,* 5873-5884.



19.21 What is the product of the Pd(0) catalyzed reaction of 3-iodotoluene and pent-1-ene.

19.22 What is the product of the Pd(0) catalyzed reaction of 4-iodoanisole and 3-ethylphenylboronic acid?



The homocoupling of aryl halides with copper is called the *Ullmann reaction*, named after Fritz Ullmann (Germany; 1875–1939).[12] The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls. When a mixture of two different aryl halides is used Ar^1X and Ar^2X, there are three possible products (Ar^1–Ar^1, Ar^1–Ar^2, Ar^2–Ar^2), but often only one is the major product. The best leaving group is iodo so the reaction is most often done with aryl iodides, but bromides, chlorides, and even thiocyanates have been used. An example is heating iodobenzene with copper at 230 °C in a sealed tube to give biphenyl in 82% yield.[13] Intramolecular reactions are known.

Ei-ichi Negishi

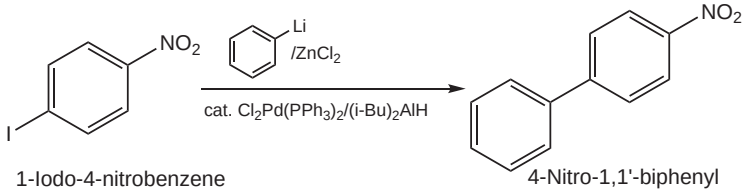
Nobel laureate Ei-ichi Negishi (Japan/USA; 1935–2021) was an organic chemist at Purdue University who developed the *Negishi coupling*.[14] The Negishi coupling condenses organic zinc compounds and organic halides with a palladium or nickel catalyst. Organic triflates or

[12] (a) Fanta, P.E. *Chemical Reviews* 1946, 38, 139–196; (b) Lin, H.; Sun, D. *Organic Preparation and Procedures International* 2013, 45, 341–394.

[13] Ullmann, F. *Annalen* 1904, 332, 38–81.

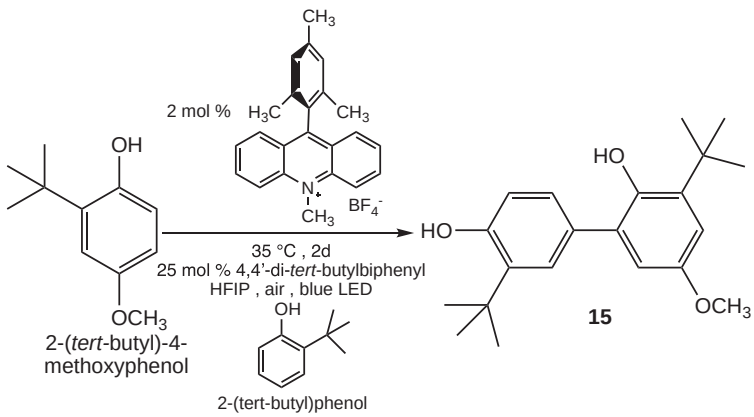
[14] Urrego-Riveros, S.; Ramirez y Medina, I.-M.; Duvinage, D.; Lork, E.; Sönnichsen, F.D.; Staubitz, A. *Chemistry a European Journal* 2019, 25, 13318–13328.

organic halides are mixed with organozinc compounds to form "Cp_2Zr" (the *Negishi reagent*) in situ. This reagent can be used to couple alkene and alkynes[15] and to form biaryls. An example is the addition of zinc chloride to phenyllithium in THF, which gave phenylzinc chloride. 4-Iodonitrobenzene reacted with a mixture of the catalyst dichlorobis(tripheny lphosphine)palladium(II) and diisobutylaluminum hydride, followed by phenylzinc chloride. After quenching with aq HC1, 4-nitrobiphenyl was isolated in 90% yield.[16]



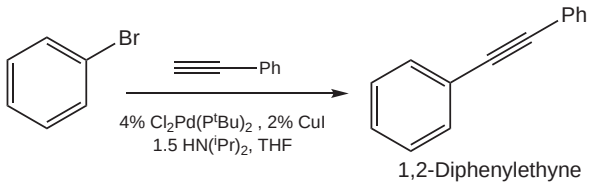
Marisa C. Kozlowski

Marisa C. Kozlowski (USA) is a professor of organic and catalysis chemistry at the University of Pennsylvania. Her research is focused on the asymmetric synthesis of biologically important molecules and the development of cost-effective catalysts. Professor Kozlowski has developed computational programs to better understand chemical reactions. Much of her work has focused on the biphenol scaffold, which is a prevalent substructure in biologically active natural compounds. She developed a photocatalytic method for phenol-phenol homo-coupling and cross-coupling that circumvents the requirement of the halide at the coupling position, thereby enhancing atom economy. Using the photocatalyst $MesAcr^+BF_4^-$ (9-mesityl-10-methylacridinium tetrafluoroborate), blue light-emitting diodes (LED) provide the activation needed for the reaction to occur. An example is the reaction of 2-(*tert*-butyl)phenol and 2-(tert-butyl)-4-methoxyphenol with 2 mol% of $MesAcr^+BF_4^-$, 25 mol% of 4,4'-tert-butylbiphenyl in HFIP (1,1,1,3,3,3-hexafluoroisopropanol), exposed to air and photolyzed with blue LED.[17] The product is the biaryl **15** in 74% yield.



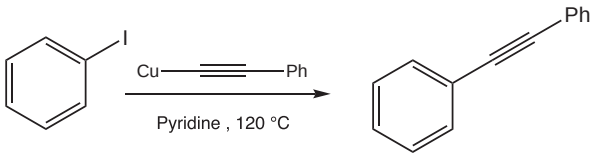
[15] King, A.O.; Okukado, N.; Negishi, E. *Journal of the Chemical Society, Chemical Communications* 1977, 683–684.
[16] Negishi, E.; King, A.O.; Okukado, N. *Journal of Organic Chemistry* 1977, 42, 1821–1823.
[17] Niederer, K.A.; Gilmartin, P.H.; Kozlowski, M.C. *ACS Catalysis* 2020, 10, 14615–14623.

Aryl derivatives can be coupled to alkynes. A Pd-catalyzed reaction of aryl halides with a terminal alkyne to give 1-aryl alkynes is called *Sonogashira coupling*, named after Kenkichi Sonogashira (Japan).[18] Terminal aryl alkynes react with aryl iodides and Pd(0) to give the corresponding diaryl alkyne. Aryl iodides are more reactive than aryl fluorides. An example of this coupling is the reaction of bromobenzene and phenylethyne with 4% bis(tri-*tert*-butylphosphine)palladium (0) and 2% CuI with 1.5 diisopropylamine in THF, which gave 1,3-diphenylethyne in >95% yield.[18c] Alkynes can be coupled to heteroaromatic compounds.



1,2-Diphenylethyne

When aryl halides react with copper acetylides to give 1-aryl alkynes, the reaction is known as *Castro-Stephens coupling*, named after Charles E. Castro (USA) and Robert D. Stephens (USA).[19] Both aliphatic and aromatic substituents can be attached to the alkyne unit, and a variety of aryl iodides have been used. An example is the reaction of cuprous phenylacetylide reacted with iodobenzene in pyridine was heated to 120 °C for 10 h to give 87% of 1,2-diphenylethyne. The copper-alkyne was prepared by the reaction of cuprous iodide in aqueous ammonia with phenylacetylene to give cuprous phenylacetylide.



1,2-Diphenylethyne

19.7 REDUCTION AND AROMATIC COMPOUNDS

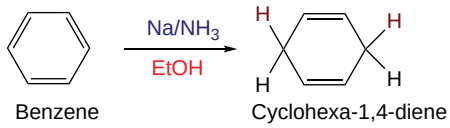
Reduction of Benzene Derivatives

The aromatic character of benzene rings makes reduction more difficult. Hydrogenation, for example, requires higher catalyst loading (higher percentage of the catalyst), higher temperatures, and/or higher pressures of hydrogen gas. The hydrogenation of benzene to cyclohexane requires three molar equivalents of hydrogen gas and a Ni(R), a Pd or a rhodium (Rh) catalyst. The reaction of benzene with two molar equivalents of hydrogen gas gives cyclohexene, which is more reactive than benzene so it may react further. The reaction of benzene with one molar equivalent of hydrogen gas is expected to give cyclohexa-1,3-diene, but it is often difficult to isolate in good yield. A mixture of cyclohexadiene, cyclohexene, and cyclohexane is common. For problems in this book *assume* that one equiv of hydrogen will give cyclohexadiene and that two molar equivalents of hydrogen will give cyclohexene. With an excess of hydrogen gas (three or more molar equivalents) benzene is cleanly converted to cyclohexane.

Benzene Cyclohexa-1,3-diene Benzene Cyclohexane

[18] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Letters* 1975, 16, 4467–4470; (b) Chinchilla, R.; Nájera, C. *Chemical Reviews* 2007, 107, 874; (c) Sonogashira, K. *Journal of Organometallic Chemistry* 2002, 653, 46–49.
[19] Stephens, R.D.; Castro, C.E. *Journal of Organic Chemistry* 1963, 28, 3313–3315.

19.23 Write out the reaction and draw the final product when 4-methylanisole is treated with 3 equiv of hydrogen gas, in the presence of a Ni(R) catalyst.



The reaction of group 1 or 2 metals such as sodium or lithium in liquid ammonia, often in the presence of ethanol, provides an alternative method for the reduction of benzene rings. This method is known as the *Birch reduction* (Section 17.5). Benzene is reduced to cyclohexa-1,4-diene with sodium and ethanol in liquid ammonia. Note that the C=C units in cyclohexa-1,4-diene are not directly attached one to the other, so they are not conjugated. The mechanism shown explains the nonconjugated nature of the product and shows that hydrogen atoms are incorporated from the solvent. This mechanism involves single electron transfer from the alkali metal to the benzene ring. This mechanism applies to substituted benzene derivatives, but different products are formed when there is an electron-withdrawing substituent versus an electron-releasing substituent. If anisole is treated with sodium in ethanol and liquid ammonia, initial electron transfer can yield resonance-stabilized intermediates **16** or **17**. Intermediate **17** has a resonance contributor with the negative charge on the ipso carbon, but there is no such resonance contributor in **16**. Electronic repulsion of the negative charge on the ipso carbon with the proximal OMe unit will destabilize **17**. Electronic repulsion is minimized, and the intermediate is more stable so **16** will form faster and give the major product. Reaction with ethanol, electron transfer from a second equivalent of sodium metal, and a second protonation with ethanol will give 1-methoxycyclohexa-1,4-diene. The oxygen atom of the methoxy group is attached to a sp^2 hybridized carbon atom (Figure 19.8).

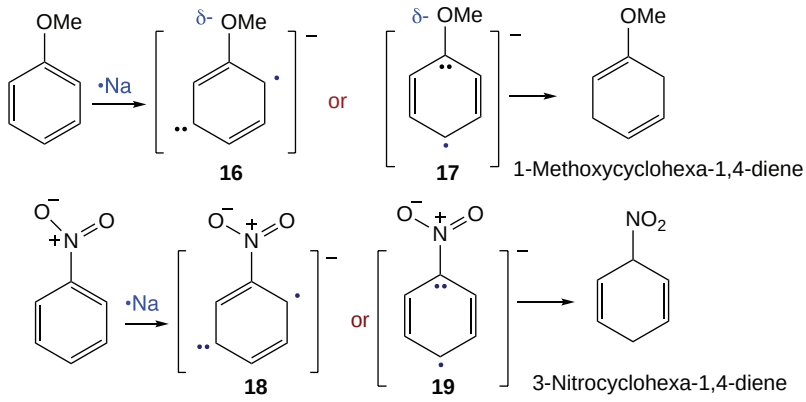


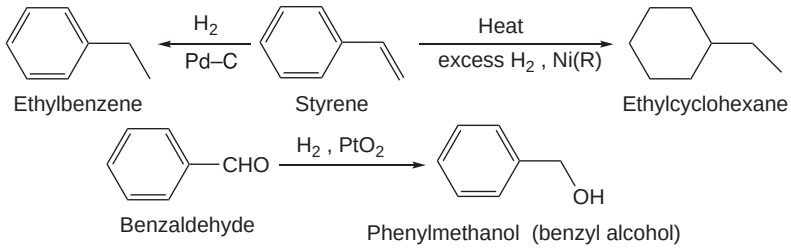
FIGURE 19.8 Birch reduction of anisole and nitrobenzene

Birch reduction of nitrobenzene differs in that the substituent is the electron-withdrawing nitro group, with a positively charged nitrogen atom. Initial electron transfer from sodium can generate radical anion **18** or **19**, as shown in Figure 19.8, and both are resonance-stabilized. The negative charge is on the ipso carbon adjacent to the positively charged nitrogen atom of the nitro group in **19**. The attraction of positive and negative charges is stabilizing so this intermediate is more stable and formed faster than the alternative **18**. In **18**, the negative and positive charges are never adjacent to each other. Therefore, **19** leads to the major product, 3-nitrocyclohexa-1,4-diene, via reaction with ethanol, electron transfer, and a final reaction with ethanol. The electron-withdrawing substituent in 3-nitrocyclohexa-1,4-diene is attached to a sp^3 hybridized carbon atom.

19.24 Draw all resonance forms of **16** and of **17**.

19.25 Draw the major product formed when 3-nitroanisole is treated with Na metal in ethanol and liquid ammonia.

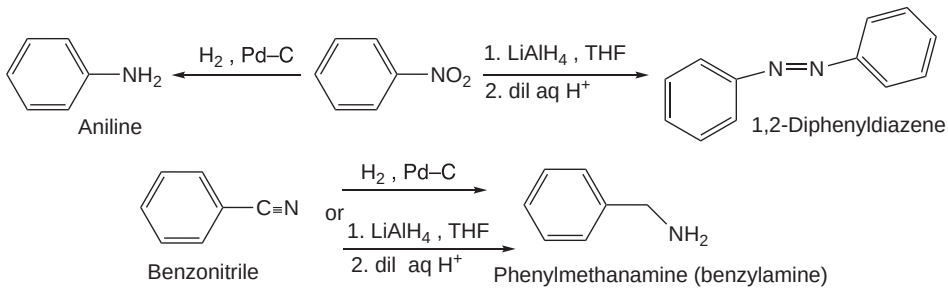
The side chains or functional groups attached to a benzene ring can be reduced without reduction of the benzene ring. The C=C unit of an alkene and the C=O unit of an aldehyde or ketone are examples. If styrene (ethenylbenzene) reacts with hydrogen gas and a Pd catalyst, for example, the C=C unit of the alkene is much more susceptible to hydrogenation than the benzene ring. The product is ethylbenzene. If a large excess of hydrogen is used with heat and pressure, ethylcyclohexane is formed. In the case of benzaldehyde, catalytic hydrogenation gives benzyl alcohol (phenylmethanol), particularly in the presence of a Pt catalyst (Section 17.4). Both $LiAlH_4$ and $NaBH_4$ reduce the carbonyl of benzaldehyde to the corresponding alcohol (Section 17.2). Both catalytic hydrogenation and hydride agents reduce aldehyde and ketone derivatives to give an alcohol. Benzophenone or acetophenone, for example, are reduced to dimethylmethanol or 1-phenylethan-1-ol, respectively.



19.26 Write out all steps to prepare 1-(3-bromophenyl)-1-bromoethane from benzene.

The nitration of benzene followed by catalytic hydrogenation is an important method for the synthesis of aniline and many of its derivatives. Hydrogen with a transition metal such as Pd, Pt or Ni converts nitrobenzene to aniline. While catalytic hydrogenation of nitrobenzene gives aniline, reaction with $LiAlH_4$ (Section 17.2) does *not* give aniline. The latter product is an azo compound, 1,2-diphenyldiazene, which can exist as (*E)* and (*Z)*- isomers. Sodium borohydride is too weak to reduce a nitro group. Catalytic hydrogenation and hydride reagents reduce a nitrile group to an amine. Catalytic hydrogenation of benzonitrile (cyanobenzene) affords phenylmethanamine (called benzylamine). The treatment of benzonitrile with $LiAlH_4$ also yields phenylmethanamine after a hydrolytic workup.

19.27 Write out the reaction sequence that converts toluene to 4-nitrotoluene, and then to 4-methylaniline, supplying all reagents that are required.



Carboxylic acid derivatives attached to a benzene ring can be reduced without reduction of the benzene ring. When benzoic acid is treated with $LiAlH_4$, the final product after hydrolysis is benzyl alcohol. Catalytic hydrogenation of benzoic acid does *not* yield benzyl alcohol, since carboxylic acids are particularly resistant to hydrogenation. Catalytic hydrogenation of

esters and amides is quite slow. Indeed, ethyl benzoate ($PhCO_2Et$) and benzamide are usually not reduced via catalytic hydrogenation. An ester such as ethyl benzoate is reduced to phenylmethanol (benzyl alcohol) upon treatment with $LiAlH_4$ (Section 17.2). Similar hydride reduction of the amide group in benzamide yields aminomethyl benzene (benzylamine).

Aromatic Compounds

19.8 AROMATICITY IN MONOCYCLIC MOLECULES OTHER THAN BENZENE

Benzene is identified as an aromatic compound because it meets certain unique criteria. There are six π-electrons confined to a ring, and every carbon atom in that ring is sp^2 hybridized with a p-orbital attached. Further, the p-orbitals are contiguous and continuous. In other words, every carbon in the ring has a p-orbital and there are no intervening sp^3 atoms. To be *aromatic* a compound must satisfy three criteria: it must be cyclic, there must be an unbroken chain of p-orbitals (no sp^3 hybridized atoms), and there must be a number of π-electrons equal to one of the numbers from the $4n$+2 rule.

There are many examples of neutral molecules and charged intermediates that follow *Hückel's rule* (Section 19.1) Neutral molecules that are *cyclic polyenes* can be aromatic if Hückel's rule otherwise known as the "4n+2 rule" is observed. If there are 2, 6, 10, 14, 18, etc. π-electrons in a cyclic polyene, where every atom is sp^2 hybridized, then the molecule is planar and aromatic. Benzene clearly has 6 π-electrons and cyclotetradeca-1,3,5,7,9,11,13-heptaene has 14 π-electrons (Figure 19.9) and both are aromatic. Larger planar cyclic polyenes may also be aromatic. Cyclooctadeca-1,3,5,7,9,11,13,15,17-nonaene has 18 π-electrons and every carbon is sp^2 hybridized, so it also satisfies the Hückel rule and is aromatic. Cyclic compounds such as these are called *annulenes, which* are completely conjugated aromatic hydrocarbons. Annulene is also a nomenclature system. Benzene is named [6]-annulene, cyclotetradeca-1,3,5,7,9,11,13-heptaene is named [14]-annulene, and cyclooctadeca-1,3,5,7,9,11,-13,15,17-nonaene is [18]-annulene. This nomenclature is used mostly for larger ring polyenes.

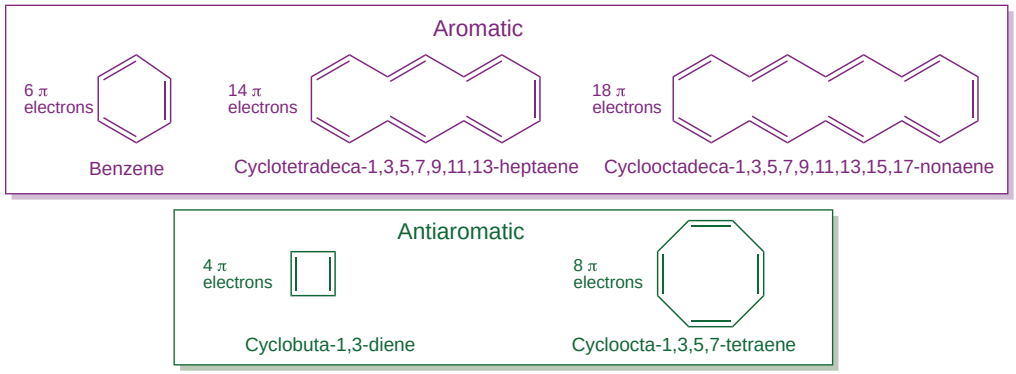


FIGURE 19.9 Aromatic and antiaromatic compounds.

Cyclobuta-1,3-diene (4 π-electrons) and cycloocta-1,3,5,7-tetraene (with 8 π-electrons) in Figure 19.9 have ($4n$) π-electrons. These compounds do *not* follow the Hückel rule. If the number of π-electrons *does not* equal $4n$+2, the compound is *not* aromatic, and the system is rather unstable. Compounds with $4n$ π-electrons are *antiaromatic*. Cyclobuta-1,3-diene is a cyclic compound, and every carbon is sp^2 hybridized, but it has only 4 π-electrons and does not satisfy the $4n$+2 rule. Cyclobuta-1,3-diene is not aromatic. Likewise, cycloocta-1,3,5,7-tetraene is cyclic and has a continuous array of sp^2 carbons, but it has 8 π-electrons and does not fit the $4n$+2 series so it is not aromatic. Such compounds cannot be prepared, although they can be observed if extremely low temperatures and specialized conditions are used.

In addition to neutral molecules, certain cation and anion intermediates meet the criteria for aromaticity, and examples are shown in Figure 19.10. The cyclopropenyl cation and the

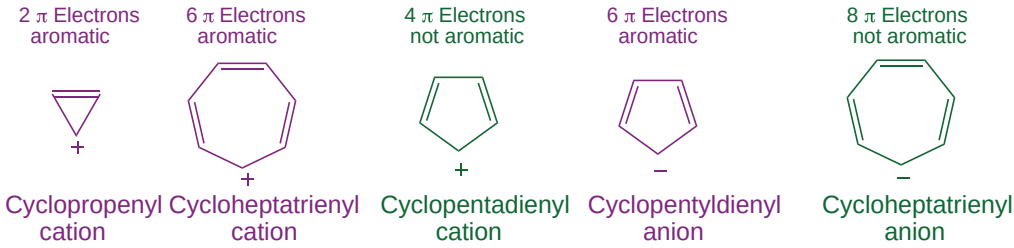
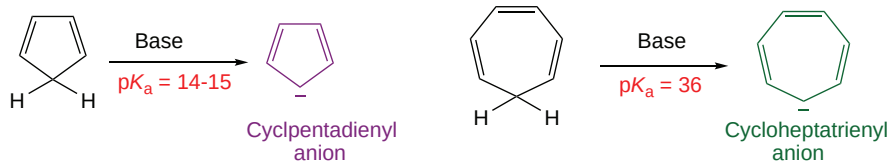


FIGURE 19.10 Aromatic and antiaromatic cations and anions.

cyclohepta-1,3,5-trienyl cation both have a continuous array of p-orbitals confined to a ring, and a number of π-electrons that fits the $4n+2$ series (2 and 6). Both carbocations are aromatic so they are stable and relatively easy to form as reactive intermediates. The cyclopentadienyl cation has a continuous array of p-orbitals confined to a ring, but it has $4n$ π-electrons and it is *not* aromatic. It is anti-aromatic, is unstable, and very difficult to form.

Anion intermediates may also be aromatic or anti-aromatic. The cyclopentadienyl anion has six π-electrons and meets all criteria for aromaticity. It is aromatic and easy to form. The cyclopentadienyl anion is formed from cyclopenta-1,3-diene in an acid-base reaction. It is known that cyclopenta-1,3-diene has a pK_a of 14 to 15,[20] which reflects the aromatic stability of the aromatic conjugate base. The cyclopentadienyl anion contrasts sharply with the cyclohepta-1,3,5-trienyl anion, which has $4n$ π-electrons, is *not* aromatic, is particularly unstable, and difficult to form. The pK_a is ~36,[20] which reflects the difficulty in forming the antiaromatic conjugate base in an acid-base reaction.

19.28 Draw the structures of [26]-annulene and [12]-annulene, and determine if they are aromatic.
19.29 Suggest a reaction scheme to make 1-benzylcyclopenta-2,4-diene from cyclopenta-1,3-diene.



19.9 POLYNUCLEAR AROMATIC HYDROCARBONS

Polycyclic Aromatic Compounds

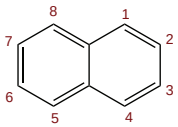
Many aromatic compounds meet the $4n+2$ rule with structures where the π-electrons are not confined to one ring, but they are in several rings that are fused together. They are called *polynuclear (or polycyclic) aromatic molecules*. These compounds undergo electrophilic aromatic substitution.

19.9.1 NAPHTHALENE, ANTHRACENE, AND PHENANTHRENE

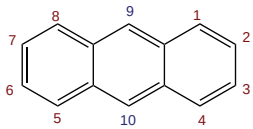
There are many polycyclic aromatic compounds. Three simple examples are naphthalene, anthracene, and phenanthrene. Naphthalene is a toxic bicyclic aromatic compound with the formula $C_{10}H_8$. It was the main constituent of "mothballs" for many years. It was replaced with 1,4-dichlorobenzene, which is characterized as an insecticidal fumigant. Anthracene is a polycyclic aromatic compound (14 π-electrons) with three rings fused

[20] Cram, D. *Fundamentals of Carbanion Chemistry*, Academic Press, NY, 1965, pp. 4, 10, 13, 14, 43, 48.

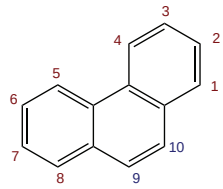
together and the formula $C_{14}H_{10}$. Anthracene is used in wood preservatives and in insecticides. Phenanthrene is an isomer of anthracene. Like anthracene, phenanthrene is derived from coal tar and is used in the synthesis of dyes, explosives, and drugs. In naphthalene only the eight carbons on the periphery of the rings are numbered. The "bridgehead" carbons are not numbered because they cannot undergo substitution reactions. Similarly, anthracene and phenanthrene have only 10 numbered carbons since each has four bridgehead positions.



Naphthalene



Anthracene



Phenanthrene

19.30 Draw all resonance contributors to anthracene.

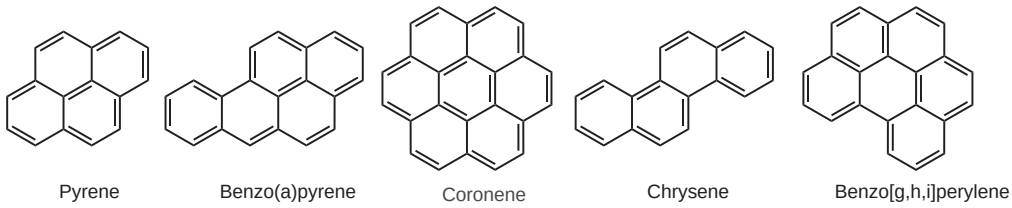
19.31 Draw the structures of (a) 2-nitronaphthalene, (b) 2-fluoroanthracene, (c) 4-methylphenanthrene, (d) 4,5-dibromophenanthrene, (e) 6-ethyl-1,4-dimethylanthracene, and (f) naphthalene-2,7-diol.

Polycyclic Aromatic Hydrocarbons (PAH)

A polycyclic aromatic hydrocarbon (PAH) is a hydrocarbon that has multiple aromatic rings. Many of them are found in coal and oil deposits and are formed by the thermal decomposition of organic matter, as in engines and incinerators or when biomass burns in forest fires. They are transported in the atmosphere in gas and/or particle phases and deposited by wet and dry deposition. Particulate matter plays a significant and continuous role in the chemistry of the atmosphere. They also play a significant role in human health.[21] Daily exposure to particulate matter is associated with increased incidences of premature death, chronic asthma as well as respiratory problems in children and cardiovascular disease in adults. They are found in tobacco smoke and particulate air pollution and may contribute to cardiovascular disease resulting from such exposures. Light-transformation of these compounds can lead to detoxification by degradation to small and less harmful molecules. This process can generate more toxic species, however. Because humans are exposed to the combination of PAHs and light, the study of human skin cancer is particularly important.

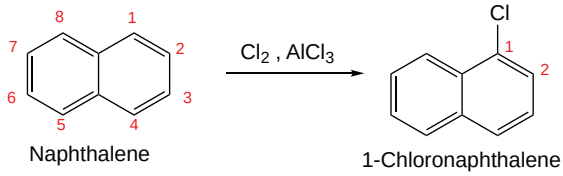
Examples of PAHs include benzo[a]pyrene, a Group I carcinogen, which means it is carcinogenic to humans. First isolated from coal tar, it is also produced by combustion as in automobiles. Chrysene is a natural constituent of coal tar, and it is found in creosote. It is suspected to be a human carcinogen, but chrysene is often contaminated with more strongly carcinogenic compounds. Derivatives of chrysene are estrogenic compounds, sex hormones that are responsible for the development and regulation of the female reproductive system and secondary sex characteristics. Benzo[*ghi*]perylene occurs naturally in crude oil and coal tar. It is a product of incomplete combustion and is found in tobacco smoke, automobile exhausts, industrial emissions, grilled meat products and edible oils. It is suspected to be a mutagen and a carcinogen. Coronene occurs naturally as the very rare mineral carpathite. This mineral may be created by ancient hydrothermal vent activity. Coronene has been used in the synthesis of graphene. Graphene is an allotrope of carbon that is a single layer of atoms arranged in a two-dimensional honeycomb lattice (Figure 8.16b). Graphene is a semimetal that conducts heat and electricity very efficiently along its plane. Graphene is also about 100 times stronger than would be the strongest steel of the same thickness.

[21] (a) Yu, H. *Journal of Environmental Science and Health Part C Environmental Carcinogenesis & Ecotoxicology Reviews* 2002, 20, 1–42; (b) Abdel-Shafy, H.I.; Mansour, M.S.M. *Egyptian Journal of Petroleum* 2016, 25, 107–123.



19.9.2 AROMATIC SUBSTITUTION REACTIONS OF POLYCYCLIC HYDROCARBONS

Polynuclear aromatic hydrocarbons (e.g., naphthalene, anthracene, and phenanthrene) undergo electrophilic aromatic substitution reactions. Naphthalene has two different positions for substitution in the reaction of with $Cl_2/AlCl_3$, C1 and C2. The major product is 1-chloronaphthalene. In naphthalene, C1, C4, C5, and C8 are chemically identical and C2, C3, C6, and C7 are chemically identical. Therefore, substitution at C1, C4, C5, or C8 gives only 1-chloronaphthalene via the arenium ion shown in Figure 19.11. A similar reaction at C2 yields the arenium ion in Figure 19.11.



There is a subtle difference in these two intermediates that makes substitution at C1 preferred to C2. Note that the arenium ions have Kekulé structures for some of the resonance contributors. These contributors have fully aromatic benzene rings (an "*intact benzene ring*"), and there is an additional Kekulé structure for each intact ring. The arenium ion for attack at C1 has four Kekulé structures and a total of seven resonance structure. The arenium ion for attack at C2 has only two Kekulé structures and a total of six resonance contributors. The extra resonance contributors make the arenium ion for substitution at C1 more stable than the arenium ion for substitution at C2. Therefore, 1-chloronaphthalene as the major product. Anthracene has three different positions (C1, C2, and C9) and phenanthrene has five different positions (C1, C2, C4, C5, and C9). Electrophilic aromatic substitution for both compounds will occur primarily at C9 since that arenium ion has the most resonance forms and the most "intact benzene rings." There is also product from attack at C1, however. In

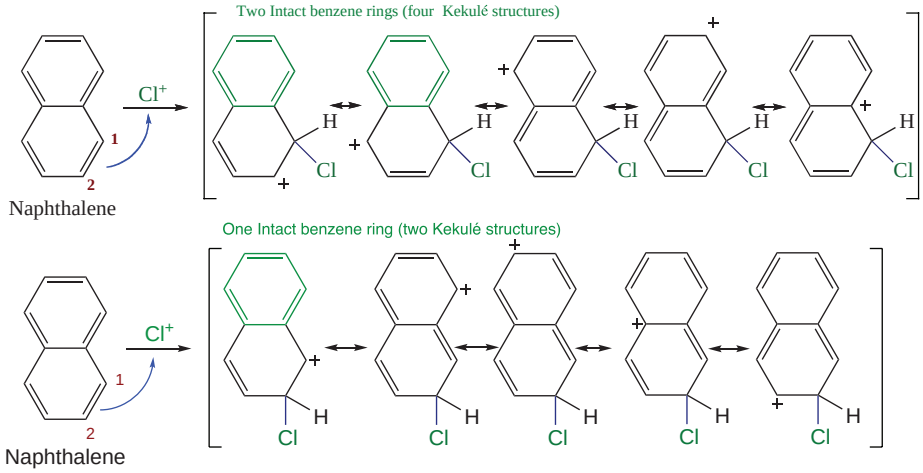
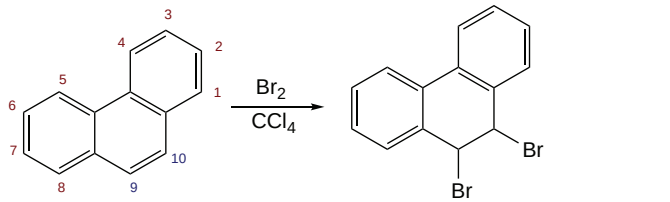


FIGURE 19.11 Arenium ions for chlorination at C1 and at C2 of naphthalene.

general, if there are more carbon atoms there are more potential sites for substitution and more arenium ion structures must be considered.

19.32 Draw all resonance forms for reaction of Cl^+ at the C9 of anthracene.



Phenanthrene 9,10-Dibromo-9,10-dihydrophenanthrene

In phenanthrene the "middle" ring is not stabilized by aromaticity to the same extent as the others. It is "less aromatic." The two rings that flank the central ring can be drawn as Kekulé structures, with two resonance contributors. Indeed, C9 and C10 are susceptible to reactions possible for benzene or naphthalene. Those positions are commonly referred to as the *"bay region"* of phenanthrene. Phenanthrene reacts with diatomic bromine in the *absence* of a Lewis acid to yield 9,10-dibromo-9,10-dihydrophenanthrene. Dihydroxylation (Section 15.3) at C9 and C10 also occurs.

Nucleophilic Aromatic Substitution

19.10 NUCLEOPHILIC AROMATIC SUBSTITUTION

Substitution reactions are known in which a nucleophile donates electrons to a benzene ring. Both a nucleophile and a benzene ring are electron-rich, however, so bringing them together in a reaction has a high E_{act} and requires high temperatures. This reaction is an example of a *nucleophilic aromatic substitution*, a *S_NAr reaction.* The S_NAr reaction of chlorobenzene and NaOH requires heating to 200–400 °C to give phenol as the product. The mechanism requires attack of the nucleophilic hydroxide on the sp^2 carbon that bears the chlorine (the

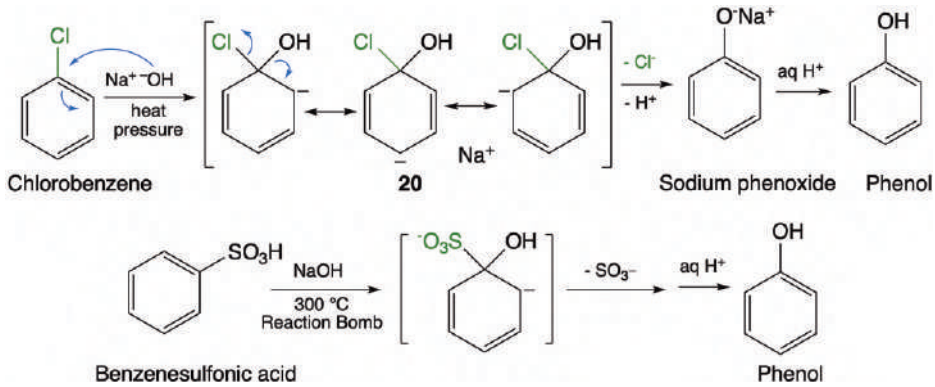
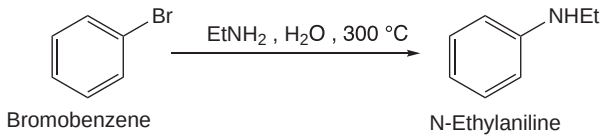


FIGURE 19.12 The S_NAr reactions of chlorobenzene and also benzenesulfonic acid with hydroxide to give phenol.

ipso carbon) to generate resonance-stabilized carbanionic intermediate **20** (Figure 19.12). The chloride ion in **20** is a good leaving group and is rapidly expelled to form phenol, which is formed in a basic solution of aqueous hydroxide. The pK_a of phenol is ~ 10 so it reacts with hydroxide to form sodium phenoxide. Neutralization with dilute acid regenerates phenol.

19.33 Write out all steps in a preparation of 4-methylphenol from toluene.

An older example of a S_NAr reaction heats benzenesulfonic acid and aqueous NaOH to 300 °C in a reaction bomb, so it is under pressure. Initial deprotonation of the sulfonic acid by hydroxide ion affords sodium benzenesulfonate. This anion reacts with hydroxide to give a resonance-stabilized carbanionic intermediate by an S_NAr pathway. Loss of sodium sulfite (Na_2SO_3) gives the phenoxide ion. Neutralization with acid yields phenol and this is an important industrial preparation of phenol.



The S_NAr reaction can be used to make aniline derivatives. When bromobenzene is heated with ethylamine ($EtNH_2$) in aqueous solution to ~ 300 °C, the S_NAr reaction is slow in water or alcohol solvents but the product is *N*-ethylaniline. The S_NAr reactions is much faster in tertiary amide solvents such as *N,N*-dimethylformamide (DMF) or *N,N*-dimethylacetamide. The reaction of bromobenzene with ethylamine, for example, produces a good yield of *N*-ethylaniline at a reaction temperature of only 160–200 °C when DMF is used as the solvent.

19.34 Write out a preparation of *N,N*-dimethylaniline from benzene.

When the substrate for nucleophilic aromatic substitution has an electron-withdrawing substituent on the ring, the S_NAr reaction can proceed under very mild conditions. Electron-withdrawing substituents at C2, C4 and C6 relative to the ipso carbon have a δ^+ dipole that will stabilize the carbanionic intermediate of an S_NAr reaction. Such stabilization lowers the E_{act} and increases the rate of reaction, allowing milder reaction conditions. The reaction of 2,4,6-trinitrochlorobenzene with dilute aqueous hydroxide, for example, occurs at room temperature to give 2,4,6-trinitrophenol. Initial reaction with hydroxide gives intermediate **21** as shown in Figure 19.13.

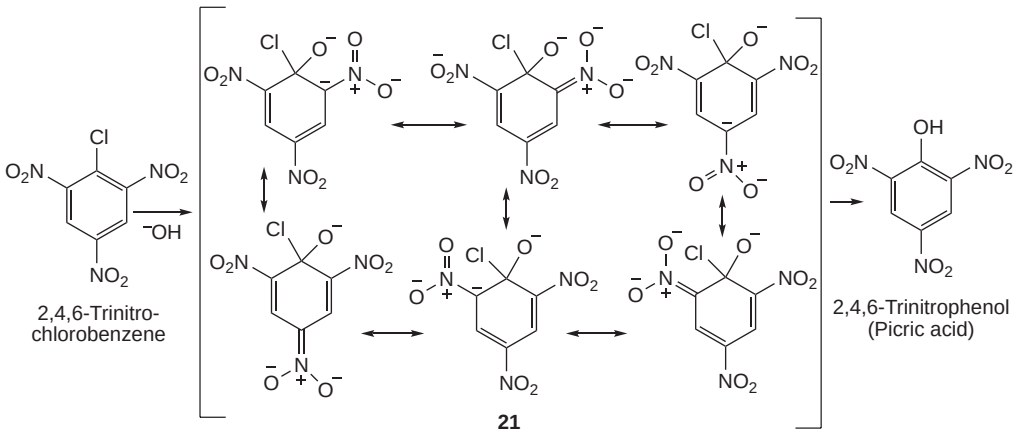


FIGURE 19.13 Nucleophilic aromatic substitution of trinitrochlorobenzene.

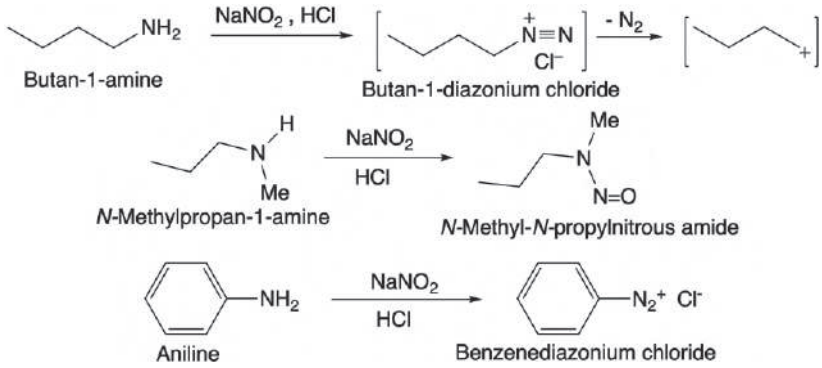
There are six resonance structures with the positive charge on C2, C4 and C6 because there is delocalization onto each of the three nitro groups. Due to the increased resonance delocalization, a S_NAr reaction is very facile. Note that 2,4,6-trinitrophenol is also known as *picric acid*, and it is used in munitions and explosives. A solution of picric acid (known as *Bouin solution*) is used as a fixative for histology specimens. The greater the number of electron-withdrawing groups at the ortho-para positions, the faster the reaction and the reaction conditions are milder. Conversely, the presence of electron-releasing groups (OR, NR_2, alkyl, etc.) on the ring makes the rate of an S_NAr reaction slower and more difficult.

19.35 Determine why the aromatic substitution reaction of hydroxide with 3-nitro-1-bromobenzene is much slower than the identical reaction with 4-nitro-1-bromobenzene.

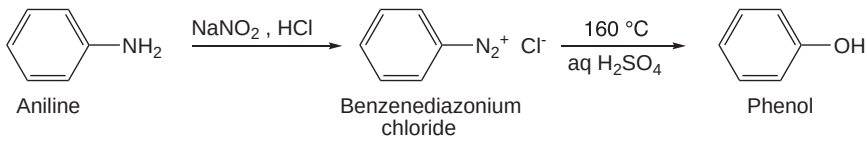
19.11 AROMATIC AMINES AND DIAZONIUM SALTS

Diazonium Salts

There is a class of highly reactive compounds derived from aniline derivatives called *diazonium salts*. When hydrochloric acid is mixed with sodium nitrite ($NaNO_2$), the resulting reaction generates *nitrous acid* (HONO). Nitrous acid reacts rapidly with amines to generate a highly reactive product called a *diazonium salt*. Diazonium salts (RN_2^+) contain the nitrogen gas unit ($N_2{=}N{\equiv}N$), an excellent leaving group. An aliphatic primary amine such as butan-1-amine reacts with nitrous acid to yield butan-1-diazonium chloride. This diazonium salt is extremely unstable and loses nitrogen gas to generate a primary carbocation, which rapidly undergoes rearrangement and further reaction. Secondary amines react with HONO to yield *N*-nitrosamines. The reaction of *N*-methylpropan-1-amine affords *N*-methyl-*N*-propylnitrous amide, an unstable nitrosamine that rapidly decomposes. Nitrosamines may be present in many foodstuffs (e.g., processed fish, bacon) and they have been labeled as cancer suspect agents.

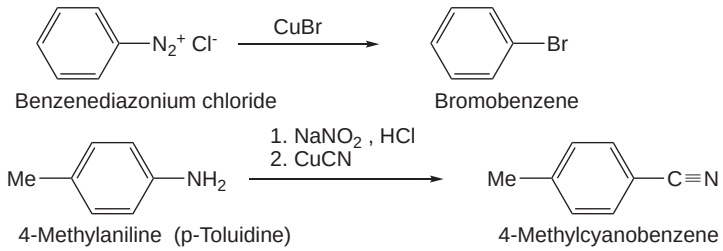


The diazonium salts derived from the reaction of aromatic amines are characterized by a $-N_2^+$ unit attached to the aromatic ring. In aqueous media, aromatic diazonium salts are significantly more stable than aliphatic diazonium salts. The reaction of $NaNO_2$/HCl gives HONO *in situ* and reaction with aniline gives benzenediazonium chloride. There are several important reactions of aromatic diazonium salts. For the most part, this reaction is restricted to primary aromatic amines (e.g., aniline) and many if not most aromatic diazonium salts are *dangerously explosive* if allowed to dry.



Reactions of Diazonium Salts

Once an aryl diazonium salt is formed in aqueous solution, reagents are added that give isolable products. Heating benzenediazonium chloride in aqueous H_2SO_4 at temperatures ~ 160 °C leads to substitution of N_2 by H_2O and formation of phenol (aniline ⟶ phenol). The presumed mechanism for the reaction of the diazonium salt is S_NAr.

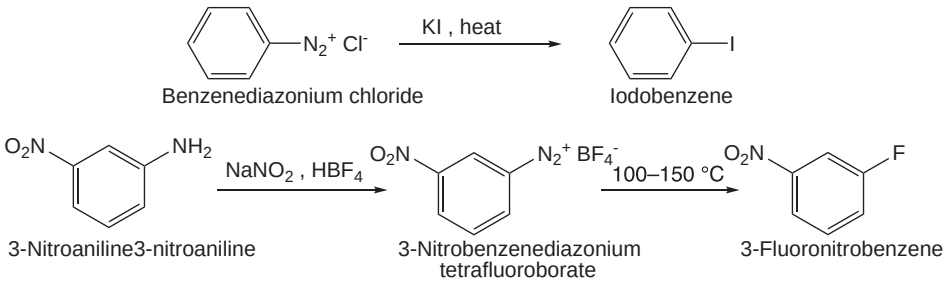


Aryl diazonium salts are also converted to aryl halides by reaction with cuprous salts (CuX) in what is known as the *Sandmeyer reaction*, named after Traugott Sandmeyer (Switzerland; 1854–1922). When benzenediazonium chloride reacts with cuprous bromide (CuBr), for example, the product is bromobenzene. Heating benzenediazonium chloride with cuprous chloride (CuCl) yields chlorobenzene. A variation of this reaction treats benzenediazonium chloride with cuprous cyanide (CuCN) to afford benzonitrile. Similarly, reaction of 4-methylaniline with HONO and then with CuCN gave 4-methylcyanobenzene.

19.36 Draw the product of a reaction between 1-aminonaphthalene and sodium nitrite in HCl.

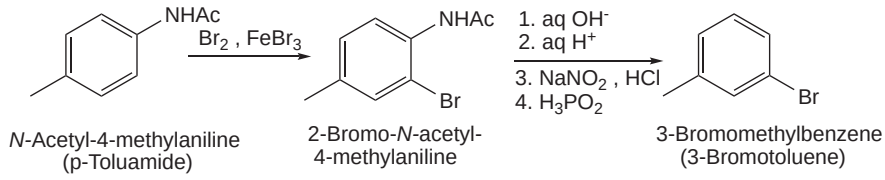
19.37 Draw the product of a reaction between 3,4-dimethylaniline and $NaNO_2$ in HCl, followed by treatment with aq H_2SO_4 at 160°C.

Iodobenzene or fluorobenzene can also be prepared from aryldiazonium salts. When benzenediazonium chloride is heated with potassium iodide (KI), the product is iodobenzene. Fluorides can be prepared by changing the acid used to prepare the diazonium salt. The reaction of $NaNO_2$ and tetrafluoroboric acid (HBF_4) gives a diazonium salt, $N_2^+BF_4^-$. Reaction with 3-nitroaniline gives 3-nitrobenzenediazonium tetrafluoroborate. When this salt is heated to 100–150 °C, the product is 3-fluoronitrobenzene.



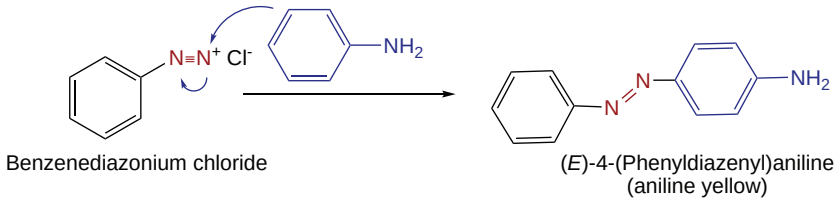
19.38 Write out a the reactions that will convert benzene to 4-fluorobromobenzene.

It is possible to *remove* nitrogen completely from the molecule and replace it with a hydrogen atom (a reduction) by heating a diazonium salt with hypophosphorus acid (H_3PO_2). Conversion of aniline to benzenediazonium chloride and subsequent heating with H_3PO_2 gives benzene. This reaction is used to prepare aromatic derivatives that are difficult to obtain by any other method. An example is the preparation of 3-bromotoluene from toluene. Analysis of 3-bromomethylbenzene shows that both bromine and methyl are ortho-para directors. The starting material is *N*-acetyl-4-methylaniline. Bromination occurs ortho to the more activating acetamide group, which is hydrolyzed the amine. Subsequent reaction with $NaNO_2$/HCl and then H_3PO_2 gives 3-bromomethylbenzene. A S_EAr reaction of either bromobenzene or toluene will not give 3-bromomethylbenzene. The amido group allows the bromine to be properly positioned. Removal of the amine via the diazonium salt gives the desired product.



19.39 Write out the reaction sequence for conversion of toluene to 2-bromo-*N*-acetyl-4-methylaniline and then to 3-bromomethylbenzene.

Highly colored and important compounds known as *azo dyes* can be prepared from aryl diazonium salts. Diazonium salts only react with benzene derivatives that contains a powerful activating substituent. The mechanism involves attack of one benzene ring at the diazo unit of the second. An example is the reaction of benzenediazonium chloride with aniline to produce the diazo compound, (*E*)-4-(phenyldiazenyl)aniline (*aniline yellow*), which is an orange powder in solid form.



Aniline yellow was first produced in 1861 and is believed to be the first commercial azo dye. It is used today in pyrotechnics for yellow colored smokes and in yellow pigments and inks, including inks for inkjet printers. *N,N*-Dimethylaniline gives *methyl yellow*, *N,N*-dimethyl-4-(phenyldiazenyl)aniline, which is used as a pH indicator. A solution of methyl yellow turns red below pH 2.9 and turns yellow above pH 4.0. *Methyl orange* is another azo dye derived from *N,N*-dimethylaniline and benzenesulfonic acid. It is used as a pH indicator. It exhibits a clear and distinct color change in titrations for acids, turning red < pH 3.1 and yellow < 4.4. Apart from the use as an indicator dye, methyl red it is also used in microbiology for the *Methyl Red (MR) Test*. This test is used to identify bacteria producing stable acids from mixed acid fermentation of glucose. The coupling reaction of benzenediazonium

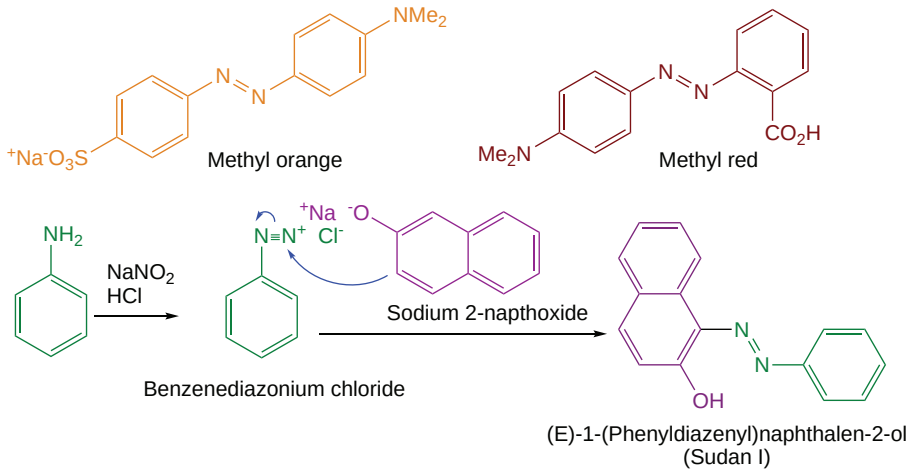
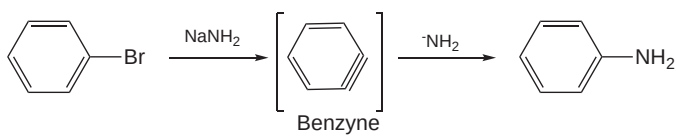


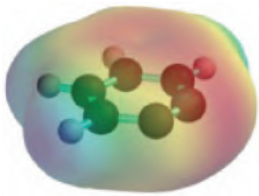
FIGURE 19.14 Azo dyes and preparation of Sudan I.

chloride and the sodium salt of 2-hydroxynaphthalene (sodium 2-napthoxide) affords *Sudan I* as shown in Figure 19.14. Sudan I is an orange-red solid and a fat-soluble dye (a lysochrome).

Benzyne Intermediates

19.12 BENZYNE INTERMEDIATES





The hydrogen atoms of benzene have a pK_a of about 43, so it is a remarkably weak acid. In halobenzene derivatives, the polarizing influence of the halogen slightly enhances the acidity of the ortho protons. The ortho hydrogen atoms of bromobenzene, for example, can be removed by a very strong base (e.g., $NaNH_2$ or an organolithium reagent) to form a carbanion. In bromobenzene, bromine is a leaving group and once the carbanion is formed loss of bromine gives an intermediate called *benzyne,* with a π-bond that is in the plane of the benzene ring. The new π-bond on benzene is a triple bond. The electron potential map of benzyne shows a region of high electron density (in red) that is perpendicular to the aromatic cloud, consistent with the π-bond of *benzyne.* A benzyne intermediate can be formed from many aromatic derivatives and they are highly reactive intermediates. They are susceptible to reaction with a suitable nucleophile such as the amide anion. In this simple example the product is aniline (PhBr ⟶ $PhNH_2$).

There is a regiochemistry issue for the reaction of benzene derivatives that have substituents on the ring. An example is the deprotonation of 2-bromoanisole with sodium amide in ammonia to give **22**, as shown in Figure 19.15. Once **22** is formed, the electrons of the carbanion unit expel the leaving group bromide to form the new π-bond in the *benzyne* intermediate, **23**. The new π-bond generates a triple bond that is orthogonal to the aromatic cloud.

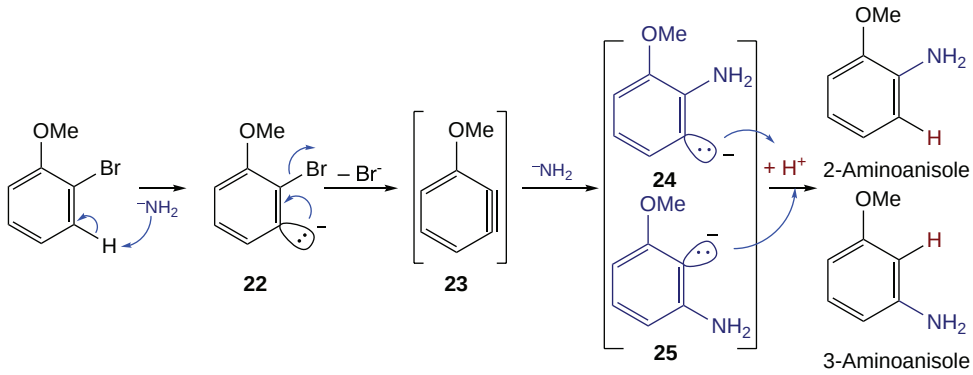


FIGURE 19.15 Mechanism of nucleophilic substitution via a benzyne intermediate.

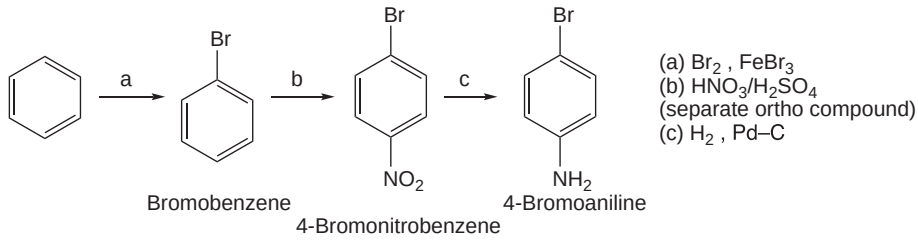
The amide anion (NH_2^-) reacts with the π-bond of benzyne **23** to give amine-substituted intermediates **24** and **25**. Once formed, carbanions are powerful bases that react with a weak acid such as ammonia to give 2-aminoanisole from **24** and 3-aminoanisole from **25** in relatively equal amounts. Benzyne reactions can be quite useful for the preparation of aromatic derivatives that are not available by other methods.

19.40 Write out an acid-base reaction in which benzene is the acid and sodium amide is the base.

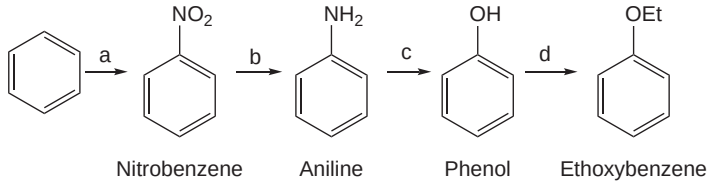
19.13 SYNTHESIS OF AROMATIC COMPOUNDS

Synthesis of Benzene Derivatives

Aromatic compounds can be prepared by a sequence of the reactions presented in this chapter in a sequence that will give the target. This process is known as *synthesis* (Section 7.1) For electrophilic aromatic substitution, the choice of a reaction sequence will depend on the substituent, electron-releasing or withdrawing, activating or deactivating, and if it is an ortho-para director or a meta director.



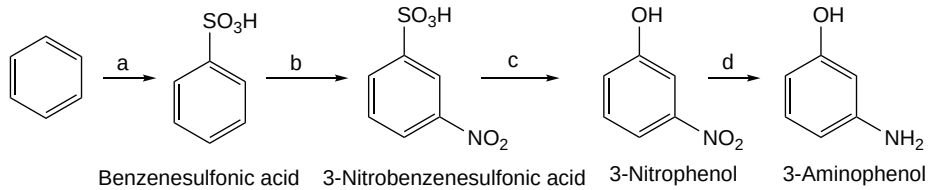
This section will provide a few examples of the synthesis of substituted aromatic hydrocarbons to illustrate the general strategy used. The first problem will prepare 4-bromoaniline from benzene. Bromination of benzene gives bromobenzene, and nitration leads to a mixture of ortho and para-bromonitrobenzenes. Separation of the para-isomer is followed by reduction of the nitro group by catalytic hydrogenation to give 4-bromoaniline. The second problem is the preparation of ethoxybenzene (phenetole) from benzene.



(a) HNO_3/H_2SO_4 (b) H_2 , Pd/C (c) i. $NaNO_2$, HCl ii. aq H_2SO_4 , 160 °C (d) i. NaH ii. EtBr

Since ethoxybenzene is an ether, the most likely precursor is phenol, which is prepared from aniline via the diazonium salt. Aniline is prepared directly from benzene via nitration followed by reduction of the nitro group by catalytic hydrogenation. The reaction of the amine group with HONO and heating with aqueous sulfuric acid gives phenol. Deprotonation of the phenol by treatment with base give the nucleophilic phenoxide anion that reacts with bromoethane to give ethoxybenzene.

The third problem prepares 3-aminophenol from benzene, but the OH and NH_2 group, both activating and ortho–para directors, are meta to each other. This means that these groups must be derived from other groups that were meta directors. The NH_2 group in 3-aminophenol is derived from a nitro group so one precursor is probably 3-nitrophenol since the OH group can be prepared from an NH_2 group and therefore from a nitro group. It is known that phenol is prepared from a sulfonic acid via an aromatic S_NAr reaction. Following this sequence, 3-aminophenol is prepared from 3-nitrophenol, which is derived from 3-nitrobenzenesulfonic acid. The nitro compound is prepared by nitration of benzenesulfonic acid. Since benzenesulfonic acid is prepared directly from benzene.



(a) SO_3/H_2SO_4 (b) HNO_3/H_2SO_4 (c) aq NaOH , 200 °C (d) H_2 , Pd/C

19.41 Write out the preparation of 3-chlorobromobenzene from benzene.

Spectroscopy of Benzene Derivatives

19.14 SPECTROSCOPY OF AROMATIC COMPOUNDS

Several absorption peaks in the infrared can be used to determine the substitution pattern on benzene rings. Using the *out-of-plane bands*, a monosubstituted benzene ring shows two strong bands (five adjacent H), whereas a disubstituted benzene ring may have at least three variants: 1,2-, 1,3-, and 1,4-. A 1,2-disubstituted benzene ring will have four adjacent protons (one peak at 770–735 cm^{-1}) and a 1,4-disubstituted benzene ring will have only two adjacent protons (one peak at 860–800 cm^{-1}). A 1,3-disubstituted benzene ring has one isolated proton and three adjacent protons and will show one peak at 900–860 cm^{-1} and another at 810–750 cm^{-1}. The IR spectra of ortho, meta, and para-xylene are shown in Figure 19.16 to illustrate the out-of-plane bands that are used for identification of the substitution pattern on the benzene ring.

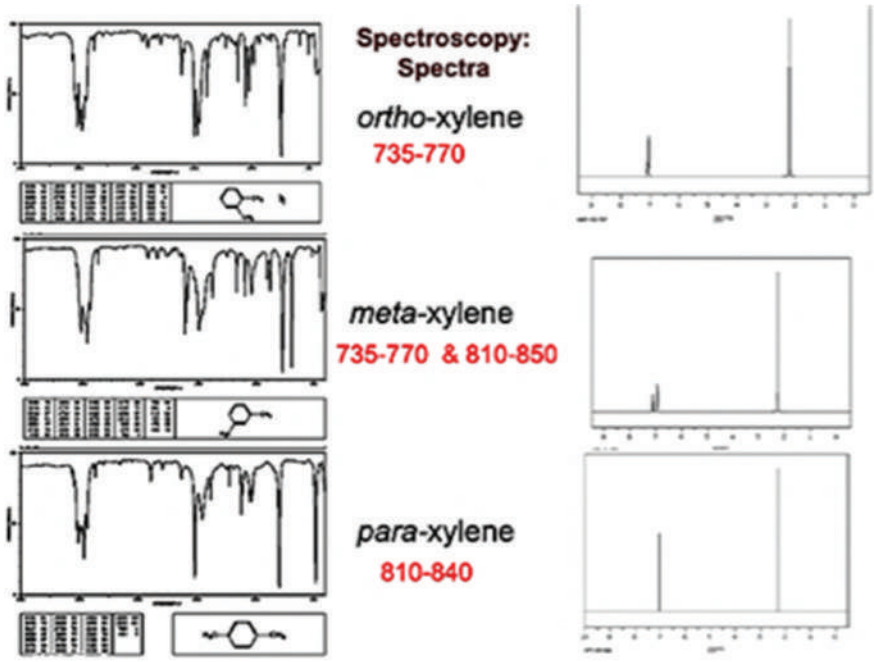
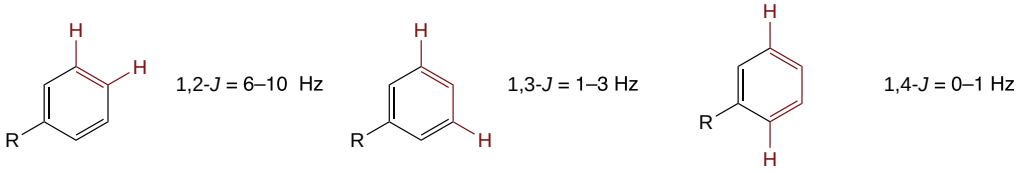


FIGURE 19.16 The infrared spectra and proton NMR or ortho, meta and para-xylene.

The region of the NMR where signals for a benzene ring are found may be quite complicated due to coupling between the protons, especially when there are substituents on the benzene ring. A benzene ring with two substituents may have a 1,2-, a 1,3-, or a 1,4-relationship for two substituents. Different structural patterns lead to different coupling constants for the hydrogen atoms on the benzene ring, as shown. Modern instruments can usually distinguish these coupling constants to identify the position of substituents as a 1,2-, 1,3-, or 1,4-relationship. With instruments that have a lower Gauss magnet, the aromatic ring often appears as a multiplet or as broad peaks in the proton NMR. In such cases, the integration of the phenyl group region is used only to give the number of aromatic protons.

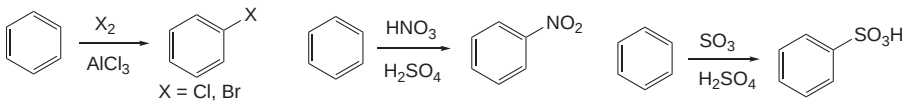


19.15 ORGANIZATION OF REACTION TYPES

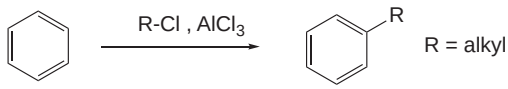
The reaction of benzene derivatives can be organized as follows:

What reactions are possible for benzene?

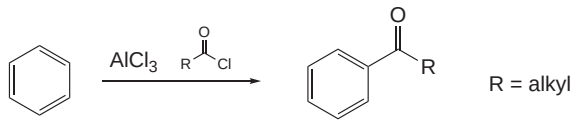
1. Benzene reacts with bromine, chlorine, nitric acid-sulfuric acid, or SO_3-sulfuric acid in the presence of a Lewis acid catalyst via electrophilic aromatic substitution.



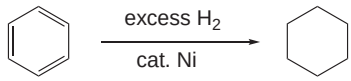
2. Benzene reacts with alkyl halides in the presence of a Lewis acid catalyst via electrophilic aromatic substitution to give an arene.



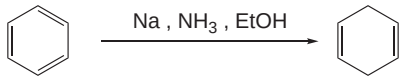
3. Benzene reacts with acid chlorides in the presence of a Lewis acid catalyst via electrophilic aromatic substitution to give a ketone.



4. Benzene is reduced to cyclohexane with an excess of hydrogen and a transition metal catalyst.

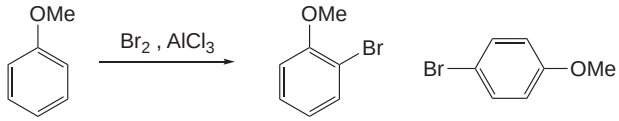


5. Benzene is reduced to cyclohexa-1,4-dienes with sodium in liquid ammonia and ethanol.

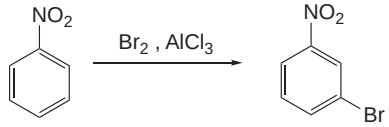


What reactions are possible for substituted benzenes?

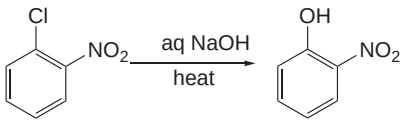
1. Benzene derivatives with electron-releasing groups attached undergo electrophilic aromatic substitution to yield ortho and para disubstituted products.



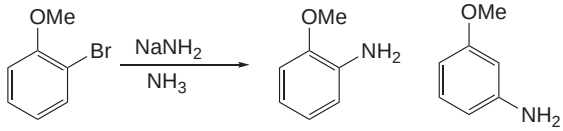
2. Benzene derivatives with electron-withdrawing groups attached undergo electrophilic aromatic substitution to yield meta disubstituted products.



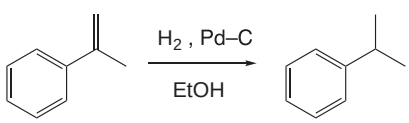
3. Halobenzene derivatives react with nucleophiles under vigorous conditions to yield a nucleophilic aromatic substitution product.



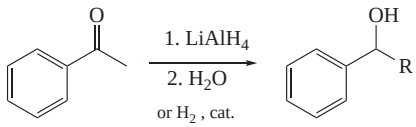
4. Halobenzene derivatives react with base to give a benzyne intermediate, which reacts with a nucleophile to yield substitution products.



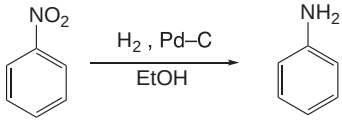
5. Alkene and alkyne units attached to a benzene ring are reduced to yield alkane or alkene substituents.



6. Aldehydes, ketones, and carboxylic acid units attached to a benzene ring are reduced to yield alcohols.

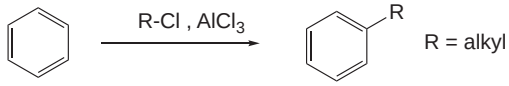


7. Nitro units attached to a benzene ring are reduced to yield aniline derivatives.

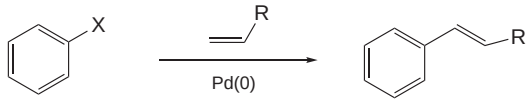


What reactions are possible for alkyl halides?

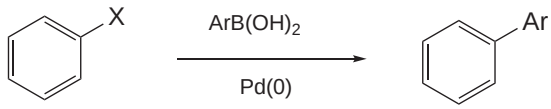
1. Alkyl halides react with Lewis acids to yield carbocations, which react with benzene to yield arenes.



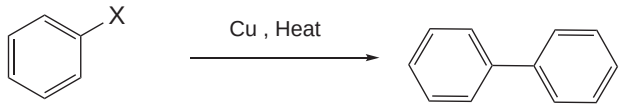
2. Aryl halides react with alkenes in the presence of a palladium catalyst to give aryl alkenes.



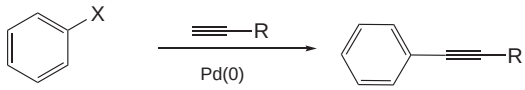
3. Aryl halides react with arylboronic acids in the presence of a palladium catalyst to give biaryls



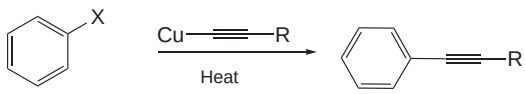
4. Aryl halides are heated with copper to give biaryls.



5. Aryl halides react with alkynes in the presence of a palladium catalyst to give aryl alkynes.

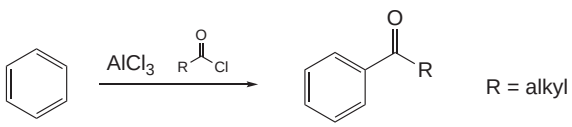


6. Aryl halides are heated with cuprous alkynes to give aryl alkynes.



What reactions are possible for acid chlorides?

1. Acyl halides react with Lewis acids to yield acylium ions, which react with benzene to yield ketones.



19.16 BIOLOGICAL RELEVANCE

Aromatic compounds and aromatic substitution reactions are part of many biological systems. Aromatic substitution chemistry is important for the production of many prescription drugs, as well as also over-the-counter medicines. Aniline, for example, is a starting material for the manufacture of drugs [e.g., Acetaminophen/Paracetamol (Tylenol), which is *N*-acetyl-4-hydroxyaniline].

19.42 Draw the structure of acetaminophen.

The biosynthesis of tyrosine in some mammals involves an aromatic substitution of phenylalanine, as shown in Figure 19.17.[22] Phenylalanine is obtained from food in a normal diet,

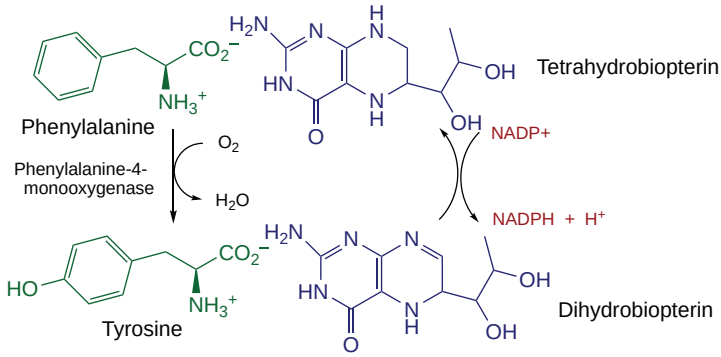


FIGURE 19.17 Biosynthesis of tyrosine.

and in the presence of tetrahydrobiopterin, oxygen and the enzyme phenylalanine-4-monooxygenase, tyrosine is formed along with dihydrobiopterin. In the body, dihydrobiopterin is converted by NADPH back to tetrahydrobiopterin and $NADP^+$ (Section 17.7). The conversion of $NADP^+$ to NADPH is formally a Birch reduction (Section 19.7).

The biosynthesis of vancomycin involves regioselective chlorination by a flavin-dependent *halogenase*. One of these enzymes is *tryptophan 7-halogenase* (PrnA). The biosynthetic and regioselective chlorination of tryptophan uses HOCl (Section 10.5.3), as shown in Figure 19.18.[23]

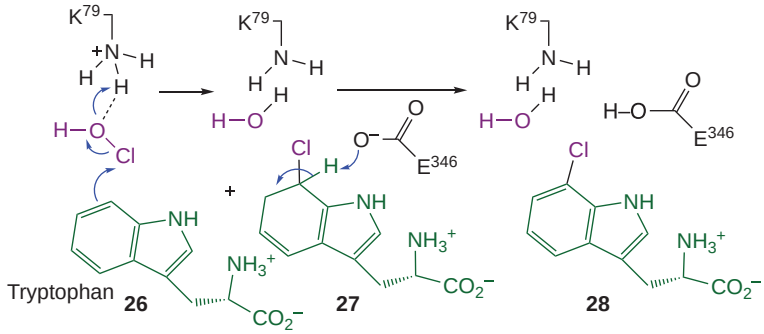


FIGURE 19.18 Enzyme mediated chlorination of tryptophan. [From Dong, C.; Flecks, S.; Unversucht, S.; Haupt, C.; van Pée, K.-H.; Naismith, J.H. *Science*, 2005, 309, 2216–2219. Reprinted with permission from AAAS.]

[22] Garrett, R.F.; Grisham, C.K. *Biochemistry* Saunders, Fort Worth, TX, 1995, pp. 859–860.
[23] Dong, C.; Flecks, S.; Unversucht, S.; Haupt, C.; van Pée, K.-H.; Naismith, J.H. *Science* 2005, 309, 2216–2219.

Using amino acid residue ^{79}K (a lysine residue in **26**), binding HOCl allows electrophilic substitution on the indole ring as shown in tryptophan to yield an arenium ion, **27**. Indole is discussed in Section 23.1. Loss of the proton to amino acid residue E^{346} (a glutamic acid residue) leads to the chlorinated indole unit in **28**. The numbers associated with the amino acid residue refer to their position in the enzyme, and the one-letter codes for the amino acids are presented in Section 24.3.

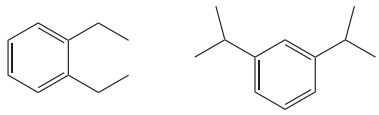
CORRELATION OF HOMEWORK WITH CONCEPTS

- Benzene is an aromatic molecule. A molecule is aromatic if it is cyclic, has a continuous and contiguous array of sp^2 hybridized atoms, and has $4n+2$ π-electrons (Hückel's rule). Both anions and cations derived from cyclic hydrocarbons can be aromatic if they fit the usual criteria: 1, 28, 29, 46, 51.
- Benzene derivatives with an alkyl substituent are called arenes: 2, 3, 43.
- Benzene derivatives bearing heteroatom substituents include phenol (OH), aniline (NH_2), anisole (OMe), benzoic acid (COOH), benzonitrile (CN), benzaldehyde (CHO), acetophenone (COMe), and benzophenone (COPh): 74, 5, 6, 7, 8, 42, 43, 44.
- Benzene and benzene derivatives react via S_EAr reactions: 9, 10, 45, 47, 48, 49, 50, 55, 56.
- Friedel–Crafts alkylation is the reaction of benzene with a carbocation to give an arene. Friedel–Crafts acylation is the reaction of benzene with an acylium ion to give a phenyl ketone: 11, 12, 13, 47, 49.
- Substituents on benzene give regioselective S_EAr reactions. Substituents that yield ortho/para products and react faster than benzene are called activators. Substituents that yield meta products and react slower than benzene are called deactivators: 14, 15, 16, 17, 18, 19, 20, 47, 48, 49, 55, 56.
- Benzene and derivatives are reduced by catalytic hydrogenation or dissolving metal reduction. Aryl substituents are reduced using catalytic hydrogenation or hydride reducing agents: 23, 24, 25, 26, 50, 55, 57, 60.
- Aryl halides with alkenes, alkynes or other aryl halides with a transition metal catalyst to give aryl alkenes, aryl alkynes or biaryls: 21, 22, 47, 56.
- Polycyclic aromatic compounds include naphthalene, anthracene, and phenanthrene and they react via S_EAr reactions: 30, 31, 32, 46, 52, 53, 54, 55.
- Nucleophilic substitution at the sp^2 carbon of a halobenzene derivative does not occur unless high heat and pressure are used: 33, 34, 35, 56.
- Aniline reacts with nitrous acid to give benzenediazonium salts, which react with a variety of reagents via a substitution reaction: 36, 37, 38, 39, 58, 59, 61.
- When halobenzene derivatives are heated with powerful bases (e.g., sodium amide), deprotonation is followed by elimination to yield a benzyne, which reacts rapidly with the nucleophile: 40, 56.
- The synthesis of aromatic compounds uses S_EAr reactions and S_NAr reactions: 27, 39, 41, 56, 62, 63.
- Spectroscopy can be used to determine the structure of a particular molecule (Chapter 13): 64, 65, 66.

ANSWERS TO IN-CHAPTER QUESTIONS

19.1 The π-bond in cyclohexene is localized between the two carbon atoms and the electrons are readily donated to a hydrogen atom of HBr to generate a carbocation intermediate. There are four π-electrons in cyclohexadiene and it is also reactive. The greater stability of the resonance-stabilized allylic carbocation intermediate makes cyclohexadiene more reactive with HBr.

19.2



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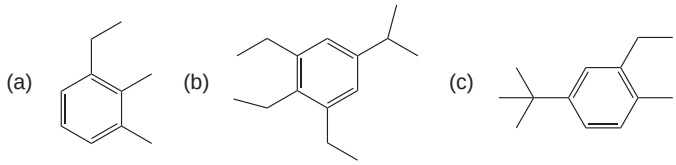

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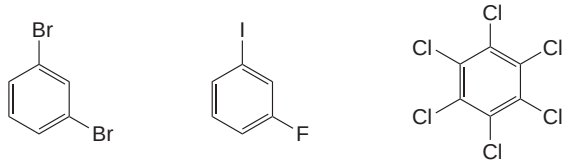

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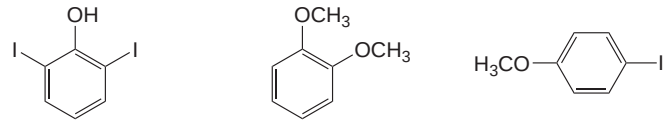

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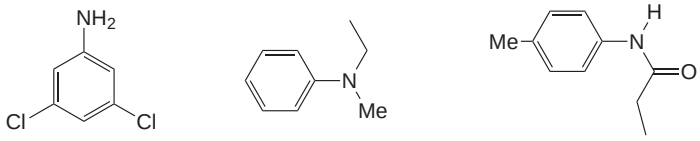

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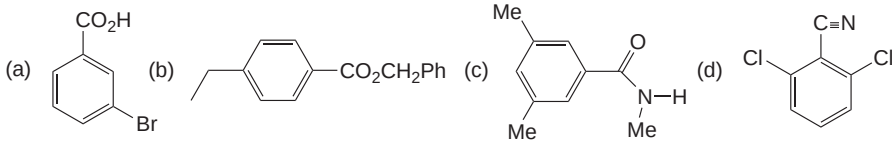

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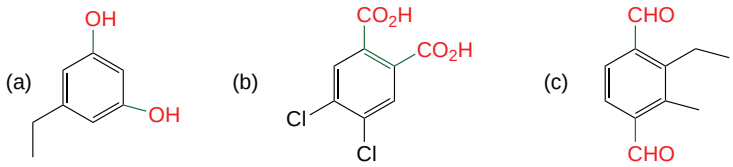

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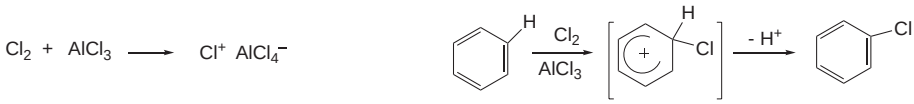

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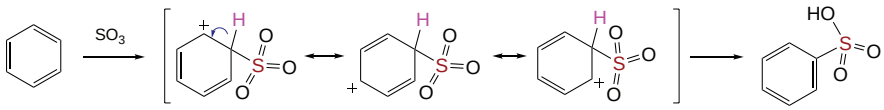

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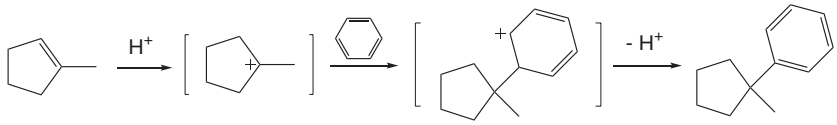
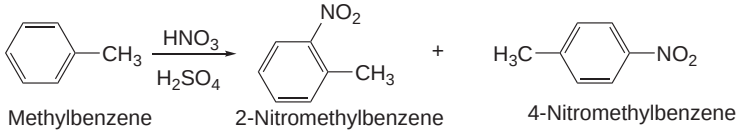


19.12

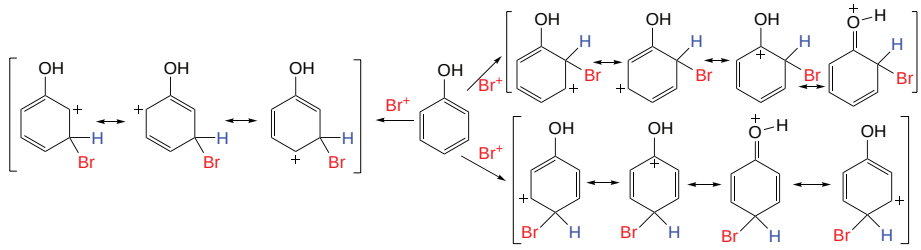
19.13

19.14



Methylbenzene 2-Nitromethylbenzene 4-Nitromethylbenzene

19.15



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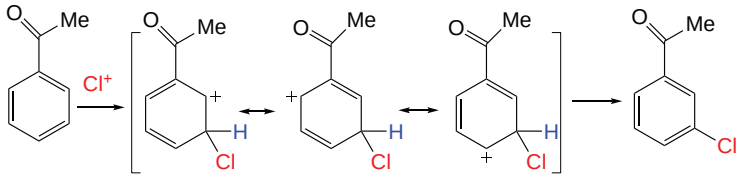

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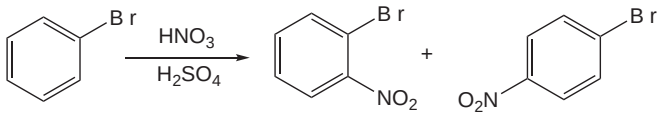

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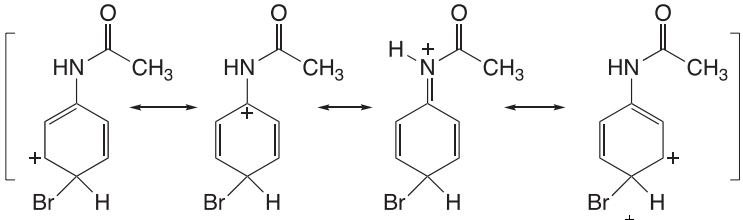
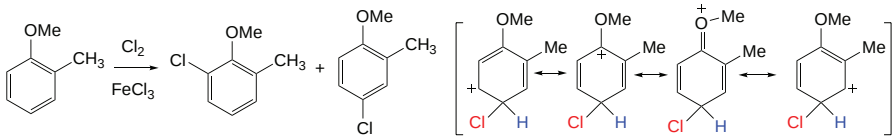


19.19



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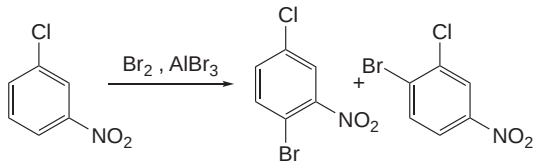
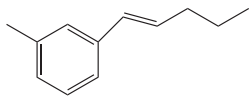


Cl is less deactivating, and it is an ortho–para director

19.21



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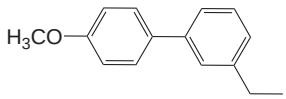

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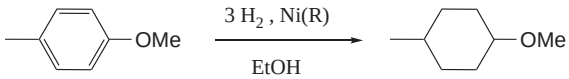

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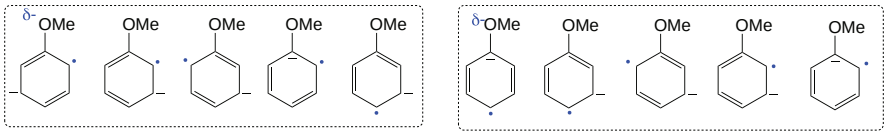

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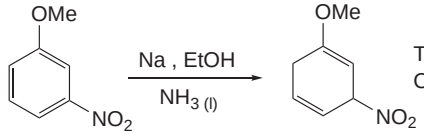
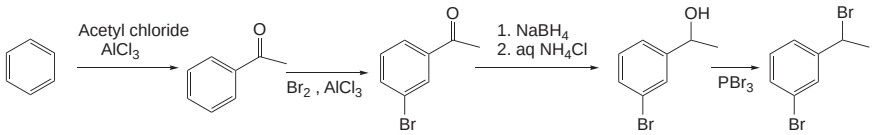


This products satisfies both substituents - OMe on sp^2 C and NO_2 on sp^3 C

19.26



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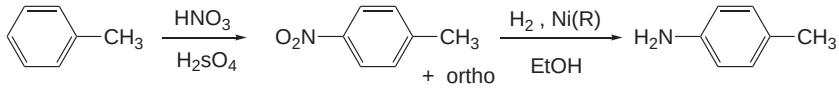

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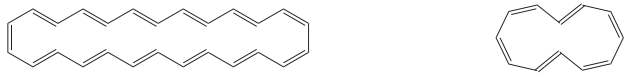
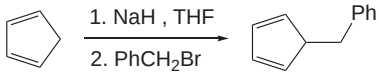


[26]-Annulene — fits 4n+2 rule where n = 6
Therefore, with 26 π-electrons this is aromatic

[12]-Annulene — does not fit the 4n+2 rule so it is not aromatic. It fits the 4n rule (n = 3) and is actually anti-aromatic

19.29



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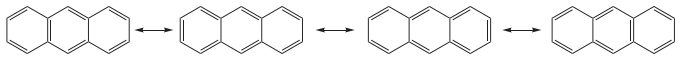
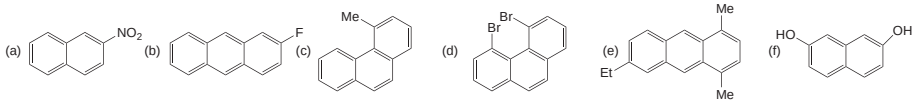
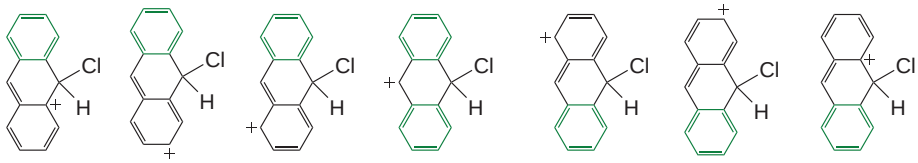


19.31



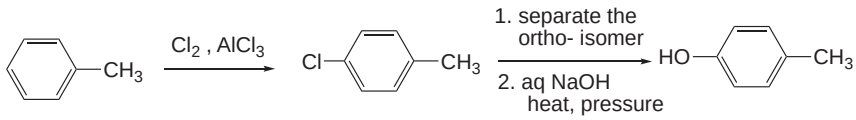
2-Nitronaphthalene — 2-Fuoroanthracene — 4-Methylphenanthrene — 4,5-Dibromophenanthrene — 6-Ethyl-1,4-dimethylanthracene — Naphthalene-2,7-diol

19.32

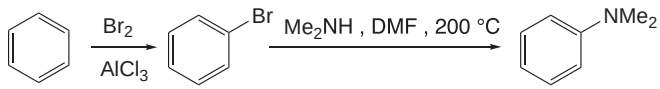


Eight intact rings, so 16 Kekulé structures

19.33

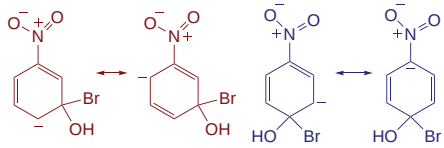


19.34



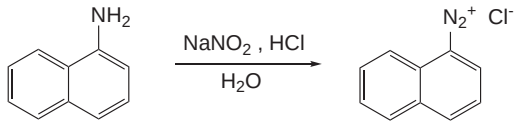
19.35

The negative charge is never on the carbon adjacent to the positive nitrogen atom



The negative charge is on the carbon adjacent to the negative nitrogen atom in one resonance form. This makes this intermediate more stable, and it leads to the major product

19.36



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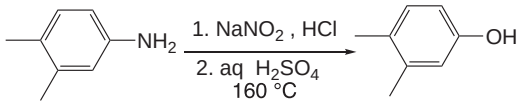

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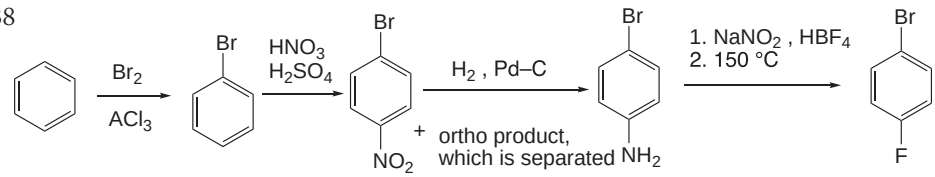

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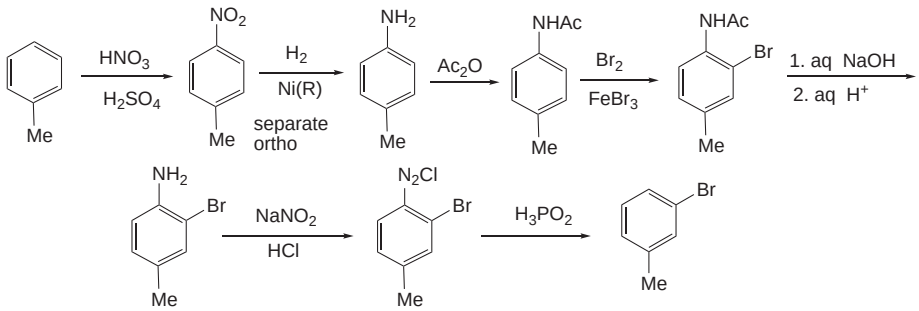
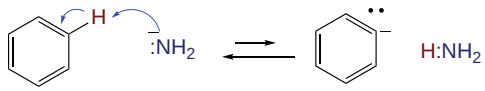
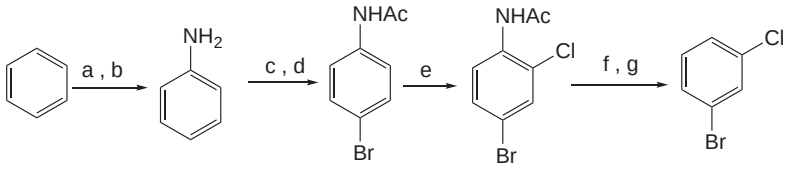


19.40

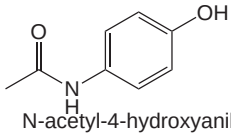


19.41



(a) HNO_3 , H_2SO_4 (b) H_2 , Pd–C (c) acetic anhydride (d) Br_2 , $FeBr_3$ (separate ortho compound) (e) Cl_2 , $AlCl_3$ (f) i. aq NaOH ii. neutralize (g) i. $NaNO_2$, HCl ii. H_3PO_2

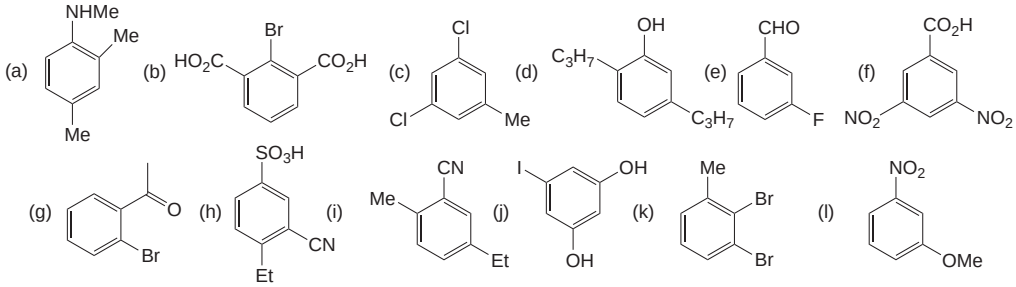
19.42



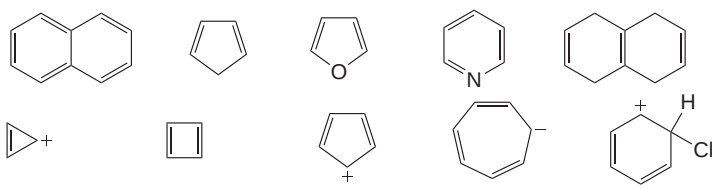
N-acetyl-4-hydroxyaniline

HOMEWORK

43. Draw the structure of each of the following:
    (a) 1,3,5-Trimethylbenzene (b) *m*-Chlorophenol (c) 3,5-Dinitroanisole (d) Hexachlorobenzene
    (e) 4-Bromophthalic acid (f) *p*-Iodobenzenesulfonic acid (g) 2-Cyanobenzoic acid (h) Phenetole
    (i) 4-Bromo-3'-chlorobenzophenone (j) 2,6-Dinitrohydroquinone (k) *o*-Bromobenzonitrile
    (l) *m*-Xylene (m) 2,2'-Dimethylstilbene (n) *N*-Acetyl-3-methylaniline (o) 2,2-Dimethyl-4-phenylhexane.
44. Give the correct IUPAC name to each of the following molecules:

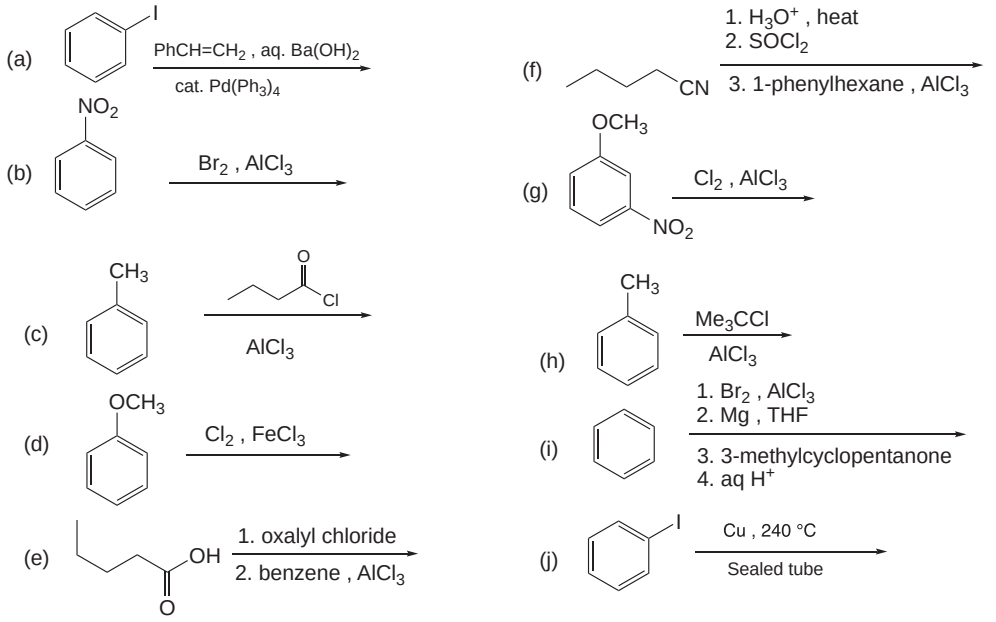


45. Give the major product for each of the following.
    (a) Benzene + 2-bromo-3-methylbutane + $AlCl_3$
    (b) Toluene + phenylacetyl chloride + $AlCl_3$
    (c) Anisole + 2-bromo-2-methylpropane + $AlCl_3$
    (d) Nitrobenzene + propanoyl chloride + $AlCl_3$
    (e) Benzene + 1-bromopentane + $AlCl_3$ (f) *p*-Xylene + acetyl chloride + $AlCl_3$
46. Identify the aromatic compounds in the following:

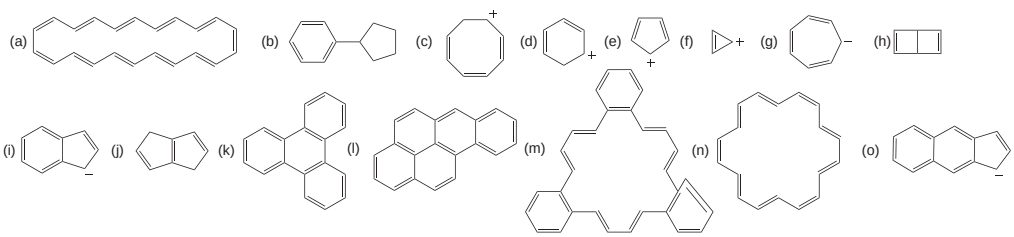


47. It is known that anisole reacts with bromine to yield aromatic substitution products without the need for a Lewis acid, whereas benzene does not react without the Lewis acid. Offer an explanation.

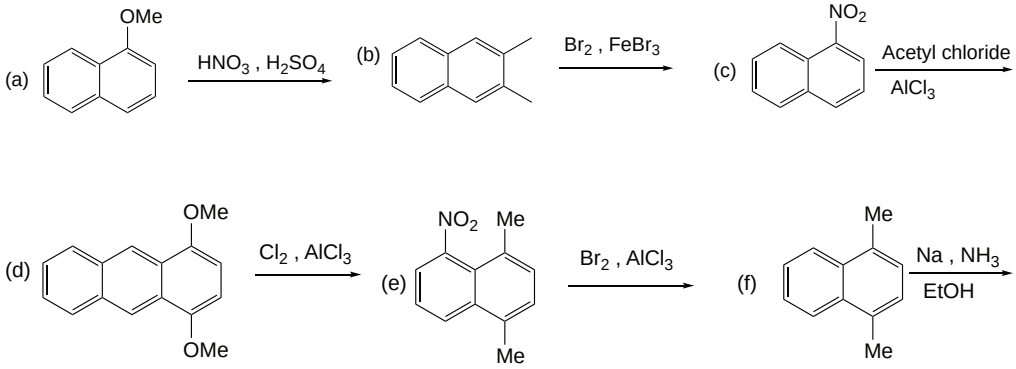
48. Give the major product for each of the following reactions:



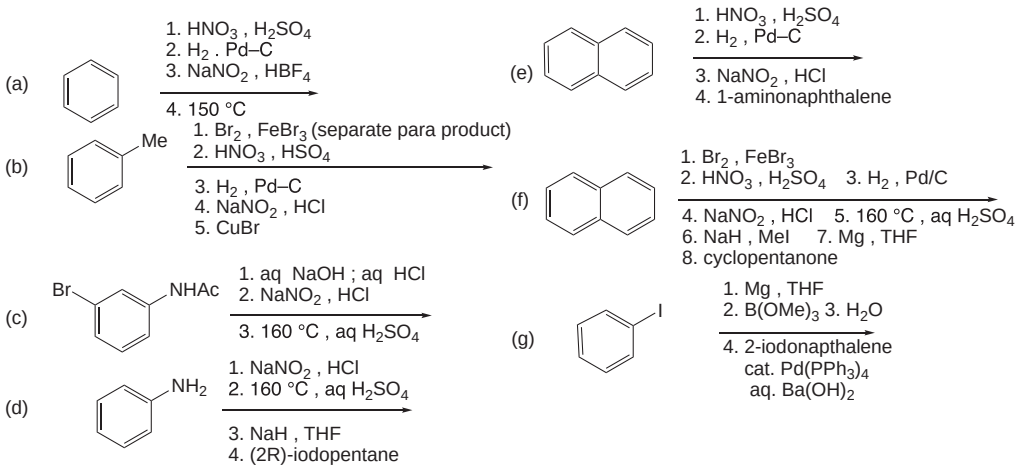
49. Give the major product for each of the following reactions:
    (a) 3-Nitroanisole + HNO_3/H_2SO_4 (b) 1,3,5-Trimethylbenzene + $Cl_2/AlCl_3$
    (c) 2-Methylbenzoic acid + SO_3/H_2SO_4 (d) 1,3-Dinitrobenzene + $Br_2/AlCl_3$
    (e) 3-Chloronitrobenzene + $Cl_2/AlCl_3$ (f) 4-Methylanisole + acetyl chloride + $AlCl_3$
    (g) *N*-Acetyl-3,5-dimethylaniline + acetyl chloride/$AlCl_3$
    (h) 2-Ethylanisole + *t*-butyl bromide/$AlCl_3$
50. Give the major product of the following reactions:
    (a) Nitrobenzene + H_2 + Pd (b) 2-Phenylhex-2-ene + H_2 + Pd–C
    (c) Toluene + 3 H_2 + Rh, heat (d) *p*-Xylene + Na/NH_3/EtOH
    (e) Benzene + 1. acetyl chloride/$AlCl_3$ 2. $NaBH_4$ 3. hydrolysis
    (f) Phenyllithium + 1. CO_2 2. hydrolysis 3. Na/NH_3/EtOH
    (g) Butanoic acid + 1. thionyl chloride 2. toluene/$AlCl_3$ 3. NH_2NH_2/KOH
    (h) Nitrobenzene + 1. H_2, Pd–C 2. acetic anhydride 3. $LiAlH_4$ 4. hydrolysis
    (i) Benzene + 1. $Br_2/FeBr_3$ 2. Mg, THF 3. propanal 4. PCC 5. Zn(Hg), HCl
51. Why does bromination of 1-methoxy-8-nitronaphthalene occur preferentially in the ring bearing the OMe unit?
52. Draw all resonance forms for the intermediate generated with 2-methoxyphenanthrene reacts with $Br_2/FeBr_3$ with attack at C7.
53. Give the major product formed when 1-aminonaphthalene is treated with HCl/$NaNO_2$ and then):
    (a) 160 °C, aq H_2SO_4 (b) CuCN (c) CuBr (d) CuCl (e) KI, heat
    (f) $PhNH_2$ (g) H_3PO_2
54. Give the number of π-electrons and indicate whether or not it is aromatic.



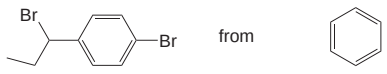
55. What is the major product(s) from the following reactions?



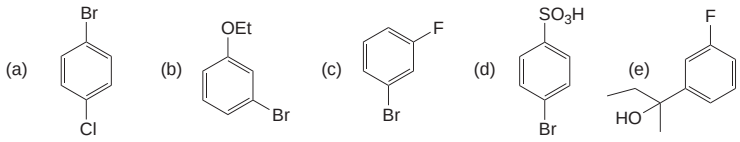
56. Give the major product of each of the following and show the intermediate product for each step.



57. Suggest the major product formed when 1-methoxynaphthalene is treated with sodium metal in a mixture of liquid ammonia and ethanol. What product is formed when 1-nitronaphthalene reacts under the same conditions?
58. What products result from each reaction and what is the final product of the following sequence?
    (i) nitrobenzene + H_2/Ni(R) (ii) HCl/$NaNO_2$ (iii) KF, THF.
59. Draw the diazonium salt formed when 2-aminonaphthalene reacts with acetic acid/$NaNO_2$. When this diazonium salt reacts with *N*-methyldiphenylamine, what is the structure of the resulting product? If the diazonium salt reacts with 1,3,5-trimethoxybenzene, what is the resulting product?
60. What is the product formed when benzaldehyde is treated with (i) H_2, PtO_2 (ii) PBr_3 (iii) $NaC{\equiv}CCH_3$, THF (iv) 1 equivalent of H_2 with a Pd–$BaSO_4$ catalyst that is poisoned with quinoline.
61. When aniline is converted to benzenediazonium chloride using $NaNO_2$ and HCl, heating with water can give phenol. Offer a reasonable mechanism that explains this reaction. If the diazonium salt is heated with CuBr, what is the product?
62. Show a synthesis for the following with all intermediate products and reagents. No mechanisms.

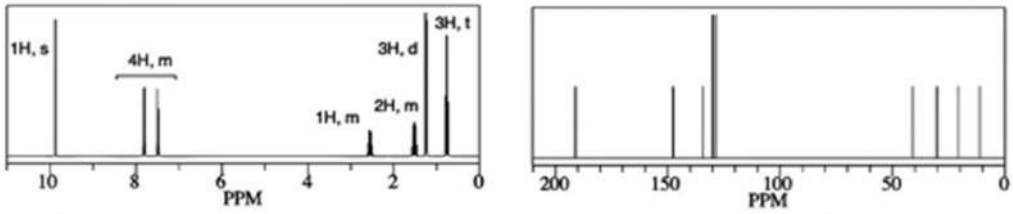


63. Provide a synthesis of each of the following from benzene:



Spectroscopic problems. Do not attempt these problems until Chapter 13 has been read and understood.

64. Describe the ^1H NMR spectrum of hexachlorobenzene.
65. Identify the molecule with the formula $C_{11}H_{14}O$ and the spectral data that are provided. IR: 2800-3000, 2815, 1727, 1580, and 660 cm^{-1}.



66. Identify the molecule with the formula C_7H_8O and the spectral data that are provided. IR: broad peak at 3333, 3036, 2922, 1614, 1514, 1237, 816, 740 cm^{-1}. ^1H NMR: 7.00–6.72 (m, 4H), 5.20 (broad s, 1H; this peak is diminished when treated with D_2O), 2.25 (s, 3H) ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-20.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

20

Enolate Anions

Acyl Addition and Acyl Substitution

Carbonyl derivatives with a proton on an α-carbon react with a suitable base to generate a carbon nucleophile called an enolate anion. Enolate anions react as a nucleophile in acyl addition, acyl substitution and alkylation reactions.

To begin this chapter, you should know the following points:

- Aldehydes, ketones, and acid derivatives (Sections 5.6, 16.1, 18.1, and 18.2).
- Ketones and aldehydes (Sections 10.8, 15.2, and 15.5).
- Acid-base strength (Sections 6.2 and 6.3).
- Equilibrium reactions (Sections 2.3 and 7.8).
- Resonance (Sections 2.6, 6.3, and 19.1).
- Rate of reaction (Section 7.11).
- Rotamers and conformations (Sections 8.1–8.6).
- Keto-enol tautomerism (Sections 10.8 and 15.5).
- E2 reactions (Sections 12.1–12.3).
- S_N2 reaction (Sections 11.2 and 11.3).
- Grignard reagents and organolithium reagents (Sections 14.1–14.3 and 16.2).
- Amines react as acids in the presence of a strong base (Section 6.5).
- Acyl addition reactions of nucleophiles (Sections 16.2–16.4).
- Acyl substitution reactions (Sections 18.2–18.9).
- Electron-releasing and -withdrawing substituents (Sections 10.1 and 19.4.2).
- (*E*) and (*Z*) nomenclature (Section 9.7).
- Absolute configuration and stereogenic centers (Sections 9.1 and 9.2).
- Diastereomers (Section 9.5).

Aldehydes, Ketones and Enols

20.1 ALDEHYDES AND KETONES ARE WEAK ACIDS

Keto-enol tautomerism was discussed in Sections 10.7.2,4,5 in connection with the hydration, oxymercuration and hydroboration reactions of alkynes. Ketones and aldehydes exist in equilibrium with small amounts of the enol form. Keto-enol tautomerism favors the carbonyl form since it is more stable.

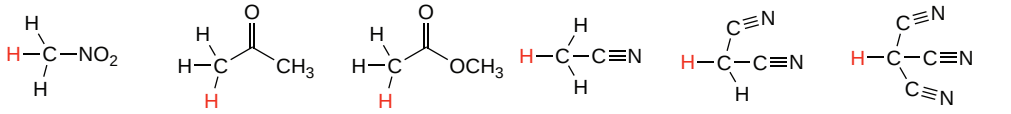
20.1.1 ACIDITY OF THE A-PROTON OF KETONES AND ALDEHYDES

Methane is a remarkably weak acid, with a pK_a of about 48.[1] When an electron-withdrawing functional group is attached to a sp^3 carbon, the α-carbon, is polarized δ^- due to the inductive effect of the carbonyl. The hydrogen atom attached to an α-carbon is called the α-hydrogen or the α-proton, and it is polarized δ^+. Therefore, the α-proton is a weak acid. The acidity of the α-proton will vary with the electron-withdrawing ability of the attached functional group.

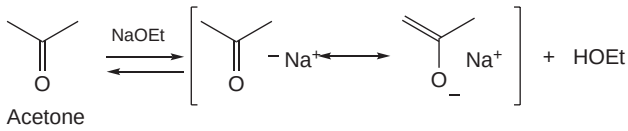
[1] Smith, M.B. *March's Advanced Organic Chemistry*, 8th ed, John Wiley & Sons, Hoboken, NJ, 2020, p. 345.

DOI: 10.1201/9781003174929-20

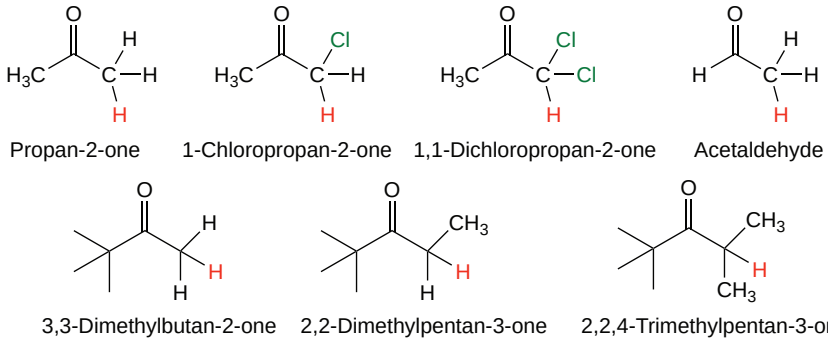
Nitromethane has a very polarized α-proton and it has a pK_a of about 11.1.[2] The α-proton of acetone is less polarized and has a pK_a of about 20.[3] An ester is less electron-withdrawing than a ketone and it is a weaker acid, and the pK_a of methyl acetate is about 25.6.[4] The cyano group (–C≡N) is less electron-withdrawing than a carbonyl group, and the pK_a of cyanomethane (acetonitrile) has a 24.[5] Multiple functional groups such as cyano attached to the α-proton will increase the acidity of the α-proton. Dicyanomethane has a pK_a of 11.2 and tricyanomethane has a pK_a of -5.[5,6] Note that tricyanomethane is more acidic than nitric acid, which has a pK_a of about 1.4.



The acidity of these compounds is important because the acid-base reaction gives a carbanion conjugate base. Using acetone as an example, the reaction with sodium ethoxide gives an *enolate anion* as the conjugate base. The enolate anion is resonance stabilized and it will be shown to react as a nucleophile in S_N2 reactions (Section 20.3), in acyl addition reactions (Section 20.4), and in acyl substitution reactions (Section 20.8).



The presence of an electron-withdrawing substituent on the α-carbon will enhance the δ⁺ dipole of the α-proton. An electron-withdrawing chlorine atom, for example, makes the α-proton more acidic. The pK_a of propan-2-one is 20[3] but the pK_a of chloroacetone (1-chloropropan-2-one) is 15.8.[5] A second electron-withdrawing chlorine atom in 1,1-dichloroacetone makes the α-proton more polarized and therefore more acidic. The pK_a of 1,1-dichloroacetone (1,1-dichloropropan-2-one) is 14.9.[7] Indeed, as the number of electron-withdrawing substituents attached to the α-carbon increase, the acidity increases (smaller pK_a).



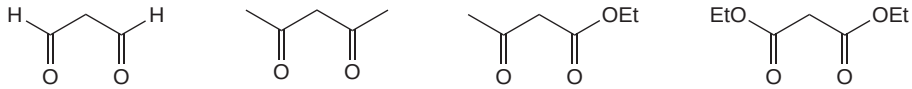
20.1 Indicate the acidic proton in propanal. Why is the O=C—H hydrogen atom not acidic?

[2] Bordwell, F.G.; Satish, A.V. *Journal of the American Chemical Society* 1994, *116*, 8885–8889.
[3] Chiang, Y.; Kresge, A.J.; Tan, Y.S.; Wirz, J. *Journal of the American Chemical Society* 1984, 106, 460–462.
[4] Grabowski, J.J. *Chemical Communications* 1997, 255–256.
[5] Pearson, R.G.; Dillon, R.C. *Journal of the American Chemical Society* 1953, 75, 2439–2443.
[6] Stewart, R., *The Proton: Applications to Organic Chemistry*, Academic Press, NY, 1985, p. 54.
[7] Kemp, D.S.; Casey, M.L. *Journal of the American Chemical Society* 1973, 95, 6670–6680.

20.2 Draw the enol expected from 1-bromopropan-2-one and indicate the intramolecular hydrogen bonding that is possible for this structure.

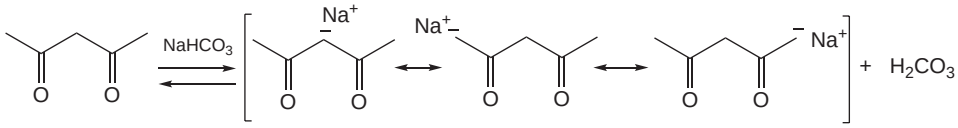
20.3 Predict whether acetone or 2,4,4-trimethylpentan-3-one is more acidic.

Alkyl groups are electron-releasing, so the α-proton on a carbon with an alkyl substituent is less polarized and less acidic. A hydrogen atom on a less substituted carbon is more acidic than a hydrogen atom on a more substituted carbon. A comparison of acetone (pK_a, 20) and 3,3-dimethylbutan-2-one (pK_a of 20.8) shows the latter is a slightly weaker acid. However, 3,3-dimethylbutan-2-one is a stronger acid that 2,2-dimethylpentan-3-one, with a pK_a of 21.3.[8] 2,2,4-Trimethylpentan-3-one is an even weaker acid, with a pK_a of 23.5.[8] It is apparent that the presence of the alkyl substituents leads to a higher pK_a (a less acidic proton). The presence of an electron releasing alkyl group also makes the α-proton of a ketone less acidic than that of an aldehyde. An aldehyde has a carbon group and a hydrogen atom attached to the carbonyl whereas a ketone has two attached carbon groups. The two electron-releasing alkyl groups make the carbonyl of a ketone less polarized than the carbonyl of an aldehyde with only one. Therefore, the α-proton of an aldehyde is more acidic than that of a ketone. The measured pK_a of the α-proton in propan-2-one (a ketone) is 20,[3] and that of ethanal (acetaldehyde) is 16.5.[1]



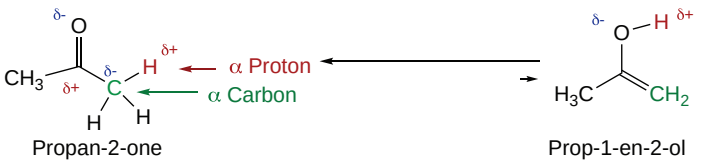
Propanedial (malonaldehyde) | Pentane-2,4-dione | Ethyl 3-oxobutanoate | Diethyl propanedioate (diethyl malonate)

Apart from the influence of electron-withdrawing substituents, an α-proton becomes increasingly acidic if an α-carbon has more than one electron-withdrawing functional group. Dicarbonyl compounds with a 1,3-relationship of the carbonyls (O=C—CH_2—C=O) will therefore be more acidic. Examples include 1,3-propanedial (malonaldehye), pentane-2,4-dione, 3-oxoesters β-ketoesters such as methyl 3-oxobutanoate, and 1,3-dioic esters such as diethyl malonates. The α-protons are on the CH_2 unit of pentane-2,4-dione and the pK_a is ~ 9.[5] The pK_a of pentane-2,4-dione is 9.0,[5] malonaldehdye is 5.9,[5] ethyl 3-oxobutanoate is 10.68,[5] and the pK_a of diethyl malonate is 13.3.[5]



Pentane-2,4-dione

Difunctional molecules (e.g., pentan-2,4-dione) are more acidic than simple aldehydes or ketones. Therefore, a weaker base may be used to remove the α-proton. Reaction of pentane-2,4-dione with $NaHCO_3$, for example, leads to the enolate anion, sodium 2,4-dioxopentan-3-ide. Bicarbonate does *not* react with pentan-3-one under the same conditions. The increase in acidity is due in large part to the stability of the enolate anion formed. The 2,4-dioxopentan-3-ide anion has three resonance contributors due to the presence of the second carbonyl unit, so it is more stable (less reactive) and a weaker base. The increased stability of this conjugate base leads to a smaller pK_a for pentane-2,4-dione.



Propan-2-one | Prop-1-en-2-ol

[8] Zook, H.D.; Kelly, W.L.; Posey, I.Y. *Journal of Organic Chemistry* 1968, 33, 3477–3480; (b) House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, Menlo Park, CA, 1972, p. 494 and references 1, 2b cited therein.

Aldehydes and ketones exist primarily in the keto form, but a tiny amount of enol is present. For example, there is only 1.5 x 10^{-4} % enol (prop-1-en-2-ol) in neat acetone.[9] The α-proton on the α-carbon is acidic, as described previously, but the O—H proton of the enol is also acidic. The pK_a of the OH unit in prop-1-en-2-ol is about 8.2. There is a relationship between greater enol content of a ketone or aldehyde and the acidity of the α-proton. Electron-withdrawing substituents at the α-carbon will lead to a greater percentage of the enol form, which is consistent with the greater acidity of those compounds. The two carbonyl units in pentane-2,4-dione leads to an increased enol content due to (79.7%) and the α-protons are more acidic.

Enolate Anions

Treatment of an aldehyde or ketone with a strong base will initiate an acid-base reaction as shown previously, but either the α-proton in the keto form or the acidic proton of the enol form can be deprotonated as shown in Figure 20.1. The product of the acid-base reaction is a

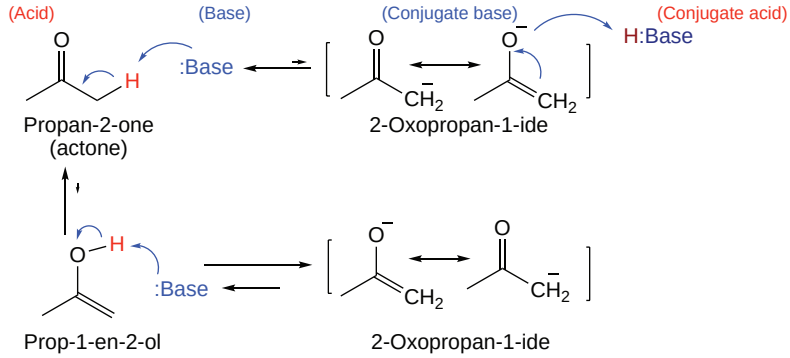


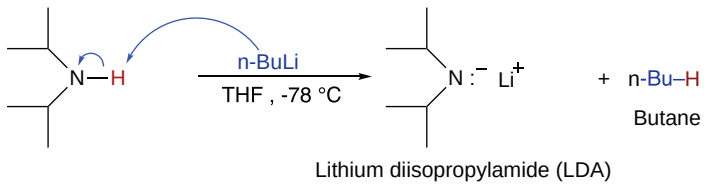
FIGURE 20.1 Formation of the enolate anion from acetone.

resonance-stabilized conjugate base known as an *enolate anion*. Acetone gives the enolate anion, 2-oxopropan-1-ide. A major contributing factor to K_a of the α-proton is the charge delocalization (resonance-stability) of the conjugate base. A more stable enolate anion shifts the acid-base equilibrium so the K_a is larger (smaller pK_a) and the α-proton is more acidic. Examination of the two resonance contributors for the enolate anion shows that the negative charge is delocalized on oxygen in one resonance contributor and on carbon in the other. Enolate anions usually have a larger concentration of electron density on the carbon relative to the oxygen atom. This charge distribution indicates that an enolate anion should react via carbon rather than oxygen.

20.4 Draw all resonance forms for sodium 2,4-dioxopentan-3-ide.
20.5 Draw the enol expected from 2-methylbutanal, as well as the enolate anion that is expected when this ketone reacts with a base.

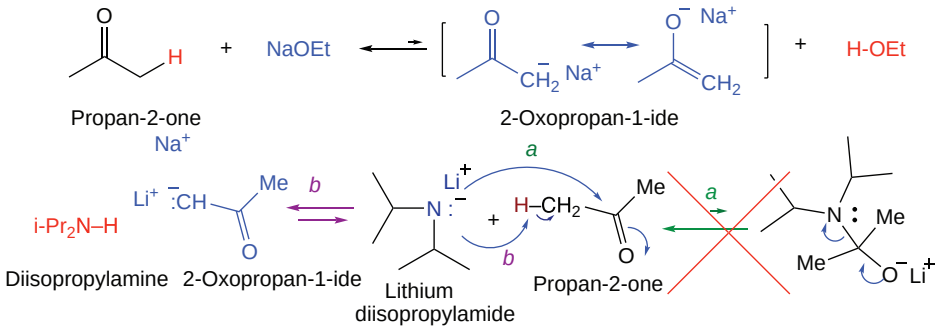
20.2 NONNUCLEOPHILIC BASES

A secondary amine (e.g., diisopropylamine) is a weak acid (pK_a ~ 36–40). A powerful base such as an organolithium is required to remove the proton from nitrogen. The product is the amide base *lithium diisopropylamide* (commonly abbreviated as LDA). The reaction is carried out at a low temperature, -78 °C, in the aprotic solvent THF. The conjugate acid of this reaction is butane, which is a remarkably weak acid. Therefore, the reaction generates a large concentration of LDA, which is a strong base.



[9] Gero, A. *Journal of Organic Chemistry* 1954, 19, 469–471.

An acid-base reaction is an equilibrium. The nature of the base plays a major role in the position of the equilibrium after deprotonation of an aldehyde or ketone. In order to promote a large K_a for the acid-base reaction, the pK_a of the conjugate acid derived from the base must be weaker than that of the ketone. The pK_a of the conjugate acid is usually >22–25 in order to shift the equilibrium toward the enolate anion product. The reaction of acetone with two different bases, sodium ethoxide and LDA, will illustrate. Acetone reacts with NaOEt in ethanol to form the enolate anion, sodium 2-oxopropan-1-ide, and the conjugate acid ethanol. Ethanol, with a pK_a of ~15.7 is more acidic than acetone with a pK_a of ~20. The 2-oxopropan-1-ide can react with ethanol to regenerate acetone and ethoxide, so the acid-base equilibrium lies to the left (a small K_a). The reaction with sodium ethoxide is contrasted with the reaction of LDA. The reaction of LDA and the α-proton of acetone (*path b*) gives the enolate anion lithium 2-oxopropan-1-ide and diisopropylamine as the conjugate acid. Diisopropylamine has a pK_a of about 36 so it is a much weaker acid than the α-proton of a ketone or aldehyde. The acid-base equilibrium lies to the right (a large K_a) since 2-oxopropan-1-ide reacts poorly with diisopropylamine. Therefore the equilibrium concentration of the enolate anion is large.



In the reaction of LDA and butan-2-one, LDA does not attack the acyl carbon via *path a* because there is significant steric hindrance around the basic nitrogen atom. The large isopropyl groups of LDA interact with the alkyl groups flanking the carbonyl as shown in Figure 20.2. This interaction inhibits the nitrogen from approaching and reacting with the acyl carbon so acyl addition is very slow and not competitive with the acid-base reaction.

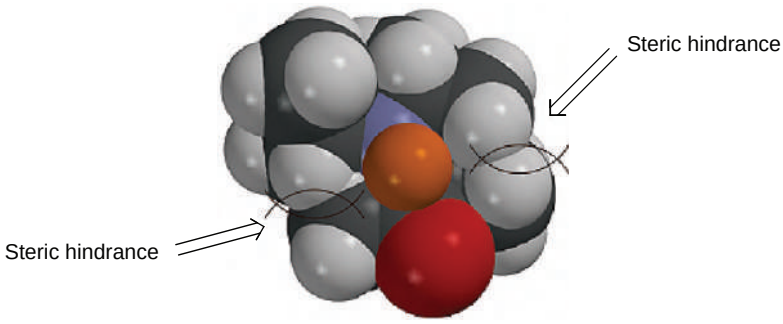


FIGURE 20.2 Steric hindrance that inhibits nucleophilic acyl addition of LDA (*top*) as it approaches butan-2-one (*bottom*). The N—Li is aligned with the C=O unit in the front of the diagram.

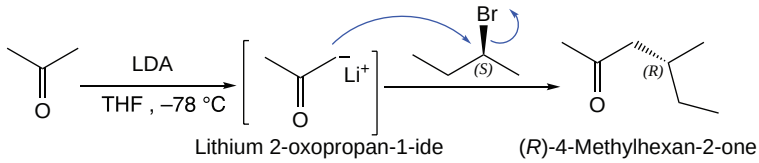
Indeed, acyl addition for virtually all ketones and aldehydes is not competitive and an acid-base reaction is faster. In other words, the *LDA is a poor nucleophile in an acyl addition reaction.* Dialkylamide bases such as LDA are commonly called *nonnucleophilic bases.* Conversely, there is little steric hindrance to approach of the proton on the α-carbon so LDA is a very strong base and reacts with acetone to form the enolate anion.

20.6 Draw and name the product of a reaction between 2,2,6,6-tetramethylpiperidine (LTMP) and butyllithium and then between hexamethyldisilazane [$(Me_3Si)_2NH$] and butyllithium.

Enolate Alkylation

20.3 ENOLATE ALKYLATION

In Sections 11.2 and 11.3, various nucleophiles were shown to react with primary and secondary alkyl halides via a S_N2 reaction to give the coupling product. Enolate anions react as carbanion nucleophiles in reactions with alkyl halides. Enolate anions also react with alkyl halides via a S_N2 reaction in what is known as *enolate alkylation*. An example is the reaction of propan-2-one (acetone) with LDA in THF at -78 °C to give lithium 2-oxopropan-1-ide.

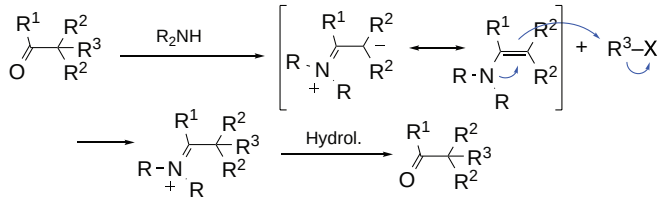


The enolate anion reacts with (2*S*)-bromobutane to give (4*R*)-methylhexan-2-one. Since this is an S_N2 reaction, there is inversion of configuration at the bromine-bearing carbon. Indeed, enolate alkylation reactions of ketone enolate anions with alkyl halides proceed with 100% inversion of configuration. The alkylation of the enolate anions derived from aldehydes may be problematic. Aldehydes tend to undergo self-condensation acyl addition reactions (Section 20.4) rather than alkylation reactions under when the enolate anion is formed. The sensitivity and reactivity of the aldehyde functionality usually requires activated substrates or specialized additives.[10]

20.7 Draw the product formed when the enolate anion of cyclopentanone reacts with 4*R*-benzyl-2*R*-iodoheptane.

Another alkylation reaction is related to enolate alkylation. Secondary amines react with ketones to give enamines, as introduced in Section 16.4.3. Enamines react with alkyl halides by a S_N2 reaction to give an iminium salt. A hydrolytic workup of the iminium salt gives a ketone. This reaction is known as the *Stork enamine reaction.* Some primary and secondary halides show sluggish reactivity. Conversion of the iminium salt to the ketone by reaction with aqueous acid completes a monoalkylation transformation. The reaction is named after Gilbert Stork (Belgium-USA; 1921–2017) an organic chemist at Columbia University. In this reaction an enamine reacts as a "nitrogen enolate anion" with a carbon nucleophile. Alkylation usually takes place at the less substituted α-carbon of the original ketone. Commonly used amines for the enamine are the cyclic amines piperidine, morpholine, and pyrrolidine.

Stork Enamine Reaction



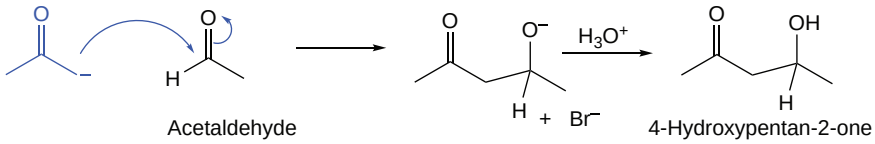
20.8 Draw all reactions and the final product when 3,3-dimethylbutan-2-one reacts with pyrrolidine and then 2-ethyloxirane, followed by reaction with aqueous acid.

[10] Capacci, A.G.; Malinowski, J.T.; McAlpine, N.J.; Kuhne, J.; MacMillan, D.W.C. *Nature Chemistry* 2017, 9, 1073–1077.

20.4 THE ALDOL CONDENSATION

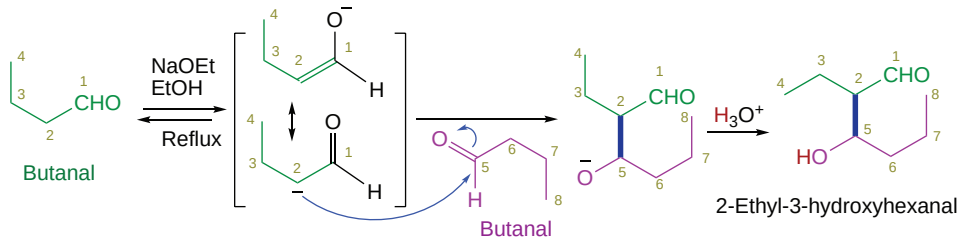
The Aldol Condensation

The discussion of acyl addition reactions in Section 16.2 clearly showed that carbon nucleophiles such as a Grignard reagent react with aldehyde or ketones to form an alkoxide product. Enolate anions also react as carbon nucleophiles in acyl addition reactions with aldehydes or ketones. In 1872 Luigi Chiozza (Italy; 1828–1889) and Adolphe Wurtz (France; 1817–1884) independently reported that an aldehyde reacted by self-condensation to give a β-hydroxy aldehyde when treated with an alkoxide base. A β-hydroxy aldehyde is known as an aldol and this reaction has come to be called the *aldol condensation*. An example is the reaction of the enolate anion of acetone with acetaldehyde to give the alkoxide. Hydrolytic workup (reaction *with aqueous acid*) gives 4-hydroxypentan-2-one.



Acetaldehyde 4-Hydroxypentan-2-one

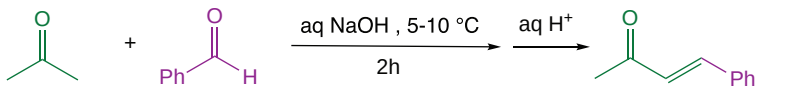
Note that in the aldol condensation the alkoxide product is called an *aldolate* and treatment with aqueous acid converts this anion to the aldol product. Another example of the aldol condensation (or aldol reaction) is the reaction of butanal with NaOEt in ethanol heated to reflux. The reaction product is the enolate anion. Subsequent hydrolytic workup gives the aldol product, 2-ethyl-3-hydroxyhexanal in 75% yield.[11] The reaction of one molecule of the aldehyde with a second molecule of the same aldehyde is called *"self-condensation."* Remember that the structure drawn for butanal in this reaction or any other molecule in any other reaction does not represent one molecule.



Butanal Butanal 2-Ethyl-3-hydroxyhexanal

Writing the structure of butanal implies one molar equivalent, or Avogadro's number of molecules (6.023×10^{23} molecules). After one half-life there are 3.01×10^{23} molecules of the enolate anion product and 3.01×10^{23} molecules of butanal in equilibrium. It is therefore perfectly reasonable that one molecule of the enolate anion can react with a molecule of unreacted butanal, which is self-condensation.

Using mild hydrolytic workup conditions, it is relatively easy to isolate the alcohol product, the aldol. However, if 2-ethyl-3-hydroxyhexanal is isolated and purified and then heated with aqueous acid, 2-ethylhex-2-enal is the product. Vigorous hydrolytic workup can lead to the dehydration product as the major product of the aldol condensation. An example is the reaction of acetone with benzaldehyde in aqueous sodium hydroxide to give an 85% yield of 4-phenylbut-3-en-2-one.[12] 4-Phenylbut-3-en-2-one is a *conjugated ketone* (also called an α,β-unsaturated ketone, Section 21.2) because the carbonyl is attached directly to one of the sp^2 carbon atoms of the alkene unit. The major product is usually the (*E*)-isomer, which is more stable than the (*Z*)-isomer. When the product can form a *conjugated* alkene unit, dehydration is very easy and it is sometimes difficult to isolate the aldol. In general, assume that a mild acid hydrolytic workup will yield the alcohol product (the aldol) rather than the alkene.

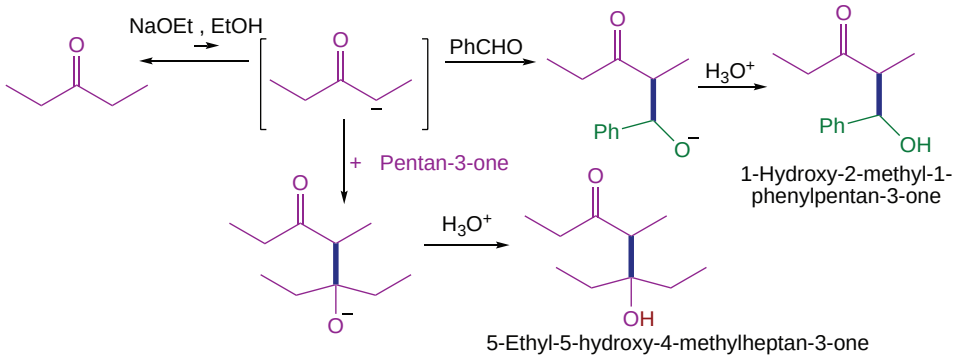


4-Phenylbut-3-en-2-one

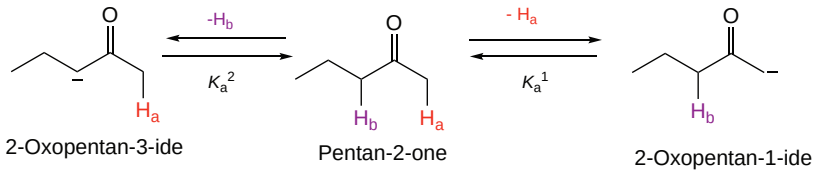
[11] Nielsen, A.T.; Houlihan, W.J. *Organic Reactions* 1968, 16, 1–438.
[12] Paul, S.; Gupta, M. *Synthetic Communications* 2005, 35, 213–222.

Mixed Aldol Condensations

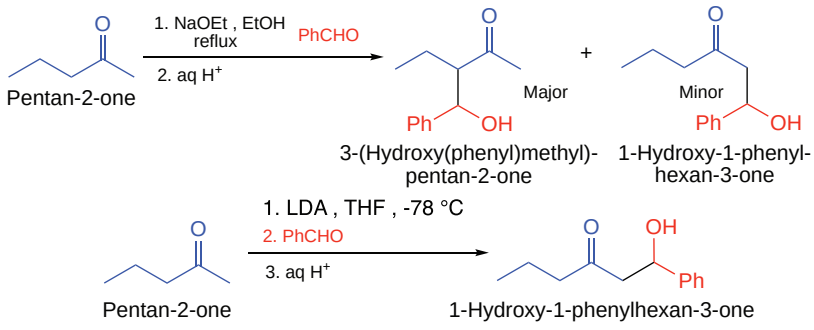
20.9 Draw the aldol sequence for self-condensation of pentan-3-one with sodium ethoxide (NaOEt) in ethanol.



An aldol condensation with different ketones can lead to very interesting aldol products. When a ketone or aldehyde is converted to an enolate anion, subsequent reaction with a different ketone or aldehyde leads to what is known as a *mixed aldol condensation*. If pentan-3-one is heated with benzaldehyde and NaOEt in ethanol, only one enolate anion is possible. Benzaldehyde has no α-proton and cannot form an enolate anion. Therefore, the enolate anion from acetone can react with benzaldehyde to give an aldolate or with itself (self-condensation) to give a different aldolate. Hydrolytic workup of the aldolate from reaction with benzaldehyde generates the mixed aldol product, 1-hydroxy-2-methyl-1-phenylpentan-3-one. Self-condensation would afford 5-ethyl-5-hydroxy-4-methylheptan-3-one. The mixed aldol condensation is favored if a large excess of benzaldehyde is used. For nearly 100 years, this self-condensation problem limited mixed aldol condensation reactions, especially in reactions with aldehydes. Only ketones or aldehydes that can form only one enolate anion and then react with aldehydes or ketones that have no α-hydrogen atoms gave synthetically useful yields of products.



There is another issue that must be considered for aldol condensation reactions of unsymmetrical ketones. Pentan-2-one has two different acidic protons, H_a and H_b. The pK_a of H_a is about 20 and the pK_a of H_b is about 21.0–21.5. Sodium ethoxide is a good enough base to remove both H_a and H_b. In an acid-base reaction the more acidic H_a is *always* removed first, so sodium pent-1-en-2-olate is always the initial product.



If K_a is large, there is a large concentration of pent-1-en-2-olate and a small concentration of pentan-2-one. However, an acid-base reaction is by definition a reversible equilibrium. If

K_a is small, pent-1-en-2-olate is formed first but the reaction is reversible so there is a large concentration of pentan-2-one at equilibrium. In such an equilibrium H_b is acidic enough to be removed by sodium ethoxide to form sodium pent-2-en-2-olate. In this latter reaction, a new equilibrium is established with three species, pentan-2-one, sodium pent-1-en-2-olate and sodium pent-2-en-2-olate. An aldol condensation reaction is possible for both enolate anions in this equilibrium mixture. If pentan-2-one reacts with LDA under conditions that favor a large K_a, there is a large concentration of sodium pent-1-en-2-olate that reacts with benzaldehyde to give 1-hydroxy-1-phenlhexan-3-one as the major product. If NaOEt is the base, however, K_a[1] is small and the equilibrium favors pent-1-en-2-olate and reaction with benzaldehyde gives 3-(hydroxy(phenyl)methyl)pentan-2-one as the major product.

Reaction Conditions and Equilibria

Once the equilibrium is established in the reaction with NaOEt, why is pent-1-en-2-olate favored when there are two different enolate anions at equilibrium? The stability of the enolate anion is a major influence on the position of the equilibrium. The aldol condensation reaction of pentan-2-one is shown in Figure 20.3 using sodium ethoxide in ethanol as the base. The reaction conditions that favor the equilibrium also favor formation of the more stable (lower energy) enolate anion. Comparing 2-oxopentan-1-ide and 2-oxopentan-3-ide, the C=C unit in 2-oxopentan-1-ide has only two substituents whereas the C=C unit in 2-oxopentan-3-ide has three substituents. Carbon groups are electron-releasing, so more electron density is donated to the π-bond in 2-oxopentan-3-ide. It has a stronger π-bond (see Section 5.1). This more highly substituted enolate anion is more stable and favored under thermodynamic conditions. Since the more highly substituted enolate is more stable, 2-oxopentan-3-ide is favored.

The ability to control the equilibrium of an aldol condensation reaction was accomplished when non-nucleophilic bases were developed (Section 20.2). A second reaction is shown in Figure 20.3 that uses lithium diisopropylamide (LDA) in THF as the base. While both LDA and NaOEt react with the more acidic proton to give the same conjugate base, enolate anion 2-oxopentan-1-ide, the conjugate acids are different. The reaction with LDA generates diisopropylamine as the conjugate acid but the reaction with NaOEt generates ethanol as the conjugate acid. Pentan-2-one has a pK_a for H_a of ~ 20, diisopropylamine has a pK_a of ~ 36–40, and ethanol has a of pK_a, 15.75.[1] Pentan-2-one is a stronger acid than the conjugate acid diisopropylamine, so deprotonation of the ketone has a larger K_a.

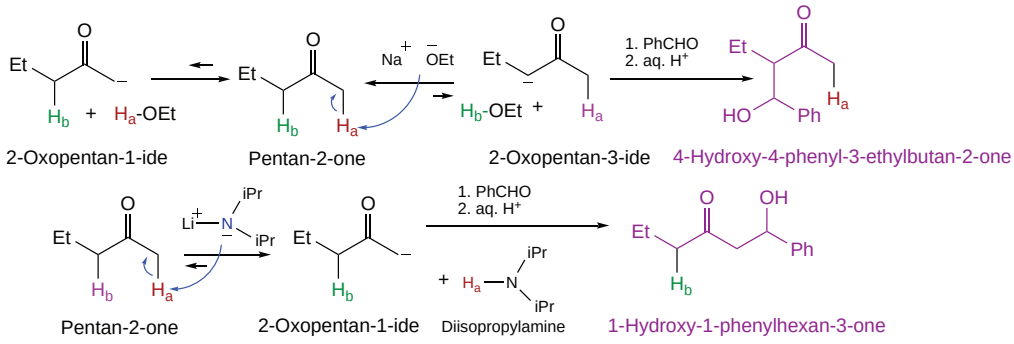


FIGURE 20.3 Kinetic and thermodynamic control in the aldol condensation of pentan-2-one.

Kinetic and Thermodynamic Conditions

Conversely, the conjugate acid ethanol is a stronger acid than pentan-2-one which favors a smaller K_a. In the LDA reaction with a large K_a, there is a large concentration of

2-oxopentan-1-ide and a small amount of unreacted pentan-2-one. These reaction conditions effectively suppress the equilibrium when the reaction is done at low temperatures and are known as *kinetic control conditions.* The reaction conditions that lead to a small K_a promote an equilibrium favoring 2-oxopentan-3-ide. These reaction conditions are known as *thermodynamic control conditions.* The aldol condensation product formed under kinetic conditions is called the *kinetic product*. The product formed under thermodynamic conditions is known as the *thermodynamic product*. Adjusting reaction conditions to favor one product over the other is known as *kinetic-thermodynamic control*.

The solvent plays a major role in kinetic control vs. thermodynamic control in the aldol condensation. The solvent THF does not have an acidic proton and it is classified as an *aprotic solvent.* Since it has no acidic hydrogen atoms it cannot react with the conjugate base and so does not participate in the reaction. The reaction of LDA in THF with an α-proton generates diisopropylamine, which is a weaker acid than the ketone or aldehyde. These are kinetic control conditions. When sodium ethoxide is used as the base, the conjugate acid ethanol is a stronger acid than the ketone or aldehyde and it is a protic solvent with a pK_a of ~ 15.9. The enolate anion is the conjugate base and it reacts with ethanol to regenerate the ketone. In other words, the protic solvent *participates in the reaction* to shift the equilibrium back to the left (K_a^1 is small) and promote the acid-base equilibrium. A protic solvent and an alkoxide base favor a small K_a and thermodynamic control. An aprotic solvent and a non-nucleophilic base favor a large K_a and kinetic control.

The aldol condensation of pentan-2-one with LDA in THF at -78 °C is under typical kinetic control conditions and the reaction with NaOEt in ethanol at reflux is under typical thermodynamic control conditions. The enolate anion of pentan-2-one generated by either kinetic control or thermodynamic control reacts with benzaldehyde. Hydrolytic workup of the aldolate gives the corresponding aldol product. Under kinetic control conditions the first-formed enolate anion 2-oxopentan-1-ide reacts with benzaldehyde to give 1-hydroxy-1-phenylhexan-3-one after hydrolytic workup. Under thermodynamic control conditions the more stable enolate anion 2-oxopentan-3-ide leads to 4-hydroxy-4-phenyl-3-ethylbutan-2-one.

20.10 Draw the conjugate acid for a reaction of butan-2-one with each of the following bases in a different reaction, and then indicate if K_a is large or small: NaOEt. N_aNH_2. N_aF.

There are two additional parameters of a reaction that must be discussed, temperature and time. In general, higher temperatures favor equilibration and thermodynamic control whereas low temperatures favor kinetic control. Reaction time influences the enolate-forming reaction, but this effect is difficult to explain in general terms. A long reaction time is obviously a relative term. If the half-life of the reaction is 0.33 minutes, then a reaction time of 10 minutes is 30 half-lives. In 10 minutes the reaction will have long since been complete. If the half-life is 10 days, then a reaction time of 2 days is only 0.2 half-lives. After 2 days the reaction has barely begun. It is assumed the reaction is allowed to proceed through at least five or six half-lives (Section 7.11.3).

Return to Mixed Aldol Condensations

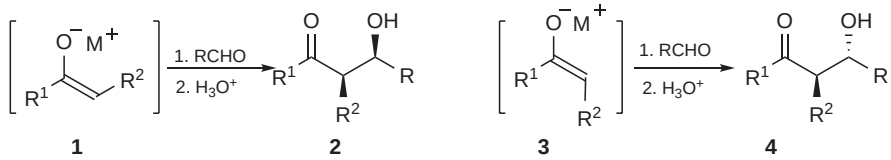
20.11 Draw the product that results from a reaction of hexan-3-one and LDA (-78 °C, THF) that is treated first with 3-phenylpropanal and second with dilute aqueous acid at 0 °C?

An understanding of kinetic and thermodynamic control in a reaction allows a return to the issue of mixed aldol reactions. The reaction of two symmetrical ketones, pentan-3-one, and cyclopentanone under thermodynamic control with sodium ethoxide in ethanol at reflux emphasizes the importance of using kinetic conditions rather than thermodynamic conditions. Both ketones react with the base to form enolate anions 3-oxopentan-2-ide and 2-oxocyclopentan-1-ide. With thermodynamic conditions, 3-oxopentan-2-ide and 2-oxocyclopentan-1-ide each react with pentan-3-one and cyclopentanone since all are in solution at the same time. Therefore, there are four alkoxide products. The hydrolytic workup converts the alkoxide products to the aldol products: 5-ethyl-5-hydroxy-4-methylheptan-3-one, 2-(1-hydroxycyclopentyl)-pentan-3-one, 2-(3-hydroxypentan-3-yl)-cyclopentanone, and 1'-hydroxycyclopentylcyclopentan-2-one. An

attempt to synthesize a specific unsymmetrical aldol under these conditions requires that the targeted product be separated from the other isomers. Therefore, the yield of an individual aldol product is usually poor. Kinetic control conditions are much preferred. The reaction of pentan-3-one with LDA in THF at -78 °C, for example, followed by reaction with cyclopentanone gives 2-(1-hydroxycyclopentyl)-pentan-3-one as the near exclusive product.

The Zimmerman-Traxler Model

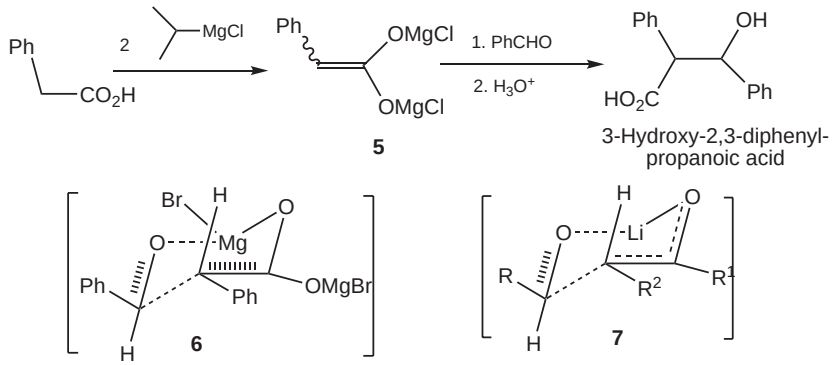
20.5 THE ZIMMERMAN-TRAXLER MODEL



1 **2** **3** **4**

In all of the enolate anions previously discussed, the enolate anions are drawn without an emphasis on stereochemistry. In fact, enolate anions exist as *E*- and *Z*-isomers. A mixed aldol reaction can generate two or more stereocenters, which leads to diastereomers. Aldol condensation reactions are diastereoselective, but the ratio of *E*- and *Z*-isomers determines the relative amount of each diastereomer. The *Z*-enolate has the alkoxide oxygen and the alkyl group R^2 on the same side (**1**). A (*Z*)-enolate such as **1** will react with an aldehyde to generate a *syn diastereomer* (**2**). An *E*-enolate has the alkoxide oxygen and the alkyl group R^2 on opposite sides (**3**). An (*E*) enolate such as **3**, which will react with an aldehyde to generate the *anti-diastereomer* (**4**). The relative percentages of *E*- and *Z*-isomers can be controlled to some extent.[13] To analyze the reaction of the *E*- or the *Z*-isomer, a cyclic transition state model is used to predict diastereoselectivity.

The most popular model is based on a closed or chelated transition state,[14] first proposed by Howard Zimmerman (USA; 1926–2012) and Marjorie D. Traxler (USA) for the *Ivanov condensation* of phenylacetic acid and benzaldehyde. The Ivanov condensation[15] named after Dimitar Ivanov Popov (Bulgaria; 1894–1975), treats a carboxylic acid with an excess of a Grignard reagent to give a bis(magnesium) ketene acetal (**5**).[15] Subsequent reaction with a carbonyl compound (benzaldehyde) led to an aldol-like product (3-hydroxy-2,3-diphenylpropanoic acid) as shown in Figure 20.4. The cyclic model proposed to describe the Ivanov reaction (model **6**) can be modified and used for aldol condensations. Magnesium in the model is replaced with lithium to give cyclic model **7**. When **7** is used to predict



5

6 **7**

FIGURE 20.4 The Ivanov Condensation, the model for the Ivanov condensation and the Zimmerman-Traxler model for predicting diastereoselectivity in the aldol condensation.

[13] Evans, D.A. in *Asymmetric Syntheses, Vol. 3*, Morrison, J.D. (Ed.), Academic Press, NY, 1984, pp. 1–110.
[14] Zimmerman, H.E.; Traxler, M.D. *Journal of the American Chemical Society* 1957, 79, 1920–1923. Also see Heathcock, C.H. in *Asymmetric Synthesis Vol. 3*, Morrison, J.D. (Ed.), Academic Press, NY, 1983.
[15] (a) Ivanoff, D.; Spassoff, A. *Bulletin of the Chemical Society of France* 1931, 49, 19; (b) Ivanoff, D.; Mihova, M.; Christova, T. *Bulletin of the Chemical Society of France* 1932, 51, 1321; (c) Ivanoff, D.; Nicoloff, N.I. *Bulletin of the Chemical Society of France* 1932, 51, 1325, 1331.

stereochemistry in the aldol condensation, it is referred to as the *Zimmerman-Traxler model*,[14] shown in Figure 20.4.

The reaction of butan-2-one with LDA generates both lithium (*E*)-but-2-en-2-olate, and lithium (*Z*)-but-2-en-2-olate. The reaction of each enolate anion with benzaldehyde is shown in Figure 20.5 using the Zimmerman-Traxler model. The reaction with lithium (*Z*)-but-2-en-2-olate generates model **8**, which predicts aldolate **9**. Hydrolysis gives (3*R*,4*R*)-4-hydrox y-3-methyl-4-phenylbutan-2-one. The reaction with lithium (*E*)-but-2-en-2-olate generates model **10**, which predicts aldolate **11**. Hydrolytic workup gives (3*R*,4*S*)-4-hydroxy-3-methyl -4-phenylbutan-2-one.

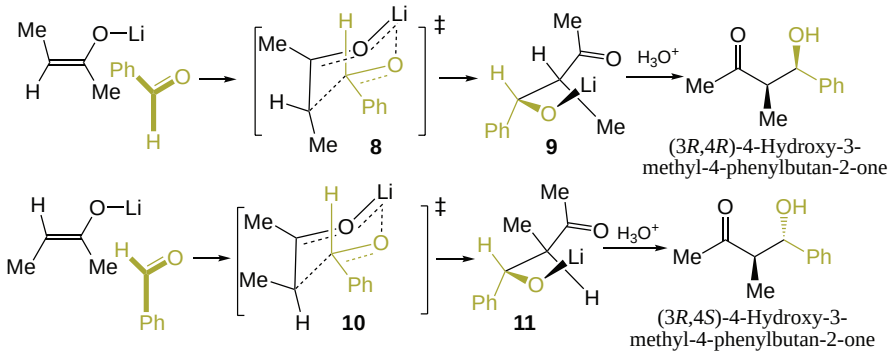


FIGURE 20.5 Application of the Zimmerman-Traxler model to the aldol condensation of the *Z*-enolate anion and the *E*-enolate anion of butan-2-one and benzaldehyde.

If the Z-enolate anion is assumed to be the major isomer, then using the Zimmerman-Traxler model predicts (3*R*,4*R*)-4-hydroxyl-3-methyl-4-phenylbutan-2-one as the major product. Note that the enolate anion approaches the aldehyde from the rear in Figure 20.5 but approach from the front is just as facile. Therefore, the model predicts that one diastereomer is favored, but it will be racemic.

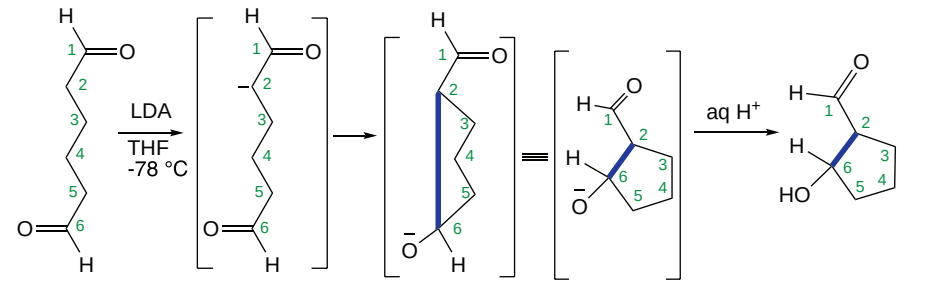
20.12 Use the Zimmerman-Traxler model to predict the aldol formed by the reaction of the *E*-enolate anion formed from 3-methylpentan-2-one and LDA in a reaction with $PhCH_2CHO$. The aldehyde approaches the enolate anion from the "front" face and the aldolate that is formed is treated with aqueous acid.

Intramolecular Aldol Condensation

20.6 THE INTRAMOLECULAR ALDOL CONDENSATION

All of the examples shown for the aldol condensation in previous sections involved an intermolecular reaction, which is the reaction of two different molecules. If a molecule has two carbonyl units as well as at least one acidic α-hydrogen and it is treated with base, an *intramolecular aldol condensation* is possible. A simple example is hexane-1,6-dial (adipaldehyde). The carbon atoms are numbered so the reaction can be tracked. There are two α-carbons in hexanedial, but it is a symmetrical molecule so the protons on *both* α-carbon atoms are chemically identical. In other words, when treated with lithium diisopropylamide in THF under kinetic control conditions, deprotonation at C2 or C5 gives the same enolate anion, 1,6-dioxohexan-2-ide. Deprotonation at C2 gives an enolate anion that reacts with the aldehyde carbonyl on the other end of the molecule (labeled C6). This intramolecular acyl addition gives the aldolate and hydrolytic workup gives 2-hydroxycyclopentanecarbaldehyde. Note that the aldolate anion is drawn first with a peculiar looking "extended" bond in order to keep the relative shape the same and make it easier to follow the bond-forming process and ring formation. The aldolate is redrawn in its proper five-membered ring form. The numbers used for the molecule are arbitrary and used for clarity but they are not derived from IUPAC nomenclature.

The intramolecular reaction is faster than the intermolecular self-condensation of 1,6-dioxohexan-2-ide with hexane-1,6-dial due to entropy. In most reactions studied so far, the energy of the entropy term is so small that it can be assumed to be zero without introducing a significant error. This intramolecular reaction is more ordered than the reaction between two molecules (e.g., there is less disorder), the entropy term is larger and it must be included. The entropy contribution is sufficient that the intramolecular process is favored over the intermolecular process. It is easy to make five-, six-, and even seven-membered rings by an intramolecular aldol reaction, and three- or four-membered rings may be formed. Making rings of eight atoms or more is very difficult using this cyclization method due to the transannular strain involved in bringing the two ends of the molecule together (see Section 8.7).



1,6-Hexanedial (adipaldehyde) 1,6-Dioxohexan-2-ide 2-Hydroxycyclopentanecarbaldehyde

Hexanedial are retained in the aldol product, although this is not the IUPAC numbering for that product.

20.13 Draw the product formed of a reaction between octane-2,7-dione with 1. LDA, THF, -78 °C and 2. dilute aqueous acid.
20.14 Draw the product of a reaction between octane-2,7-dione and 1. NaOEt in EtOH at reflux 2. dilute aqueous acid.

Aldol Reactions

The Acid-Catalyzed Aldol Condensation

20.7 THE ACID-CATALYZED ALDOL CONDENSATION

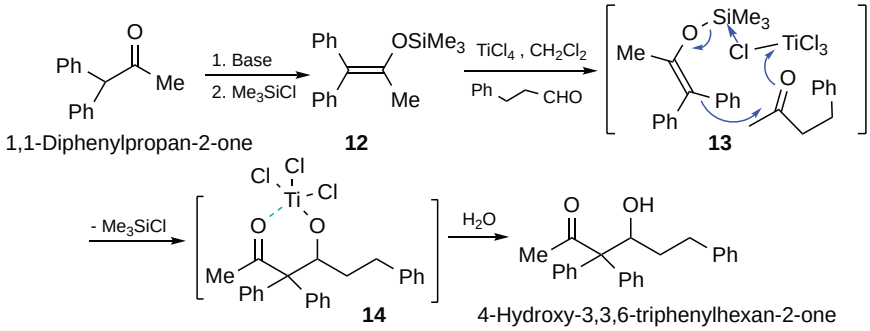
Aldol condensation reactions can be done under acidic conditions. Many credit Alexander Borodin (Russia; 1833–1887) with discovery of the aldol condensation reaction. Borodin was a Russian Romantic composer, a doctor as well as a chemist.[16] Borodin reported the self-condensation reaction of acetaldehyde to give 3-hydroxybutanal when treated with acid.[17] While the base-catalyzed reaction is more common, acid-catalyzed condensation reactions are well known. While Brønsted-Lowry acids can be used, many modern aldol condensation reactions use Lewis acids as catalysts. In the presence of a catalytic amount of $TiCl_4$,[18] butan-2-one was condensed with benzaldehyde in toluene to give an 83% yield of the aldolate product. The reaction was highly regioselective for the thermodynamic product. The use of traditional Brønsted-Lowry acids can promote reversible processes and poor yields can result due to deleterious cationic side reactions. Therefore, this variation is not as widely used as the base-catalyzed aldol condensation. The base catalyzed reaction, however, can sometimes lead to dimers, polymers, self-condensation products or α,β-unsaturated carbonyl derivatives. Teruaki Mukaiyama (Japan; 1927–2018) was an organic chemist at the Tokyo Institute of Technology who helped establish the field of organic chemistry in Japan after World War II. Mukaiyama exploited the concept of the redox condensation reaction in which a weak acid and weak base catalyze a condensation by means of a redox reaction. This concept was applied

[16] As a composer he is noted for "In the Steppes of Central Asia," the opera "Prince Igor," and many symphonies
[17] Borodin's earliest results are reported in von Richter, V. *Berichte der Deutschen Chemischen Gesellschaft* 1869, 2, 552–554. See Borodin, A. *Berichte der Deutschen Chemischen Gesellschaft* 1873, 6, 982–985.
[18] Mahrwald, R.; Gündogan, B. *Journal or the American Chemical Society* 1998, 120, 413–414.

to the formation of a variety of other functional groups. Mukaiyama used titanium(IV) chloride to activate aldehydes for reaction with silyl enol ethers in the Mukaiyama aldol reaction. He found that a reaction with silyl enol ethers, derived from carbonyl compounds, produced aldol-like products in the presence of titanium tetrachloride ($TiCl_4$) and other Lewis acids (e.g. BF_3•OEt_2).[19]

Teruaki Mukaiyama

The requisite silyl-enol ether is prepared by treatment of a ketone such as 1,1-diphenylpropan-2-one with base and trapping the thermodynamic enolate anion with chlorotrimethylsilane. The product is silyl enol ether **12**. When **12** was mixed with 3-phenylpropanal, in the presence of $TiCl_4$, a condensation occurred via a transition state such as **13**. The product is the titanium aldolate **14** via loss of chlorotrimethylsilane. Hydrolytic workup provided the aldol product, 4-hydroxy-3,3,6-triphenylhexan-2-one. At -78 °C the reaction proceeds without self-condensation. This reaction is now called the *Mukaiyama aldol reaction*.[20]



20.15 What is the final product when 3-butan-2-one is treated with (1) LDA, THF (2) Me_3SiCl (3) $TiCl_4$, CH_2Cl_2, cyclopentanecarbaldehyde?

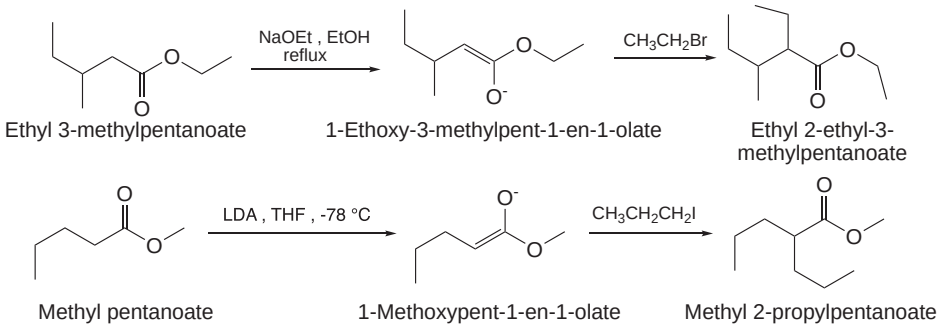
20.8 ESTER ENOLATE ANIONS

The discussion of enolate anions has so far been restricted to ketones and aldehydes. Esters and other acid derivatives also have a carbonyl group. The enolate anions are formed by reaction with a suitable base, but only the reactions of ester enolate anions will be discussed. Enolate anions from acid chlorides or acid anhydrides and even amides have reactivity

[19] Inomata, K.; Muraki, M.; Mukaiyama, T. *Bulletin of the Chemical Society of Japan* 1973, 46, 1807–1810.
[20] (a) Mukaiyama, T. *Angewandte Chemie International Edition* 1977, 16, 817–826; (b) Mukaiyama, T. *Organic Reactions* 1982, 28, 203–331(see pp. 238–248).

problems. The pK_a of the α-hydrogen of an ester is ~ 24 to 25, so esters are *weaker* acids than ketones. Once formed, ester enolate anions react as carbanion nucleophiles via a S_N2 reaction, via acyl addition and also via acyl substitution.

20.8.1 ALKYLATION OF ESTER ENOLATE ANIONS



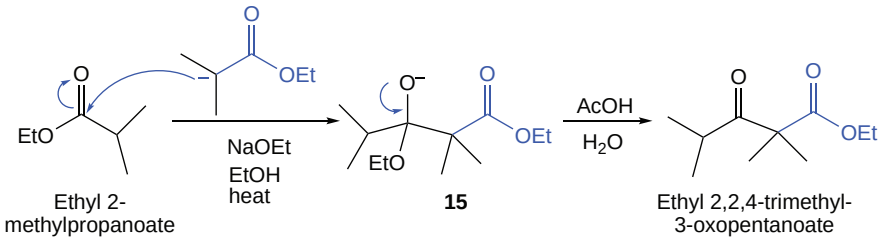
Ester enolate anions react with alkyl halides by a S_N2 reaction to give alkylated esters. An example is the reaction of methyl pentanoate with sodium ethoxide in ethanol and then with iodopropane to give methyl 2-propylpentanoate. Note that methyl pentanoate has only one α-carbon so there is only one possible enolate anion. This reaction is done under thermodynamic control conditions, so self-condensation of the ester is possible. When the reaction is done under kinetic control conditions, the product is the same, but self-condensation is minimized.

20.16 Draw the enolate anion formed when ethyl 3-methylpentanoate reacts with NaOEt.

20.8.2 ACYL SUBSTITUTION AND ACYL ADDITION

Acyl Substitution of Ester Enolates

In the late 19th century, Rainer Ludwig Claisen (Germany; 1851–1930) performed an experiment in which ethyl 2-methylpropanonate was heated with sodium ethoxide in ethanol. After acidification with glacial acetic acid (i.e., 100% acetic acid) the final isolated product was ethyl 2,2,4-trimethyl-3-oxopentanoate.[21] Ethyl 2-methylpropanoate reacts with sodium ethoxide to give the enolate anion. Reaction with another molecule of ethyl 2-methylpropanoate gives a tetrahedral intermediate, **15**, which loses the ethoxy leaving group to give a β-*keto ester*, ethyl 2,2,4-trimethyl-3-oxopentanoate after the hydrolytic workup. This reaction is now called the *Claisen condensation*, and it is an *acyl substitution* reaction. This reaction is a self-condensation.

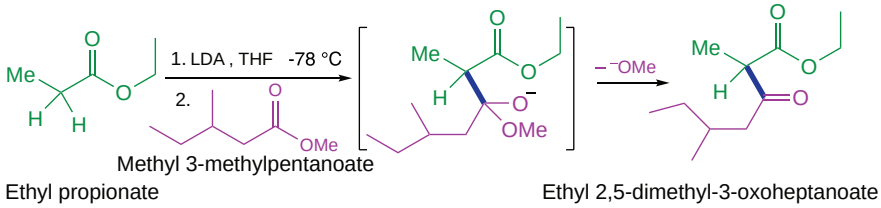


[21] See Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.176, pp. 741–742.

20.17 Draw the product formed when ethyl pentanoate is heated with sodium ethoxide in ethanol and then hydrolyzed with aqueous acid.

The reaction of two different esters gives a *mixed-Claisen condensation*. When two different esters react with base under thermodynamic conditions, there are two esters in the medium as well as two different ester enolates. Each enolate anion will react with both esters to give a different product. There are four possible Claisen condensation products, analogous to the problems encountered with the mixed aldol condensation in Section 20.4. Heating a mixture of ethyl propanoate and methyl 3-methylpentanoate at reflux in ethanol, in the presence of sodium ethoxide, gives ethyl 2-methyl-3-oxopentanoate and ethyl 2,5-dimethyl-3-oxoheptanoate from ethyl propanoate. Methyl 3-methylpentanoate reacts to give *sec*-butyl-3-oxopentanoate and a methyl 2-(2-methylpropyl)-4-methyl-3-oxohexanoate. For this reason, and to minimize self-condensation, kinetic control conditions are used. Kinetic control conditions for a mixed-Claisen condensation lead one isomer rather than four. The reaction of ethyl propionate with LDA gives the enolate anion. Subsequent reaction with methyl 3-methylpentanoate gives the tetrahedral intermediate shown and loss of methoxide gives ethyl 2,5-dimethyl-3-oxoheptanoate.

When an alcohol solvent is used in reactions under thermodynamic conditions, the alcohol solvent should be the same as the alcohol part of the ester. If a methyl ester reacts with NaOEt in ethanol, the OEt unit displaces OMe to yield an ethyl ester in the product. If a different alcohol solvent is used, transesterification may lead to a mixture of ethyl and methyl esters.



20.18 Draw the product of the reaction of benzyl pentanoate with LDA in THF at -78 °C, when it subsequently treated with methyl cyclohexane carboxylate and then hydrolyzed with aqueous acid.

Ester enolate anions react with aldehydes or ketones via acyl addition. Kinetic control conditions are the most suitable for this reaction in order to minimize self-condensation. If ethyl propanoate is treated first with LDA and then with butanal, for example, the initial acyl addition product is the expected alkoxide. Treatment with dilute aqueous acid converts the alkoxide to an alcohol, a β-hydroxy ester (ethyl 3-hydroxy-2-methylhexanoate). Aldehyde or ketone enolate anions react with esters via acyl substitution. When cyclohexanone is treated with LDA (THF, -78 °C) and then with methyl propanoate, the initial transient product is a tetrahedral intermediate. Loss of $^{-}$OMe completes the acyl substitution sequence to yield a 1,3-diketone, 4-methylheptane-3,5-dione.

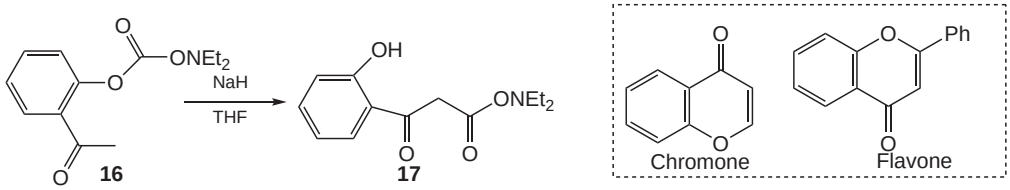
Ester Enolates and Aldehydes and Ketones

20.19 Give the reaction and final product for treatment of pentan-2-one with LDA followed by treatment with ethyl cyclopentanecarboxylate.

There are other reactions that involve the enolate anions of esters. Krishnaswami Venkataraman (India; 1901–1981), was an Indian organic chemist best known for development of the reaction of *O*-acylaryl ketones with base to give an enolate anion, which rearranges to 2-(1,3-diketoalkyl)phenols. This reaction is known as the *Baker-Venkataraman rearrangement.* The Baker-Venkataraman rearrangement is often used in the synthesis of chromones and flavones. The reaction is named after Professor Venkataraman and Wilson Baker (1900–2002), a British organic chemist. An example is the reaction of aryl ketone **16** with sodium hydride to give the phenol product, **17**.[22] Formation of the enolate anion of the

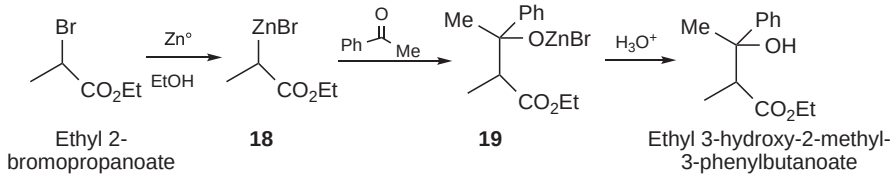
[22] Kalinin, V.; A. Da Silva, J.M.; Lopes, C.C.; Lopes, R.S.C.; Snieckus, V. *Tetrahedron Letters* 1998, 39, 4995–4998.

methyl ketone allows an intramolecular attack at the acyl carbon to form a tetrahedral intermediate. Loss of the phenol unit as a leaving group leads to **17**.



The *Reformatsky reaction*[23] is an enolate-like reaction, discovered by Sergey Nikolaevich Reformatsky (Russia; 1860–1934). The Reformatsky reaction employs a nucleophilic organozinc intermediate, generated from an α halo carbonyl and zinc metal. The organozinc reagent (**18**) is derived from ethyl 2-bromopropanoate and it attacks the carbonyl of an aldehyde or ketone (such as acetophenone) to give **19**.

The Reformatsky Reaction

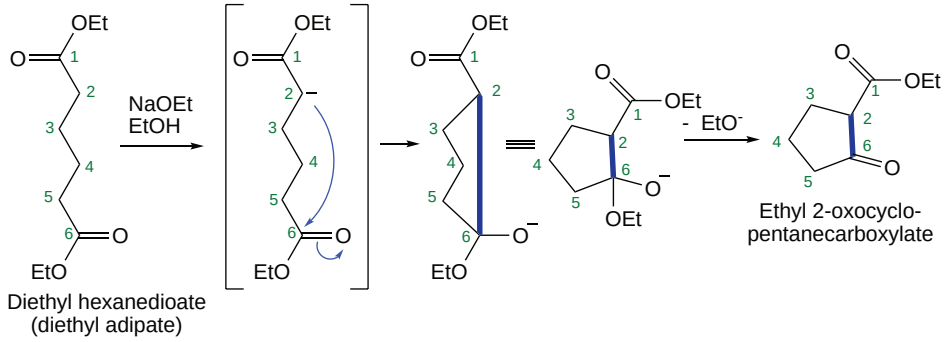


A hydrolytic workup gives the condensation product, a β hydroxyester, ethyl 3-hydroxy-2-methyl-3-phenylbutanoate. Preparation of the organozinc complex in the Reformatsky reaction can be difficult, and often requires special preparation of the zinc (activated zinc). Indeed, activated zinc has been prepared by various procedures.[24] As noted above, hydrolytic workup gives the hydroxy ester to complete this two-carbon chain extension process.

Ester Enolate Anion Reactions

20.8.3 INTRAMOLECULAR CONDENSATION: THE DIECKMANN CONDENSATION

Just as there is an intramolecular version of the aldol condensation (see Section 20.7), there is an intramolecular version of the Claisen condensation. A simple illustration is the reaction of an α,ω-diester such as diethyl 1,6-hexanedioate (diethyl adipate) with sodium ethoxide in ethanol. The intramolecular Claisen condensation product is ethyl 2-oxocyclopentanecarboxylate. Since C2 and C5 are identical in this symmetrical molecule, removal of either of the α-protons will give the same enolate anion. Once the enolate is formed by reaction at C2, the C6 carbonyl unit at the other end of the molecule is the only site available for reaction.



[23] (a) Reformatsky, S. *Chemische Berichte* 1887, 20, 1210–1211; (b) Diaper, D.G.M.; Kuksis A. *Chemical Reviews* 1959, 59, 89–178; (c) Rathke, M.W. *Organic Reactions* 1975, 22, 423–460.

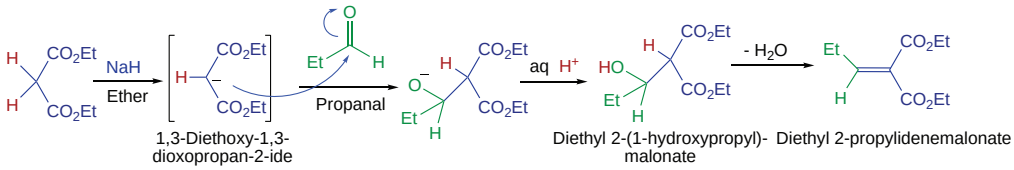
[24] Rieke, R.D.; Li, P.T.-J.; Burns, T.P.; Uhm, S.T. *Journal of Organic Chemistry* 1981, 46, 4323–4324.

The intramolecular Claisen condensation leads to the tetrahedral intermediate, and loss of ethoxide ($^{-}$OEt) leads to a cyclic β-ketone-ester, ethyl 2-oxocyclopentanecarboxylate. The tetrahedral intermediate is shown in a distorted conformation to highlight exactly where the new bond is formed, but the five-membered ring is drawn properly in the second structure. This intramolecular Claisen condensation is formally known as the *Dieckmann condensation*, named after Walter Dieckmann (Germany; 1869–1921). Diesters derived from four- to eight-carbon dicarboxylic acids give three- to seven-membered ring cyclic ketones via Dieckmann condensation. An excellent source of the dicarboxylic acid precursors to diesters is the oxidative cleavage of cyclic alkenes described in Section 15.5.

20.20 Show a reaction sequence that converts octanedioic acid to 2-benzylcycloheptanone.

20.8.4 MALONIC ESTER ENOLATE ANIONS

Propanedoic acid (malonic acid) was introduced in Section 8.12, and conversion to the corresponding ethyl diester (e.g., diethyl malonate; diethyl 1,3-propanedioate) is straightforward. Inductive effects of the two carbonyl units as well as the stability of the resonance-stabilized enolate anion (the conjugate base) enhance the acidity of the α-hydrogen in diethyl malonate. The pK_a is ~ 15[5] as compared to a pK_a of ~ 20 for acetone or about 26 for ethyl acetate.[4] A weaker base can be used to remove the α-hydrogen relative to that used for a simple ester. These bases include sodium hydride (NaH) and sodium carbonate, but alkoxide bases (NaOR) are commonly used.



The reaction of diethyl malonate with sodium hydride generates the enolate anion (1,3-diethoxy-1,3-dioxopropan-2-ide) as the conjugate base and hydrogen gas is the conjugate acid. This enolate anion, called the malonate anion, has three resonance contributors and is very stable. The malonate anion readily reacts as a carbanion nucleophile with both aldehydes and ketones. If propanal is added, for example, acyl addition to the aldehyde carbonyl leads to the expected acyl addition product. Subsequent aqueous acid workup yields the alcohol, diethyl 2-(1-hydroxypropyl) malonate. With malonic ester derivatives, loss of water to form the alkene occurs easily upon treatment with dilute acid or with gentle heating. Elimination is facile because the C=C unit is conjugated to two carbonyl groups**.** The enolate anion of malonate esters react with esters in acyl substitution reactions to give β-keto diesters.

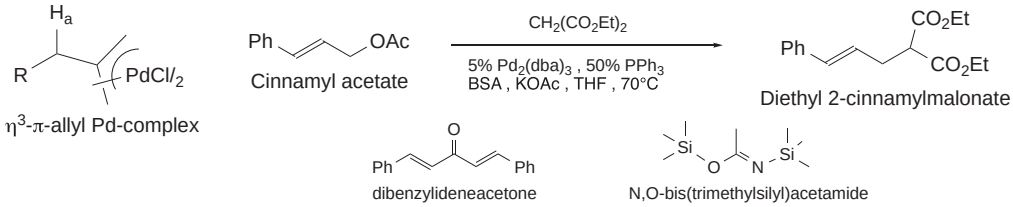
20.21 Draw the enolate anion formed when diethyl malonate reacts with NaH, and show all resonance contributors for the malonate anion.

Allylic acetates ($C{=}CCH_2OAc$) react with a palladium catalyst to form η^3-π-allyl Pd-complexes and subsequent reaction with malonate esters and other nucleophiles give an alkylated product. This coupling reaction is usually called the *Tsuji-Trost reaction*.[25] The reaction is named after Jiro Tsuji (Japan) and Barry Trost (USA). Potassium acetate reacts with diethylmalonate to form the enolate anion which reacts with the allylic acetate in the presence of the palladium catalyst. A typical transformation is shown for the reaction of an allylic acetate such as cinnamyl acetate with diethyl malonate in the presence of

[25] (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Letters* 1965, 6, 4387–4388; (b) Trost, B.M. *Tetrahedron Letters* 2015, 71, 5708–5733.

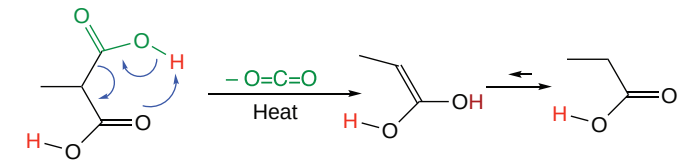
$Pd_2(dba)_3$, BSA (*N,O*-bis(trimethylsilyl)acetamide) and potassium acetate, which gives coupling product diethyl 2-cinnamylmalonate in the presence of the Pd-catalyst. Note that dba is dibenzylideneacetone.

Tsuji-Trost Reaction

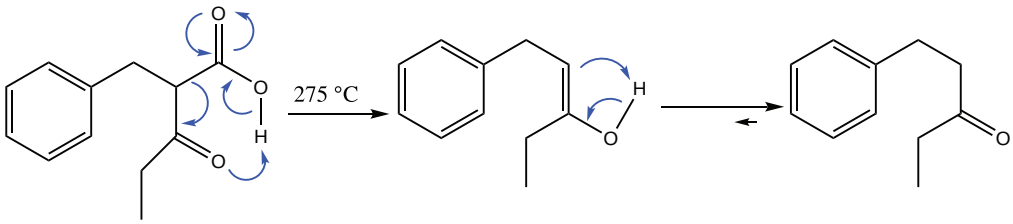


Decarboxylation

20.9 DECARBOXYLATION



There is an elimination reaction known as *decarboxylation* that occurs by heating 1,3-dicarboxylic acids and β-keto acids. Decarboxylation requires the presence of a carboxyl group (COOH) attached to a carbon with another carbonyl substituent that can react as an electron donor. With this structural motif, an internal acid-base reaction leads to cleavage of a C—C bond. Loss of the neutral molecule carbon dioxide (CO_2 is O=C=O) generates an enol that tautomerizes to a carboxylic acid or a ketone. Malonic acid derivatives have the requisite structural features, and when heated to 200 °C carbon dioxide (CO_2) is lost from the molecule. This reaction is known as *decarboxylation*. A specific example is 2-methyl-1,3-propanedioic acid (2-methylmalonic acid), which yields propanoic acid upon heating. The oxygen atom of one carboxyl unit acts as a base, donating electrons to the proton of the other carboxyl unit. A conformation that mimics a six-membered ring is required, which is why the COOH unit and the carbonyl unit must have a 1,3-relationship.



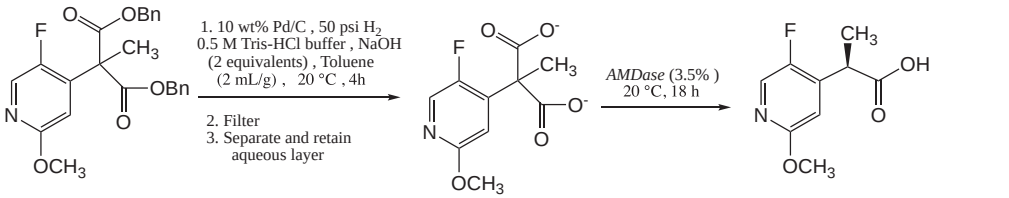
The product is prop-1-ene-1,1-diol, the enol of a carboxylic acid. Keto-enol tautomerization favors the keto form, propionic acid. The β-keto ester products from the Claisen condensation fit the structural criterion for decarboxylation. Decarboxylation requires a somewhat higher reaction temperature than is required for 1,3-dicarboxylic acids, but it is usually a facile reaction at 200–300 °C. Heating 2-benzyl-3-oxopentanoic acid to 275 °C led to decarboxylation and formation of the enol that tautomerized to 1-phenylpentan-3-one. Heating a 1,3-dicarboxylic acid leads to a mono-carboxylic acid, but heating a β-keto acid leads to a ketone product.

20.22 Write out a sequence of reactions that will produce 2-methylheptan-3-one from pentanoic acid.

20.23 What is the enol product formed when 2,5-dimethyl-3-oxohexanoic acid is heated to 275 °C? What is the ketone product generated from this enol?

Caroline Blakemore

Caroline Blakemore (USA) is currently a Principal Scientist at Pfizer Inc. who has worked on multiple projects in a range of therapeutic areas, contributing to the design strategy of projects from exploratory to late stage discovery. One of those projects involved the synthesis of chiral α-methylated aryl acetic acid derivatives. α-Aryl propionic acid derivatives are synthetically useful building blocks and are common fragments in drug discovery. The work targeted *N*-heteroaryl and substituted aryl propionic acids using a biocatalytic approach. Enantiopure α-aryl propionic acids could be accessed from the corresponding malonic acids enzymatically, using *arylmalonate decarboxylases (AMDases*). *N*-heterocyclic malonic acids were found to be unstable to isolation resulting in spontaneous decarboxylation and the generation of racemic propionic acids.[26]



Dibenzyl 2-(5-fluoro-2-methoxypyridin-4-yl)-2-methylmalonate

2-(5-Fluoro-2-methoxypyridin-4-yl)-2-methylmalonate

(*R*)-2-(5-Fluoro-2-methoxypyridin-4-yl) propanoic acid

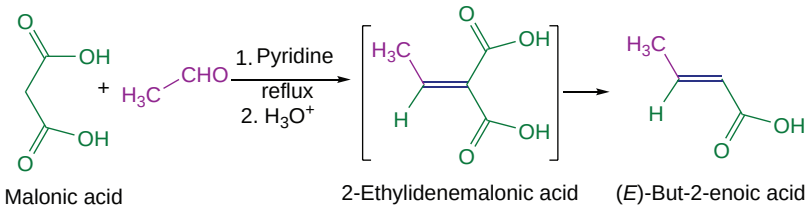
This problem was solved by using a hydrogenolysis procedure in a biphasic toluene-basic aqueous buffer mixture. In this approach the malonic acid intermediate is not isolated but rather formed in an aqueous buffer at pH 8.0, where spontaneous decarboxylation was minimized. After filtration of Pd/C catalyst, the layers were partitioned, and the basic aqueous phase retained. To this was charged *AMDase* enzyme to give enantioenriched *N*-heteroaryl propionic acids that were isolated after acidification to pH 2.5 and extraction into organic solvent. An example is the hydrogenation reaction of dibenzyl 2-(5-fluoro-2-methoxypyri din-4-yl)-2-methylmalonate to give 2-(5-fluoro-2-methoxypyridin-4-yl)-2-methylmalonate in situ, followed by reaction with 3.5 wt % of *AMDase* to give the desired (*R*)-2-(5-fluoro-2 -methoxypyridin-4-yl)propanoic acid in 80% yield and 99% ee.[26] This approach was suitable for large-scale applications.

Malonic Esters and the Knoevenagel Reaction

[26] Blakemore, C.A.; France, S.P.; Samp, L.; Nason, D.M.; Yang, E.; Howard, R.M.; Coffman, K.J.; Yang, Q.; Smith, A.C.; Evrard, E.; Li, W.; Dai, L.; Yang, L.; Chen, Z.; Zhang, Q.; He, F.; Zhang, J. *Organic Process Research & Development* 2021, 25, 421–426.

20.10 THE KNOEVENAGEL REACTION, THE MALONIC ESTER SYNTHESIS, AND THE ACETOACETIC ACID SYNTHESIS

An interesting combination of a condensation reaction and decarboxylation treats malonic acid with an aldehyde (e.g., acetaldehyde), using pyridine as a base. The enolate anion is formed by reaction with the basic pyridine, and it condenses with the carbonyl group of the aldehyde.

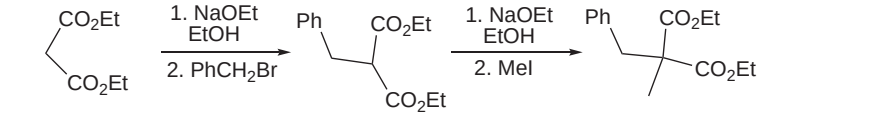


Malonic acid — 2-Ethylidenemalonic acid — (*E*)-But-2-enoic acid

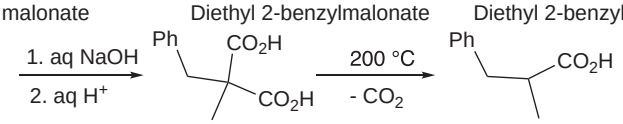
After treatment with aqueous acid, the final product isolated was but-2-enoic acid in 60% yield as the (*E*)-stereoisomer.[27] This specialized version of condensation with malonic acid is a variation of the so-called the *Knoevenagel reaction*, named after Emil Knoevenagel (Germany; 1865–1921). The Knoevenagel reaction gives a mixture of both (*E*)- and (*Z*)-isomers, but the more stable (*E*)-isomer is usually the major product. Note that dehydration occurs during the hydrolytic workup. The COOH unit is lost as CO_2 and decarboxylation accompanies the reaction once 2-ethylidenemalonic acid is formed.

20.24 Write out the reactants and product of the reaction of ethyl 2-methylmalonate with LDA, followed by treatment with cyclohexanone and a hydrolytic workup.

Alkylation of malonate derivatives is possible by simply treating the malonate anion with an alkyl halide. The reaction of diethyl malonate and NaOEt in ethanol, followed by reaction with benzyl bromide gives diethyl 2-benzylmalonate. This new malonate derivative also has an acidic α-proton, so in a second reaction, diethyl 2-benzylmalonate reacts with NaOEt in ethanol and then with iodomethane to give diethyl 2-benzyl-2-methylmalonate.



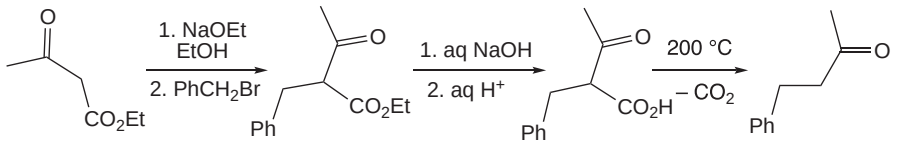
diethyl malonate — Diethyl 2-benzylmalonate — Diethyl 2-benzyl-2-methylmalonate



2-Benzyl-2-methylmalonic acid — 2-Methyl-3-phenylpropanoic acid

Saponification of the ester units (Section 18.5.2) gives the dicarboxylic acid, 2-benzyl-2-methylmalonic acid, and heating this 1,3-diacid leads to decarboxylation and formation of the final product, 2-methyl-3-phenylpropanoic acid. This overall sequence converted diethyl malonate to a substituted carboxylic acid, and it is known as the *malonic ester synthesis*.

20.25 Show a synthesis of 2-ethylhexanoic acid from 1,3-propanedioic acid.



Ethyl 3-oxobutanoate — Ethyl 2-benzyl-3-oxobutanoate — 2-Benzyl-3-oxobutanoic acid — 4-Phenylbutan-2-one

[27] Jones, G. *Organic Reactions* 1967, 15, 204–599.

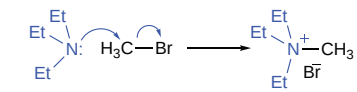
The β-keto esters obtained from Claisen condensation are useful in a variation of the malonic ester synthesis. When ethyl 3-oxobutanoate is converted to the enolate anion with NaOEt in ethanol, reaction with benzyl bromide yields the alkylation product ethyl 2-benzyl-3-oxobutanoate. After saponification, the product is a β-keto acid, 2-benzyl-3-oxobutanoic acid. Decarboxylation of this 1,3-dicarbonyl compound by heating gives 4-phenylbutan-2-one. This reaction sequence is known as the *acetoacetic acid synthesis*. Both the malonic ester synthesis and the acetoacetic acid synthesis employ enolate alkylation reactions to build larger molecules from smaller ones.

20.26 Show a synthesis of 1-phenyl-2,2,4-trimethylpentan-3-one from 2-methylpropanoic acid

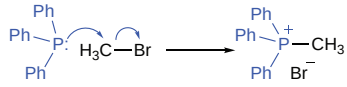
Wittig Reaction

20.11 YLID REACTIONS

An enolate anion is a carbanion unit that is stabilized by an electron-withdrawing group, the carbonyl. A different stabilized carbanion has a positively charged phosphorus atom connected to a carbanionic carbon. A molecule that has a positive and a negative charge in the same molecule is called a *zwitterion.* When those two charges are on adjacent atoms it is called an *ylid*. A typical structure is $Ph_3P^+—CH_2^-$, triphenylphosphonium methylid. Note that these compounds may be spelled as *ylide*.

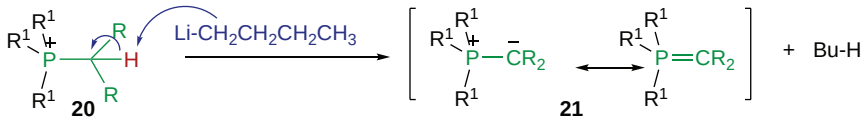


Triethylamine Triethylmethylammonium bromide



Triphenylphosphine Methyltriphenylphosphonum bromide

An amine is a trisubstituted nitrogen compound (e.g., NR_3) and a phosphine is a trisubstituted phosphorous compounds (PR_3). A phosphine reacts with an alkyl halide to give a phosphonium salt (R_4P^+) via an S_N2 reaction, analogous to the reaction of an amine that gives an ammonium salt (R_4N^+). Triethylamine reacts with bromomethane to give triethylammonium bromide. Triphenylphosphine reacts with bromomethane to give methyltriphenylphosphonium bromide in 99% yield.[28] The α-hydrogen of the methyl unit in a phosphonium unit is more acidic than a proton attached to a methyl group in an ammonium salt. Methyltriphenylphosphonium bromide has a pK_a of ~22[29] and reaction with a strong base (e.g., butyllithium) gives the ylid, $Ph_3P^+—CH_2^-$.



20.27 Write the structures of trimethylphosphine and methylphenylphosphine.

The acid-base reaction of a generic phosphonium salt **20** with the powerful base *n*-butyllithium affords ylid **21**, where "R" can be almost any alkyl group. However, the R^1 must be a group that does not contain an α-hydrogen. If the group attached to phosphorus has more than one type of α-proton, two or more different ylids can be formed that would give more than one product in subsequent reactions. Triphenylphosphine has no α-hydrogen atoms, and it is the most commonly used phosphine. The ylid is resonance-stabilized with two

[28] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. (Eds.). *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, Essex, UK, 1994, Exp. 5.17, pp. 498–499.
[29] Zhang, X.-M.; Bordwell, F.G. *Journal of the American Chemical Society* 1994, 116, 968–972.

resonance contributors. Bases used to deprotonate phosphonium salts include KO*t*-Bu, NaH, $LiNH_2$, $LiNEt_2$, $LiN(iPr)_2$, as well as other organolithium reagents.

20.28 Draw the ylid that results from each of the following reactions: (a) PPh_3 + 2-bromobutane then BuLi and (b) PPh_3 + benzyl bromide then BuLi.

Phosphorous ylids react with aldehydes or ketones to give an alkene. A specific example is shown in Figure 20.6, in which methyltriphenylphosphonium bromide is formed by the reaction of triphenylphosphine with a bromomethane. Conversion of the phosphonium salt to the corresponding ylid by reaction with *n*-butyllithium yields triphenylphosphonium methylid. In reactions with carbonyl compounds, triphenylphosphonium methylid can be viewed as a phosphorus-stabilized carbanion. Nucleophilic acyl addition to the carbonyl carbon of cyclohexanone gives a product known as a *betaine*, as shown in Figure 20.6. Since phosphorus has d-orbitals, it can expand its valence, which allows the alkoxide unit to attack phosphorus to form a new P—O bond to give what is known as an *oxaphosphetane*. The oxaphosphetane

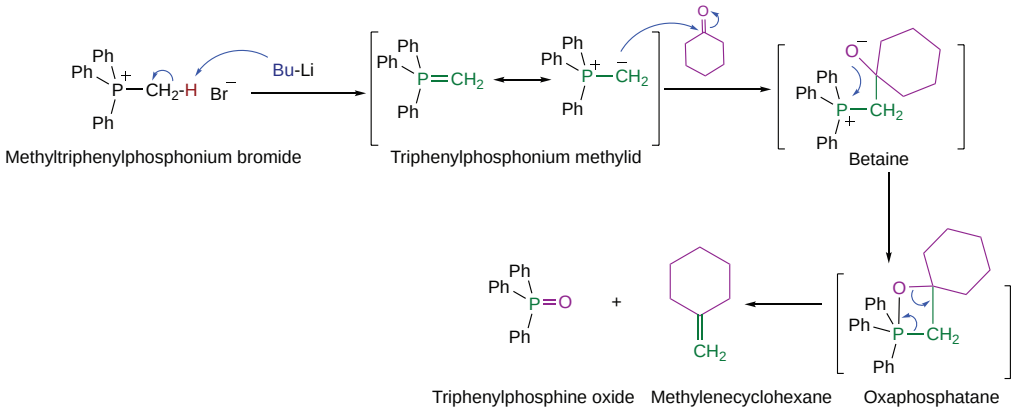
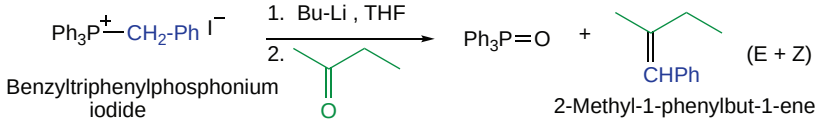


FIGURE 20.6 The Wittig reaction of methyltriphenylphosphonium methylid with cyclohexanone to give methylenecyclohexane and triphenylphosphine oxide.

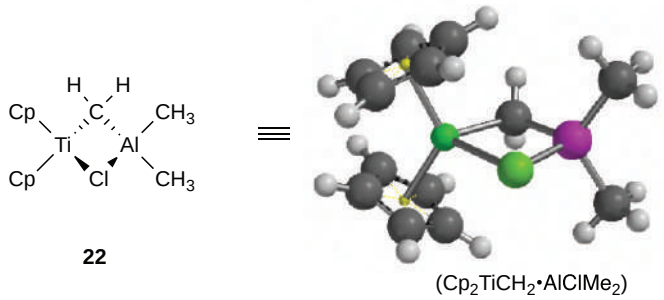
decomposes to give triphenylphosphine oxide with concomitant formation of an alkene. It is known that the P=O bond is rather strong and formation of triphenylphosphine oxide as the oxaphosphetane decomposes is an exothermic process. The overall process converts a ketone or aldehyde to an alkene. This particular transformation is called the *Wittig reaction or Wittig olefination* using the older terminology. Phosphonium ylids are often called *Wittig reagents.* The reagent and the reaction are named after Georg Wittig (Germany; 1897–1981), who examined the reactions of phosphonium salt ylids.

Many alkyl halides may be converted to the corresponding phosphine, and then to ylids, where they react with a variety of aldehydes and ketones. The Wittig reaction is, therefore, quite versatile. Another example is the conversion of benzyltriphenylphosphonium iodide to the ylid, which reacts with butan-2-one to give 2-methyl-1-phenylbut-1-ene along with the phosphine oxide. The reason for showing this second example is to illustrate that the alkene product is formed as a *mixture of (E) and (Z)-isomers*, which is typical of the Wittig reaction. Although the alkene formed in the greatest yield usually has the two largest groups attached to the C=C unit trans to each other, a mixture is almost always formed.



20.29 Write the reactions that will form each of the following alkenes from an appropriate halide, using the Wittig reaction: (a) hex-2-ene and (b) 2-methylpent-2-ene.

Tebbe and Petasis Reactions



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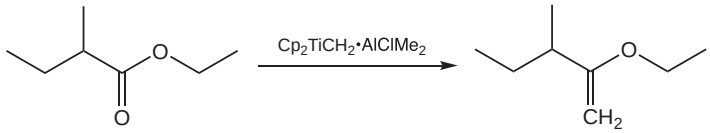
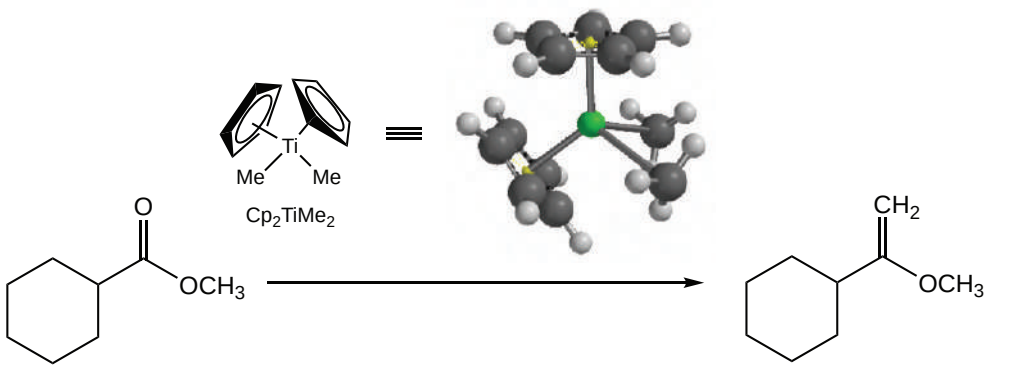
Several different transition metal reagents have been developed for the conversion of carbonyl compounds to alkenes. An example is the *Tebbe reagent*, which exists as a bridged methylene species (**22**) where Cp is cyclopentadienyl,[30] and the reaction with carbonyl compounds that leads to alkene derivatives is called *Tebbe olefination*. The most common reagent is the aluminum dimethylaluminum chloride compound shown. The Tebbe reagent is named after Frederick N. Tebbe (USA; 1935–1995).



Ethyl 2-methylbutanoate — 2-Ethoxy-3-methylpent-1-ene

The Tebbe reagent reacts with ketones or aldehydes to give an alkene, analogous to the Wittig reagent. The Tebbe reagent also reacts with the carbonyl of esters or lactones to give vinyl ethers, in contrast to common Wittig reagents. For example, ethyl 2-methylbutanoate reacts with the Tebbe reagent to give 2-ethoxy-3-methylpent-1-ene.

The titanium compound Cp_2TiMe_2 is a very useful alternative to the Tebbe reagent and is called the *Petasis reagent*.[31] The Petasis reagent is named after Nicos A. Petasis (Greece-USA). The Petasis reagent is prepared by reaction of methyllithium with titanocene dichloride (Cp_2TiCl_2)], which avoids the high cost, long preparation times, short shelf-lives, extreme sensitivity to air and water, and residual aluminum reagents that are problems with of the Tebbe reagent. Aldehydes and ketones react with the Petasis reagent to give an alkene, and in the absence of an aldehyde or ketone moiety, an ester[32] or even an amide moiety can react. Esters react with give a vinyl ether, illustrated by the conversion of methyl cyclohexanecarboxylate to (1-methoxyvinyl)cyclohexane.



Methyl cyclohexanecarboxylate — (1-Methoxyvinyl)cyclohexane

[30] Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *Journal of the American Chemical Society* 1978, 100, 3611–3613.
[31] Petasis, N.A.; Bzowej, E.I. *Journal of the American Chemical Society* 1990, 112, 6392–6394.
[32] See Smith III, A.B.; Mesaros, E.F.; Meyer, E.A. *Journal of the American Chemical Society* 2006, 128, 5292–5299.

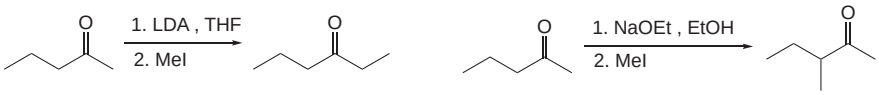
20.30 What product is formed when tetrahydro-2*H*-pyran-2-one (δ-valerolactone) reacts with Tebbe reagent? What is the product when *N,N*-diethyl-3-methylbutanamide reacts with the Petasis reagent?

20.12 ORGANIZATION OF REACTION TYPES

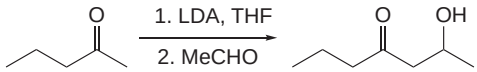
Condensation reactions can be organized as follows. A hydrolytic workup is understood to follow all reactions that generate an alkoxide, although that step is not shown.

What reactions are possible for ketones or aldehydes?

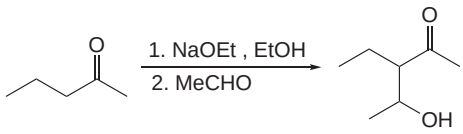
1. Enolate anions of aldehydes and ketones react with alkyl halides to yield alkylated aldehydes or ketones.



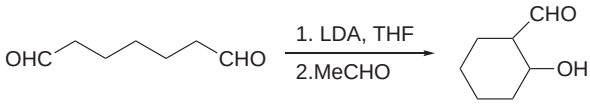
2. Enolate anions of aldehydes and ketones react with aldehydes or ketones under kinetic conditions to yield β-hydroxy aldehydes or ketones by the aldol condensation at the less substituted α-carbon.



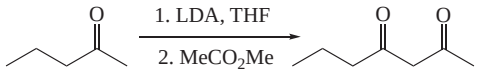
3. Enolate anions of aldehydes and ketones react with aldehydes or ketones under thermodynamic conditions to yield β-hydroxy aldehydes or ketones by the aldol condensation at the more substituted α-carbon.



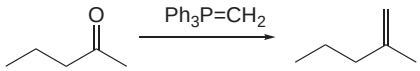
4. Diketones and dialdehydes react with strong base to yield an enolate anion, and an intramolecular aldol condensation leads to a cyclic β-hydroxy aldehydes or ketones.



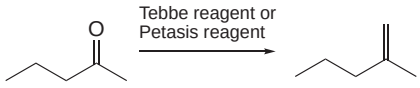
5. Enolate anions of aldehydes and ketones react with esters to yield β-diketones.



6. Aldehydes and ketones react with phosphonium ylids to yield alkenes by the Wittig reaction.

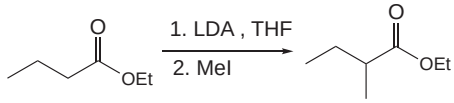


7. Aldehydes and ketones react with the Tebbe reagent or the Petasis reagent to give an alkene

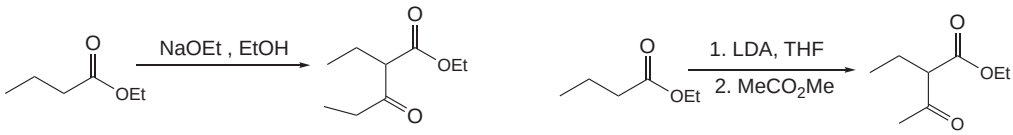


What reactions are possible for esters?

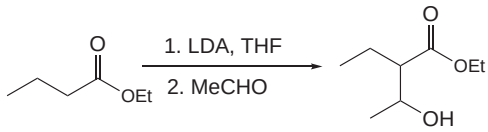
1. Enolate anions of esters react with alkyl halides to yield alkylated esters.



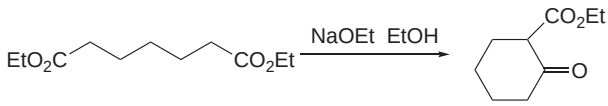
2. Esters react to yield β-keto esters via the Claisen condensation.



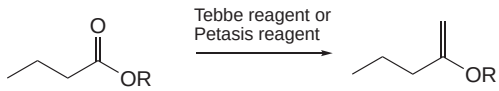
3. Enolate anions of esters react with aldehydes or ketones to yield β-hydroxy esters.



4. The intramolecular Claisen condensation is known as the Dieckmann condensation.

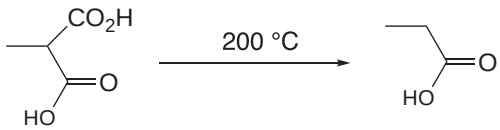


5. Esters react with the Tebbe reagent or the Petasis reagent to give a vinyl ether.



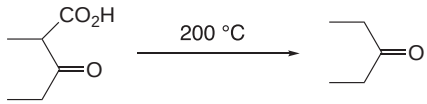
What reactions are possible for diacids?

1. 1,3-Diacids undergo decarboxylation when heated to yield a mono-carboxylic acid.



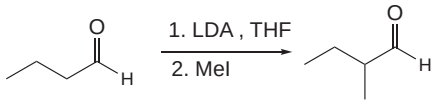
What reactions are possible for keto-acid?

1. β-Keto-acids undergo decarboxylation when heated to yield a ketone.

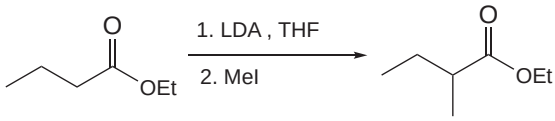


What reactions are possible for alkyl halides?

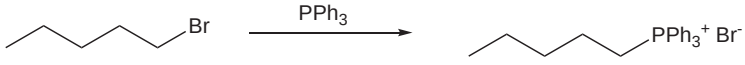
1. Alkyl halides react with enolate anions of aldehydes or ketones by an S_N2 reaction to yield the alkylated product.



2. Alkyl halides react with enolate anions of esters by an S_N2 reaction to yield the alkylated product.

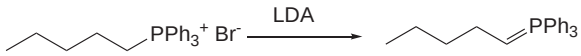


3. Alkyl halides react with phosphines to yield phosphonium salts.



What reactions are possible for phosphines?

1. Phosphines react with alkyl halides to yield phosphonium salts, which yield an ylid when treated with a strong base.



20.13 BIOLOGICAL RELEVANCE

The aldol condensation is reversible under certain circumstances. Enzymes known as aldolases catalyze both the forward and reverse aldol reactions. An example is the retro-aldol-aldol mechanism mediated by the enzyme *L-ribulose-5-phosphate-4-epimerase*, found in both prokaryotes and eukaryotes. This enzyme inverts the stereochemistry of the hydroxyl-bearing carbon in **23** to that in **26**. In other words, L-ribulose-5-phosphate *epimerizes* the stereogenic center to give D-xylulose-5-phosphate (Section 25.1), as shown in Figure 20.7.[33] The first step is a retro-aldol of the Zn^{2+} coordinated L-ribulose-5-phosphate (**23**), induced by the enzyme to yield the aldehyde 2-oxoethyl phosphate (glycoaldehyde phosphate) and the zinc-coordinated enolate anion **24** (dihydroxacetone enolate).[33] Before the aldol reaction occurs, there is a bond rotation to generate a different rotamer of 2-oxoethyl phosphate (**25**). The aldehyde unit is now positioned differently, such that an aldol reaction will give the aldolate **26**, but with a different absolute stereochemistry for the hydroxyl-bearing carbon.

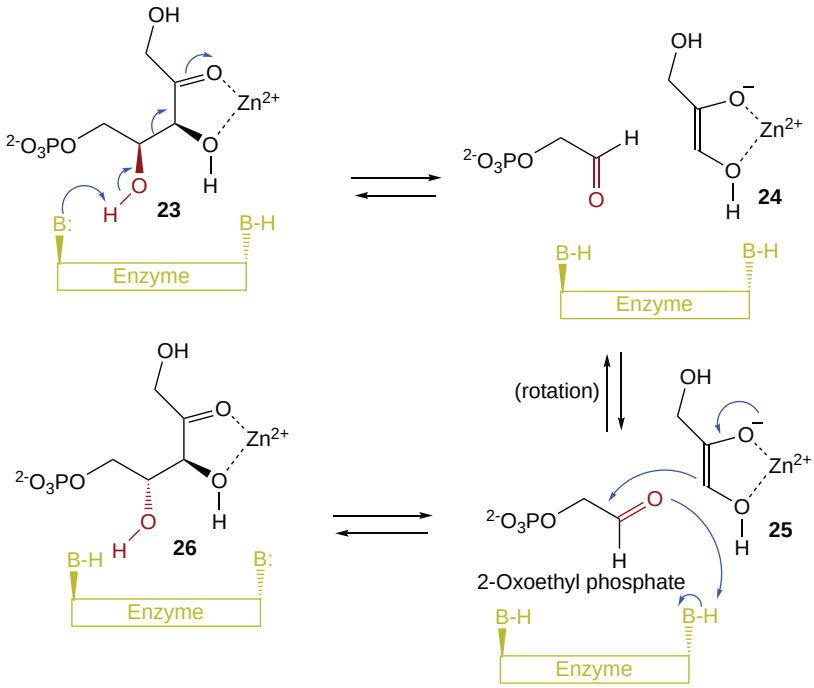
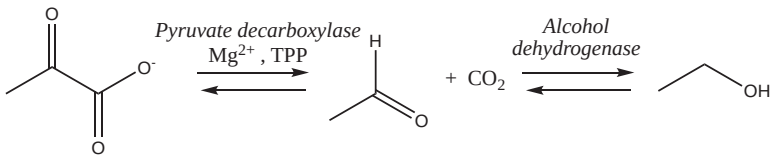


FIGURE 20.7 Enzyme mediated epimerization of L-ribulose-5-phosphate to D-xylulose-5-phosphate. (Reprinted with permission from Tanner, M.E. *Acc. Chem. Res.* 2002, 35, 237. Copyright 2002 American Chemical Society).

Production of alcohol in the presence of yeast is important for the brewing of beer. Under anaerobic conditions, the *pyruvate decarboxylase* enzyme is part of the fermentation process that occurs in yeast, especially of the *Saccharomyces* genus, to produce ethanol by

[33] Tanner, M.E. *Accounts of Chemical Research* 2002, 35, 237–246.

fermentation. *Pyruvate decarboxylase* starts this process[34] by converting pyruvate into acetaldehyde and carbon dioxide. A decarboxylase is an enzyme of the lyase class that catalyzes the removal of a carbon dioxide molecule from carboxylic acids. A lyase is a class of enzymes that remove groups from their substrates (other than by hydrolysis or oxidation), leaving double bonds, or that conversely add groups to double bonds. The reaction of pyruvate with pyruvate decarboxylase requires Mg^{2+} and a cofactor known as thiamine pyrophosphate (TTP). Loss of carbon dioxide yields ethanal (the common name is acetaldehyde). A second enzymatic reaction reduces acetaldehyde to ethanol using alcohol dehydrogenase, which requires NADH and a biological acid to effect the reduction of the aldehyde, while being reduced to NAD^+ (nicotinamide adenine dinucleotide, where NADH is the reduced from of NAD^+).



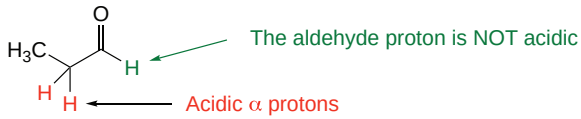
CORRELATION OF HOMEWORK WITH CONCEPTS

- The reaction of a ketone or aldehyde with base gives a resonance-stabilized enolate anion: 1, 2, 3, 4, 5, 31, 32.
- Dialkyl amides are formed by the reaction of an amine with an organolithium reagent, and they are used as non-nucleophilic bases: 6, 34.
- Enolate anions of aldehydes, ketones, and esters react with alkyl halides by a S_N2 reaction to give alkylated carbonyl compounds: 7, 33, 38.
- Enamines react with alkyl halides to give an iminium salt, which is hydrolyzed to an alkylated ketone: 8, 38.
- The condensation reaction of an aldehyde or ketone enolate anion with another aldehyde or ketone is called an aldol condensation: 9, 10, 11, 33, 35, 36, 37, 38, 41.
- The Zimmerman-Traxler model is used to predict the diastereoselectivity an aldol condensation: 12, 40.
- The intramolecular aldol condensation of an α,ω-dialdehyde or diketone leads to a cyclic compound: 13, 14, 39.
- Ester enolates react with alkyl halides: 16, 40.
- The condensation reaction of one ester with another is called a Claisen condensation and it generates a β-keto ester: 17, 18, 19, 40, 41, 42, 43.
- The intramolecular Claisen condensation is called a Dieckmann condensation, and it generates a cyclic compound: 20, 42, 43.
- Malonic esters and β-keto esters can be converted to the enolate anion and condensed with aldehydes, ketones, or acid derivatives. The reaction of malonic acid with an aldehyde using pyridine as a base is called the Knoevenagel condensation: 21, 24, 40, 47.
- Malonic acid derivatives, as well as β-keto acids decarboxylate upon heating: 22, 23, 25, 26, 46.
- Organolithium bases react with alkyltriphenylphosphonium salts to yield phosphorus ylids, which react with aldehydes and ketones to give alkenes in what is known as the Wittig reaction: 27, 28, 29, 44, 45.
- Ketones, aldehydes and esters are converted to alkene derivatives by reaction with the Tebbe reagent or the Petasis reagent: 30, 40.
- Spectroscopy can be used to determine the structure of a particular molecule (see Chapter 13): 48, 49, 50, 51.

[34] Begley, T.P.; McMurry, J. *The Organic Chemistry of Biological Pathways*, Roberts and Co. Publishers, Englewood, CO, 2005, p. 179.

ANSWERS TO IN-CHAPTER QUESTIONS

20.1



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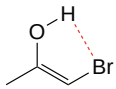
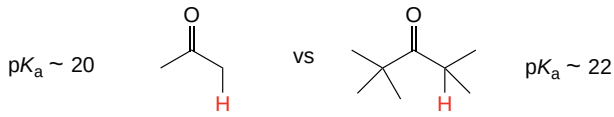


20.3 There is only one acidic hydrogen in 2,4,4-trimethylpentan-3-one and the two electron-releasing methyl groups make it less acidic than the proton in acetone. An estimated pK_a is ~ 22.



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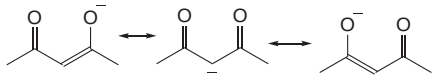
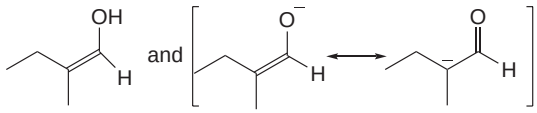


Greater charge dispersal (three resonance contributors) make the enolate anion more stable (less basic),which leads to a larger K_a

20.5



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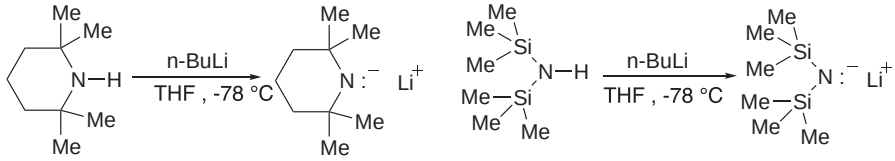
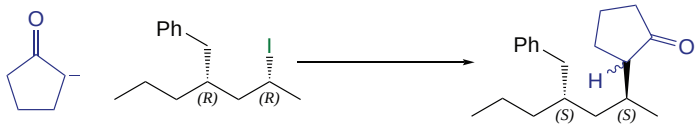


Lithium 2,2,6,6-tetramethylpiperidide

Lithium hexamethyldisilazide

20.7



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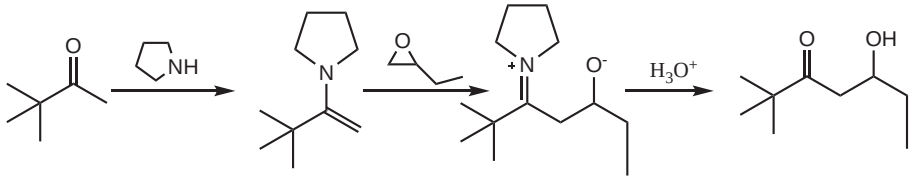
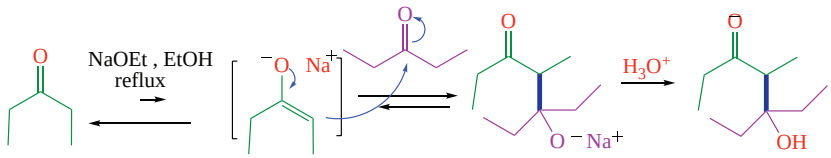
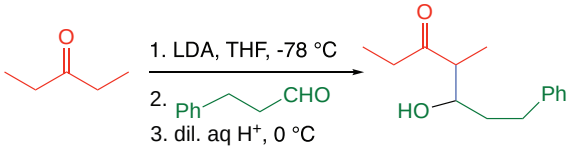


20.9

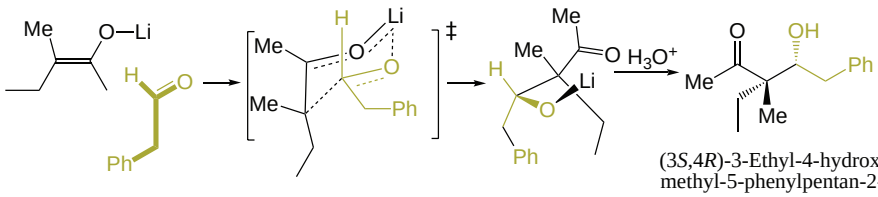


20.10 For NaOEt, the conjugate acid is ethanol (EtOH), with a pK_a of ~ 17. Therefore, K_a is small. For the reaction with $NaNH_2$, the conjugate acid is ammonia (NH_3) with a pK_a of ~ 25. Therefore, *K*a is small. For NaF, the conjugate acid is HF, with a pK_a of ~ 3.2. This result means that K_a is very large.

20.11

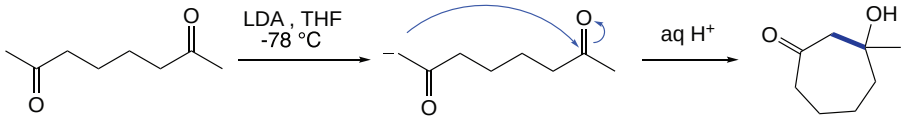


20.12

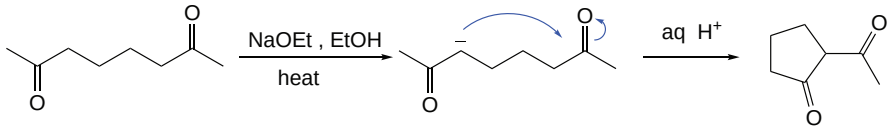


(3*S*,4*R*)-3-Ethyl-4-hydroxy-3-methyl-5-phenylpentan-2-one

20.13 In the diketone the more acidic proton is one of the methyl protons. The enolate produced attacks the other ketone–carbonyl unit to yield the seven-membered ring product.



20.14 Under thermodynamic conditions, the enolate anion shown is formed in this symmetrical molecule, and reaction with the ketone unit leads to a 5-membered ring product.



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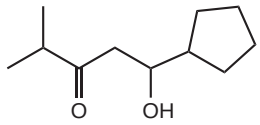

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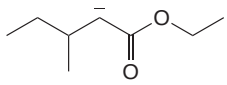
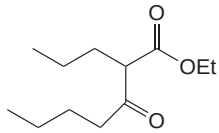


1-Ethoxy-3-methyl-1-oxopentan-2-ide

20.17



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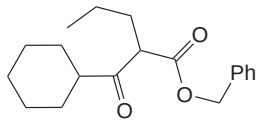

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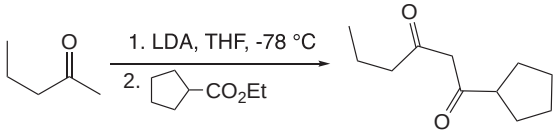
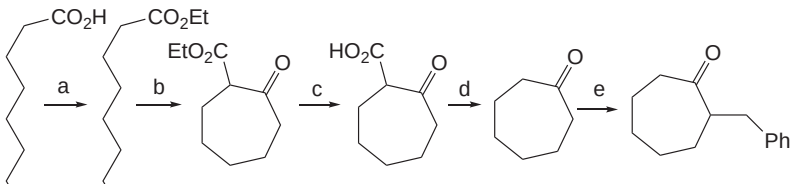
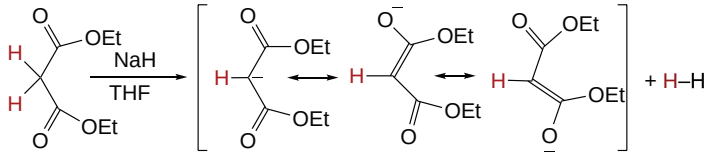


20.20



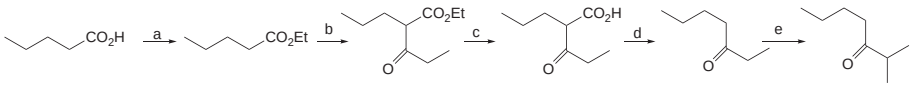
(a) $SOCl_2$; EtOH (b) NaOEt, EtOH, reflux
(c) H_3O^+ (d) 200 °C (e) 1. LDA, THF. -78 °C 2. $PhCH_2Br$

20.21



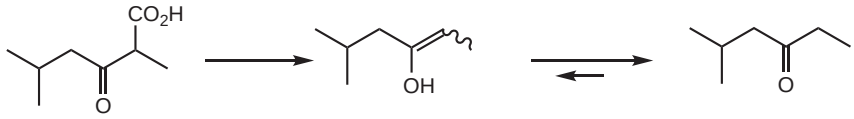
1,3-Diethoxy-3-oxoprop-1-en-1-olate

20.22



(a) $SOCl_2$;EtOH (b) 1. LDA, THF, -78 °C 2. ethyl propanoate 3. aq H^+
(c) 1. aq NaOH 2. aq H^+ (d) 200 °C (-CO_2) (e) LDA , THF , -78 °C then MeI. The 4-methyl isomer is also formed, and must be separated.

20.23



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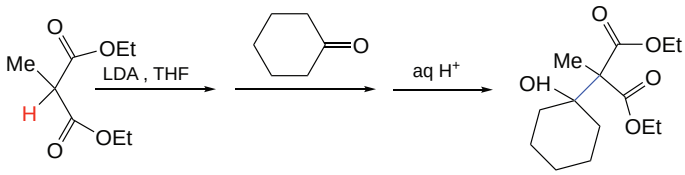
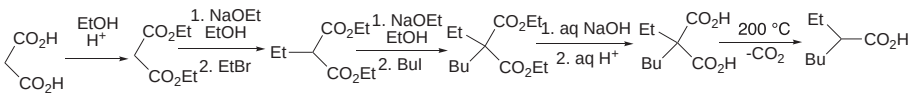
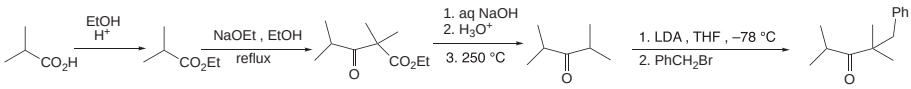


20.25

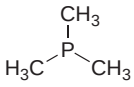


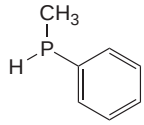
20.26



20.27

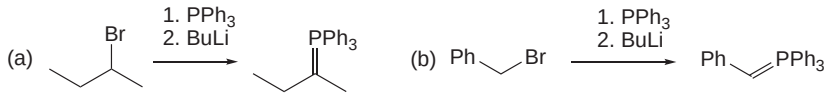
Trimethylphosphine





Methylphenylphosphine

20.28



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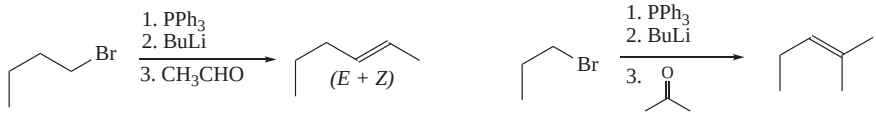


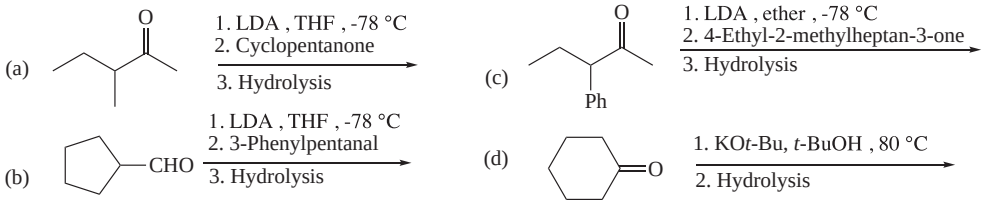
20.30

2-Methylenetetrahydro-2*H*-pyran *N*,*N*-Diethyl-4-methylpent-1-en-2-amine

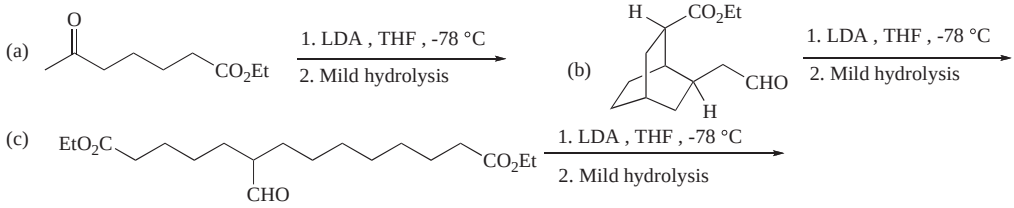
HOMEWORK

31. Look up the relative acidities of 1-phenylethan-1-one, 1-phenylpropan-1-one, 2-methyl-1-phenylpropan-1-one, and 2,2-dimethyl-1-phenylpropan-1-one.
32. Draw the carbanion formed from dicyanomethane, $CH_2(CN)_2$. Draw the resonance contributors.
33. Draw the product formed when the kinetic enolate anion of 2-methylhexan-3-one reacts with benzaldehyde. With ethyl butanoate. With (2*S*)-iodohexane.
34. Draw the complete acid-base reaction between pentan-3-one and (a) LDA (b) lithium 2,2,6,6-tetramethylpiperidide (c) lithium amide (d) sodium hydride (assume it is a strong enough base).

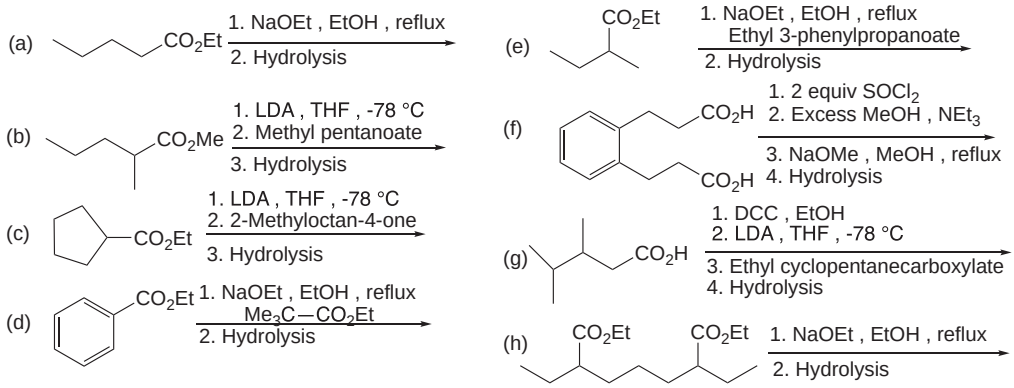
35. Pentanal has only one type of α-hydrogen. Does it matter whether kinetic or thermodynamic control conditions are used to form the enolate anion? Briefly justify your answer.
36. The aldehyde hydrogen of an aldehyde is not acidic, and reaction of an aldehyde with LDA removes the α-proton rather than the aldehyde hydrogen. Explain.
37. Draw the structure of all aldol condensation products for each of the following reactions.



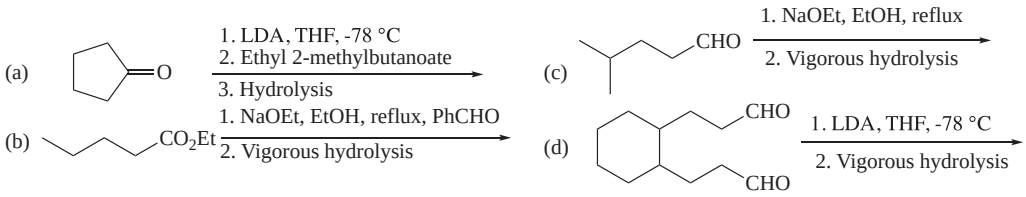
38. Draw the product formed from the following reactions:
    (a) 2-Methylcyclopentanone: (1) pyrrolidine, EtOH (2) $PhCH_2Br$.
    (b) Methyl 2-bromopentanoate: (10 Zn, EtOH (2) pentan-2-one (3) aqueous acid.
    (c) 4-Methylpent-2-en-1-ol: (1) acetyl chloride, cat. H^+ (2) diethyl malonate, cat. $Pd_2(dba)_3$, 0.5 PPh_3, KOAc. (d) Ethyl cyclopentanecarboxylate + $Cp_2TiCH_2 \bullet AlClMe_2$.
39. Give the major product formed when nonane-2,4,8-trione is treated with 1. LDA, THF, -78 °C and 2. hydrolysis. Briefly explain your answer.
40. Give the major product for each of the following: (a) *N*-Ethyl-*N*,3-dimethylbutanamide + Cp_2TiMe_2.
    (b) Diethyl succinate: 1. LDA, THF, -78 °C 2. ethyl butanoate and 3. Hydrolysis. (c) Malonic acid: 1. oxalyl chloride 2. MeOH, NEt_3 3. LDA, THF, -78 °C 4. cyclopentanone and 5. Hydrolysis. (d) Glutaric acid: 1. excess EtOH, cat H^+ 2. $LiNEt_2$, THF, -78 °C 3. methyl 4-phenylbutanoate and 4. Hydrolysis. (e) Ethyl butanoate: (1) LDA, THF, -78°C (2) iodomethylcyclohexane. (f) 3-Methylpentan-2-one: (1) LDA, THF, -78 °C (2) methyl 2-methylpropanoate (3) hydrolysis. (g) Diethyl malonate: (1) NaOEt, EtOH, reflux (2) iodocyclopentane (3) hydrolysis & heat
41. Give the major product for the following reactions and explain your answer if there is more than one possibility.



42. Give the product(s) of all the following reactions:



43. Give the major product of the following reactions:



44. Draw the final product expected from each of the following reactions:
    a. (a) Triphenylphosphine + 2-Bromohexane (b) Me_3P + Bromocyclobutane
    b. (c) Ph_3P + 1. Bromoethane 2. BuLi (d) Ph_3P + 1. 1-Iodopentane 2. BuLi 3. Acetone
    c. (e) Tributylphosphine + Iodomethane (f) Ph_3P + 3-Iodopentane 2. PhLi
45. In each case, give the final product of the reaction.
    (a) 4-Phenyl-1-iodocyclohexane + 1. PPh_3 2. BuLi 3. cyclopentanone
    (b) Cyclopentanecarbonitrile + 1. MeLi 2. H_3O^+ 3. $Ph_3P{=}CMe_2$
    (c) 5-Bromopentanoic acid + 1. $(COCl)_2$ 2. Bu_2CuLi 3. $C_5H_{11}CH{=}PPh_3$
    (d) 5-Bromopentanoic acid + 1. $(COCl)_2$ 2. $EtOH/NEt_3$ 3. PPh_3
    (e) 1-Iodobutane + 1. PPh_3 2. BuLi 3. aqueous acetone
    (f) Butanoic acid + 1. excess MeLi 2. hydrolysis 3. $Ph_3P{=}CHCH_2CH_2CHPh$
    (g) $Ph_3P^+CH_2(CH_2)_5CH_2Br\ I^-$ + 1. BuLi 2. butan-2-one 3. PPh_3 4. BuLi 5. cyclobutanone
46. Explain why heating butanedioic acid derivatives does not lead to decarboxylation.
47. Draw the product that is formed when 6,6-dicyanohexan-2-one is treated with LDA in THF at 0 °C, and then subjected to an aqueous acid workup.

Spectroscopy Problems. Do not attempt these problems until Chapter 13 has been read and understood.

48. After a Claisen condensation the subsequent acid hydrolysis may have been too vigorous and decarboxylation may have occurred. What characteristics in the IR spectrum and ^1H NMR spectrum will determine if your product is a ketoester or a ketoacid? Discuss differences in the ^{13}C NMR spectra.
49. Give the structure for a molecule with the formula is $C_7H_{12}O_3$, and the spectral data given.
    IR: 2984, 2909, 1745, 1716, 1647, 1629, 1313, 1250, 1160, 1028 cm^{-1}. ^1H NMR: 4.2 (q, 2H), 3.46 (s, 2H), 2.58 (q, 2H), 1.28 (t, 3H), 1.08 (t, 3H) ppm. ^{13}C NMR: 206.4, 168.1, 61.0, 48.6, 31.3, 14.1, 7.6 ppm.
50. Give the structure for a molecule with the formula is $C_6H_{12}O_2$, and the following spectral data.
    IR: broad peak at 2876, 2936, 1717, 1471, 1361-1310, 1262-1183, 955, 916 cm^{-1}.
    ^1H NMR: 3.81 (broad s, 1H; this peak is diminished when treated with D_2O), 2.64 (s, 2H), 2.18 (s, 3H),
    1.26 (s, 6H) ppm. ^{13}C NMR: 211.0, 71.1, 60.6, 30.4, 29.3 ppm.
51. Molecule **A** has the formula C_5H_{10}. It exhibits a sharp peak in the IR at 1640 cm^{-1}, and the ^1H NMR shows peaks at 5.70 (m, 1H), 5.07 (m, 1H), 5.02 (m, 1H), 2.52 (m, 1H), 1.06 (d, 6H) ppm. The reaction of **A** with (1) mercuric acetate in water followed by (2) $NaBH_4$ in ethanol and then (3) hydrolysis to yield **B**. The reaction of **B** with pyridinium dichromate in dichloromethane yields **C**, which exhibits a strong peak in the IR at 1716 cm^{-1}. The ^1H NMR is: 1.11 (d, 6H), 2.141 (s, 3H), and 2.58 (m, 1H) ppm. The reaction of **C** with LDA in THF at -78 °C gives an intermediate that reacts with propanal to yield a product **D**. When **D** is treated with dilute aqueous acid at ambient temperatures, **E** is formed. Compound **E** has the formula $C_8H_{16}O_2$ and shows strong peaks at 3300 and 1725 cm^{-1} in the IR. It also shows peaks in the ^1H NMR: 0.90 (t, 3H), 1.06 (d, 6H), 1.48 (m, 2H), 2.48–2.73 (m, 4H), 3.44 (m, 1H), and 3.58 (broad s, 1H; this peak is diminished when treated with D_2O) ppm. ^{13}C NMR: 216.6, 68.8, 47.3, 41.3, 30.1, 17.6, 9.5 ppm. Identify **A, B, C, D**, and **E**.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-21.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

21

Difunctional Molecules

Dienes and Conjugated Carbonyl Compounds

When a starting material has two or more functional groups, one may influence how another functional group in the molecule reacts if the groups are close enough. This chapter discusses difunctional molecules and their chemical reactions. The fundamental principles of photochemistry are also introduced.

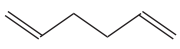
To begin this chapter, you should know the following points:

- Alkenes and alkynes (Sections 5.1–5.3).
- Ketones or aldehydes (Sections 5.6.1,2).
- Alkenes and alkynes (Sections 10.2–10.8).
- Molecular orbitals (Section 3.4)
- Carbocations (Sections 7.2.1 and 10.1).
- Acyl addition reactions of aldehydes and ketones (Sections 16.1–16.5).
- Grignard reagents and organolithium reagents (Sections 14.1–14.3).
- Organocuprates (Section 14.4).
- Reversible reactions and reaction energetics (Sections 7.4–7.9).
- Kinetic and thermodynamic control (Section 20.4).
- Rate of reaction (Section 7.11).
- (*E*) and (*Z*)-stereoisomers (Section 9.7).

Conjugated Dienes and Conjugated Carbonyl Compounds

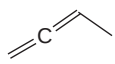
21.1 CONJUGATION

A molecule that contains one C=C unit is called an alkene (see Section 5.1). When a molecule contains two C=C units it is called a *diene*. There are three fundamental structural categories for a diene: (1) the C=C units are separated by sp^3 hybridized atoms, (2) the C=C units are connected together to form a C=C—C=C unit, and (3) there are two π-bonds that share a sp hybridized atom (C=C=C). Dienes in category (1) are called *nonconjugated dienes* and an example is hexa-1,5-diene. Dienes in category (2) are called *conjugated dienes* illustrated by hexa-1,3-diene, which can exist as a mixture of (*E,E*), (*E,Z*), or (*Z,Z*)-isomers. Dienes in category (3) are 1,2-dienes but they have the common name of *allenes* and an example is buta-1,2-diene. An allene is an example of a *cumulative π-system*, a *cumulative diene*. These compounds are sometimes called cumulenes.



Hexa-1,5-diene

Hexa-1,3-diene

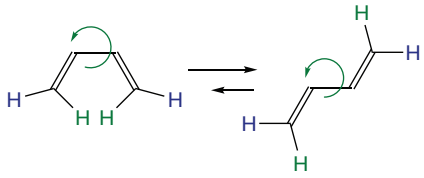


Buta-1,2-diene

21.1 Draw hepta-(2*E*, 4*Z*)-diene.

DOI: 10.1201/9781003174929-21

A carbon-carbon single bond connects the two C=C units in a conjugated diene (C=C—C=C). The C=C bond length in buta-1,3-diene is 1.34 Å (134 pm),[1] which compares favorably with the ~ 1.337 Å, (133.7 pm) bond distance of a typical alkene C=C unit.[1] These bonds distances show that the π-electrons of a diene are *localized* in the π-bonds of the C=C units. The C—C bond length of 1.48 Å (148 pm)[1] in buta-1,3-diene is a bit shorter than the C—C bond distance of 1.54 Å (154 pm) in an alkane.[1] There is a small amount of interaction of the p-orbitals that makes the C—C bond slightly shorter than expected but *butadiene is not resonance stabilized*. Buta-1,3-diene has distinct single and double bonds. Just as it is possible to have two C=C units conjugated in a diene, two C≡C units may be conjugated to form a diyne. Conjugated diynes are not as common as conjugated dienes.



s-cis-Buta-1,3-diene *s-trans*-Buta-1,3-diene

Since C3–C4 in buta-1,3-diene is a single covalent bond there is rotation about that bond with high and low energy rotamers in equilibrium. When the C=C units have an eclipsed-relationship buta-1,3-diene is said to be in a *cisoid-conformation*, or *s-cis conformation*. When the two C=C units have a staggered relationship, buta-1,3-diene is said to be in a *transoid conformation, or s-trans conformation*. The steric interactions of the $=CH_2$ units in the s-cis conformation leads to a greater concentration of the less sterically hindered s-trans conformation.

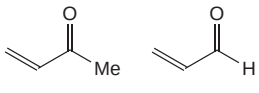
In addition to acyclic compounds, cyclic molecules with conjugated π-bonds are common. An important cyclic diene is cyclopenta-1,3-diene. With cyclohexadiene derivatives there is a conjugated cyclohexa-1,3-diene and a nonconjugated cyclohexa-1,4-diene as shown. With dienes that have larger rings, there is one conjugated isomer but several nonconjugated isomers.

Cyclopenta-1,3-diene

Cyclohexa-1,3-diene

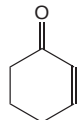
Cyclohexa-1,4-diene

21.2 Draw buta-1,3-diyne and hexa-2,4-diyne.
21.3 Draw 2,4,4-trimethylhex-1-en-5-yne and 1-chloro-6-methylhept-(1*Z*)-en-3-yne.

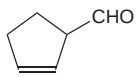


But-3-en-2-one (methyl vinyl ketone)

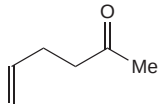
Prop-2-enal (Acrolein)



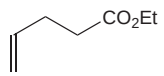
Cyclohex-2-en-1-one



Cyclopent-2-ene-1-carbaldehyde



Hex-5-en-2-one



Ethyl pent-4-enoate

Conjugated alkene-aldehydes, alkene-ketones, and conjugated alkene-carboxylic acid derivatives are characterized by the presence of a C=C—C=O unit. Conjugated carbonyl compounds are also known as *α,β-unsaturated carbonyl compounds*: α,β-unsaturated ketones, α,β-unsaturated aldehydes, α,β-unsaturated esters, etc. Typical examples include

[1] (a) Dean, J.A., *Handbook of Organic Chemistry,* McGraw-Hill, NY, 1987, pp. 3–12 to 3–15; (b) Smith, M. *March's Advanced Organic Chemistry,* 8th ed., John Wiley and Sons, Inc., Hoboken, NJ, 2020, pp. 23–27.

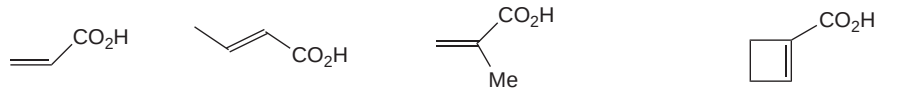
but-3-en-2-one (methyl vinyl ketone) and prop-2-enal (acrolein). As in buta-1,3-diene, there is some overlap of the p-orbitals of the carbonyl carbon and an α-carbon, but as with buta-1,3-diene there is no resonance. Cyclic ketones have a conjugated carbonyl unit within the ring as seen in cyclohex-2-enone. A conjugated cyclic aldehyde has the CHO unit attached to a ring and the conjugating C=C unit is in the ring. An example is cyclopent-1-encarbaldehyde. In these molecules, the presence of the carbonyl will influence reactions at the C=C unit and the presence of the alkene will influence reactions at the C=O unit. In other words, it is difficult to do a chemical reaction at one functional group without the other either reacting or influencing the course of the reaction.

Nonconjugated compounds have sp^3-hybridized carbon atoms that separate the C=C and C=O units. Nonconjugated carbonyl compounds include hex-5-ene-2-one and ethyl pent-4-enolate where the C=C unit and the C=O units react more or less independently of each other in chemical reactions. This reactivity depends on the proximity of the two functional groups, but it is a good working assumption in most cases. Hydrogenation of hex-5-ene-2-one using a palladium catalyst, for example, generally yields hexan-2-one by reduction of the C=C unit whereas switching to a PtO_2 catalyst leads to reduction of the C=O unit to yield hex-1-ene. In other words, one functional group reacts faster than another with the correct choice of catalyst.

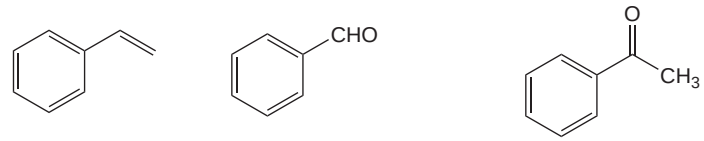
21.4 Draw (a) 5-phenylhex-(3*E*)-en-2-one, (b) methyl 2,2-diethylhept-(4*E*)-enoate, and (c) 4-methylpent-2-ynal.

21.5 Draw (a) 1-phenylhex-(2*Z*)-en-1-one, (b) 3-ethylpent-2-enal, and (c) 2,3,4-trimethylhex-4-en-3-one.

21.6 Draw the structures of cyclopent-2-en-1-one, cyclohex-2-en-1-one, cyclohex-3-en-1-one, 1-cyclohexene-1-carbaldehyde, and 3-cyclohexene-1-carbaldehyde.



Prop-2-enoic acid (Acrylic acid) | But-(2E)-enoic acid | 2-Methylprop-2-enoic acid (Methacrylic acid) | Cyclobut-1-enecarboxylic acid



Styrene | Benzaldehyde | Acetophenone

There are several difunctional compounds with a C=C unit and the carbonyl unit of a carboxylic acid, an acid chloride, an ester, or an amide. Typical conjugated carboxylic acids are prop-2-enoic acid (acrylic acid), but-(2*E*)-enoic acid (crotonic acid), and 2-methylpropenoic acid (methacrylic acid). There are cyclic derivatives of the carboxylic acids in which the carboxyl unit is attached to the ring such as cyclobut-1-enecarboxylic acid. The acid chloride, ester or amide derivatives of these compounds are formed in the usual manner (Sections 18.5–18.8). A C=C unit or a C=O unit connected to an aromatic ring is conjugated. Ethenylbenzene (styrene) for example, is a conjugated alkene and both benzaldehyde and acetophenone are conjugated.

21.7 Draw (a) 2,3-diphenylhex-(2*Z*)-enoic acid, (b) 3-methylbut-2-enoyl chloride, and (c) methyl 3-phenylprop-(2*E*)-enoate.

21.8 Draw (a) ethyl 7,7-dimethylcyclopent-1-en-1-carboxylate, (b) cyclobut-2-en-1-carboxamide, and (c) 2-phenylcyclohex-1-en-1-oyl chloride.

General Principles of Photochemistry

21.2 GENERAL PRINCIPLES OF PHOTOCHEMISTRY

Photochemistry refers to reactions brought about by the absorption of light.[2] Both UV and visible light can excite molecules to higher electronic states. The application of light increases the energy of a molecule according to $E = h\nu$, where $\nu = c/\lambda$ where h is Planck's constant (6.63×10^{-34} *J* sec), c is the speed of light (3×10^{8} m sec^{-1}), and ν is its frequency in sec^{-1}. The wavelength of the light λ is measured in nanometers (1 nm = 1 mμ = 1×10^{-7} cm), and it is inversely proportional to frequency. Ultraviolet light is probably used most often. Light in the UV region is 400–200 nm, or 71.48–142.96 kcal (299.1–598.1 kJ) mol^{-1}. Organic molecules absorb energy in the region of ~ 80–200 kcal (334.7–836.8 kJ) mol^{-1}, easily accessible by exposure of the molecule to a UV light source.

Different functional groups absorb light according to their individual structure. The wavelength of maximum absorption (λ_{max}) is a good guide as to which wavelength of light that should be chosen for irradiation. The wavelength of light absorption and the corresponding energy for several common functional groups has been determined. A carbonyl absorbs at 200 nm, for example, a C=C absorbs at 250 nm, a C—H bond at 300 nm and a C—C bond at 50 nm. The energy of the wavelength of light used for irradiation correlates with the amount of energy necessary to break a given bond.

If a molecule is irradiated with a light source generating several different wavelengths of light, more than one functional group in a molecule may absorb the light and react. The product of the reaction may also absorb the light during the reaction, which can have deleterious effects. To mitigate this problem, the wavelength of light and thereby the energy of irradiation is filtered to control which functional group is more likely to absorb the energy. Irradiation through a filter will block higher energy and lower energy wavelengths so only a narrow range of wavelengths will irradiate the reactants. Common filters include Pyrex glass and Quartz crystal, both with a transmittance range of >200 nm. The so-called Schott color glass filters are useful for different wavelength transmissions.[3] A filter is inserted between the light source and the reactants. A Pyrex™ or quartz glass reaction vessel can act as a filter, but a filter may be also attached to the light source.

When a molecule absorbs a photon of light, an electron is promoted from the bonding molecular orbital to an anti-bonding molecular orbital ($n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, or $\pi \rightarrow \pi^*$) generating a *SOMO (singly occupied molecular orbital)*. There are several ways a molecule can dissipate excess energy from an excited state, as shown in the Jablonski diagram in Figure

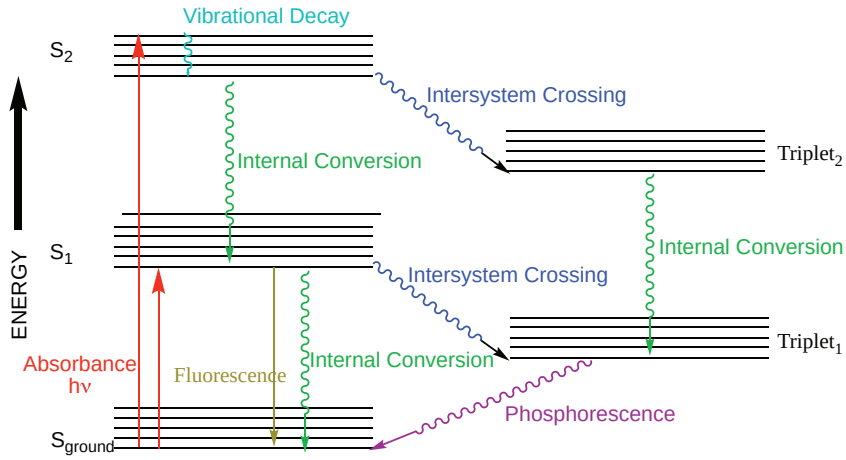


FIGURE 21.1 Jablonski diagram. [Reprinted with permission from Leermakers, P.A.; Vesley, G.F. *J. Chem. Educ. 1964, 41*, 535–541. See Figure 1, 535. Copyright 1964, American Chemical Society].

[2] Wayne, R.P. *Principles and Applications of Photochemistry,* Oxford University Press, Oxford, 1988, p. 1.
[3] www.pgo-online.com/intl/schott-filters.html.

21.1.[4] During photochemical processes *fluorescence* (light emitted from a species that has absorbed radiation) and *chemiluminescence* (light emitted as a product of a chemical reaction) can occur.[2] The light energy is absorbed and excess energy is lost by emission of light, *radiative deactivation* or *fluorescence*, which occurs with spin conservation. Energy is also lost by *phosphorescence*, which occurs with spin inversion. If the deactivation is nonradiative, the transition can occur between two states of the same spin (*internal conversion*) or with inversion of spin (*intersystem crossing*). Excess energy is liberated as heat in both cases. Deactivation must occur in such a way that there is no motion of the atoms during the electronic transition (the *Franck-Condon principle*).

In some cases, an organic molecule does not directly absorb UV radiation, or absorbs it very slowly. In such a case, an excited molecule called a *sensitizer* (S*), which is in a triplet state, can facilitate electron transfer between two molecules.[5] A sensitizer transfers energy

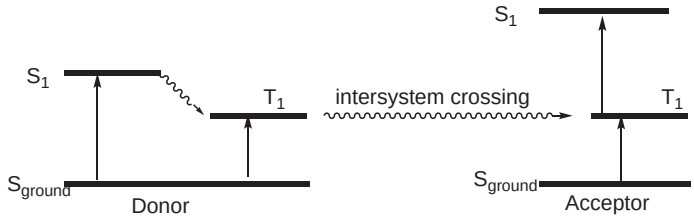
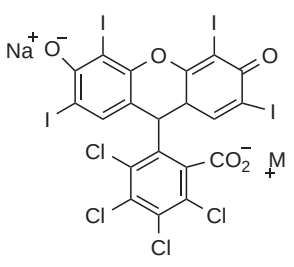


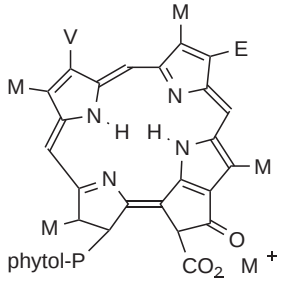
FIGURE 21.2 Singlet to Triplet Intersystem Crossing for Sensitized Reactions. [Reprinted with permission from Leermakers, P.A.; Vesley, G.F. *J. Chem. Educ.*, 1964, 41, 535–541. See Figure 3, 537. Copyright 1964, American Chemical Society].

to another molecule that is in the singlet state. As seen in Figure 21.2,[4] a sensitizer transfers excitation energy from an electronically excited donor molecule (the sensitizer) to the ground state of another molecule, the acceptor. The acceptor is usually excited to a triplet excited state. Triplet energy transfer requires that the triplet energy of the donor be higher than that of the acceptor molecule by 3 kcal (12.6 kJ) mol^{-1} or more. Once excited, the acceptor molecule is susceptible to the processes shown in Figure 21.1 and chemical reactions are possible.

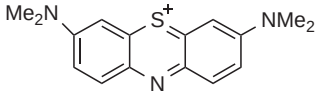
Benzophenone is a common triplet sensitizer. The electron transfer occurs by intersystem crossing ($S_1 \rightarrow T_1$, where S is the singlet and T is the triplet) with great efficiency in molecules such as benzophenone. Irradiation at 366 nm [78.1 kcal (327.1 kJ mol^{-1}] of a mixture of buta-1,3-diene and benzophenone led to exclusive absorption by benzophenone. Triplet buta-1,3-diene has an energy of ≈60 kcal (251.2 kJ) mol^{-1}. The triplet energy of benzophenone [69 kcal (288.8 kJ) mol^{-1}] is transferred with 100% efficiency via intersystem crossing to buta-1,3-diene, which can then undergo photochemical transformations. Acetophenone and naphthalene are widely used sensitizers. More exotic sensitizers are readily available and commonly used including Rose Bengal, chlorophyll A and methylene blue.



Rose bengal



Chlorophyll A



Methylene blue

[4] Leermakers, P.A.; Vesley, G.F. *Journal of Chemical Education* 1964, 41, 535–541.
[5] Eaton, D.F. *Pure and Applied Chemistry* 1984, *56*, 1191–1202.

The use of a sensitizer will influence the choice of the irradiation wavelength. Tuning of the wavelength plays a key role in the outcome of a photochemical path. A different wavelength may activate a different chromophore in a single molecule, or it may induce the population of different reactive excited states. A particular wavelength may sequentially populate the excited state of a compound and the excited state of an intermediate photogenerated from it. These two photoexcited species show a different reactivity. A complex molecule may bear different chromophores, each characterized by its unique reactivity and molar absorption coefficient at a given wavelength. Modification of the wavelength of irradiation can therefore modify a reaction outcome

In photochemical reactions, it is important to measure the efficiency of the photolysis, which is done by the parameter known as *quantum yield* (*quantum efficiency*) defined as the number of molecules reacted or formed per light quanta absorbed. The quantum yield for formation of a product is $\Phi_{form} = \frac{\text{Number of molecules of product formed}}{\text{Number of quanta absorbed}}$. Quantum yield expressed in terms of disappearance of the starting material (SM) per quantum of light is $\Phi_{dis} = \frac{\text{Number of molecules of starting material destroyed}}{\text{Number of quanta absorbed}}$. For photochemical reactions that give a single product, $\Phi_{form} = \Phi_{dis}$. If several products are formed, $\Phi_{dis} = \Sigma\ \Phi_{form}$. If a reaction does *not* go through a chain mechanism, Φ will have a value between 0 and 1.

Ultraviolet Spectroscopy

21.3 DETECTING CONJUGATION WITH SPECTROSCOPY

There are many difunctional molecules that contain C=C, C≡C, or C=O units. Some are conjugated, whereas others are not. Infrared (IR) spectroscopy, introduced in Section 13.3 can be used to identify conjugation in organic molecules because conjugation will shift an IR stretching absorption to lower frequency (longer wavelength), which is lower in energy. Alkenes show a weak-to-moderate absorption at ~ 1645–1670 cm^{-1} for C=C in the IR. Conjugated dienes show two peaks for C=C units centered at ~ 1650 and 1600 cm^{-1}. When a C=C unit is conjugated to a carbonyl, the carbonyl absorption shifts to lower frequency by ~ 30 cm^{-1}. The conjugation of a C=C unit also leads to an enhanced signal so the C=C absorption is stronger when compared to a nonconjugated C=C. Conjugation to a benzene ring shifts the carbonyl signal to ~ 1690 cm^{-1}. A nonconjugated ester shows a carbonyl signal at ~ 1735 cm^{-1}, but conjugation to a C=C or a benzene ring shifts that signal to ~ 1720 cm^{-1}.

Ultraviolet (UV) spectroscopy is particularly useful for the detection of conjugated dienes and conjugated carbonyl compounds. The normal range of UV radiation is 400–200 nm, or 71.48–142.96 kcal (299.1–598.1 kJ) mol^{-1}. A smaller value of nm corresponds to higher energy radiation and a larger value of nm corresponds to a lower energy radiation. Therefore, a 200-nm signal is higher in energy than a 400-nm signal.

21.9 Determine the higher energy absorption, an absorption at 310 or one at 210 nm?

The instrument used to measure the effect of UV light on a molecule is called an *ultraviolet spectrophotometer*. A simplified diagram for a typical instrument is shown in Figure 21.3.[6] There is a UV light source and a series of prisms and mirrors to split the light into two equal components. One beam is directed through a chamber that contains the molecule of interest (the sample). That sample is dissolved in a solvent that does not absorb UV light in the region where the molecule of interest absorbs UV light. Typical solvents include water, ethanol, methanol. The other beam is directed through a chamber that does not contain the sample and it is used as a reference. After passage through the sample and the reference, the beams are recombined and analyzed for absorption of UV light by the sample. A molecule

[6] Altemose, I.R. *Journal of Chemical Education* 1986, 63, pp. A216–A223. See Figure 4.

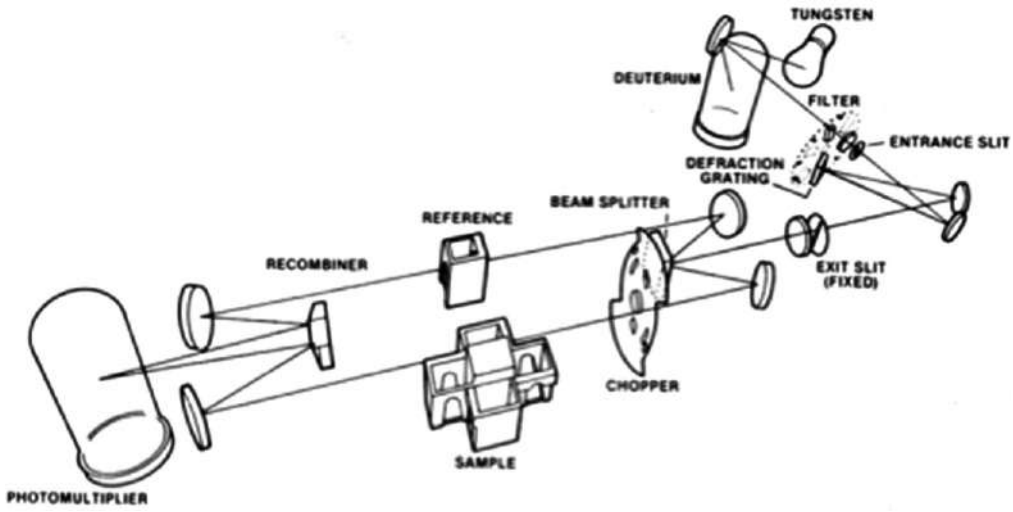


FIGURE 21.3 Diagram of UV spectrophotometer. (Reprinted with permission from Altemose, I.R. *Journal of Chemical Education.*, 1986, 63, p. A216. See Figure 4. Copyright 1986 American Chemical Society).

strongly absorbs UV light *only* if there is a functional group that interacts with the light. Therefore, a UV spectrum is an indication of the presence or absence of certain functional groups in a molecule. The wavelength of UV light is varied in the instrument, and both the wavelength and the amount of light absorbed is recorded. The detection system leads to a plot of wavelength vs absorption to show how much energy was absorbed for a given wave-

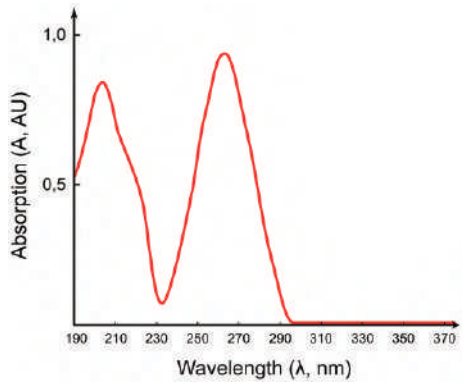


FIGURE 21.4 A typical UV absorption spectrum. Royalty-free stock vector ID: 273874901

length of UV light. This plot is the *UV spectrum.* When light is absorbed, it registers as a "peak" at that wavelength (Figure 21.4). A more intense peak is produced when more light is absorbed. The intensity of the absorption is the *extinction coefficient (ε).* The larger the extinction coefficient, the stronger the signal. The wavelength with the largest extinction coefficient (the largest peak) is referred to as λ_{max}.

For a given wavelength of light, the amount of light that passes through the molecule is measured by the intensity (I) of that light. The amount of light used as a reference is labeled I_o, and the amount of light transmitted through the solution is $\frac{I_o}{I}$. The amount of light that passes through the solution is the *transmittance.* The amount of light *absorbed* by the molecule is the *inverse* of this equation, which is $\frac{I}{I_o}$. The amount of light absorbed or transmitted

is proportional to how many molecules are present (the concentration, *c*) and also the length of the chamber through which the light must pass (path length, *d*). *Beer's Law* shows this relationship as log $\frac{I_o}{I} \propto c \bullet d$ but a proportionality constant is required to set these terms equal. This constant is ε, *the extinction coefficient*. Therefore, Beer's Law is log $\frac{I_o}{I} = \varepsilon \bullet c \bullet d$. This equation shows that when I_o and I are measured using a UV spectrophotometer, the concentration and path length are known and ε can be calculated. If ε is very large, it means that the molecule absorbs UV light readily, but if ε is small it means the molecule does *not* absorb UV light very well.

21.10 If ε = 20 for c = 0.1 g mL^{-1} and a path length of 10 dm, calculate log $\frac{I_o}{I}$.

A discussion of how a molecule interacts with UV light requires a return to the concept of molecular orbitals introduced in Section 3.4. Absorption of UV light by a molecule is usually associated with the promotion of an electron from a lower energy to a higher energy orbital. A C—C bond with sp^3 hybridized carbon atoms has bonding and antibonding orbitals. Electrons used to form covalent bonds are found in the bonding molecular orbital (MO), whereas the antibonding orbital is "empty." The bonding orbital in sp^3 hybridized bonds is labeled as a σ-orbital and the antibonding orbital is labeled σ*-orbital. The energy of UV-visible-IR light does not correlate with the energy of a σ→σ* absorption of an alkane in Figure 21.5. There is no absorption of UV light by an alkane. Unshared electrons in a molecule are much easier to displace since less energy is required for the unshared electron to go from a bonding to an antibonding orbital. The orbital containing unshared electrons is known as an *n-orbital* (a nonbonding orbital). Such a compound can absorb UV light and there is an absorption that corresponds to an n→σ* transition. There is another transition that corresponds to a n→n* transition (Figure 21.5). For example, 1-iodobutane shows an absorption peak at 224 nm [160.2 kcal (670.3 kJ) mol^{-1}] that corresponds to the *n*→σ* transition. For the C=C unit the π-electrons are easily displaced. The molecular orbitals associated with π-electrons are labeled the π-orbitals and π*-orbitals, respectively. Absorption of UV light leads to a transfer of a π-electron from the π-orbital to a π*-orbital (known as a π→π* transition). Ethene shows a π→π* absorption at 165 nm. The carbonyl group also has a π-bond, so there is a π→π* transition.

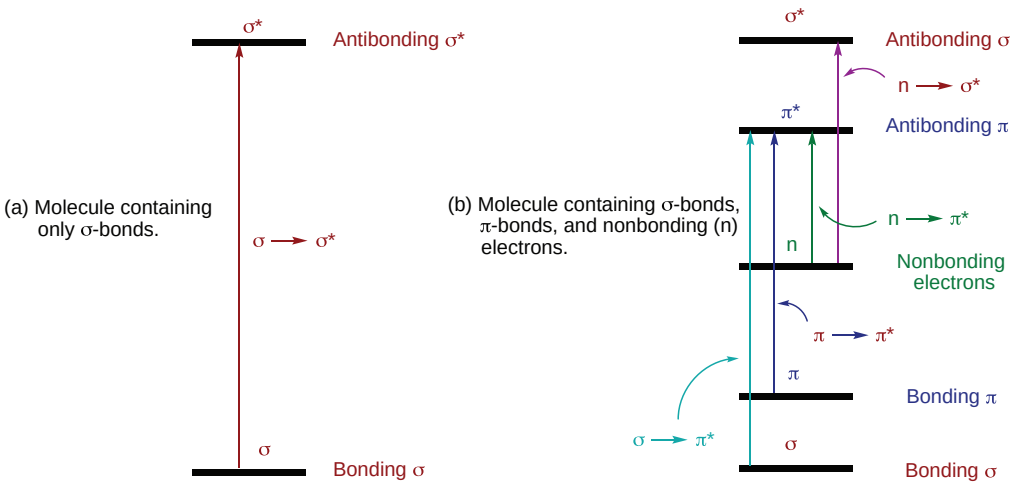
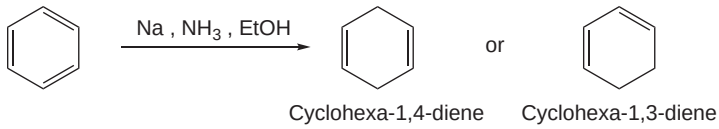


FIGURE 21.5 Transitions within electronic energy levels.

The oxygen of a carbonyl has unshared electrons, whereas the C=C of an alkene does not, so n→n* transitions and n→π* transitions are possible for the carbonyl. Another transition is

possible, the n→σ* transition. In the case of acetone, the π→π* transition occurs at 150 nm, the n→σ* transition appears at 188 nm, and the n→π* transition appears at 279 nm. The ΔE for the n→π* is smaller than that for any other transition, and this is generally true for functional groups containing both nonbonded electrons and π-electrons. The energy of UV light for the π→π* transition of acetone is higher than that for ethene (150 vs 165 nm).

Irradiation with UV light can distinguish the structure of a conjugated compound. Conjugation shifts the absorption bands in the UV. The actual π→π* transition UV absorption band for buta-1,3-diene is 217 nm compared with 165 nm for ethene. Therefore, a conjugated diene is distinguished from a nonconjugated diene by a lower energy absorption band. A similar argument is made for conjugated carbonyl compounds. The conjugated aldehyde acrolein shows a π→π* absorption occurs at 210 nm.[7] The energy required for acrolein to absorb UV light is higher than for buta-1,3-diene (217 nm). Acrolein shows a second absorption band that does *not* appear for buta-1,3-diene, a n→π* transition at 315 nm.[7] Sufficient information is now available to use UV spectroscopy to obtain structural information about molecules containing two C=C units or a C=C unit and a C=O unit. This information is used to determine if there is conjugation.



21.11 Which absorbs at shorter wavelength, hexa-1,5-diene or hexa-1,3-diene?

Birch reduction of benzene was shown to yield the non-conjugated cyclohexa-1.4-diene in Section 19.7 rather than the conjugated diene cyclohexa-1,3-diene Conjugation can be detected by their UV spectrum. The UV spectrum of cyclohexa-1,4-diene shows an absorption band at 224 nm with a low extinction coefficient of 32. Cyclohexa-1,3-diene shows a band at 256 nm with an extinction coefficient of 10,000.[8] The characteristic shift to lower energy associated with conjugation clearly identifies cyclohexa-1,3-diene as conjugated. The larger extinction coefficient is also characteristic of conjugation. When there is no data in the literature and no authentic sample is available a prediction can be made to compare with an experimentally obtained spectrum. The Woodward-Fieser rules[9] were developed to assist in the predication of UV absorption peaks.[10]

CONJUGATED DIENES

The base value for a conjugated diene is 214 nm and buta-1,3-diene is assumed to be the "parent."
If the diene is contained in a ring, the base number is 253 nm.
For each C=C unit that extends conjugation, +30. For each alkyl group attached to the C=C, +5. For an exocyclic C=C, +5. For an *O*-alkyl substituent, +6 and for an *S*-alkyl substituent, +30. For a Cl or Br substituent, +5. For a $B(R)_2$ substituent, +60.

[7] Yadav, L.D.S. *Organic Spectroscopy* Klumer Academic Publishing, Norwell, MA, 2005, p. 13.
[8] Yadav, L.D.S. *Organic Spectroscopy* Klumer Academic Publishing, Norwell, MA, 2005, p. 21.
[9] Woodward, R.B. *Journal of the American Chemical Society* 1941, 63, 1123–1126; Fieser, L.F.; Fieser, M.; Rajagopalan, S. *Journal of Organic Chemistry* 1948, 13, 800–806.
[10] Silverstein, R.M.; Bassler, G.C.; Morrill, T. *Spectrophotometric Identification of Organic Compounds*, 5th ed., John Wiley & Sons, Inc., NY, 1991, Tables 7.5 and 7.6, pp. 299–300. Also see, Yadav, L.D.S. *Organic Spectroscopy*, Klumer Academic Publishing, Norwell, MA, 2005, p. 20 and p. 27.

CONJUGATED CARBONYLS

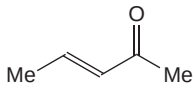
The base value for an acyclic ketone is 215 nm; it is 210 nm for an acyclic aldehyde; it is 195 nm for a conjugate acid. There are two carbon atoms of the C=C unit. The carbon closest to the carbonyl (proximal) is the α-carbon and the carbon furthest from the carbonyl (distal) is the β-carbon.

The base value for a cyclohexenone derivative is 215 nm and it is 214 for a cyclopentenone.

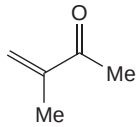
For each conjugating C=C unit, +30. For each alkyl group +10 for α-alkyl and +12 for a β-alkyl.

The values are +35 for an α-OH and +30 for a β-OH; +6 for an α-OAc; +35 for an α-OMe and +30 for a β-OMe. Add +15 for an α-Cl and +12 for a β-Cl; +25 for an α-Br and +30 for a β-Br. Add +95 for a β-NR_2.

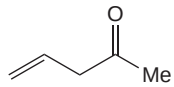
Consider three structures, pent-(3*E*)-en-2-one, 3-methylbut-3-en-2-one, or pent-4-en-2-one. Predictions are made by first assigning a base value for a conjugated diene (214 nm), a conjugated ketone (215 nm), a conjugated aldehyde (210 nm), or a conjugated acid (195 nm). Values are added to the base value for each substituent. The sum of these values is taken to be the λ_{max} for that molecule. Using these rules, pent-(3*E*)-en-2-one has a base value of 215 + 12 for a methyl on the β-carbon = 227 nm. For 3-methylbut-3-en-2-one, the base value is 215 + 10 for a methyl on the α-carbon = 225 nm. Pent-4-en-2-one is *not* conjugated so it should show an absorption for the C=C at ~ 170–180 nm and an absorption for the C=O ~ 150–160 nm.



Pent-(3*E*)-en-2-one



3-Methylbut-3-en-2-one



Pent-4-en-2-one

21.12 Estimate λ_{max} for (a) hept-(5*E*)-en-2-one, (b) hept-(3*E*)-en-2-one, (c) hept-(3*E*,5*E*)-dien-2-one, and (d) 3,4-dimethylhept-(3*Z*)-en-2-one.

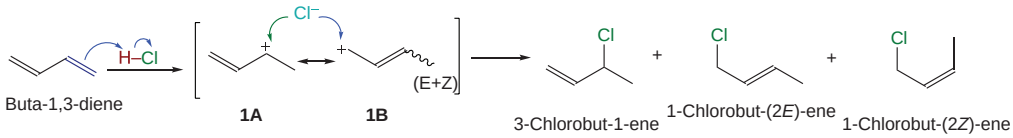
21.13 Estimate λ_{max} differentiate: pent-(2*E*)-enal vs 2-methylbut-(2*E*)-enal and also hex-(3*E*)-en-2-one vs hexa-(3*E*,5*E*)-dien-2-ol.

Reactions of Dienes

21.4 REACTIONS OF CONJUGATED Π-BONDS

Several chemical reactions of simple alkenes were discussed in Chapter 10. Acid-base reactions generate carbocations or other cation intermediates. In a nonconjugated diene, each π-bond reacts more or less independently, so hexa-1,5-diene is expected to react with one molar equivalent of HBr to give an alkenyl bromide, 5-bromohex-1-ene. One C=C unit reacts and the second C=C unit does not influence the reaction. The situation is quite different for a conjugated diene such as hexa-1,3-diene. Since the π-bonds are linked together, a reaction at one C=C unit is influenced by the presence of the other C=C unit.

When HCl reacts with buta-1,3-diene one C=C unit reacts to give a carbocation, but the second C=C unit is connected and the product is an *allylic carbocation,* **1**. Allylic carbocation **1** is resonance-stabilized because of the conjugating C=C unit. There are two resonance contributors **1A** and **1B** and an allylic carbocation is more stable than a non-allylic carbocation**.** Because of resonance, there are two electrophilic carbon atoms in **1**.

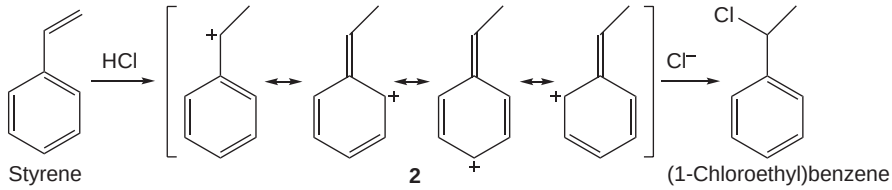


The nucleophilic chloride ion reacts with *both* positive carbons to give two regioisomeric products, 3-chlorobut-1-ene (from **1A**) and 1-chlorobut-2-ene (from **1B**). A mixture of (*E*)-1-chlorobut-2-ene and (*Z*)-1-chlorobut-2-ene is obtained in ~ 80% yield, along with ~ 20% of 3-chlorobut-1-ene.[11] The *E/Z* mixture is due to free rotation about the C2—C3 bond. There is usually a higher percentage of the disubstituted alkene because the C=C unit has more electron releasing alkyl groups and it is more stable. 3-Chlorobut-1-ene is formed by "adding" the elements of H and Cl to one C=C unit of C=C-C=C and it is called a *1,2-addition product*. Similarly, to form 1-chlorobut-2-ene the elements of H and Cl add to C1 and C4 of C=C-C=C, so it is called a *1,4-addition product*.

21.14 Write out the reaction between hexa-1,5-diene and one molar equivalent of HBr. What is the product if two molar equivalents of HBr are used?

21.15 Draw the structure of all products formed when HBr reacts with hepta-(3*E*,5*Z*)-diene; label the major product if the reaction is done at -50°C; at 55°C?

When the C=C unit is conjugated to a benzene ring, as in styrene, the reaction with HCl gives the resonance-stabilized intermediate, **2**, known as a *benzylic carbocation*. The positive charge can be delocalized into the benzene ring, leading to the four resonance contributors shown. Reaction with the nucleophilic chloride ion gives (1-chloroethyl)benzene. The chloride ion only reacts with carbon attached to the benzene ring since reaction with the other resonance contributors give a product that is not aromatic. Formation of the aromatic product is favored.



21.16 Draw all resonance contributors and the final product for a reaction between 1-(1-methyethenyl)-4-methylbenzene and HBr.

The reaction of alkenes with diatomic halogens (e.g., bromine, Br_2) to form 1,2-dibromides is facile (see Section 10.4). In this reaction, the alkene donates two electrons to the bromine atom to form a bromonium ion and reaction with the nucleophilic bromide counterion gives the trans-dibromide. When buta-1,3-diene reacts with bromine, both 1,2- and 1,4-addition products are formed, 3,4-dibromobut-1-ene and a mixture of (*E*) and (*Z*)-1,4-dibromobut-2-ene. Initial reaction with bromine generates bromonium ion **3**, as shown in Figure 21.6. The bromide ion will attack the less substituted carbon to give the 1,2-dibromo product. However, **3** is attached to a C=C unit. Reactivity is extended because inductive effects lead to a δ^+ dipole at the terminal carbon of the alkene unit. The extension of reactivity due to conjugating π-bonds is known as *vinylogy*. Reaction of the bromide ion at the C=C unit yields the two stereoisomeric products, 1,4-dibromobut-(2*E*)-ene and 1,4-dibromobut-(2*Z*)-ene. Nucleophilic attack of this type is called an S_N2' *reaction*, nucleophilic substitution at an allylic carbon with displacement of the leaving group.

[11] Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry*, Reinhold Pub., NY, 1961, p. 199.

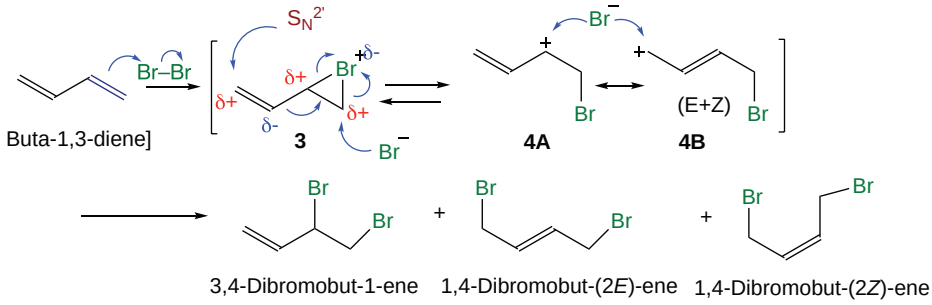
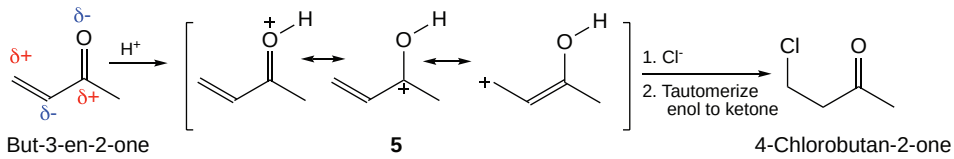


FIGURE 21.6 Mechanism of the reaction of buta-1,3-diene with diatomic bromine.

In an aqueous medium, formation of the three-membered ring bromonium ion (**3**) is followed by opening to generate allyl carbocation **4**. Reaction with the bromide ion affords three observed products. Assume the ionization mechanism dominates in aqueous media and the S_N2' mechanism is dominant in nonaqueous solvents. The 1,4-dibromobut-2-enes are disubstituted alkenes and thermodynamically more stable than the terminal alkene 3,4-dibromobut-1-ene. There is a temperature dependence on the reaction of buta-1,3-diene with bromine. Bromonium ion **3** should form first and fastest at low temperatures and reaction with the bromide ion will lead to primarily to the 1,2-dibromo product. At higher temperatures, the S_N2' reaction is more competitive and ionization to **4** is also more likely in a thermodynamic process. If an allylic cation is formed at higher temperatures, there is an equilibration that will give the thermodynamically more stable alkene products. To summarize, buta-1,3-diene reacts with Br_2 at low temperatures to yield 3,4-dibromobut-1-ene as the major product. At higher temperatures, the major products are 1,4-dibromobut-(2*E*)-ene and 1,4-dibromobut-(2*Z*)-ene.

21.17 Draw all products formed when hexa-(2*E*, 4*Z*)-diene reacts with chlorine.

Just as conjugated dienes undergo addition reactions with HX or X_2, conjugated carbonyl derivatives also react. The presence of the carbonyl makes the reaction follow a somewhat different path relative to dienes, however. A simple conjugated ketone, but-3-en-2-one (methyl vinyl ketone), illustrates the difference. The electronegative oxygen polarizes the carbonyl unit, but inductive effects extend to the conjugating C=C unit, so the terminal carbon on the alkene unit has a δ^+ dipole. When but-3-en-2-one reacts with HCl, the carbonyl oxygen reacts with H^+ to generate oxocarbenium ion **5** (Section 18.1). Oxocarbenium ion **5** has three resonance contributors, however, due to the attached C=C unit.



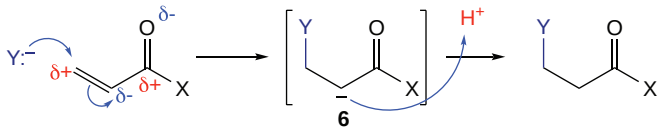
The charge delocalization due to resonance extends the positive charge to the terminal carbon, C4. The nucleophilic chloride ion reacts at C4 to give 4-chlorobutan-2-one. If chloride ion reacts at C4, the product is an enol, which tautomerizes to the final product, 4-chlorobutan-2-one. A conjugated acid derivatives such as methyl acrylate, reacts with HCl in a similar manner to but-3-en-2-one, and the product is methyl 3-chloropropanoate. α,β-Unsaturated esters react similarly.

21.18 Draw the product formed when cyclopentenone reacts with HCl.

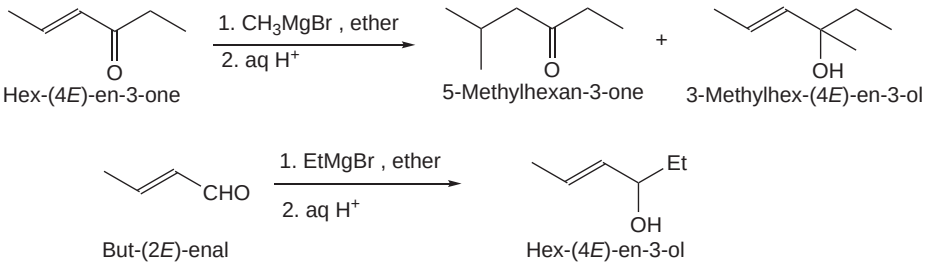
21.5 CONJUGATE ADDITION

Michael Addition

Due to vinylogy the β-carbon of an α,β-unsaturated carbonyl compound is subject to reaction with nucleophiles such as amines. There is an early body of work in which amines reacted at the β-carbon of conjugated carbonyl compounds. However, this reaction is often reversible, and it will not be discussed further in order to keep the focus on reactions that generate C—C bonds. The reaction of an enolate ion of a ketone or aldehyde with the β-carbon of an α,β-unsaturated carbonyl is commonly called *Michael addition* (or the *Michael reaction*), named after Arthur Michael (USA; 1853–1942). An example of the reaction uses a nucleophile Y^- in a reaction with a generic conjugated system. The bond polarization induced by the electronegative carbonyl oxygen atom is also shown. The δ+ dipole of the C=C unit reacts with a nucleophile (Y^-) to form enolate anion, **6**, which is resonance stabilized. In a second step, a hydrolytic workup gives the isolated product in which the nucleophile has added to C3 relative to the carbonyl carbon atom. This is a *1,4-addition, or conjugate addition*. The common term is *Michael addition.*

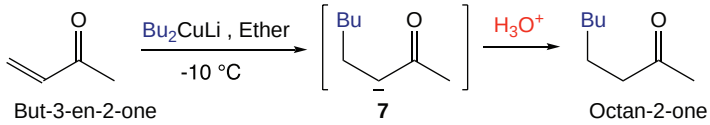


21.19 Show the reaction and product formed when dimethylamine (*N*-methylmethanamine) reacts with methyl vinyl ketone.

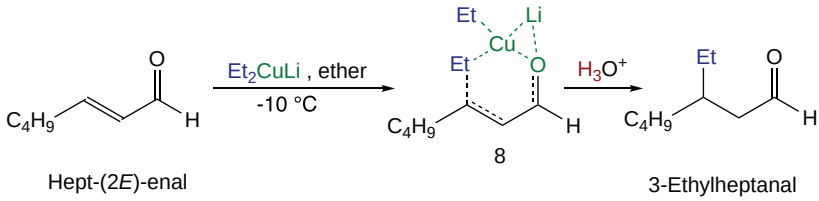


Michael addition occurs with strong nucleophiles such as Grignard reagents. With ketones, there may be a competition between 1,2- (attack at the acyl carbon) and 1,4-addition (attack at the β-carbon of the C=C unit). The reaction of hex-(4*E*)-en-3-one with the Grignard reagent methylmagnesium bromide, followed by a hydrolytic workup, leads to a mixture of 5-methylhexan-3-one and 3-methylhex-(4*E*)-en-3-ol. In general, significant amounts of 1,4-addition occur with conjugated ketones only when there is a relatively large group attached to the acyl carbon. When the group attached to the carbonyl is relatively small, 1,2-addition (normal acyl addition) tends to be the major product. When the carbonyl is relatively unhindered, as with conjugate aldehydes, Grignard reagents react primarily at the acyl carbon (1,2-addition). But-(2*E*)-enal reacts with ethylmagnesium bromide, for example, to give hex-(4*E*)-en-3-ol.

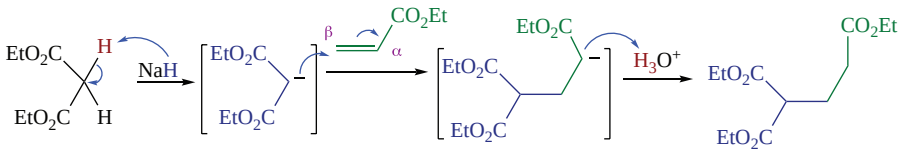
21.20 Draw both starting material and final product for the 1,2-addition product from the reaction of pent-3-en-2-one with ethylmagnesium bromide, followed by hydrolysis.



Organocuprates (Section 14.4) react with conjugated carbonyl compounds to give almost exclusively 1,4-addition. Organocuprates are generated from an organolithium reagent and a cuprous salt (e.g., CuI, cuprous iodide; Section 14.4). When two equivalents of *n*-butyllithium are mixed with CuI in ether at -10 °C, the product is lithium dibutylcuprate. Subsequent reaction with a conjugated ketone such as but-3-en-2-one via 1,4-addition gives an enolate anion product, **7**, which gives octan-2-one upon hydrolytic workup. Even an aldehyde, which is rather unhindered, gives primarily 1,4-addition as illustrated by the reaction of hept-(2*E*)-enal with lithium diethylcuprate to yield 3-ethylheptanal after hydrolytic workup.



This reaction gives 1,4-addition because there is a coordination of copper with the carbonyl oxygen, making delivery to the "4" position easy via a six-centered transition state (**8**). This type of six-centered transition state is likely involved in all reactions of organocuprates with conjugated ketones, aldehydes, or esters. Assume that organocuprates give 1,4-addition with both conjugated aldehydes and conjugated ketones.



Enolate anion nucleophiles undergo Michael addition in some cases, forming a new C—C bond by reaction at the terminal carbon of the C=C unit. Michael addition of the malonate anion to ethyl acrylate will give the conjugate addition product, enolate anion **9**. Aqueous acid workup gives the isolated product, triethyl propane-1,1,3-tricarboxylate. Other conjugated carbonyl derivatives react similarly.

21.21 Draw the product formed when pentane-2,4-dione reacts with sodium hydride and then with pent-3-en-2-one.

When tricyclic ketone **10** is heated with methyl vinyl ketone (but-3-en-2-one) in the presence of ethanolic KOH, the final product (after hydrolysis) is a steroid, **15**. This process is called the *Robinson annulation*, named after Sir Robert Robinson (England; 1886–1975). The reaction of tricyclic ketone **10** with KOH forms the enolate anion (**11**), as shown in Figure 21.7. Although it is not obvious, under these thermodynamic conditions 1,4-addition is faster than

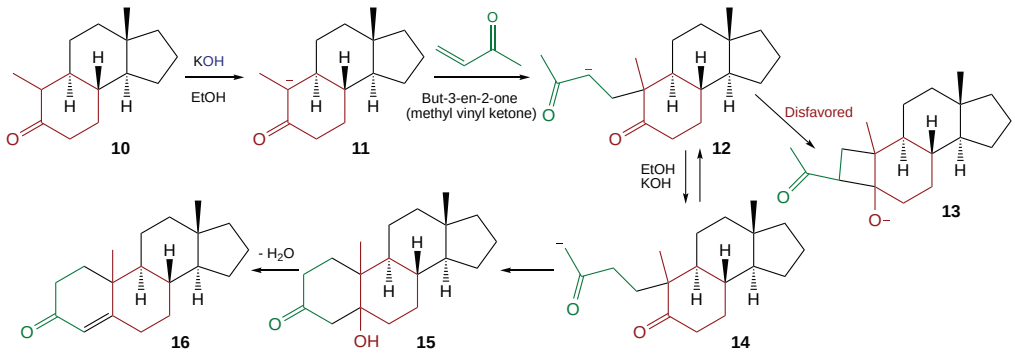


FIGURE 21.7 The Robinson annulation.

self-condensation of the ketone and the product is enolate anion **12**. One possible reaction for **12** is an intramolecular aldol condensation with the other carbonyl (Section 20.6), but that would lead to a four-membered ring product, **13**. The activation barrier to form this strained ring is high, so this reaction is *slow* and a lower energy reaction pathway is available. The reaction conditions favor thermodynamic control, which means that enolate anion **12** is in equilibrium with the neutral diketone. Reaction with hydroxide generates the kinetic enolate anion **14**. The enolate anion attacks the carbonyl in an intramolecular aldol reaction to form a six-membered ring product, **15**. A hydrolytic workup and dehydration generates steroid **16**.

21.22 Draw the Robinson annulation product formed from hex-1-en-3-one and 2-methylpentan-3-one, in the presence of NaOMe/MeOH, after aqueous acid hydrolysis at 10°C.

Nazarov Cyclization

An important cyclization reaction relies on Michael addition. The acid-catalyzed addition of diene-ketones such as **17**, involves the addition of one conjugated alkene to the other conjugated alkene. The product is a cyclopentenone (**20**) and the reaction is

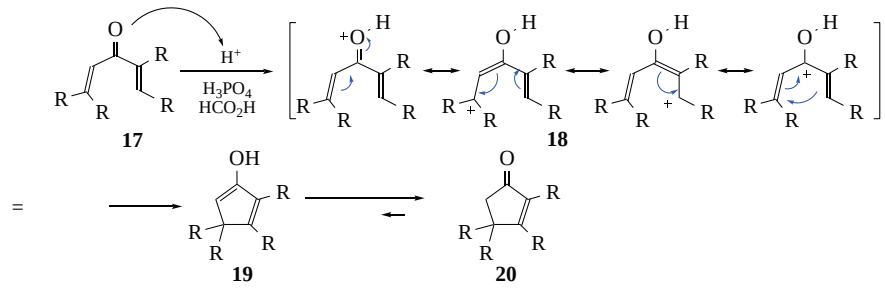
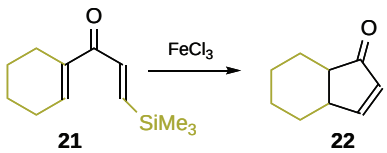


FIGURE 21.8 General mechanism of the Nazarov cyclization.

called the *Nazarov cyclization*.[12] The initial reaction of the carbonyl with the acid catalyst generates the resonance stabilized cation **18** as shown in Figure 21.8. One of the resonance contributors allows a Michael-type addition to the distal C=C unit that gives enol **19**. The enol tautomerizes to the cyclopentenone **20**. The cyclization can be accomplished mild conditions by incorporating a stabilizing group on the alkene. Both silane and stannane derivatives have been prepared. An example is the cyclization of **21** using ferric chloride ($FeCl_3$) to give **22**.[13]

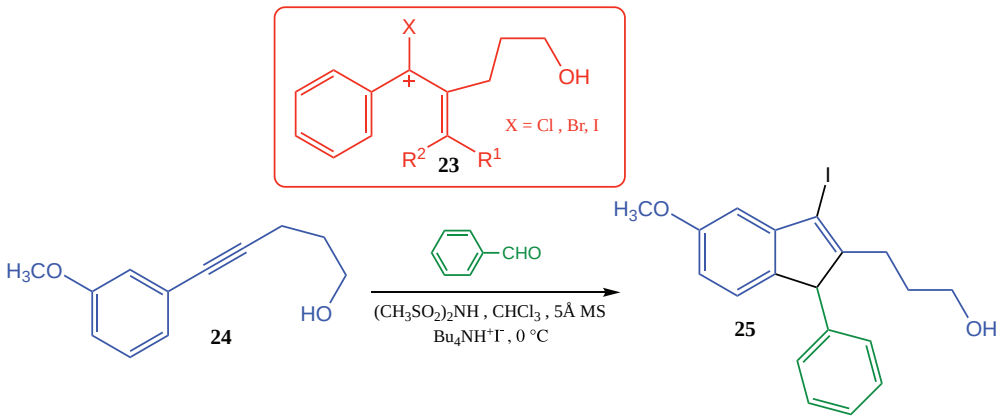


[12] (a) Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk. (*Bulletin of the Academy of Sciences of the USSR, Division of Chemical Science) 1942, 200; (b) Frontier, A.J.; Jackson, J.; Hernandez, J.J. *Accounts of Chemical Research* **2020**, *53*, 9, 1822–1832; (c) Frontier, A.J.; Collison, C. *Tetrahedron* 2005, 61, 7577–7606; (d) Tius, M.A. *European Journal of Organic Chemistry* 2005, 2193–2206.

[13] Denmark, S.E.; Jones, T.K. *Journal of the American Chemical Society* 1982, 104, 2642–2645.

Alison J. Frontier

Alison J. Frontier (USA) is a professor at the University of Rochester and a synthetic organic chemist. Professor Frontier's work has focused on cyclization reactions that produce unusual, densely functionalized ring systems from simple precursors. She has studied novel pericyclic reactions, cationic rearrangements and diastereoselective cyclization cascades, and their application to complex molecule synthesis. One area of research is her study of the Nazarov cyclization.[12b,c] During the course of that research it was discovered that the use of dienones as Nazarov cyclization precursors was problematic in that they required a multistep synthesis and that these precursors degraded tend to degrade upon prolonged storage. To avoid this problem, Professor Frontier and her student Connor Holt examined a "halo-Nazarov cyclization" approach for the preparation of substituted halo-indenes and indanones, which was postulated to proceed by an intermediate such as **23**.[14] The haloalkyne precursor **24** was treated with 1.6 equivalents of triflimide (Tf_2NH), tetrabutylammonium iodide in chloroform at 0 °C, in the presence of molecular sieves 5Å to give a 58% yield of the halo-indene product, **25**. The mild conditions and efficient nature of this halo-Nazarov cyclization allows formation of functionalized halo-indenes in a cationic, one-pot cascade reaction.

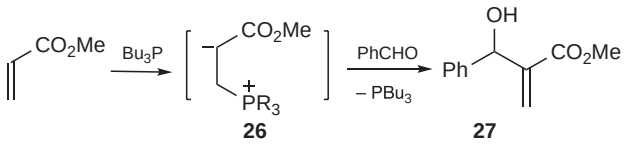


An interesting variation of the Michael addition has been used to prepare highly functionalized acylate derivatives. In its fundamental form, an acrylate ester reacts with an aldehyde in the presence of an amine or phosphine catalyst such as tributylphosphine. Presumably,

[14] Holt, C.; Alachouzos, G.; Alison J. Frontier, A.J. *Journal of the American Chemical Society* 2019, 141, 5461–5469.

Michael addition of the phosphine generates an enolate anion such as **26**, which condenses with the aldehyde and then loses the phosphine or amine to give the final product **27**. This transformation is known as the *Baylis-Hillman reaction*[15] (also known as the *Morita-Baylis-Hillman reaction*).[16] The reaction is named after Ken-ichi Morita (Japan), Anthony B. Baylis (USA) and Melville E.D. Hillman (USA). Aldol condensation, induced by the amine catalyst, can be a competing side reaction. Coupling is often slow, but the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst at 0 °C led to faster formation of Baylis-Hillman products, and in good yield.[17]

Morita-Baylis-Hillman Reaction

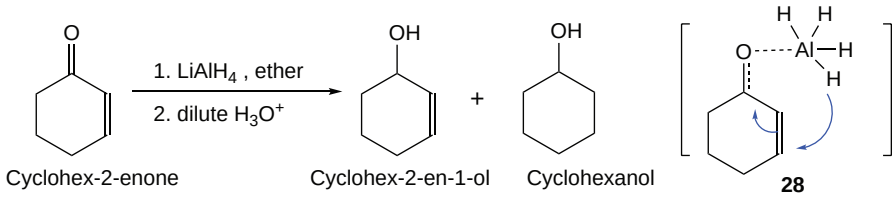


26 **27**

21.6 REDUCTION OF CONJUGATE SYSTEMS

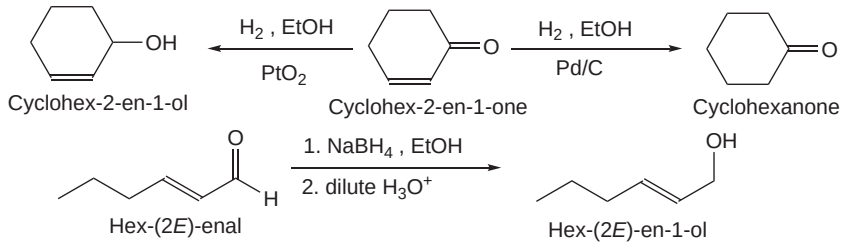
Conjugate Reduction

In Section 17.2, lithium aluminum hydride and sodium borohydride were shown to react with ketones or aldehydes via acyl addition to reduce the carbonyl to the corresponding alcohol. The presence of a conjugating π-bond leads to 1,2- and 1,4-addition, however.



Cyclohex-2-enone Cyclohex-2-en-1-ol Cyclohexanol **28**

When cyclohex-2-enone reacts with $LiAlH_4$, the product is a mixture of cyclohexenol and cyclohexanol. Cyclohex-2-enol results from 1,2-addition of the hydride, but the other product, cyclohexanol, results from 1,4- *and* 1,2-addition. The 1,4-reduction occurs by coordination of aluminum or boron to the oxygen, as in **28**, followed by intramolecular delivery of hydride to the C=C unit. The reduction of cyclohex-2-enone is contrasted with reduction of α,β-unsaturated aldehydes (e.g., hex-2-enal) with $NaBH_4$, which yields a high percentage of 1,2-reduction so the product is hex-2-en-1-ol.



Cyclohex-2-en-1-ol Cyclohex-2-en-1-one Cyclohexanone

Hex-(2*E*)-enal Hex-(2*E*)-en-1-ol

Although conjugated ketones react via both 1,2- and 1,4-addition, at temperatures < 0 °C, 1,2-reduction predominates. Reduction with $LiAlH_4$ is more likely to yield 1,2- and 1,4-reduction products, but $NaBH_4$ is more likely to give 1,2-reduction at low temperatures.

[15] (a) Ciganek, E. *Organic Reactions* 1997, 51, 201–350; (b) Basavaiah, D.; Rao, P.D.; Hyma, R.S. *Tetrahedron* 1996, 52, 8001–8062; (c) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Tetrahedron* 2003, 59, 1181–1189.

[16] (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bulletin of the Chemical Society of Japan* 1968, 41, 2815. (b) Basavaiah, D.; Rao, A.J.; Satyanarayana, T. *Chemical Reviews* 2003, 103, 811–892.

[17] Rafel, S.; Leahy, J.W. *Journal of Organic Chemistry* 1997, 62, 1521–1522.

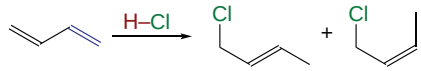
It is possible to reduce only the C=C unit of a conjugated ketone using catalytic hydrogenation when only 1 equiv of hydrogen gas is used. The reaction of cyclohex-2-enone with hydrogen gas and a Pd catalyst affords cyclohexanone in high yield. If the catalyst is changed to platinum oxide (PtO_2), however, the product is primarily cyclohex-2-enol. Assume that Pd catalysts lead to reduction of the C=C unit as the major product, but that Pt catalysts lead to reduction of the C=O unit as the major product. When hex-(2*E*)-enal reacts with $NaBH_4$, the 1,2-addition product hex-(2*E*)-en-1-ol is isolated after treatment with aqueous acid.

21.7 ORGANIZATION OF REACTION TYPES

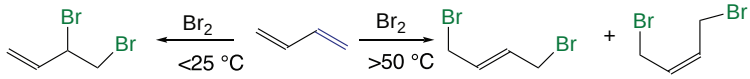
The reactions of conjugated dienes and conjugated carbonyl compounds include:

What reactions are possible for conjugated dienes?

1. Conjugated dienes undergo primarily 1,4-addition with HCl or HBr.

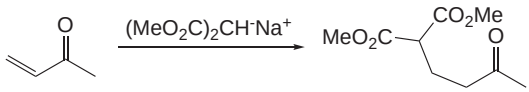


2. Conjugated dienes undergo primarily 1,4-addition with Br_2 at >50 °C and 1,2-addition at <25 °C.

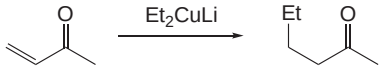


What reactions are possible for conjugated ketones or aldehydes?

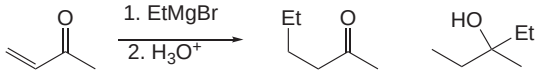
1. Conjugated ketones and aldehydes undergo primarily 1,4-addition with malonate anion derivatives.



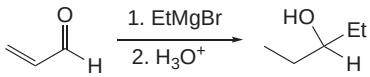
2. Conjugated ketones and aldehydes undergo primarily 1,4-addition with organocuprates.



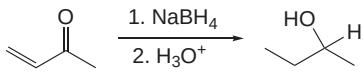
3. Conjugated ketones undergo a mixture of 1,2- and 1,4-addition with Grignard reagents.



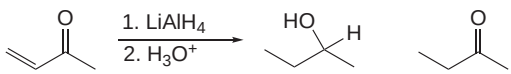
4. Conjugated aldehydes undergo a mixture of 1,2- and 1,4-addition with Grignard reagents, but mostly 1,2-addition.



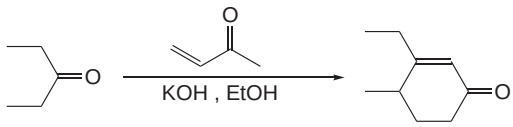
5. Conjugated ketones and aldehydes react with $NaBH_4$ to yield primarily 1,2 reduction.



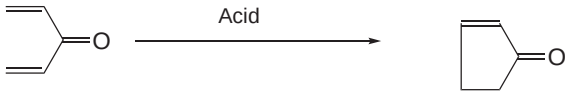
6. Conjugated ketones and aldehydes react with $LiAlH_4$ to yield a mixture of 1,2- and 1,4- reduction



7. Conjugated ketones and aldehydes react with ketones under thermodynamic enolate anion conditions to yield cyclic ketones via the Robinson annulation, and with cyclic ketones to yield bicyclic ketones.

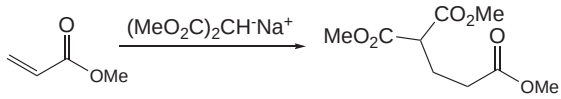


8. The reaction of dienone with acid gives cyclopentenones

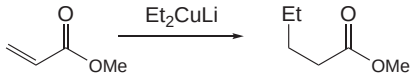


What reactions are possible for conjugated esters?

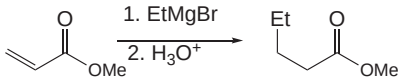
1. Conjugated esters undergo primarily 1,4-addition with malonate anion derivatives.



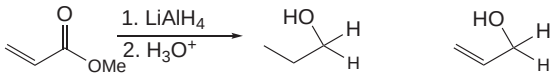
2. Conjugated esters undergo primarily 1,4-addition with organocuprates.



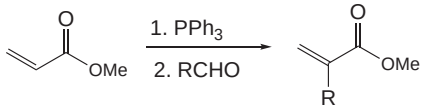
3. Conjugated esters undergo 1,4-addition with Grignard reagents.



4. Conjugated esters undergo a mixture of 1,2- and 1,4-reduction with $LiAlH_4$

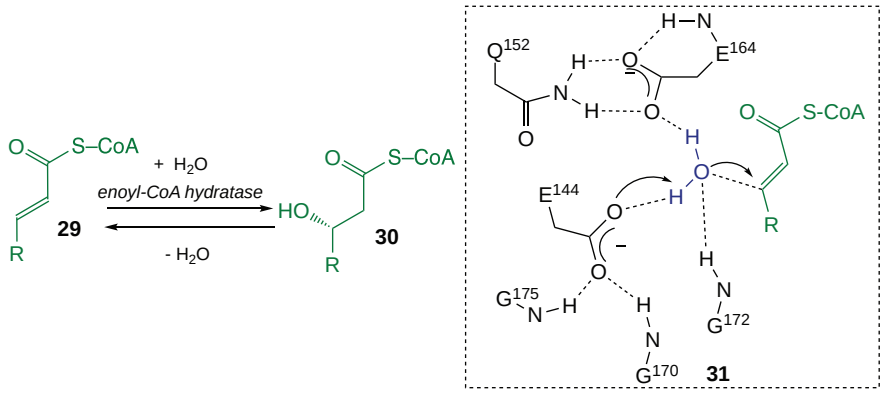


5. Conjugated esters react with tributylphosphine and then an aldehyde to give allylic alcohol esters.



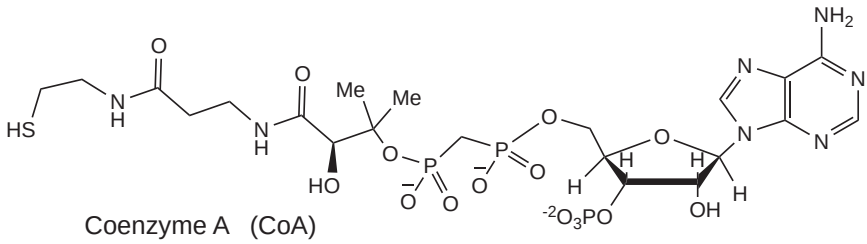
21.8 BIOLOGICAL RELEVANCE

Conjugate addition reactions occur in biological systems. There is an enzyme known as *enoyl-CoA hydratase* (also known as *crotonase*) that facilitates the conjugate addition of water the C=C unit of an acyl–CoA molecule (e.g., **29**) to yield the 3-hydroxy thioester (**30**). The fragment CoA is coenzyme A which forms a thioester unit as seen in **29** and **30**.



[This figure is reprinted in part with permission from Bahnson, B.J.; Anderson, V.E.; Petsko, G.A. *Biochemistry* ***2002****, 41,* 2621–2629. Copyright 2002 American Chemical Society.]

This process is essential for the metabolism of fatty acid and the production of energy[18] in which *enoyl-CoA hydratase* catalyzes the second step in the breakdown of fatty acids or the second step of β-oxidation in fatty acid metabolism. The active site of the enzyme involves water, coordinated to two glutamic acid residues (E) (E144 and E164; **30**), stabilized with glutamine residue (Q152) and glycine residues (G175 and G170) are also essential. The water is also held in place by G172 and reacts at C3 of the enzyme-bound conjugated thioester.[18]



Ultraviolet spectroscopy is quite useful in biochemical studies. Both $NADP^+$ and NADPH are important cofactors in enzymatic reactions. As shown in the Figure 21.9,[19] the change in structure that accompanies an enzymatic reaction may be monitored by UV. The NADPH absorbs light at 340 nm, whereas $NADP^+$ does not.

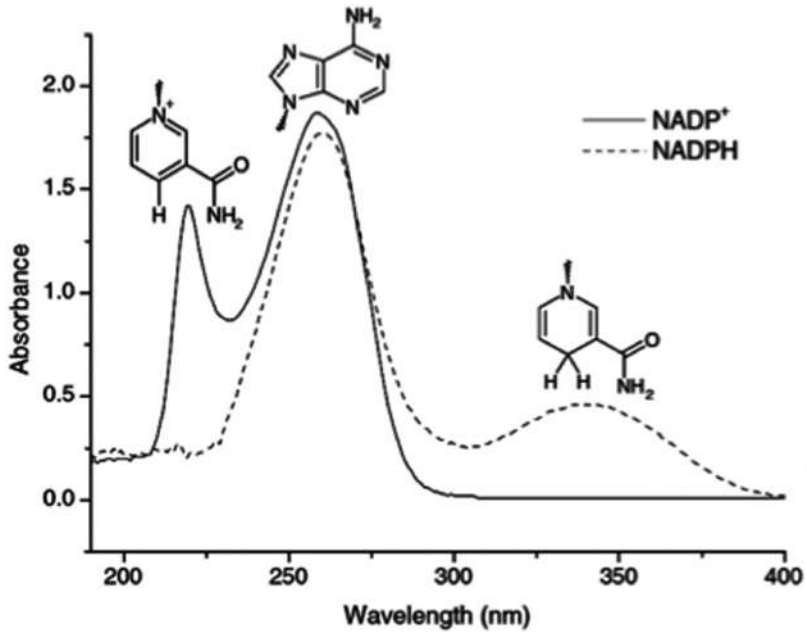


FIGURE 21.9 The UV/vis spectrum of $NADP^+$ and NADPH. [Reproduced from De Ruyck, J.; Famerée, M.; Wouters, J.; Perpète, E.A.; Preat, J.; Jacquemin, D. *Chemical Physics Letters*, 2007, 450, 119–122. Copyright 2007 Elsevier, with permission from Elsevier.]

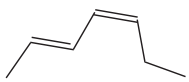
[18] Bahnson, B. J.; Anderson, V.E.; Petsko, G.A. *Biochemistry* 2002, 41, 2621–2629.
[19] De Ruyck, J.; Famerée, M.; Wouters, J.; Perpète, E.A.; Preat, J.; Jacquemin, D. *Chemical Physics Letters* 2007, 450, 119–122.

CORRELATION OF HOMEWORK WITH CONCEPTS

- Conjugated dienes are molecules that contain two C=C units connected together such that there is a continuous array of sp^2 carbons (C=C—C=C). Conjugate carbonyl compounds have a C=C unit directly attached to the carbon of a carbonyl (C=C-C=O). When a C=C or a C=O unit is attached to a benzene ring, these are also conjugated alkenes or carbonyl derivatives: 1, 2, 3, 4, 5, 7, 8, 23, 24, 25, 39.
- When a molecule absorbs UV light, the most intense absorption peak (wavelength in nm) is labeled λ_{max} and the intensity of the absorption is given by the extinction coefficient, ε. The differences in UV spectra between conjugated and nonconjugated compounds allow them to be easily distinguished via UV: 9, 10, 11, 12, 13, 26, 27, 28, 29.
- Dienes react with HCl, HBr, HI to give 1,2-addition and 1,4-addition products via formation of an allylic cation. Dihalogens (e.g., Cl_2, Br_2, and I_2) also add to dienes to yield a mixture of 1,2- and 1,4-addition products. Both HX and X_2 react with alkenes with the C=C unit conjugated to a benzene ring in essentially the same manner as with alkenes that do not contain a benzene ring: 14, 15,16, 17, 18, 30, 33.
- Michael addition is the addition of a nucleophile to the end of the C=C unit of a conjugated carbonyl, forming an enolate anion. Organocuprates usually yield conjugate addition products with both conjugated aldehydes and ketones: 19, 20, 21, 31, 32, 33.
- The reaction of a ketone enolate with a conjugated ketone under thermodynamic conditions yields a cyclic product, in what is called the Robinson annulation: 22, 32.
- Conjugated carbonyl compounds give primarily 1,2- or 1,4-reduction, depending on the reagent: 30, 33.
- Dienones react with an acid catalyst to give a cyclopentenone. α,β-Unsaturated esters react with a phosphine followed by an aldehyde to give an allylic alcohol ester: 30, 31.
- Spectroscopy can be used to determine the structure of a molecule (Chapter 13): 35, 36, 37, 38.

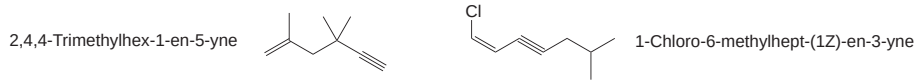
ANSWERS TO IN-CHAPTER QUESTIONS

21.1

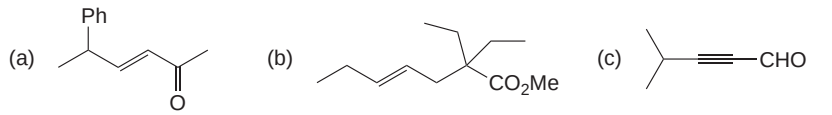


21.2

21.3

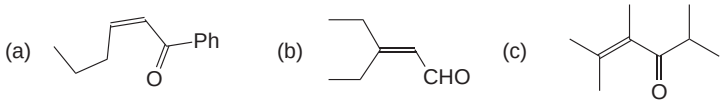


21.4



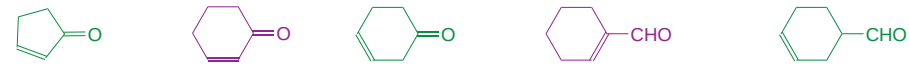
5-Phenylhex-(3E)-en-2-one Methyl 2,2-diethylhept-(4E)-enoate 4-Methylpent-2-ynal

21.5



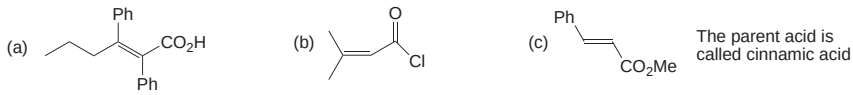
1-Phenylhex-(2Z)-en-1-one 3-Ethylpent-2-enal 2,4,5-Trimethylhex-4-en-3-one

21.6



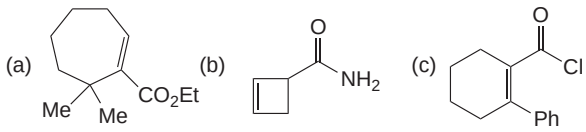
Cyclopent-2-en-1-one Cyclohex-2-en-1-one Cyclohex-3-en-1-one 1-Cyclohexene-1-carbaldehyde 3-Cyclohexene-1-carbaldehyde

21.7



2,3-Diphenylhex-(2Z)-enoic acid — 3-Methylbut-2-enoyl chloride — Methyl 3-phenylprop-(2E)-enoate

21.8



21.9 The lower value for frequency corresponds to higher energy, so an absorption at 210 nm is higher in energy than one at 310 nm.

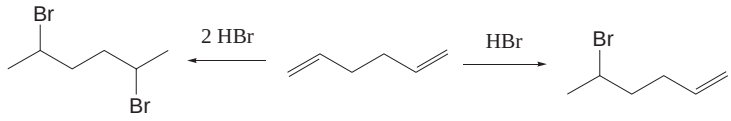
21.10 $\log \frac{I_o}{I} = 20 \times 0.1 \times 10 = 20$. If $\log \frac{I_o}{I} = 20$, then $\frac{I_o}{I} = 1 \times 10^{-20}$.

21.11 Longer wavelength is lower energy and shorter wavelength is higher energy. The conjugated diene, hexa-1,3-diene, should absorb at lower energy (longer wavelength), so hexa-1,5-diene will absorb at shorter wavelength (higher energy).

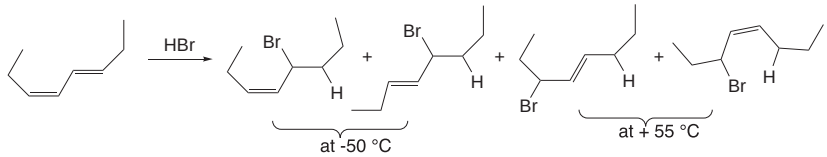
21.12 (a) Nonconjugated: the rules do not apply; (b) 215 + 12 = 227 nm; (c) 215 + 30 = 245 nm; (d) 215 + 10 + 12 = 237 nm.

21.13 (a) 215 + 12 = 227 vs 215 + 10 + 12 = 237 nm. (b) 215 + 12 = 227 nm vs 214 + 5 = 219 nm.

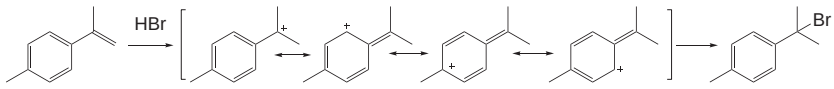
21.14



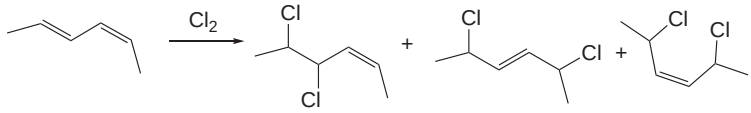
21.15



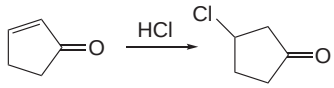
21.16



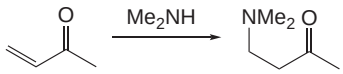
21.17



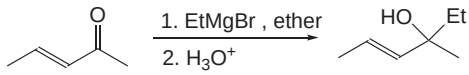
21.18



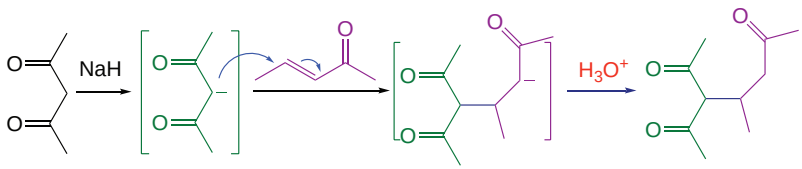
21.19



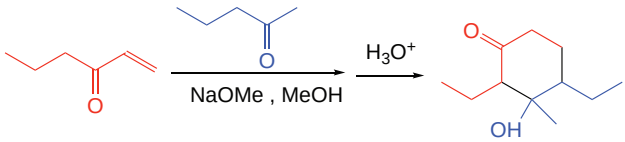
21.20



21.21

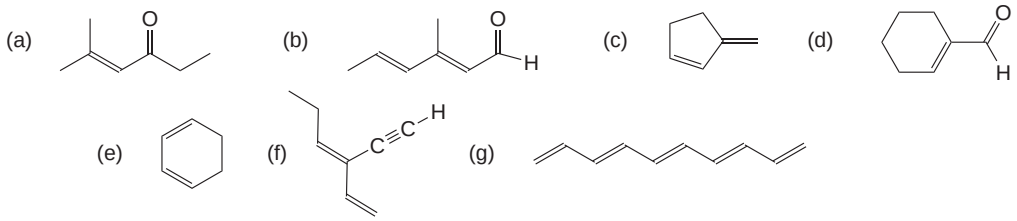


21.22

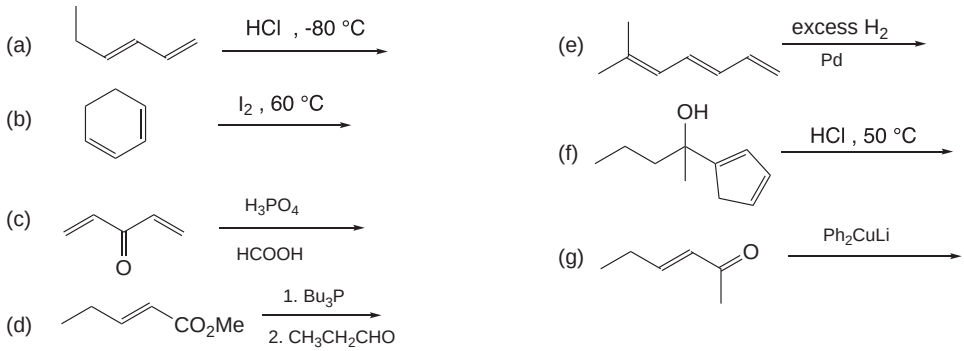


HOMEWORK

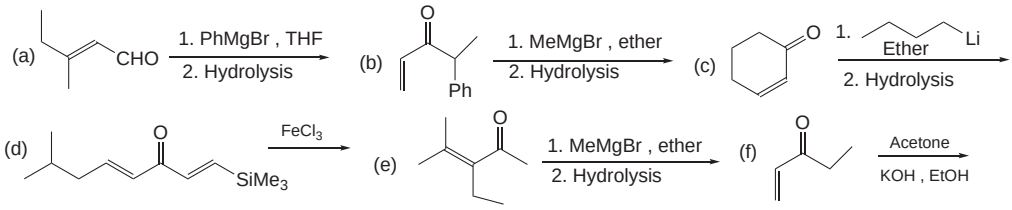
23. Draw the structure of each of the following molecules:
    (a) Nona-(2*E*,5*Z*)-diene (b) 1,2-Diethylcyclohexadiene
    (c) Hex-1-en-3-yne
    (d) 2,3-Dimethylbuta-1,3-diene (e) Penta-2,4-dienoic acid
    (f) Dodeca-(3*E*,5*E*)-dienal
    (g) Cycloocta-1,5-diene (h) 1,4-Diphenyl-(1*E*,3*E)*-butadiene
    (i) 2,3,4,5-Tetramethylhexa-2,4-diene
24. Draw the structure for each of the following molecules:
    (a) Ethyl benzoate (b) Hex-(3*E)*-en-2-one (c) Pent-2-ynenitrile
    (d) 2,7-Diethylcyclohept-2-en-1-one (e) Acrolein (f) Methyl vinyl ketone
    (g) Dimethyl fumarate (h) Hexa-(3*E)*-en-2,5-dione
    (i) 1,5-Diphenyl-1-pentene
    (j) 2-Methylhex-1-en-3-one (k) Penta-1,4-dien-3-one
    (l) Cyclopent-3-en-1-one
    (m) Acrylic acid (n) Cyclohexene-1-carboxylic acid (o) Oct-(4*Z)*-enal
25. Birch reduction of anisole (Sections 17.5 and 19.7) leads to 1-methoxycyclohexa-1,4-diene. Heating this with aqueous acid leads to cyclohex-2-en-1-one. Draw all of these products and provide a mechanism for the formation of cyclohexenone. Why should this product form?
26. Interconvert the following: (a) 345 nm to kcal; to cm^{-1} (b) $16x10^2$ cm^{-1} to kJ; to nm (c) 1765 cm^{-1} to nm; to kcal; to Å (d) 325 kJ to kcal; to nm (e) 8000 Å to kcal; to cm^{-1} (f) 185 kcal to nm; to Å; to cm^{-1}
27. If $\varepsilon = 38000$ for $c = 0.5$ g mL^{-1} (10 dm path length), calculate $\log \frac{I_o}{I}$.
28. If $\frac{I_o}{I} = 3x10^{-8}$, $c = 1.2$ g mL^{-1} and the path length is 5 dm, calculate ε.
29. Predict the maximum UV absorption peak for each of the following:



30. Give the major product for each of the following:



31. Give the structure for the major product formed in each of the following reactions:



32. Give the major product for each of the following reactions:
    (a) Cyclopent-2-en-1-one + pentan-3-one + NaOEt/ethanol/reflux followed by hydrolysis.
    (b) Hex-4-en-3-one + butan-2-one + NaOMe/methanol/reflux followed by hydrolysis.
    (c) Cyclohexanone + cyclopent-2-en-1-one + NaOEt/ethanol/reflux followed by hydrolysis.
33. Give the major product for each of the following reactions:
    (a) Hexa-(2*E*,4*E*)-diene: lithium diphenylcuprate, THF, -10 °C
    (b) Hex-4-en-3-one: Br_2, -20 °C
    (c) Cyclopentene-1-carbaldehyde: 1. $NaBH_4$/EtOH 2. aq NH_4Cl
    (d) Ethylpent-2-enoate: H_2/Pd–C
    (e) Hex-4-en-2-one: 1. $LiAlH_4$/THF 2. hydrolysis
    (f) Cyclopenta-1,3-diene: 1. $LiAlH_4$/ether 2. water
    (g) 4-Ethylhex-3-en-2-one: 1. $NaBH_4$/EtOH 2. aq NH_4Cl
    (h) Acetophenone: 1. $Ph_3P{=}CH_2$ 2. H_2, Pd
34. Discuss the major rotamer of 1-phenyl-(1*E*),3-butadiene and then 1-phenyl-(1*Z*),3-butadiene.

Spectroscopic problems. Do not attempt these problems until Chapter 13 has been read and understood

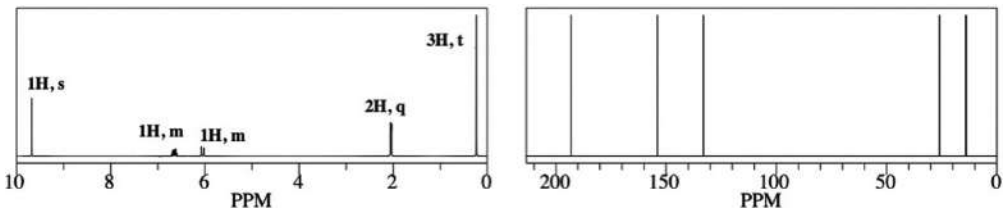
35. Discuss the UV spectroscopic differences between hexa-1,3-diene and hexa-1,5-diene. Briefly discuss any differences in chemical reactivity.
36. Identify the molecule with the formula C_5H_8, with the following spectral data. There is a significant peak in the UV spectrum at 219 nm.

IR: 3088, 3055–2853, 1797, 1666, 163, 1002, 949, 897 cm^{-1}. ^1H NMR: 6.29 (m, 1H), 6.06 (m, 1H), 5.70 (m, 1H), 5.06 (m, 1H), 4.93 (m, 1H), 1.74 (d, 3H): J(B,C)=15.1 Hz, J(A,B)=10.4 Hz, J(A,D)=17.0 Hz, J(A,E)=10.1 Hz

37. Identify the molecule with the formula $C_6H_{10}O_2$, with the following spectral data. There is a significant peak in the UV spectrum at 225 nm.

IR: 2984–2908, 1722, 1640, 1323, 1299, 1178, 1169, 1034, 942, 875 cm^{-1}. ^1H NMR: 6.1 (m, 1H), 5.54 (m, 1H), 4.21 (q, 2H), 1.94 (m, 3H), 1.30 (t, 3H) ppm: J(A,B)=1.7Hz, J(A,D)=-1.0Hz, J(B,D)=-1.6Hz

38. Identify the molecule with the formula C_5H_8O, with the following spectral data. There are no significant peaks in the UV spectrum past 215 nm. IR: 2900-3000, 2820, and 1730 cm^{-1}.



The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-22.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

Difunctional Molecules

Pericyclic Reactions

22

This chapter will discuss the reaction of 1,3-dienes with alkenes to give cyclohexene derivatives in a pericyclic reaction known as a [4+2]-cycloaddition. It is commonly known as the *Diels-Alder reaction*. Other pericyclic reactions include [2+2]-cycloaddition and [3+2]-cycloaddition reactions. Sigmatropic rearrangement reactions occur with 1,5-diene units.

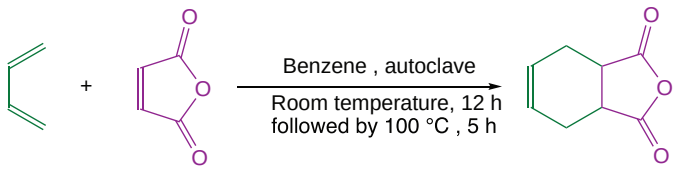
To begin this chapter, you should know the following points:

- Alkenes, dienes, and alkynes (Sections 5.1–5.3).
- Heteroatom functional groups (Sections 5.5 and 5.6).
- (*E*)- and (*Z*)-isomers of alkenes (Section 9.7).
- Conjugated compounds (Sections 21.1 and 21.4–21.6).
- Bicyclic compounds (Section 9.9).
- Molecular orbitals and π-bonds (Sections 3.2).
- Rate of reaction (Section 7.11).
- Activation energy and transition states (Sections 7.6),
- Rotamers and conformations (Sections 8.1–8.4).
- Stereogenic centers and enantiomers (Sections 9.1 and 9.2).
- Diastereomers (Section 9.5).

22.1 THE DIELS-ALDER REACTION

The Diels-Alder Reaction

Conjugated dienes react with alkenes to give cyclohexene products. An example is the reaction of buta-1,3-diene and maleic anhydride to give a bicyclic anhydride, 3a,4,7,7a-tetrahydro isobenzofuran-1,3-dione, in 90% yield[1] when heated in an autoclave.[2] This reaction generates a ring, and it is classified as a *[4+2]-cycloaddition*. The numbers refer to the four π-electrons of the diene that react with the two π-electrons of the alkene. The π-bonds in maleic anhydride and buta-1,3-diene are broken, *two* new carbon-carbon bonds are formed, and a new π-bond is generated in the six-membered ring product. There are *no* intermediates in a [4+2]-cycloaddition reaction and it is *synchronous* or *concerted.*



The [4+2]- cycloaddition is known as the *Diels-Alder reaction* to honor the work of Nobel laureates Otto Diels (Germany; 1876–1954) and Kurt Alder (Germany; 1902–1958). Nobel laureates Robert B. Woodward (USA; 1917–1979) and Roald Hoffmann (Poland-USA) worked

[1] Fieser, L.F.; Novello, F.C. *Journal of the American Chemical Society* 1942, 64, 802–809.
[2] An autoclave is a metal cylinder that can be charged with chemicals and sealed for heating, allowing reactions to be done at moderate to high pressures.

DOI: 10.1201/9781003174929-22

to understand the mechanism of the Diels-Alder and related reactions. *Frontier molecular orbital (FMO) theory,* developed by Nobel laureate Kenichi Fukui (Japan; 1918–1998), is used today to explain reactions of this type.

The Diels-Alder reaction is illustrated by the reaction of buta-1,3-diene and ethene to give cyclohexene. The reaction is *concerted* and described by a *six-centered transition state*, as illustrated in Figure 22.1. Reorganization of six π-electrons, four from the diene and two from the alkene, form two new σ-bonds in the cyclohexene product. A ball-and-stick molecular model of the transition state shows the electron flow, the elongated C—C single bonds and the changes to the C=C units.

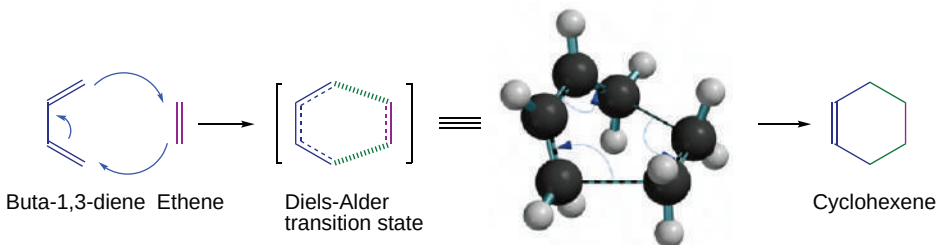


FIGURE 22.1 The Diels-Alder reaction of buta-1,3-diene and ethene.

22.1 Give the major products formed when cyclohexadiene reacts with ethyl acrylate; when 2,3-dimethyl-1,3-butadiene reacts with methyl ethyl ketone.

Only the π-orbitals of buta-1,3-diene and ethene are involved in the Diels-Alder reaction. The molecular orbitals on butadiene and on ethene have a p-orbital on each carbon atom, as shown in Figure 22.2. Ethene has two π-electrons, so it has two π-molecular orbitals and buta-1,3-diene has four π-electrons with four π-molecular orbitals. Both the diene and the alkene have a HOMO and a LUMO. The *HOMO* is the highest energy MO that contains electrons. The *LUMO* is the lowest energy MO that does not contain electrons. The reaction proceeds by transfer of π-electrons from a filled molecular orbital of the diene to an empty molecular orbital of the alkene.

For buta-1,3-diene and for ethene, the orbitals are labeled "+" or "–" to represent the sign of the wavefunction for each orbital. The wavefunctions arise from wave theory and the solution to the Schrödinger equation for this set of π-electrons (Section 3.1.1). The four orbitals of buta-1,3-diene have four different energy levels. Likewise, the two orbitals of ethene have two different energy levels. An MO that contains electrons is lower in energy than a MO with no electrons. There are four π-electrons in butadiene, and they reside in the two lowest energy orbitals, spin paired, with two electrons in each orbital. The two spin-paired π-electrons in ethene reside in the lowest energy orbital. The HOMO for both buta-1,3-diene and ethene are marked in Figure 22.2. The LUMO for both molecules is also marked. For a Diels-Alder reaction, the $HOMO_{diene}$ interacts with the $LUMO_{alkene}$, and transfers two electron to form a bond. The destructive overlap of orbitals that have opposite signs (+ -) is higher in energy than the constructive overlap of orbitals with the same sign (+ +) or (- -). In other words, there can only be overlap of orbitals that have the same sign.

The molecular models of the MOs are color-coded blue for + and red for -. Note that for buta-1,3-diene there are the four π-orbitals and four lobes for each *molecular orbital.* In the lowest energy orbital of buta-1,3-diene, all "+" lobes are on the same side, so this MO has the most favorable interactions. The next highest molecular orbital has a + + - - array of lobes and the next higher molecular orbital has a + - - + array. The highest energy orbital has a + - + - array. When a "+" lobe is adjacent to a "-" lobe there is a *node.* Each node represents a point of zero electron density as the wavefunction changes sign. The highest energy MO has the most nodes, and the lowest energy MO has zero nodes. There are four π-electrons in buta-1,3-diene and four π-MOs, but the four electrons are found in the two lowest energy orbitals, which each contain two spin paired electrons. The highest energy MO of the diene that contains electrons is the + + - - orbital, so it is the

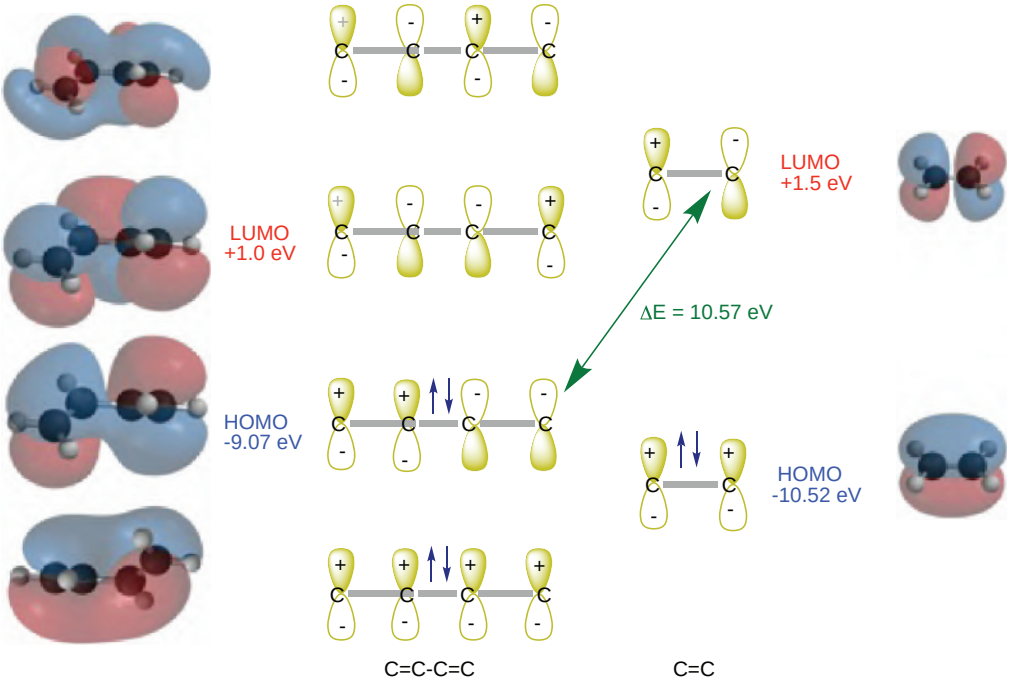


FIGURE 22.2 Frontier MOs for 1,3-butadiene and ethene.

HOMO. The next highest MO has two nodes with a + - - + array but it does not contain electrons and it is the LUMO. There are two π-MOs for ethene. The lowest energy MO contains two electrons, so it is the HOMO, and the highest energy MO does not contain electrons is the LUMO.

The experimentally determined energy of each orbital is provided in Figure 22.2, reported in electron volts (eV). The energy required to lose an electron from the diene, or the alkene is the first *ionization potential (IP)* (Section 3.2), and these values are taken to be the energy of the HOMO. Similarly, *electron affinity (EA)*, (Section 3.2) is the energy associated with gaining one electron, and EA is taken to be the energy of each LUMO. The electron rich HOMO is associated with electron donation and the electron deficient LUMO is associated with electron capture.

22.2 Draw the lowest energy MO for hexa-1,3,5-triene that has zero nodes.

The HOMO and LUMO for the diene and the alkene are the frontier molecular orbitals. Figure 22.3 is a simplified MO diagram for the reaction of buta-1,3-diene with ethene, and the energy of each HOMO and LUMO is provided. Frontier Molecular Orbital (FMO) theory

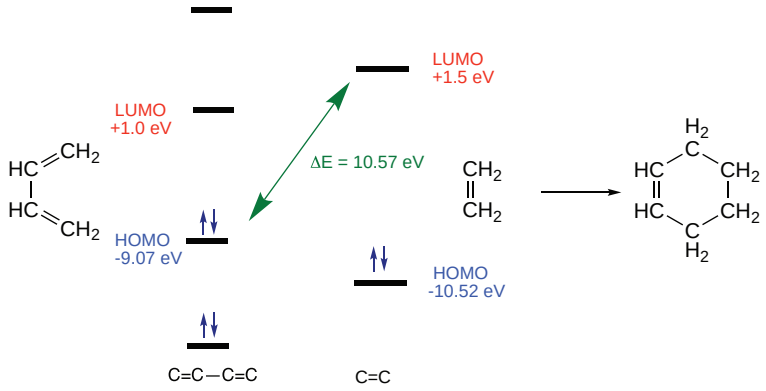


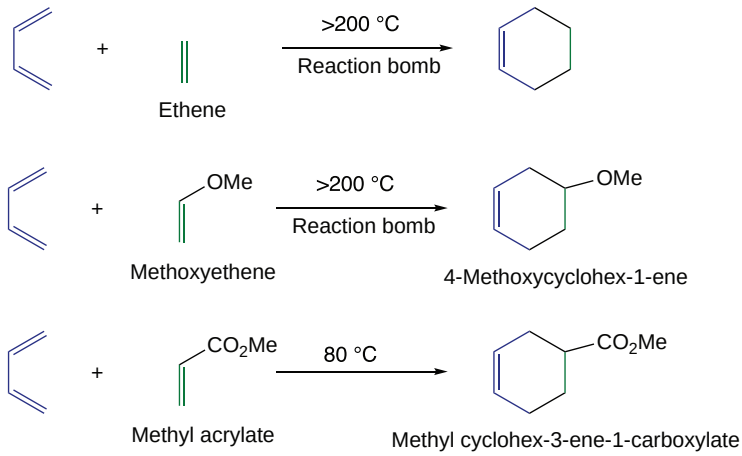
FIGURE 22.3 The MO diagram for the $HOMO_{diene}$ of buta-1,3-diene and the $LUMO_{alkene}$ of ethene showing the ΔE, which is the E_{act} for the reaction.

describes electron transfer from the electron-rich $HOMO_{diene}$ with four electrons to the electron-poor $LUMO_{alkene}$ in the Diels-Alder reaction. As identified by the work of Woodward and Hoffmann, MOs can only react with lobes of the same symmetry (+ with + or – with -). If the symmetry of the orbitals does not match, the reaction cannot occur. The reactive C1 and C4 lobes for the HOMO of buta-1,3-diene and the C1–C2 lobes for the LUMO of ethene have the same symmetry (+ with + or – with -). In Figure 22.3, for a Diels-Alder reaction, the difference in energy between the $HOMO_{diene}$ and the $LUMO_{alkene}$ (ΔE) is taken to be the *activation energy* (E_{act}, Section 7.4). A larger value of E_{act} (larger ΔE) indicates the reaction is more difficult to initiate, requiring higher heat and/or pressure for the reaction to proceed. Conversely, a lower E_{act} (smaller ΔE) indicates the reaction is more facile and requires less heat for the reaction to proceed. Based on a knowledge of the E_{act} for each reaction, a diene is predicted to react faster with some alkenes and slower with others.

22.3 Suggest a reason why the Diels-Alder reaction is driven by the $HOMO_{diene}$-$LUMO_{alkene}$ interaction rather than the $HOMO_{alkene}$-$LUMO_{diene}$ interaction, using Figure 22.2.

The Diels-Alder Reaction-Reactivity

22.2 REACTIVITY OF DIENES AND ALKENES



In the reaction of buta-1,3-diene with ethene, high temperatures in an autoclave[2] are required for a reaction that gives cyclohexene. If methoxyethene (methyl vinyl ether) is heated with buta-1,3-diene, even higher temperatures and pressures are required. The yield of 4-methoxycyclohex-1-ene is low. The reaction of buta-1,3-diene and methyl acylate, however, requires heating to only 80 °C at atmospheric pressure to give methyl cyclohex-3-ene-1-carboxylate. It is clear that the reaction with methyl acrylate is much more facile and faster and the reaction with either ethene or methoxyethene is slower. Figure 22.4 compares the HOMO and LUMO energy for butadiene, ethene, methyl acrylate, and methoxyethene. Methyl acrylate has an electron withdrawing CO_2Me group attached to the C=C unit, whereas the electron releasing OMe group is attached to the C=C unit in methoxyethene. The carbonyl group of the carboxyl group withdraws electrons from the π-bond of the C=C unit in methyl acrylate. Therefore the π-bond has less electron density and is weaker than the π-bond in ethene. Since the π-bond is weaker, the HOMO and LUMO energies of methyl acrylate are lower. Conversely, the methoxy group of methoxyethene releases electrons to the π-bond of the C=C unit. More electron density makes the π-bond stronger so the HOMO and LUMO energies are higher. The higher or lower energy of the HOMO and LUMO are reflected in the E_{act} values for the reactants. The ΔE and therefore the E_{act} for the buta-1,3-diene-methyl acrylate reaction is 9.07 eV, which is lower than the 10.57 eV for buta-1,3-diene-ethene reaction. The E_{act} of 11.07 eV for the buta-1,3-diene-methoxyethene reaction is the highest. In accord with the E_{act} values, methyl acrylate reacts faster under milder conditions and the methoxyethene reaction requires higher reaction temperatures.

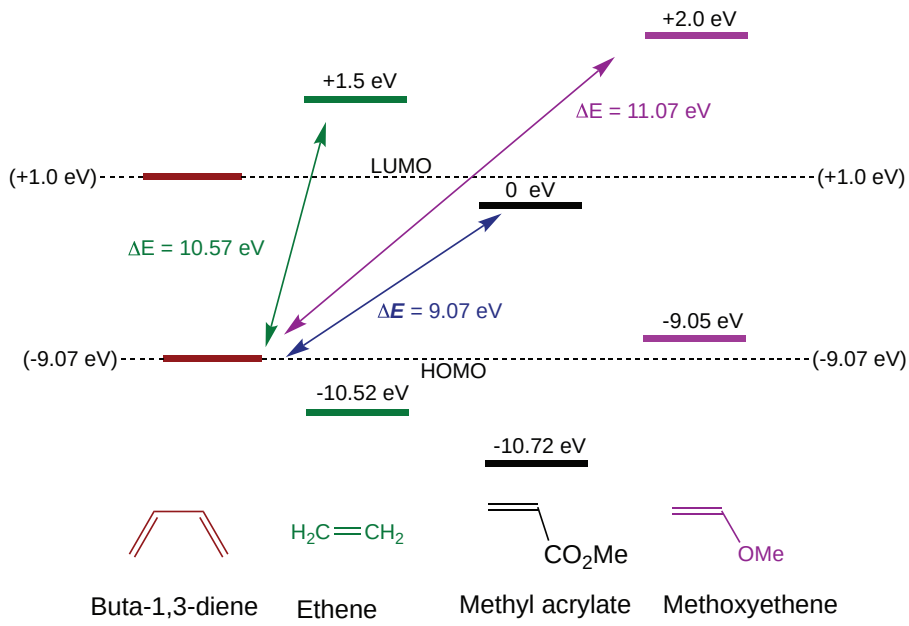


FIGURE 22.4 The HOMO and LUMO energies for the reaction of buta-1,3-diene with ethene, methyl acrylate, and methoxyethene.

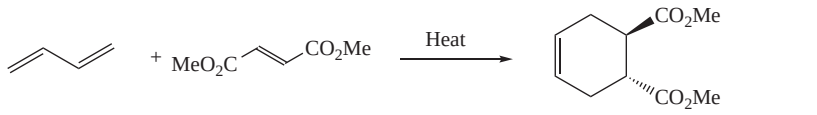
To summarize, if an alkene has an electron-withdrawing group attached, both the $HOMO_{alkene}$ and the $LUMO_{alkene}$ are lower in energy because there is less electron density in the π-bond. Since the $LUMO_{alkene}$ is lower, in reactions with a diene there is a smaller E_{act} and a faster reaction under milder reaction conditions. Therefore, the reaction of methyl acrylate reacts faster. When the alkene has an electron-releasing group attached to it (e.g., OR), both the $HOMO_{alkene}$ and the $LUMO_{alkene}$ are higher in energy than ethene. An electron releasing group increases the electron density in the π-bond. In reactions with a diene, there is a larger E_{act} and a slower reaction requiring more vigorous reaction conditions. Therefore, methoxyethene reacts slower.

22.4 Determine which diene, (a) or (b), will react fastest with maleic anhydride [LUMO = -0.57 eV]. (a) 1-phenylbuta-1,3-diene [HOMO = -8.16 eV] or (b) penta-2,4-dienoic acid [HOMO = -9.41 eV].

22.3 SELECTIVITY IN THE DIELS-ALDER REACTION

There are no stereogenic centers when the sp^2 hybridized carbon atoms of a diene and those of an alkene react in a Diels-Alder reaction. In the cyclohexene product there are four sp^3 hybridized carbon atoms, and depending on the substitution, there may be one to four new stereogenic centers. Both the diene and the alkene are planar so reaction can occur from via either face. Cycloaddition leads to one enantiomer if the reaction occurs from one face and the other enantiomer if it occurs from the opposite face. The cyclohexene products are therefore *racemic*, but diastereomers are possible.

The stereochemistry of the alkene is retained in the cyclohexene product. In the reaction of buta-1,3-diene and dimethyl fumarate, where the carbomethoxy groups are trans, the Diels-Alder reaction gives *trans*-dimethyl cyclohex-4-ene-1,2-dicarboxylate as the only product. None of the cis diastereomer is formed so this reaction generates one racemic diastereomer and the cycloaddition is diastereospecific. For all Diels-Alder reactions assume that the stereochemistry of groups in the alkene is transferred without change to the cycloadduct.



Buta-1,3-diene Dimethyl fumarate Dimethyl cyclohex-4-ene-1,2-dicarboxylate

When there is one substituent on the diene and one substituent on the alkene there is the possibility of diastereomers in the cyclohexene product. An example is the reaction of cyclopentadiene and maleic anhydride to give bicyclic products **2** and **4** as shown in Figure 22.5. The Diels-Alder transition states are shown for both products. Transition state **1** leads to the

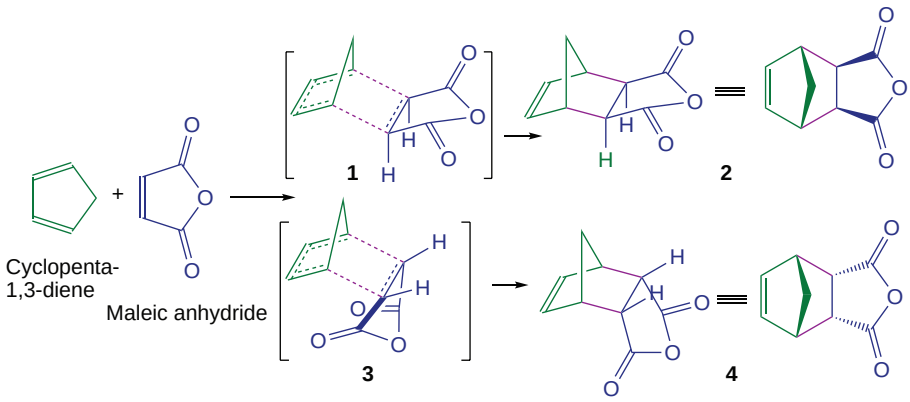


FIGURE 22.5 Exo and endo products in the Diels–Alder reaction.

formation of **2** and transition state **3** leads to **4**. Cyclopenta-1,3-diene has a —CH_2— unit (methylene) that bridges the 1,3-diene unit. In effect, the bridge is a substituent on the diene. The methylene of cyclopentadiene connects C1 and C4 in the bicyclic cyclohexene products. The cis relationship of the carbonyl groups in maleic anhydride is retained in **2** and **4**. The ester units are on the same side as the —CH_2— unit in **2** but on the opposite side in **4** so they are diastereomers. The anhydride unit is "up" relative to the methylene bridge in **2** (they have a *syn-relationship*) and "down" in **4** (they have an *anti-relationship*). The carbonyl groups in **2** are said to be *exo* to the bridge and the carbonyl groups in **4** are said to be *endo* to the bridge. Cycloadduct **2** is the *exo* product and cycloadduct **4** is the *endo* product. The endo diastereomer **4** is the major product of this cycloaddition by a factor of 3:1.

Regioselectivity and Diastereoselectivity

The preference for the endo cycloadduct **4** can be explained by examining the transition states in Figure 22.5. Transition state **1** leads to the formation of **2** and transition state **3** leads to **4**. In **3**, the π-bonds of the carbonyl groups are underneath (*endo*) the ring relative to the π-bonds of the dienes. In this orientation, the π-orbitals of the carbonyls interact with the π-orbitals of the diene unit. The overlap of the π-orbitals of the carbonyl units with those of the diene provides additional stabilization that is maximized with an endo approach. This interaction is called a *secondary orbital interaction* and it stabilizes transition state **3** more than **1**, which leads to a preference for the endo product, **4**. This preference for the endo product **4** is called the *Alder endo rule.* The Alder endo rule states "endo addition was the consequence of a plane-to-plane orientation of diene and dienophile with "maximum accumulation of double bonds."[3] In transition state **1** there is an exo approach, and the carbonyl units are projected away from the diene units (*exo*). There is no possibility for secondary orbital interactions, so the energy of that transition state is higher.

22.5 Draw the major product of a reaction between cyclopenta-1,3-diene and diethyl fumarate [diethyl but-(2*E*)-endioate].

[3] Alder, K.; Stein, G. *Angewandte Chemie* 1937, 50, 510.

Alder Endo Rule

The Alder endo rule applies to all Diels-Alder reactions, including acyclic dienes. This preference can only be observed for an acyclic diene when there are substituents on both the diene and the alkene. Penta-(1,3*E*)-diene has a methyl substituent at C1 and dimethyl maleate has a cis relationship for the two CO_2Me substituents. Both the exo and endo transition states are shown in Figure 22.6, **5** and **6** respectively. In this example, the alkene approaches

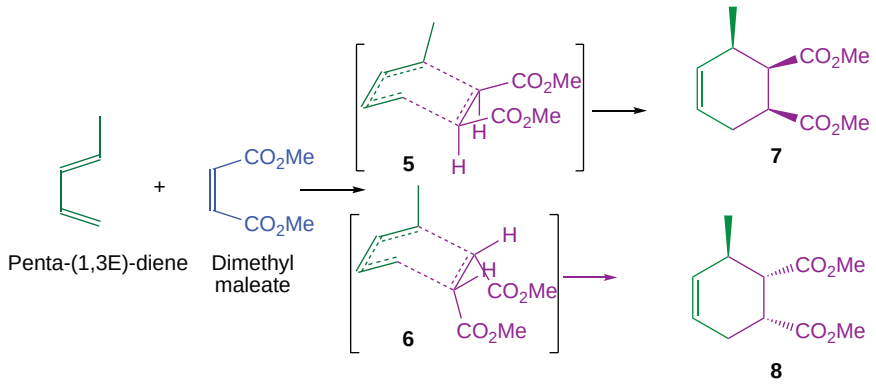


FIGURE 22.6 Diastereoselective Diels-Alder reaction of penta-(1,3*E*)-diene and dimethyl maleate.

the diene from the "bottom" so the methyl group of the diene will be pushed in the opposite direction relative to the ester units of the alkene. The alkene can also approach the diene from the "top" face so both enantiomers are possible, and the products are racemic. The transition state **5** shows an exo approach that will lead to exo diastereomer **7** with all three substituents on the same side of the ring. The transition state **6** shows an endo approach to give endo diastereomer **8**, with the two CO_2Me units cis to each other and trans to the methyl group. The product is the endo diastereomer **8**. The prediction that the endo product **8** is the major product is consistent with the *Alder endo rule.*

The reaction of 1-methoxypenta-1,3-diene and acrylonitrile shown in Figure 22.7. Acrylonitrile has π-bonds in the nitrile unit, so secondary orbital interactions lead to a

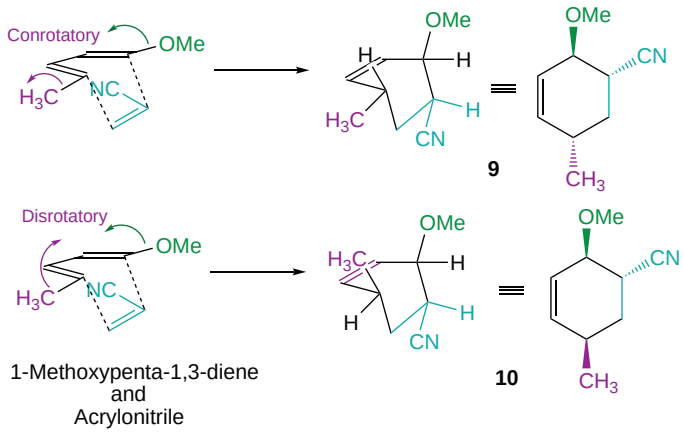
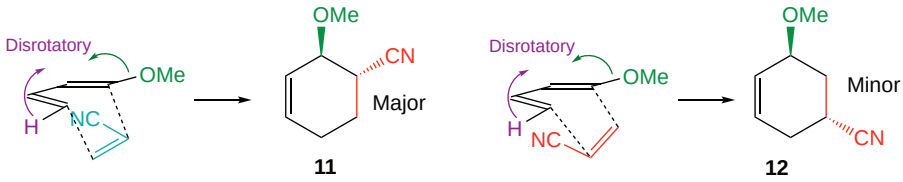


FIGURE 22.7 Conrotatory vs disrotatory cycloaddition

preferred "endo" transition state. However, there are two possible products based on an endo approach, **9** and **10**. Both C1 and C4 change hybridization from planar sp^2 carbon atoms in the diene to tetrahedral sp^3 carbon atoms in the cyclohexene product. As a consequence, the OMe group at C1 of the diene and the methyl group on C4 of the diene will literally change their spatial position as the cyclohexene ring is formed. As the reaction progresses the OMe and the methyl group may move in the same direction (away from

each other), a *conrotatory motion*, or they may move in opposite directions (towards each other), a *disrotatory motion*. The possible conrotatory and disrotatory motions are shown in Figure 22.7. *In Diels-Alder reactions a disrotatory motion of the substituents at C1 and C4 of the diene occurs*. Since acrylonitrile is shown to approach from the bottom face, the methyl at C4 and methoxy group at C1 will move toward each other, in the opposite direction from the incoming alkene. The disrotatory motion leads to **10** as the major product of this reaction.

Another important aspect of the Diels-Alder reaction can be examined in the reaction of the monosubstituted diene 1-methoxybuta-1,3-diene and the monosubstituted alkene acrylonitrile. Based on an endo approach, the diene can approach with the acrylonitrile in two different orientations. The cyano group can can be proximal to the methoxy, a 1,2-approach, or it can be distal to the methoxy group, a 1,4-approach. These two orientations of the alkene give two different regioisomers, cycloadduct **11** (1*S*,2*R*)-2-methoxycyclohex-3-ene-1-carbonitrile and **12** (1*R*,5*S*)-5-methoxycyclohex-3-ene -1-carbonitrile, respectively. The major cycloadduct is **11** with a 1,2-relationship of the methoxy group and the cyano group.



The Diels-Alder reaction is therefore *regioselective* since there a mixture of both products but there is a major regioisomer and a minor regioisomer. Predicting the major product in this situation is a bit complicated but three rules that can assist in predicting the preferred regioisomer. *1.* A diene with a substituent at C1 (electron withdrawing or releasing) reacts with either an electron rich alkene or an electron deficient alkene to give the ortho- (1,2-) product. *2.* A diene with a substituent at C2 (electron withdrawing or releasing) reacts with either an electron rich alkene or an electron deficient alkene to give the para- product (1,4-) product, with one exception. *3.* A diene with an electron releasing substituent at C2 reacts with an alkene with an electron-releasing group to yield a 1,3- product. When 1-methoxybuta-1,3-diene reacts with acrylonitrile, rule 1 predicts the 1,2- cycloadduct (**11**) to be the major product. Note that these rules are unreliable with some functional groups, particularly weakly electron-releasing or electron-withdrawing groups. The rules are also unreliable when multiple substituents are present. However, for simple systems, the predictions are reasonable.

22.6 Draw the two disrotatory products that are possible for an endo approach of acrylonitrile to 1-methoxypenta-1,3-diene from the top, using Figure 22.7 as a guide.

22.7 Predict the structure of the major product resulting from the reaction of 2-methoxybuta-1,3-diene and ethyl vinyl ether?

In principle, four stereogenic centers can be formed on the cyclohexene cycloadduct so 16 stereoisomers are possible. A shown in the previous sections, the Diels-Alder reaction is diastereoselective as predicted by (a) an endo approach of the alkene and (b) a disrotatory motion of substituent in the diene. The reaction is also regioselective. Therefore, of the four diastereomers that are possible, one is usually the major product, although it is racemic

Kathlyn A. Parker

Professor Kathlyn A. Parker (USA) at the State University of New York, Stony Brook has focused her research on the synthesis of natural products and the development of synthetic methods for compounds of biological interest that involve solving regiochemical and stereochemical problems. One project involved the synthesis of three endo bicyclooctadienol dimers that correspond to several kingianins, racemic natural products isolated from *Endiandra kingiana* Gamble. Professor Parker's strategy envisioned a bicyclooctadiene dimerization via an intermolecular Diels-Alder reaction, but there was a problem since cyclohexadienes undergo the Diels-Alder dimerization reaction with difficulty.[4] Although most Diels-Alder reactions follow a pericyclic mechanism, it has been proposed that some Diels-Alder reactions can be facilitated by treatment with a radical cation.[5] A radical cation initiation was proposed to overcome the poor reactivity of bicyclooctadiene dimerization and mimic the proposed biosynthesis of the kingianins. The radical cation $SbCl_6^{-}$ $^{+}N(p\text{-}BrPh)_3$, which is tris(4-bromophenyl)ammonium hexachloroantimonate, was used to initiate conditions the reaction with acetate **13**.

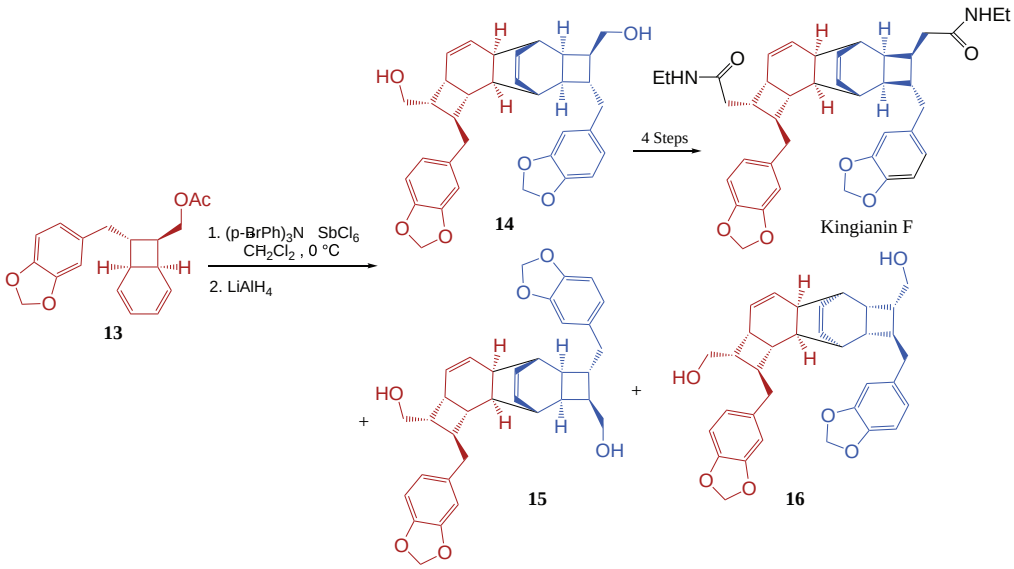


FIGURE 22.8 Key Diels-Alder radical-cation initiated step in the synthesis of Kingianin F.

[4] (a) Leverrier, A.; Awang, K.; Gueritte, F.; Litaudon, M. *Phytochemistry* 2011, 72, 1443–1452. (b) Leverrier, A.; Dau, M.E.T.H.; Retailleau, P.; Awang, K.; Gueritte, F.; Litaudon, M. *Organic Letters* 2010, 12, 3638–3641.

[5] Bellville, D.J.; Wirth, D.W.; Bauld, N.L. *Journal of the American Chemical Society*, 1981, 103, 718–720.

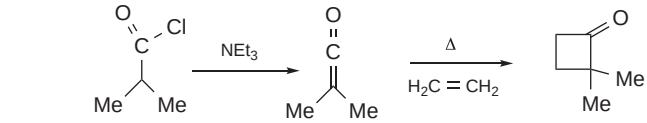
A mixture of two major products were formed, derived from endo transition states, and a minor product derived from an exo-transition state.[6] Reduction of the acetyl groups with $LiAlH_4$ gave a mixture of three diols, **14** in 46%, **15** in 30%, and **16** in 12% yield that were readily separated by preparative TLC. Kingianin F was then prepared from diol **14** in four steps. The Kingianins are reported to be inhibitors of the antiapoptotic protein Bcl-xL.[4] (Figure 22.8)

[2+2] and [3+2]-Cycloaddition Reactions

22.4 OTHER PERICYCLIC REACTIONS

Other pericyclic reactions are known. The [2+2]-cycloaddition involves the cycloaddition of two alkenes. A [3+2]-cycloaddition involves the cycloaddition of an alkene with a 1,3-dipole. Apart from the [4+2]-,[3+2]- and [2+2]-cycloaddition reactions there are [3+1]-, [3+3]-, and [4+1]-cycloadditions and several others.

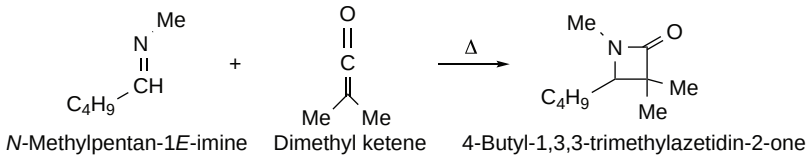
There are several examples of thermal [2+2]-cycloadditions that occur by a radical or dipolar intermediate, while others occur by HOMO-HOMO or LUMO-LUMO interactions. A useful variation of a thermal [2+2]-cycloaddition is the reaction of ketenes ($R_2C{=}C{=}O$) with alkenes to give cyclobutanones.



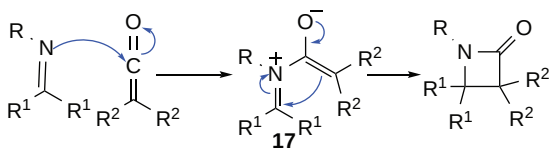
2-Methylpropanoyl chloride Dimethyl ketene 2,2-Dimethylcyclobutan-1-one

Most ketenes are unstable and when used in a chemical reaction they are generated and consumed as they are produced. A common method for the preparation of ketenes reacts a tertiary amine such as triethylamine with an acid chloride that has an α-proton. An example is the reaction of 2-methylpropanoyl chloride with triethylamine to give dimethylketene. Ketenes are highly electrophilic due to a low-lying LUMO (π^*-C=O), and the HOMO is relatively high in energy. The $HOMO_{alkene}$ has the correct symmetry to react with the $LUMO_{ketene}$.[7] For example, dimethylketene and ethene were heated to give 2,2-dimethylcyclobutan-1-one.

Ketenes react with imines via [2+2]-cycloaddition to give β-lactams in what is commonly known as the *Staudinger Synthesis*, or the *Staudinger Ketene-Imine Cycloaddition*.[8] The reaction is named after Nobel laureate Hermann Staudinger (Germany; 1881–1965). The preparation of β-lactams[9] is particularly important for the synthesis of β-lactam antibiotics. The mechanism of this reaction involves nucleophilic attack by the imine nitrogen on the carbonyl carbon of the ketene to give a zwitterion, **17**. The second step generates the β-lactam.



N-Methylpentan-1*E*-imine Dimethyl ketene 4-Butyl-1,3,3-trimethylazetidin-2-one

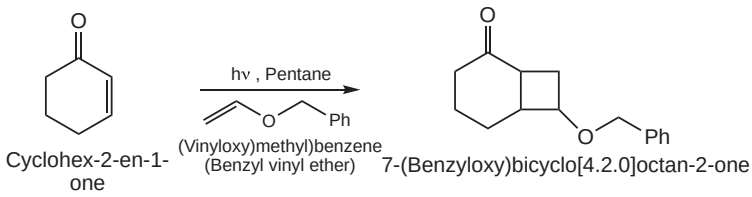


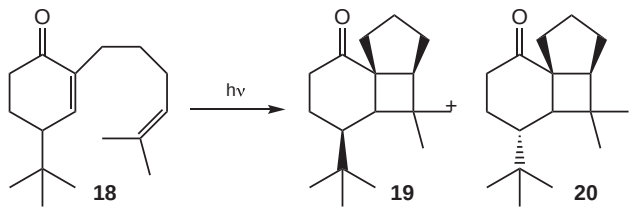
[6] Lim, H.N.; Parker, K.A. *Journal of Organic Chemistry* 2014, 79, 919–926
[7] Brady, W.T. *Tetrahedron* 1981, 37, 2949–2966.
[8] Cossio, F.P.; Arrieta, A.; Sierra, M.G. *Accounts of Chemical Research* 2008, 41, 925–936.
[9] (a) Brown, M.J. *Heterocycles*, 1989, 29, 2225–2244; (b) Isaacs, N.S. *Chemical Society Reviews* 1976, 5, 181–202.

22.8 What is the product of the reaction of dichloroketene and cyclopentene?
22.9 What is the product of *E*-*N*-phenylbutan-2-imine and dimethylketene?

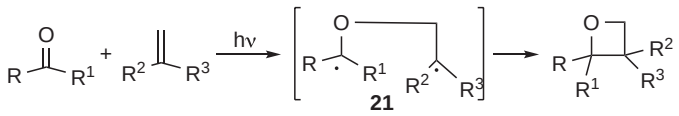
When an alkene is subjected to photochemical conditions (Section 21.1), an electron is promoted from a HOMO to a LUMO, allowing LUMO-LUMO pericyclic [2+2]-photocycloaddition reactions. This reaction occurs when alkenes, alkynes, or conjugated carbonyl compounds react with other alkenes, alkynes or conjugated systems. In general, photolysis of enones uses the $n\rightarrow\pi^*$ transition[10] (Sections 21.2,3). This reaction is usually accomplished by photolysis in a Pyrex container, which acts as a filter and is opaque to light < 300 nm. The $n\rightarrow\pi^*$ transition for acrolein occurs at 315 nm [90.8 kcal (380.1 kJ) mol^{-1}; the λ_{max} for acrolein] (Section 21.3). Ethene has a strong $\pi\rightarrow\pi^*$ transition at ≈ 165 nm 173.3 kcal (725.4 kJ) mol^{-1}]. Therefore, irradiation of alkene must be this energy or more to populate the LUMO.

There are many examples of photochemical [2+2]-cycloadditions involving enones and alkenes, or alkenes with alkenes. Irradiation of cyclohexene with benzyl vinyl ether in a Quartz vessel, for example, gave a 65% yield of 7-(benzyloxy)bicyclo[4.2.0]octan-2-one.[11] The stirred solution was irradiated with a Type L, 450-W. Hanovia mercury arc through a Corex filter and absorption occurred at 321 μ for cyclohexenone. The photocycloadditon can be done intramolecularly as in the study of the stereoselectivity of [2+2]-photocycloadditions using cyclohexenone derivatives with a 2-alkenyl substituent. An example is the photolysis of **18**, which gave a 2.3:1 mixture of **19**:**20** in >90% yield.[12] Note that **19** is formed by the C=C unit of the side chain approaching the C=C unit of the conjugated ketone from the face opposite the *tert*-butyl group.





The *Paternò-Büchi reaction*[13] is a [2+2]-photocyclization of a carbonyl compound and an alkene. This reaction was discovered by Emanuele Paternò (Italy; 1847–1935)[14] and expanded by George Hermann Büchi (Switzerland-USA; 1921–1998).[15] The cycloaddition of an alkene and a carbonyl gives an oxetane (Section 23.2). The reaction is believed to proceed via a diradical intermediate (**21**). Irradiation of aldehydes often uses light at 290 nm [98.6 kcal (412.8 kJ) mol^{-1}], generally corresponding to the $n\rightarrow\pi^*$ transition of the carbonyl. Intramolecular Paternò–Büchi reactions are known.

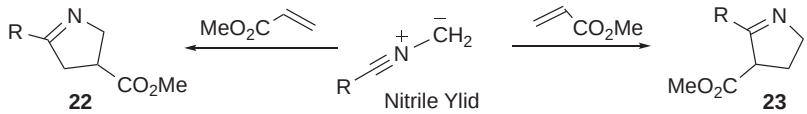


[10] Eaton, P.E. *Accounts of Chemical Research* 1968, 1, 50–57.
[11] Corey, E.J.; Bass, J.D.; LeMahieu, R.; Mitra, R.B. *Journal of the American Chemical Society* 1964, 86, 5570–5583.
[12] Becker, D.; Haddad, N. *Tetrahedron Letters* 1986, 27, 6393–6396.
[13] Smith, M.B. *March's Advanced Organic Chemistry,* 8th ed., Hoboken, NJ, 2020, pp. 1060–1061.
[14] Paternò, E.; Chieffi, C. *Gazzetta Chimica Italiana 1909, 39,* 341–361.
[15] Büchi, G.; Inman, C.G.; Lipinsky, E.S. *Journal of the American Chemical Society* 1954, 76, 4327–4331.

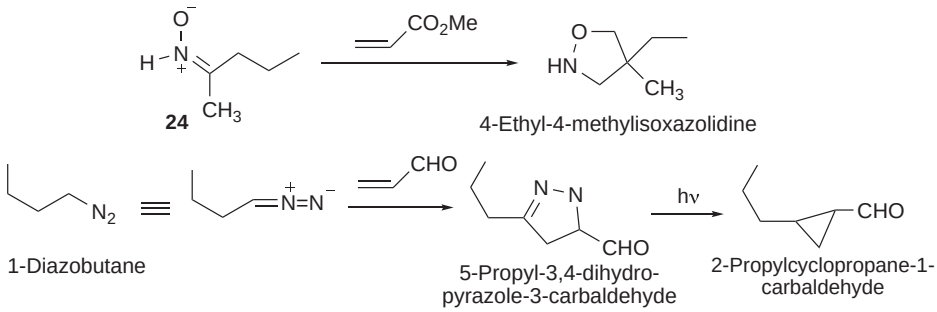
22.10 What is the photocyclization product of cyclohexanone and 2-methylpentene?

As first mentioned in Sections 15.3 and 15.5, the oxidation reactions of alkenes with potassium permanganate or osmium tetroxide and the oxidative cleavage reaction with ozone all react via an initial [3+2]-cycloaddition. Note that MnO_4^-, OsO_4 and O_3 are *1,3-dipolar compounds*. These *1,3-dipoles* react with the π-bonds of alkenes (*dipolarophiles*) to give five-membered rings. A 1,3-dipole has a sequence of three atoms *a–b–c*, and usually contains heteroatoms with four π-electrons distributed over three atoms. Apart from ozone, the permanganate anion and osmium tetroxide, examples of 1,3-dipoles include nitrile ylids ($RC{\equiv}N^+{-}CH_2^-$), nitrile oxides ($RC{\equiv}N^+{-}O^-$), diazoalkanes ($R_2C{=}N^+{=}N^-$), nitrones ($R_2C{=}NH^+{-}O^-$) and azides ($RN{=}N^+{=}N^-$). The dipolarophile is commonly an alkene or alkyne derivative.

The reaction is believed to be a concerted, thermal cyclization.[16] Both intermolecular cycloadditions and intramolecular reactions are possible. The reaction is controlled by $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interactions. Substituents that lower the dipole LUMO energy or raise the HOMO energy of the dipolarophile will accelerate the reaction. The [3+2]-cycloaddition should react fastest with electron-deficient alkenes and slowest with electron-rich alkenes. Electrostatic interactions and solvent effects can modify the regiochemical and stereochemical outcome.



A reaction to generate a heterocycle is illustrated by reaction of a generic nitrile ylid with methyl vinyl ether to give a dihydropyrrole product. There are two possible regioisomers for the reaction of a nitrile ylid with methyl acrylate, **22** and **23**, and **23** is the preferred product. Nitrile ylids are formed by the photolysis of 2H-azirines.[17] Other heterocycles can be prepared by a [3+2]-cycloaddition using other 1,3-dipoles. Examples are the reaction of nitrone **24** with methyl acrylate to give an isoxazolidine product, 4-ethyl-4-methylisooxazolidine. Nitrones are prepared by the reaction of an aldehyde or ketone with an N-alkylhydroxylamine (RNHOH). Another example is the reaction of a diazoalkane, 1-diazobutane with acrolein to give a dihydropyrazole, 5-propyl-3,4-dihydropyrazole-3-carbaldehyde. Diazoalkanes can be prepared by the reaction of an amine with nitrous acid (Section 19.11). Dihydropyrazoles such as this can be *photolyzed* to generate cyclopropane derivatives with loss of nitrogen gas. In this case, photolysis of 5-propyl-3,4-dihydropyrazole-3-carbaldehdye gives 2-propylcyclopropane-1-carbaldehdye.

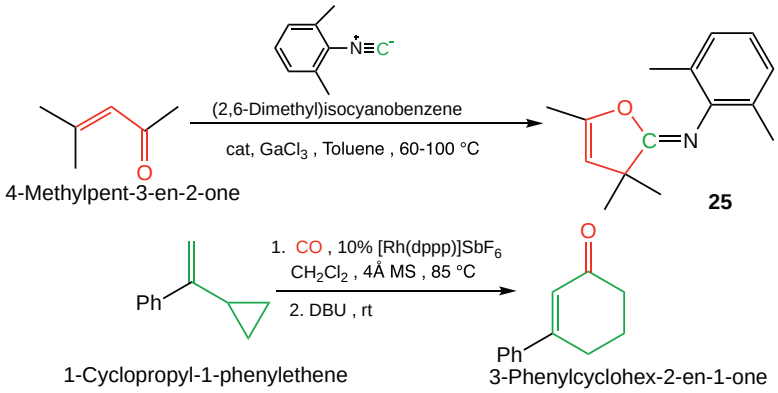


[16] (a) Hoffman, R.; Woodward, R.B. *Accounts of Chemical Research* 1968, 1, 17–22; (b) Eckell, A.; Huisgen, R.; Sustmann, R.; Wallbillich, G.; Grashey, D.; Spindler, E. *Chemische Berichte* 1967, 100, 2192–2213.

[17] Cludius-Brandt, S.; Kupracz, L.; Kirschnking, A. *Beilstein Journal of Organic Chemistry* 2013, 9, 1745–1750.

22.11 What is the product of the reaction of nitrile oxide BuC≡N^+–O^- and but-3-en-2-one? Of azide $Me_2CHN{=}N^+{=}N^-$ and methyl but-2*E*-enoate?

Other cycloaddition reactions are possible, including [3+1], [3+3], [4+1], [5+1], [4+3], and [5+2]-cycloaddition reactions, often catalyzed by transition metal catalysts. Examples include the [4+1]-cycloaddition of 4-methylpent-3-en-2-one with the isocyanide, (2,6-dimethyl)isocyanobenzene in toluene. Heating to 60–100 °C with a catalytic amount of $GaCl_3$ gave **25** in 94% yield.[18] A [5+1]-cycloaddition is the reaction of 1-cyclopropyl-1-phenylethene with carbon monoxide and 10% of [Rh(dppp)]SbF_6 in dichloromethane with 4Å molecular sieves. A second step requires reaction of the product with DBU to give 3-phenylcyclohex-2-en-1-one in 73% yield.[19] Note that dppp is 1,3-bis(diphenylphosphino)propane and DBU is 8-diazabicyclo[5.4.0]undec-7-ene.



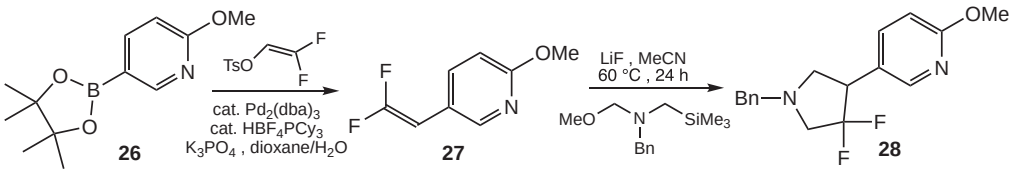
Michelle Tran-Dubé

Michelle Tran-Dubé (USA) is an oncology medicinal chemist at Pfizer, Inc. She played a key role on the chemistry team that discovered the first marketed ALK inhibitor, crizotinib. She played a pivotal role on the chemistry team that discovered the clinical candidate PF-06939999, Pfizer's oral PRMT5 inhibitor in Phase I clinical trials for oncology, a first-in-class oral arginine methyltransferase inhibitor which shows promise in treating numerous

[18] (a) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *Journal of the American Chemical Society* 2003, 125, 7812–7813; (b) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *Journal of the American Chemical Society*, 2005 127, 761–766.

[19] Jiang, G.-J.; Fu, X.-F.; Li, Q.; Yu, Z.-X. *Organic Letters* 2012, 14, 692–695.

types of cancer. She has contributed to a study of small fluorinated aliphatic amines that are important to drug discovery programs. Incorporation of a fluorine atom in the beta or gamma position relative to a basic nitrogen has major effects on the lipophilicity and thereby the permeability, solubility, efflux, and safety profile of a compound due to changes of pK_a.



Relative stereochemistry of the dipolarophile can be controlled by a concerted cycloaddition reaction to form substituted pyrrolidines. Vinyl fluorides and vinyl difluorides are readily accessible and undergo the cycloaddition reaction to give pharmaceutically relevant fluoropyrrolidines. The reaction of 2-methoxypyridine-5-boronic acid pinacol ester (**26**) with 2,2-difluorovinyl 4-methylbenzenesulfonate in the presence of $Pd_2(dba)_3$, tricyclohexylphosphine tetrafluoroborate and heated at 100 °C in a sealed vial to give 5-(2,2-difluorovinyl)-2-methoxypyridine (**27**).[20] Subsequent heating of **28** with *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine and LiF in acetonitrile gave fluorinated pyrrolidine **27** in 30% overall yield. Note that Bn is benzyl ($-CH_2Ph$) and dba is dibenzylideneacetone.

Sigmatropic Rearrangements

22.5 SIGMATROPIC REARRANGEMENTS

There are several important reactions that involve transfer of electrons and migration of atoms or groups across a π-system, but do not form rings. These reactions are categorized as *sigmatropic rearrangements*. Sigmatropic rearrangements are defined as reactions in which a σ-bond bearing an atom or a substituent moves across a conjugated system to a new site.[21] There are numbers attached to the length of each fragment associated with the move, and they are placed in brackets. As shown in Figure 22.9, a [1,3]-shift involves migration of one

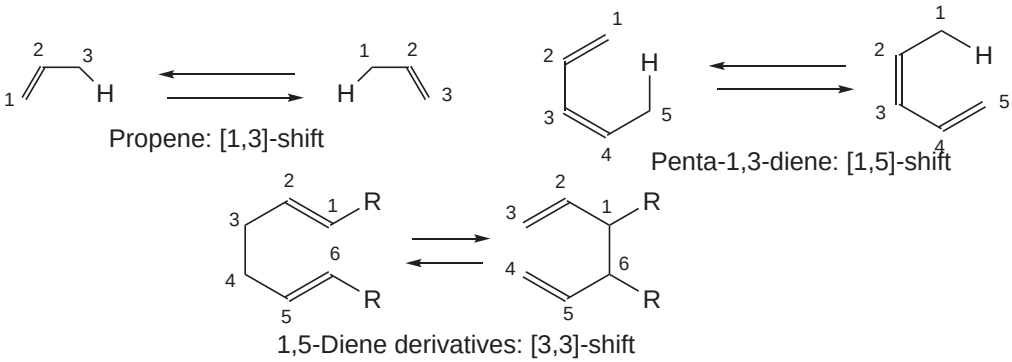


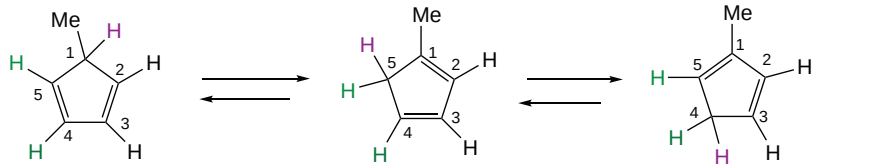
FIGURE 22.9 1,3-, 1,5-, and 1,7-Sigmatropic rearrangements.

fragment across three fragments. In a 1,3-shift of a proton, for example, a hydrogen atom migrates from C3 to C1 to yield a new propene. In the [1,5]-shift one hydrogen atom migrates from C5 in penta-1,3-diene to C1. In the dialkyl hexa-1,5-diene derivative shown in Figure 22.9, there is a three-carbon allylic unit (C1–C3) connected to another three-carbon allylic unit (C4–C6). The [3,3]-shift involves breaking the bond between C3–C4 in the starting

[20] McAlpine, I.; Tran-Dubé, M.; Wang, F.; Scales, S. Matthews, J.; Collins, M.R.; Nair, S.K.; Nguyen, M.; Bian, J.; Martinez Alsina, L.; Sun, J.; Zhong, J.; Warmus, J.S.; O'Neill, B.T. *Journal of Organic Chemistry* 2015, 80, 7266–7274.

[21] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions* Wiley, London, UK, 1976, p. 98.

diene and forming a new bond between C1–C6 in the product diene. [1,7]-Sigmatropic shifts are observed in some systems, but they will not be discussed.



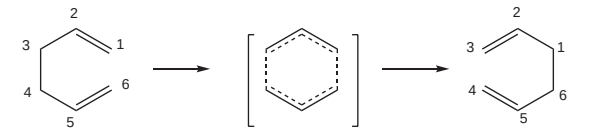
5-Methylcyclopenta-1,3-diene 1-Methylcyclopenta-1,3-diene 2-Methylcyclopenta-1,3-diene

Methylcyclopenta-1,3-diene undergoes a [1,5]-sigmatropic shift. The hydrogen atom is a one-atom fragment, and it moves across a five-carbon fragment (C1 to C5). When 5-methylcyclopenta-1,3-diene is heated, a hydrogen moves to give 1-methylcyclopenta-1,3-diene via a [1,5]-sigmatropic shift. Similarly, a hydrogen in 1-methylcyclopenta-1,3-diene moves to give 2-methylcyclopenta-1,3-diene (from C5 to C4 as marked). All these isomers are in equilibrium with each other. Rearrangement of this type is called a *suprafacial shift* because the σ-bond to the hydrogen atom is made and broken on the same side of the conjugated system. Although [1,5]-sigmatropic rearrangements are common, [1,3]-sigmatropic shifts are not because moving a hydrogen atom in a [1,3]-shift requires that the σ-bond be broken on one side of the conjugated system but made on the opposite side of that system. This movement is known as an *antarafacial shift*. Antarafacial shifts are higher in energy and are not observed that often so they will *not* be discussed.

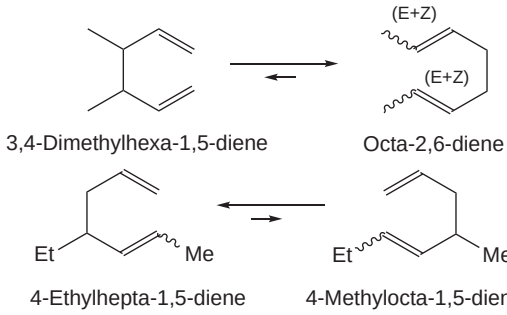
22.12 Draw the [1,7]-sigmatropic rearrangement product by heating dodeca-1,3,5-triene.

[3,3]-Sigmatropic rearrangements involve migration of alkyl groups rather than hydrogen atoms. There is no intermediate, and the prototype [3,3]-sigmatropic rearrangement involves heating a 1,5-diene (e.g., hexa-1,5-diene). The sigmatropic rearrangement proceeds by a concerted six-centered transition state represented by **29** and gives hexa-1,5-diene back again. The product is identical to the starting material, but if the C=C units of the diene are "labeled" with substituents, as with 3,4-dimethylhexa-1,5-diene, it is clear that the [3,3]-sigmatropic rearrangement has occurred because it leads to a different 1,5-diene, octa-2,6-diene. The "squiggle" lines indicate a mixture of isomers at those stereocenters. These two dienes are in equilibrium, and the equilibrium favors the diene with the more substituted C=C units. The disubstituted octa-2,6-diene is the thermodynamically the more stable diene. This rearrangement is called the *Cope rearrangement*, after Arthur C. Cope (USA; 1909–1966) who discovered the reaction. The temperatures required for a Cope rearrangement are sometimes quite high and the equilibrium established between the two dienes often leads to mixtures of products that are difficult to separate. Another example is the Cope rearrangement of 1,5-diene 4-ethylhepta-(1,5*E)*-diene, which upon heating yields 4-methylocta-(1,5*E)*-diene. There is one disubstituted C=C unit in (*E*)-4-methylocta-1,5-diene and one disubstituted C=C unit in 4-methylocta-(1,5*E)*-diene, so the equilibrium is unlikely to favor one over the other, and close to a 1:1 mixture of these two dienes is expected.

Cope Rearrangement and Claisen Rearrangement

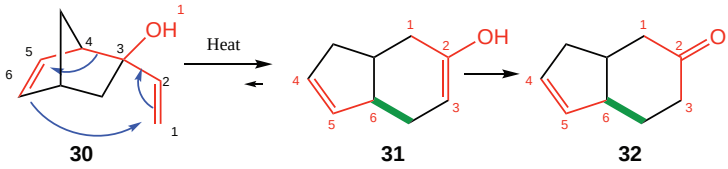


Hexa-1,5-diene **29** Hexa-1,5-diene

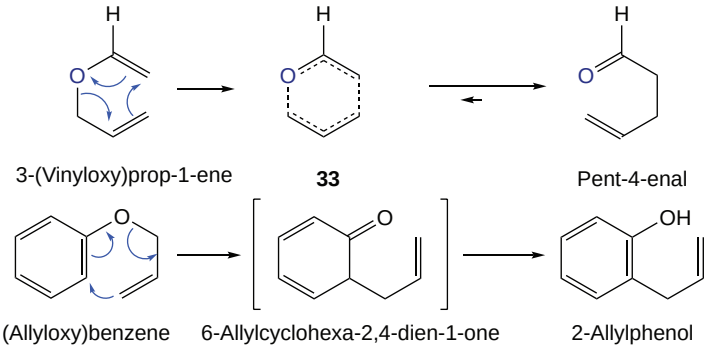


oxy-Cope Rearrangement

A variation of the Cope rearrangement is called the *oxy-Cope rearrangement*. In this variation heating a 3-hydroxy-1,5-diene leads to a [3,3]-sigmatropic shift to give an enol, which tautomerizes to an alkene aldehyde. Formation of the enol and tautomerization shifts the equilibrium toward to the aldehyde. An example is bicyclic alcohol **30**, which undergoes a [3,3]-sigmatropic rearrangement when heated to give enol **31**. Tautomerization gives ketone **32**. The 1,5-diene unit is numbered so the rearrangement can be followed more easily.



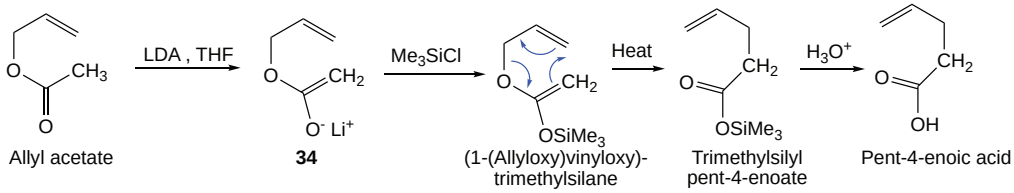
Another [3,3]-sigmatropic rearrangement is particularly useful. If one —CH_2— unit in the structure of a 1,5-diene is replaced with an oxygen atom, the resulting structure is an *allylic vinyl ether* such as 3-(vinyloxy)prop-1-ene. This ether has two C=C units and it is a 1,5-diene. Heating gives a [3,3]-sigmatropic rearrangement reaction that proceeds via transition state **33** to yield the aldehyde pent-4-enal.



The equilibrium in this reaction favors pent-4-enal and the reaction temperature is lower than that required for a Cope rearrangement. This [3,3]-sigmatropic rearrangement is called the *Claisen rearrangement*, named after Ludwig Claisen (Germany; 1851–1930). Ketones can also be formed via a Claisen rearrangement. An early example of a Claisen rearrangement heated (allyloxyl)benzene. A [3,3]-rearrangement generated the ketone 6-allylcyclohexa-2,4-dien-1-one. However, this intermediate product rapidly aromatized to generate the final isolated product, 2-allylphenol.

Ireland–Claisen Rearrangement

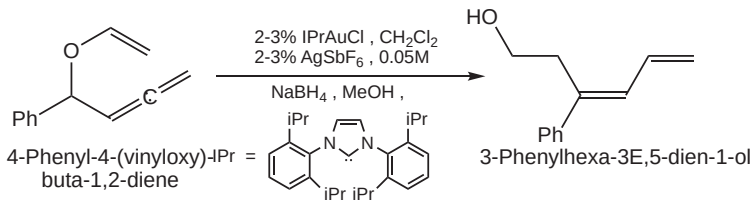
22.13 What is the product when 3-hydroxybuta-1,5-diene is heated?



A modern version of this reaction is the so-called Ireland variant of the Claisen rearrangement or the *Ireland-Claisen rearrangement*, named after Robert E. Ireland (USA; 1929–2012). If an ester such as prop-2-enyl acetate (allyl acetate) reacts with lithium diisopropylamide (LDA) under kinetic control conditions, enolate anion **34** is formed (Section 20.9). The enolate anion is "trapped" by a reaction with chlorotrimethylsilane (Me_3SiCl) to yield (1-(allyloxy)vinyloxy)trimethylsilane, an *enol ether*. Although not discussed previously, the enolate oxygen has a particular affinity for the silicon of chlorotrimethylsilane and that is where the reaction occurs**.** Enol ether (1-(allyloxy)vinyloxy)trimethylsilane has an allyl vinyl ether unit, and heating leads to a [3,3]-sigmatropic rearrangement that yields trimethylsilyl pent-4-enoate. Aqueous acid hydrolysis yields the carboxylic acid, pent-4-enoic acid.

Marie Elizabeth Krafft

Marie Elizabeth Krafft (USA; 1956–2014) was the Martin A. Schwartz Professor of Chemistry and Biochemistry at Florida State University. She was known for her seminal contributions in organometallic chemistry and synthetic organic chemistry. Among these were her investigations of the Pauson-Khand reaction[22] and the Morita-Baylis-Hillman reaction (Section 21.5).[23] The Pauson-Khand reaction is a cycloaddition between an alkyne, and alkene and carbon monoxide to form a α,β-cyclopentenone. The reaction was originally mediated by stoichiometric amounts of dicobalt octacarbonyl. She also reported gold(I) catalyzed Claisen rearrangements. In one study, the gold(I)-catalyzed Claisen rearrangement of allenyl vinyl ethers gave substituted 1,3-dienes. The best yields for this transformation were obtained by in situ reduction of the labile aldehyde product to the alcohol. The 4-phenyl-4-(vinyloxy)buta-1,2-diene was treated with the *N*-heterocyclic carbene:AuCl complex formed from 1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium-2-ide. In the presence of $AgSbF_6$, the gold(I)-induced Claisen rearrangement gave the corresponding aldehyde.[24] To obtain the best yield, the initially formed aldehyde was reduced in situ with $NaBH_4$ to give the alcohol product, 3-phenyl-3*E*,5-dien-1-ol in 86% yield.



22.14 Write out a synthesis of ethyl 2-phenylpent-4-enoate from acrolein.

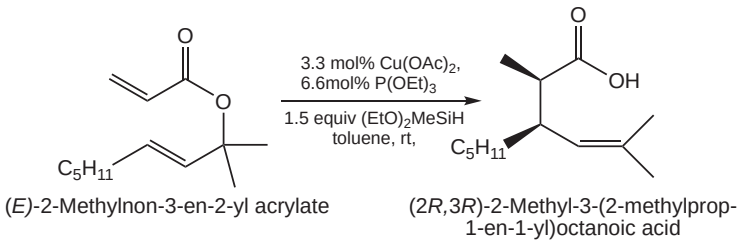
[22] (a) Krafft, M.E. *Journal of the American Chemical Society* 1988, 110, 968–970; (b) Krafft, M.E.; Romero, R.H.; Scott, I.L. *The Journal of Organic Chemistry* 1992, 57, 5277–5278; (c) Krafft, M.E.; Juliano, C.A.; Scott, I.L.; Wright, C.; McEachin, M.D. *Journal of the American Chemical Society* 1991, 113, 1693–1703.

[23] (a) Krafft, M.E.; Haxell, T.F.N. *Journal of the American Chemical Society* 2005, 127, 10168–10169; (b) Krafft, M.E.; Seibert, K.A.; Haxell, T.F.N.; Hirosawa, C. *Chemical Communications (Camb)*,2005, 5772–5774.

[24] Krafft, M.E.; Hallal, K.M.; Vidhani, D.V.; Cran, J.W. *Organic & Biomolecular Chemistry* 2011, 9, 7535–7538.

Pauline Chiu

The research of Professor Pauline Chiu (China) at the University of Hong Kong has focused on cycloaddition and cascade reactions as applied to natural product total synthesis, and the development of new methodology. She has developed copper-mediated chemical transformations that include Claisen rearrangements, aldol cyclizations, [4+3] cycloadditions, [5+2] cycloadditions and reactions to synthesize medium-sized rings. Copper hydrides are relatively non-basic species that are known to induce several different reactions, including the reductive Claisen rearrangement.[25] An example is the reaction of (*E*)-2-methylnon-3-en-2-yl acrylate with 3.3 mol% $Cu(OAc)_2$, 6.6 mol% of triethylphosphite and $(EtO)_2MeSiH$ in toluene, which gave a 90% yield of (2*R**,3*R**)-2-methyl-3-(2-methylprop-1-en-1-yl)octanoic acid in a 7:1 ratio, favoring this diastereomer.



(*E*)-2-Methylnon-3-en-2-yl acrylate

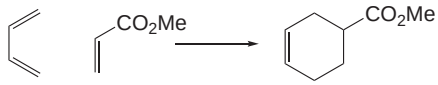
(2*R*,3*R*)-2-Methyl-3-(2-methylprop-1-en-1-yl)octanoic acid

22.6 ORGANIZATION OF REACTION TYPES

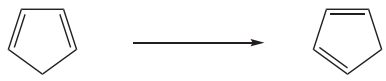
The reactions of dienes and allyl vinyl ethers can be organized as follows:

What reactions are possible for 1,3-dienes?

1. 1,3-Dienes undergo [4+2]-cycloaddition with alkenes to yield cyclohexenes.

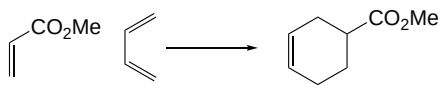


2. 1,3-Dienes can undergo 1,5-sigmatropic hydrogen shifts to yield new 1,3-dienes.



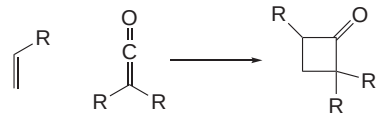
What reactions are possible for alkenes?

1. Alkenes undergo Diels–Alder reactions with 1,3-dienes to yield cyclohexenes.

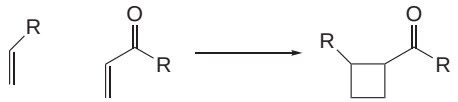


[25] Wong, K.C.; Ng, E.; Wong, W.-T.; Chiu, P. *Chemistry a European Journal* 2016, 22, 3709–3712.

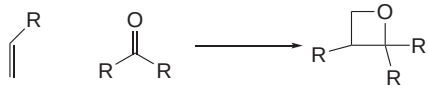
2. Alkenes undergo a [2+2]-cycloaddition with ketenes.



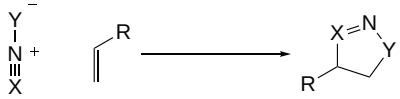
3. Alkenes undergo a [2+2]-cycloaddition with alkenes.



4. Alkenes undergo a [2+2]-cycloaddition with ketones or aldehydes.

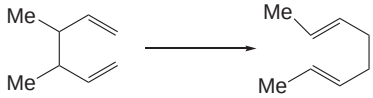


5. Alkenes undergo a [3+2]-cycloaddition with 1,3-dipoles.



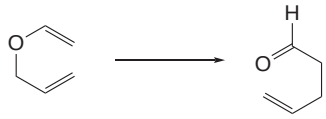
What reactions are possible for 1,5-dienes?

1. 1,5-Dienes undergo Cope rearrangement to yield new 1,5-dienes.



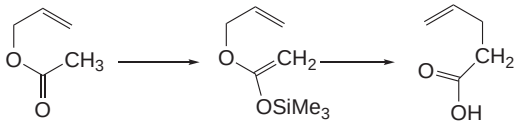
What reactions are possible for allyl vinyl ethers?

1. Allyl vinyl ethers undergo Claisen rearrangement to yield alkenyl aldehydes or alkene ketones.

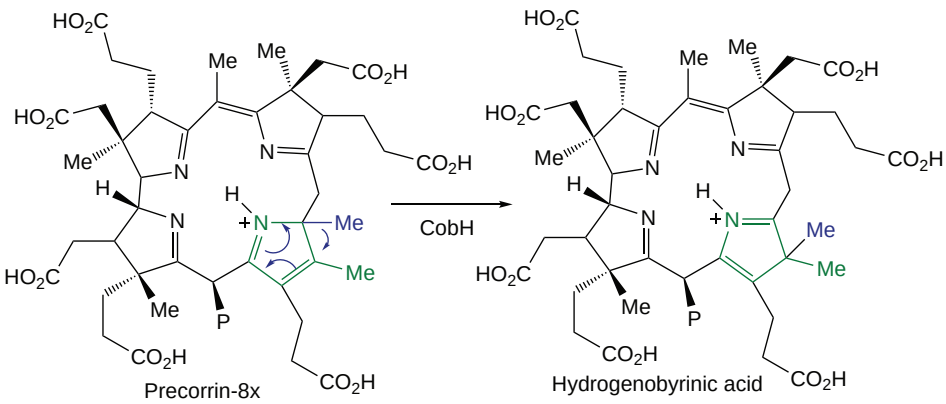


What reactions are possible for carboxylic acid?

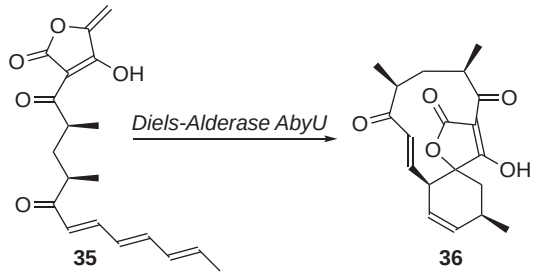
1. Alkene-esters are converted to a silyl enol ether and Claisen rearrangement followed by hydrolysis leads to a new alkene acid.



22.7 BIOLOGICAL RELEVANCE



Pericyclic reactions occur in biochemical transformations. One report shows that the last step in the aerobic biosynthesis of the corrin macrocycle of vitamin B12 in *Pseudomonas denitrificans*is is an enzyme-catalyzed reaction (*precorrin-8x methyl mutase*, abbreviated as CobH). In this process the methyl group attached to C11 of the substrate, protein-bound precorrin-8x, migrates from C11 to C12 to give the product, hydrogenobyrinic acid.[26] This transformation is a 1,5-sigmatropic methyl shift.



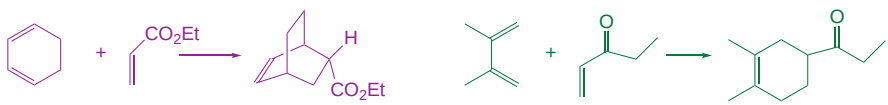
A few natural enzymes catalyze [4 + 2]-cycloaddition reactions.[27] The enzyme *Diels-Alderase AbyU* was isolated from the marine actinomycete *Verrucosispora maris* AB-18-032. This enzyme is involved in the biosynthesis of abyssomicin C, a potent inhibitor of bacterial folate metabolism.[28] This enzyme catalyzed the intramolecular [4+2] cycloaddition of the exocyclic methylene group and the conjugated diene in **35**. The product is **36**, a biosynthetic precursor to abyssomicin C.

CORRELATION OF HOMEWORK WITH CONCEPTS

- The reaction of a 1,3-diene and an alkene to give a cyclohexene derivative is a [4+2]-cycloaddition (a Diels-Alder reaction): 1, 2, 3, 4, 15, 17, 20, 21, 22, 28.
- Secondary orbitals interactions of alkenes bearing substituents having a π-bond lead to a preference for the endo product in the Diels–Alder reaction. The stereochemistry of the Diels–Alder reaction is set, in part, by a disrotatory motion of the diene substituents at C1 and C4. The Diels–Alder reaction is regioselective due to interactions of orbital coefficients on the orbitals of the reacting atoms. Substituents at C_1 and C_4 of the diene move in a disrotatory manner and opposite, relative to the incoming alkene: 1, 5, 6, 7, 18, 22.
- [2+2]-Cycloaddition reactions and [3+2]-cycloaddition reactions are known: 8, 9, 10, 11, 17.
- A sigmatropic rearrangement is a reaction where a σ-bond moves across a conjugated π-system to a new site. The Cope rearrangement occurs with 1,5-dienes and the Claisen rearrangement with allyl vinyl ethers: 12, 13, 14, 16, 19, 24, 25, 26, 27.
- Spectroscopy is used to determine the structure of a particular molecule (see Chapter 13): 29, 30, 31.

ANSWERS TO IN-CHAPTER QUESTIONS

22.1

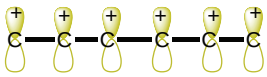


[26] Shipman, L.W.; Li, D.; Roessner, C.A.; Scott, A.I.; Sacchettini, J.C. *Structure* 2001, 9, 587–596.

[27] Tian, Z.; Sun, P.; Yan, Y.; Wu, Z.; Zheng, Q.; Zhou, S.; Zhang, H.; Yu, F.;Jia, X.; Chen, D.; Mańdi, A.; Kurtań, T.; Liu, W. *Nature Chemical Biology* 2015, 11, 259–265; Hashimoto, T.; Hashimoto, J.; Teruya, K.; Hirano, T.; Shin-ya, K.; Ikeda, H.; Liu, H.; Nishiyama, M.; Kuzuyama, T. *Journal of the American Chemical Society* 2015, 137, 572–575; Fage, C.D.; Isiorho, E.A.; Liu, Y.; Wagner, D.T.; Liu, H.; Keatinge-Clay, A.T. *Nature Chemical Biology* 2015, 11, 256–258.

[28] Byrne, M.J.; Lees, N.R.; Han, L.-C.; Marc W. van der Kamp, M.W.; Mulholland, A.J.; Stach, J.E.M.; Willis, C.L.; Race, P.R. *Journal of the American Chemical Society* 2016, 138, 19, 6095–6098.

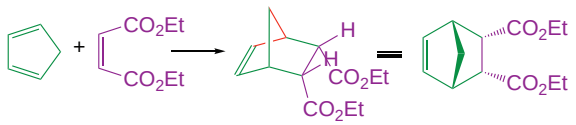
22.2



22.3 The ΔE for $HOMO_{alkene}$-$LUMO_{diene}$ is smaller than ΔE for $HOMO_{diene}$-$LUMO_{alkene}$, and the diene HOMO is more electron rich than the alkene HOMO.

22.4 The ΔE for (b) is larger than for (a), so dienoic acid (b) reacts faster than 1-phenyl-buta-1,3-diene (a).

22.5



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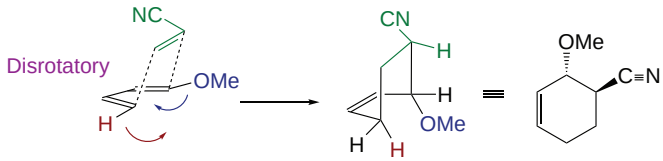

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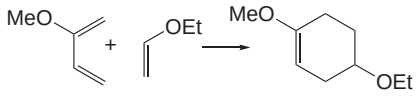

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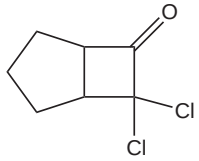
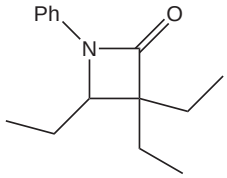


22.9



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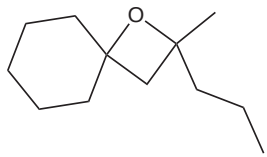
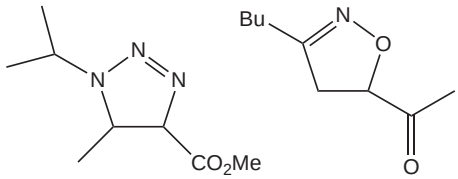
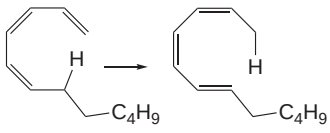


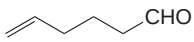
22.11



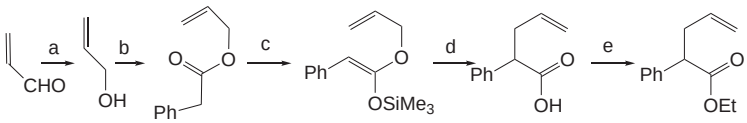
22.12



22.13



22.14



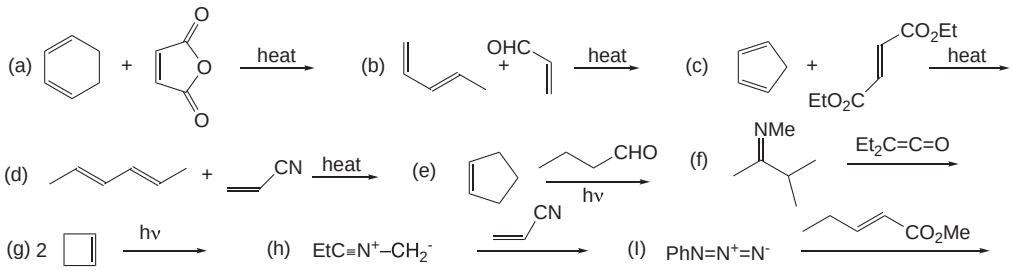
(a) $NaBH_4$, EtOH (b) $PhCH_2COCl$ (c) 1. LDA, THF, -78 °C 2. Me_3SiCl (d) heat (e) 1. $SOCl_2$ 2. EtOH

HOMEWORK

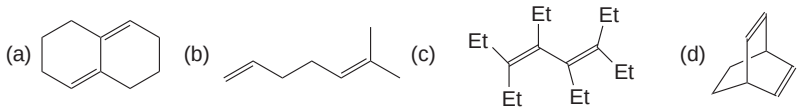
15. Which of the following molecules cannot undergo a Diels–Alder reaction? Explain.

16. Molecule **A** is known to require much lower reaction temperatures to undergo a Claisen rearrangement when compared with **B**. Explain.

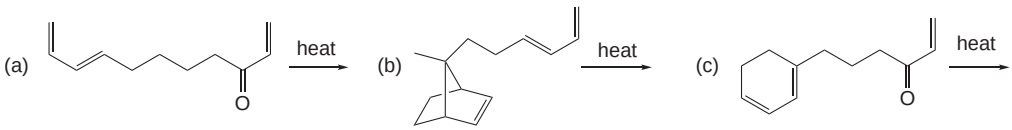
17. Cyclopentadiene reacts much faster in a Diels–Alder reaction than buta-1,3-diene. Offer a brief explanation for this observation.
18. Give the major product for each of the following reactions:



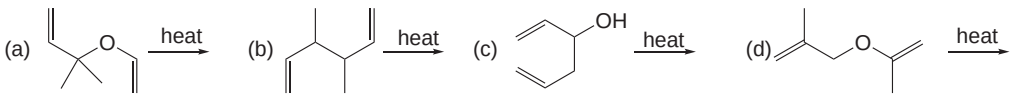
19. Heating $PhOCH_2CH{=}CH_2$ leads to a phenol derivative. Draw the reaction and the final product and categorize the reaction in terms of the reactions in this chapter.
20. Briefly explain why the following molecules do not undergo a Diels–Alder reaction:



21. Draw the major product for each of the following:

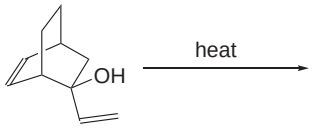


22. Draw the products of both conrotatory and disrotatory addition for each of the following:
    (a) Hexa-(2*E*,4*E*)-diene + ethyl acrylate (b) Hexa-(2*E*,4*Z*)-diene + ethyl acrylate
    (c) Phenylbuta-(1*E*),3-diene + diethyl maleate (d) 5-Phenylpenta-(2*E*-4*E*)-diene + diethyl fumarate
23. Briefly explain why maleic anhydride shows greater "endo-selectivity" in the Diels-Alder reaction than does ethyl acrylate.
24. Give the major product for each of the following.



25. What is the product formed when allyl acetate reacts with 1. LDA, THF -78 °C 2. Me_3SiCl 3. Heat 4. H_3O^+.

26. The Cope rearrangement is a reversible process. When 3,4-diphenylhexa-1,5-diene is heated, however, the equilibrium favors the rearrangement product. Why?
27. Draw the final product of the following reaction:



28. A bottle of "cyclopentadiene" is not really cyclopentadiene but another molecule. Heating generates cyclopentadiene, which is distilled off and trapped. Suggest a structure for this other product based on the known chemistry of cyclopentadiene and a reason why heating generates cyclopentadiene.

Spectroscopic problems. Do not attempt these problems until Chapter 13 is read and understood.

29. Give the structure of a molecule with the formula C_5H_8O and the spectral data and gives a new compound with a strong peak in the IR at 1725 cm^{-1} after heating: The IR shows two sharp medium intensity peaks in the region of 1640 cm^{-1}; ^1H NMR: 6.46 (m, 1H), 5.95 (m, 1H), 5.22 (m, 1H), 5.32 (m, 1H), 4.22 (d, 2H), 4.20 (m, 1H), 4.00 (m, 1H) ppm; ^{13}C NMR: 152.4, 132.1, 118.2, 87.1, 70.6 ppm.
30. Give the structure of a molecule with the formula C_7H_9N and the following spectral data: IR: 3033, 2934, 2846, 2241, 1652, 656 cm^{-1}. ^1H NMR: 5.70-5.59 (m, 2H), 2.77 (m, 1H), 2.34-2.05 (m, 4H), 1.93-1.84 (m, 2H) ppm. ^{13}C NMR: 126.0, 123.9, 122.5, 29.2, 25.6, 25.3, 24.1 ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-23.php

The scientist photographs are also available at:
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php

23

Heteroaromatic Compounds

Heterocycles or *heterocyclic aromatic compounds* are a class of aromatic compounds in which heteroatoms replace one or more of the ring carbons. Heterocycles and their chemistry comprise a vast area of chemistry and an entire course is easily built around them. However, the focus of this chapter will be nitrogen, oxygen, and sulfur heterocycles. This chapter also discusses reduced heterocycles, which are cyclic molecules that contain nitrogen, oxygen, or sulfur. Alkaloids are a class of nitrogenous organic compounds of plant origin that have pronounced physiological actions on humans.

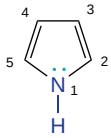
To begin this chapter, you should know the following points:

- Hydrocarbon and heteroatom functional groups (Sections 5.1, 5.2, 5.3, 5.5, and 5.6).
- Aromaticity (Sections 19.2 and 19.8).
- Organic bases (Section 6.7).
- Electrophilic aromatic substitution (Section 19.3).
- Nucleophilic aromatic substitution (Section 19.10).
- Alkene chemistry (Sections 10.1–10.7).
- Ketones and aldehydes (Sections 5.6.2, 16.1, and 116.2).
- Carboxylic acid derivatives (Sections 5.6.3, 18.4–18.90).
- Acyl addition reactions (Sections 16.2–16.4).
- Acetal and ketal formation (Section 16.4.2).
- Imine and enamine formation (Section 16.4.3).
- Acyl substitution (Section 18.4).
- Isomers (Section 4.2.2).
- The E1 reaction (Section 12.4).

N-Containing 5 and 6-Membered Rings

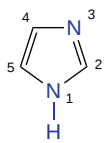
23.1 NITROGEN, OXYGEN, AND SULFUR IN AN AROMATIC RING

There are several heterocycles that contain one or two nitrogen atoms. The five-membered ring compound with one nitrogen is called *pyrrole*, a constituent of coal tar and it is found in bone oil. The IUPAC numbering scheme for pyrrole begins with nitrogen and extends around the ring. The orbital with the unshared electron pair on the nitrogen atom is parallel to those for the four π-electrons of the C=C units. This arrangement gives an aromatic six π-electron system. The hydrogen atom on nitrogen is forced to be perpendicular to the aromatic π-cloud but it is coplanar with the carbon atoms and nitrogen. Although pyrrole is a secondary amine it is not basic because electron donation would disrupt the aromaticity of the ring. Indeed, the hydrogen atom on the nitrogen of pyrrole is somewhat acidic, with a pK_a of 17.5 in water.

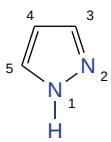


Pyrrole1*H*-pyrrole

Aromatic π-cloud of pyrrole



Imidazole



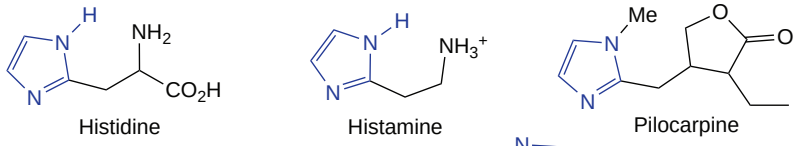
Pyrazole

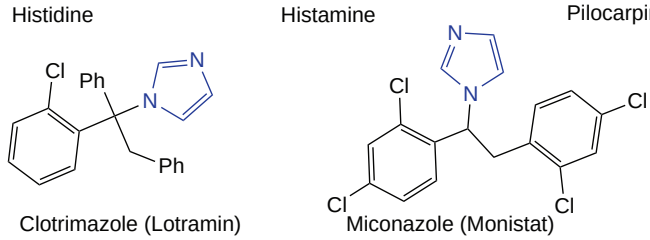
DOI: 10.1201/9781003174929-23

23.1 Draw 1-ethylpyrrole, 4-nitropyrrole, and *N*-methyl-3-phenylpyrrole.

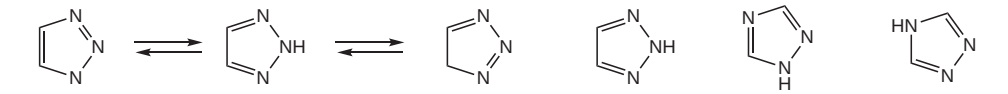
Nitrogen Heterocycles in Everyday Life

There are two heterocyclic five-membered ring amines with two nitrogen atoms in the ring. The nitrogen atoms have a 1,3-relationship in *imidazole* and a 1,2-relationship in *pyrazole*. The numbering for these compounds is shown. An older term for an imidazole is *azole*. Both heterocycles are aromatic. One electron pair on nitrogen is part of the aromatic π-cloud in both imidazole and pyrazole. The other nitrogen electron pair is perpendicular to the π-cloud and available for donation. Both imidazole and pyrazole are stronger bases than pyrrole.

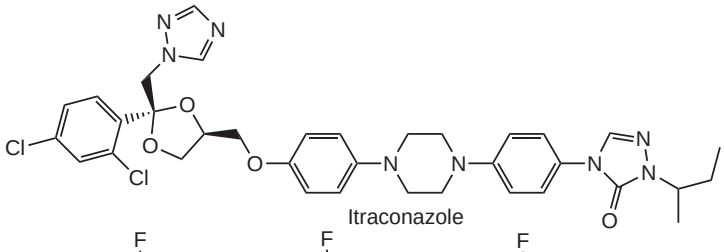


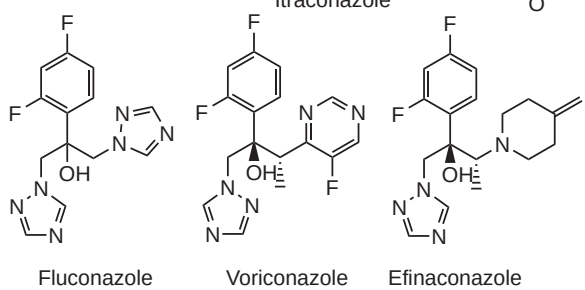


Imidazole and pyrazole are important units in many pharmaceutical preparations and also in naturally occurring compounds. *Histidine* is an amino acid (Section 24.3) and *histamine* is a neurotransmitter that is important in cells during antigen-antibody reactions. Both anaphylaxes (a drop in blood pressure that can result in shock) and allergic responses involve histamine. *Pilocarpine* is used to treat glaucoma. Both *clotrimazole* (Lotramin) and *miconazole* (Monistat, Micatin) are antifungal agents that are applied topically. Both have been used in preparations to treat athlete's foot.

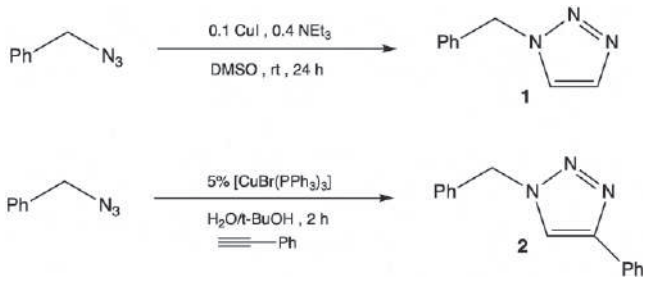


A triazole is a heterocyclic compound that has a five-membered ring with two carbon atoms and three nitrogen atoms. There are four isomeric triazoles that differ in the relative positions of the three nitrogen atoms: 1H-1,2,3-triazole, 2H-1,2,3-triazole, 1H-1,2,4-triazole and 4H-1,2,4-triazole. All are aromatic.



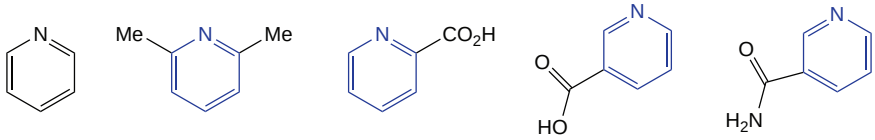


There are tautomers for each compound due to [1,5]-sigmatropic hydrogen shifts. For example, 1H-1,2,3-triazole, 2*H*-1,2,3-triazole, and 4*H*-1,2,3-triazole are three tautomers for a single triazole. Many compounds that contain one or more 1,2,4-triazole rings are potent antifungal compounds. *Itraconazole* and *fluconazole* were some of the first triazoles synthesized, but had limitations associated with their use. Second-generation triazoles such as *voriconazole*, albaconazole, *efinaconazole*, ravuconazole and isavuconazole are all derivatives of either itraconazole or fluconazole and designed to overcome the deficiencies of their parent drugs. 1,2,3-Triazoles can be prepared using copper-catalyzed "click chemistry" (see the formation of **1**[1a] and **2**[1b]) by the reaction of an alkyl azide and an alkyne.[1]



23.2 Draw 1,3-(*1H*)-dimethylpyrazole and 4-bromo-2-ethylimidazole.

There are six-membered ring heterocycles with one or more nitrogen atoms. *Pyridine* is an aromatic six-membered ring compound with one nitrogen atom, first isolated in 1846 from coal tar. The nitrogen atom is sp^2 hybridized with one electron pair that is part of the aromatic π-cloud. Another electron pair on nitrogen is perpendicular to the aromatic π-cloud so it is available for donation in acid-base reactions. Pyridine is a good base. There are several important pyridine derivatives with substituents on the aromatic ring, including *2,6-lutidine* (2,6-dimethylpyridine) and picolinic acid. Another is *nicotinic acid* (niacin, vitamin B_3), found in liver, yeast, and in meat. A deficiency of this vitamin can lead to Pellagra (a wasting disease). *Nicotinamide* (niacinamide) is one of the two principal forms of the B-complex vitamin niacin, and it may be useful for individuals with type 1 (insulin-dependent) diabetes.

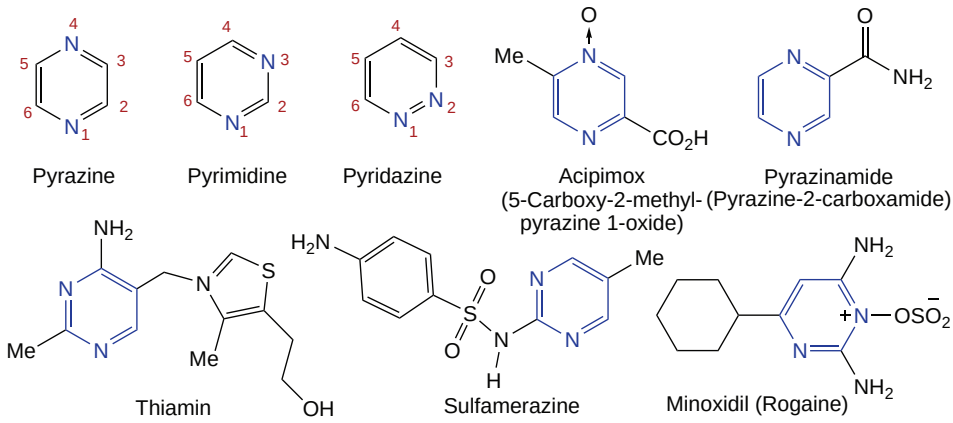


Pyridine | 2,6-Dimethylpyridine (2,6-Lutidine) | Picolinic acid | Nicotinic acid (Niacin) | Nicotinamide

The aromatic six-membered ring compounds with two nitrogen atoms in the ring are known as *diazines*. There are three isomers, *pyrazine*, *pyrimidine*, and *pyridazine*. Pyrazine has two nitrogen atoms in a 1,4-relationship, pyrimidine has two nitrogen atoms in a 1,3-relationship, and pyridazine has two nitrogen atoms in a 1,2-relationship. All three isomers are good bases. Pyrazine and alkylpyrazines are found in baked and roasted goods as flavor and aroma constituents. Three pyrimidine derivatives cytosine, thymine and uracil are nucleobases in nucleic acids (Sections 25.5,6). Pyridazines are rare in nature.

Pyrazine, pyrimidine, and pyridazine derivatives are common components of pharmaceutically important compounds. The pyrazine derivative (5-carboxy-2-methylpyrazine 1-oxide) called *Acipimox* is used to lower levels of cholesterol and triglycerides. The *N*-oxide unit of the pyrazine ring is an oxidized form of the amine. *Pyrazinamide* (pyrazine-2-carboxamide) is an antibacterial agent. A deficiency of *thiamin* (vitamin B_1) is associated with Beriberi. *Sulfamerazine* is a broad-spectrum anti-bacterial agent. *Minoxidil* (Rogaine) relaxes the smooth muscle in blood vessels and causes the vessels to dilate, a vasodilator. It is used to treat high blood pressure and is also used in hair-restoring preparations.

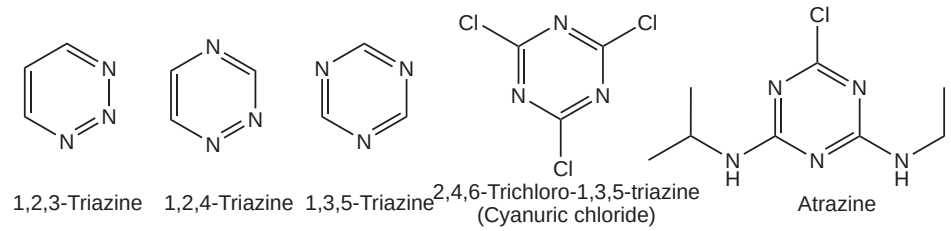
[1] (a) Wu, L.-Y.; Xie, Y.-X.; Chen, Z.-S.; Niu, Y.-N.; Liang, Y.-M. *Synlett* 2009, 1453–1456; (b) Lal, S.; Díez-González, S. *Journal of Organic Chemistry* 2011, 76, 2367–2373.



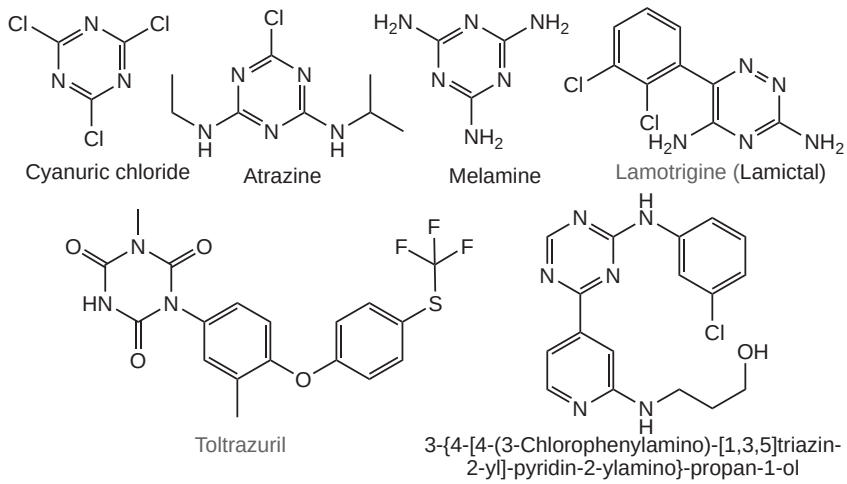
23.3 Draw the structures of (a) 2-ethyl-5-nitropyrazine, (b) 2,6-dibromopyrazine, (c) 2,4,6-triethylpyrimidine, and (d) 4,5-dinitropyridazine.

Triazines

The *triazines* are heterocycles with three nitrogen atoms. They are aromatic and there are three isomers: 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine. Triazine derivatives are constituents of many important compounds. 1,3,5-Triazine is used as the laboratory equivalent of HCN, as it is a solid and easier to handle. *Cyanuric chloride* is prepared in two steps from HCN and chlorine.



Cyanuric chloride is the main precursor to the herbicide *atrazine*, a widely used to prevent pre-emergence broadleaf weeds. However, triazine herbicides are persistent in environment. *Melamine* is a 1,3,5-triazine derivative and forms a melamine resin when combined with formaldehyde.

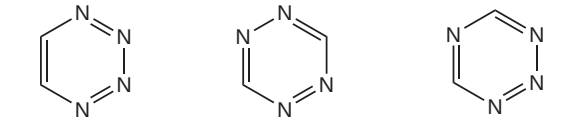


This thermosetting plastic is used in Formica, melamine dinnerware, laminate flooring and as an insulting material. *Lamotrigine* (Lamictal) is an anticonvulsant medication used

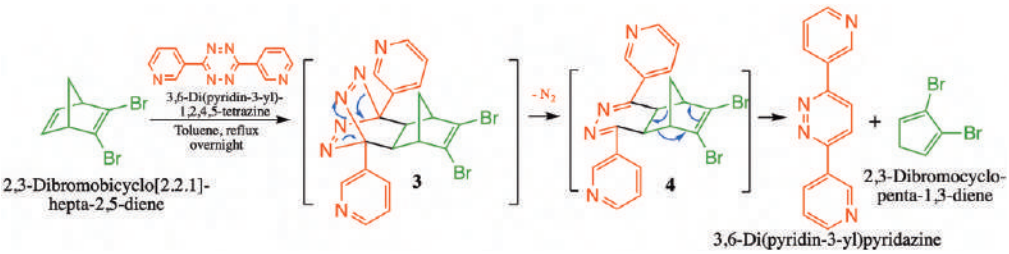
to treat epilepsy. It is also used to delay or prevent the recurrence of depressive episodes in bipolar disorder. Triazine pesticides include *atrazine*, prometon, prometryn, propyzamide, terbutylazine and terbutryne. Triazines are used in veterinary medicine. including *toltrazuril*, ponazuril, diclazuril, clazuril, and nitromezuril. Toltrazuril, for example, is used as an anticoccidial agent in chickens, turkeys, pigs, and cattle for the prevention and treatment of coccidiosis. Coccidiosis is a parasitic disease of the intestinal tract of animals caused by coccidian protozoa. *3-{4-[4-(3-Chlorophenylamino)-[1,3,5]triazin-2-yl]-pyridin-2-ylamino}-propan-1-ol* is active against CDK1, CDK2 and CDK4, respectively and showed high potency also toward the glycogen synthase kinase GSK-3b.[2] It displayed potent antiproliferative activity, both in vitro, against various cancer cell lines, including HeLa, HCT-116, U937 and A375 and in vivo, in a human melanoma A375 xenograft model. Indeed, 1,3,5-triazines are promising for the development of anticancer drugs.[3]

23.4 Draw the structures of (a) 4,5-diethyl-1,2,3-triazine, (b) 1,2,4-triazine-5-carboxylic acid, and (c) 2,4-diphenyl-1,3,5-triazine.

Tetazines



Tetrazines are aromatic compounds with four nitrogen atoms and three isomers are shown. The main use of 1,2,4,5-tetrazines appears to be in bioconjugate chemistry.



The presence of N=N unit is in 1,2,4,5-tetrazines make them highly reactive in Diels-Alder reactions. An example is the reaction of 3,6-di(pyridine-3-yl)-1,2,4,5-tetrazine with the bicyclic compound 2,3-dibromobicyclo[2.2.1]-hepta-2,5-diene, which gives the transient cycloadduct **3**. Compound **3** loses nitrogen in a retro-Diels-Alder reaction to give **4**,[4] which also undergoes a retro Diels-Alder reaction to give 3,6-di(pyridine-3-yl)pyridazine and 2,3-dibromocyclopenta-1,3-diene.

The high reaction rates, chemoselectivity and excellent biocompatibility of tetrazines coupled with their Diels-Alder reactivity to generate a pyridazine make them suitable as activating prodrugs. *Click chemistry* involves a class of reactions of biocompatible small molecules that are commonly used in bioconjugation. Bioconjugation is the formation of a stable covalent link between two molecules, of which at least one is a biomolecule. The term "click chemistry" was coined by Nobel laureate K. Barry Sharpless (USA).[5] Click chemistry involves controllable biorthogonal reactions, which are chemical reactions that occur inside of living systems without interfering with native biochemical processes. Hitting particular

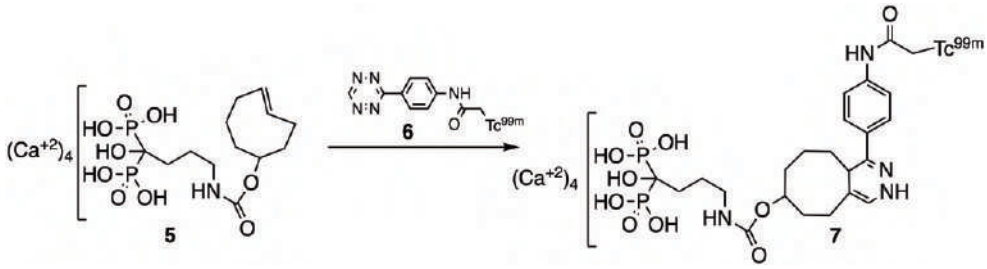
[2] Kuo, G.-H.; DeAngelis, A.; Emanuel, S.; Wang, A.; Zhang, Y.; Connolly, P.J.; Chen, X.; Gruninger, R.H.; Rugg, C.; Fuentes-Pesquera, A.; Middleton, S.A.; Jolliffe, L.; Murray, W.V. *Journal of Medicinal Chemistry* 2005, 48, 4535–4546.

[3] Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. *European Journal of Medicinal Chemistry* 2017, 142, 523–549.

[4] Dalkiliç, E., Daştan, A. *Tetrahedron* 2015, 71, 1966–1970.

[5] Kolb, H.C.; Finn, M.G.; Sharpless, K.B. *Angewandte Chemie International Edition* 2001, 40, 2004–2021.

targets in complex cell lysates is possible with this technique. A Diels-Alder reaction between 1,2,4,5-tetrazine and strained alkenes such as *trans*-cyclooctene is a well-established bioorthogonal reaction, and it is regarded as the fastest click reaction. Activated alkenes such as *trans*-cyclooctene react with tetrazines in an *inverse electron-demand Diels-Alder reaction*, which is a cycloaddition between an electron-rich dienophile and an electron-poor diene. The initial cycloaddition is followed by a *retro [4+2] cycloaddition*, the microscopic reverse reaction that forms a diene and dienophile from a cyclohexene.



A pre-targeted strategy for bone imaging and radiotherapy is based on this concept. It used a conjugated bisphosphonate and a radiolabeled tetrazines.[6] A bisphosphonate conjugate was prepared and injected into an animal model, allowing the accumulation of dienophile **5** *in skeletal tissue.* After 12 h post administration, ^{99m}Tc-labeled tetrazine **6** was administered intravenously, and **7** was formed in the skeletal tissue. SPECT/CT imaging revealed high radioactivity in the knees and shoulder, suggesting that the functionalized tetrazine targeted the bone tissue. Single photon emission computed tomography (SPECT)/computed tomography (CT) scan shows how blood flows to tissues and organs.

23.5 What is the product formed when 3,6-diphenyl-1,2,4.5-tetrazine is heated with dimethyl maleate.

There are five-membered ring aromatic compounds that contain an oxygen or a sulfur, but the analogous six-membered ring compounds are *not* aromatic. *Furan* is an aromatic compound that is distilled from pine wood rosin and its vapors are narcotic. One of the two electron pairs on oxygen is involved in the aromatic π-cloud but the other lone electron pair is perpendicular to the π-cloud. Furan is a weak base, but it is a much *stronger* base than pyrrole because of the availability of those electrons.

O and S-Containing 5 and 6-Membered Rings

If the oxygen atom in furan is replaced with sulfur, the resulting compound is the aromatic compound *thiophene*, an aromatic thioether. As with furan, one electron pair is involved in the 6 π-electron aromatic cloud, and the other is perpendicular to that π-cloud. Thiophene is obtained from coal tar and coal gas, and it is used in the manufacture of dyes and pharmaceuticals. The heteroatom is numbered 1 in both furan and thiophene.

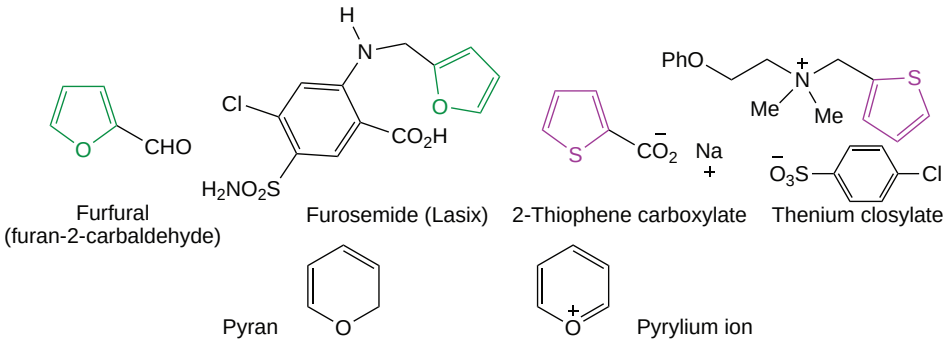
Furan Electron π-cloud of furan Thiophene

23.6 Draw the structures of (a) 3,4-dimethylfuran, (b) furan-3-carboxylic acid, (c) thiophene-2-carbaldehyde, and (d) 2,5-dibromothiophene.

Many important compounds contain furan or thiophene rings. *Furfural*, for example, contains the furan ring and is found in cereal straws and brans. It is used in the manufacture of

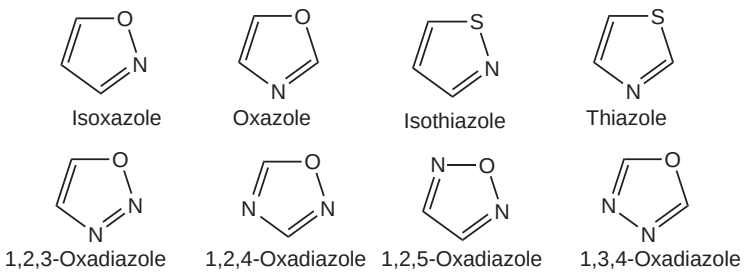
[6] (a) Yazdani, A.; Bilton, H.; Vito, A.; Genady, A.R.; Rathmann, S.M.; Ahmad, Z.; Janzen, N.; Czorny, S.; Zeglis, B.M.; Francesconi, L.C.; Valliant, J.F. *Journal of Medicinal Chemistry* 2016, 59, 9381–9389; (b) Mushtaq, S.; Yun, S.-J.; Jeon, J. *Molecules* 2019, 24, 3567–3597.

plastics and varnishes, and it is used as an insecticide and fumigant. *Furosemide* (Lasix) has diuretic and anti-hypertensive properties and inhibits sodium ion reabsorption. It is used to treat edema (swelling caused by fluid in body tissues), hypertension, and cardiac insufficiency. The sodium salt of 2-thiophene carboxylic acid, is used as a lubricant grease thickener. *Thenium closylate* has anthelmintic properties, which means it is active against parasitic worms. Oxygen and sulfur are divalent, so incorporation into a six-membered ring does not allow an aromatic system to be generated. Pyran is the six-membered ring ether. A double bond to oxygen would generate a positively charged pyrylium ion, a transient intermediate in some reactions.

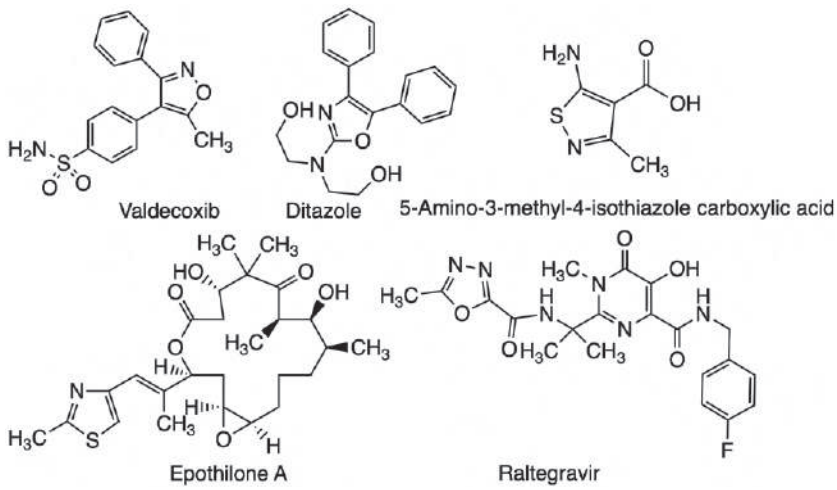


23.7 Draw the sulfur analog of pyran, known as thiopyran.

Other N, O, S Heterocycles

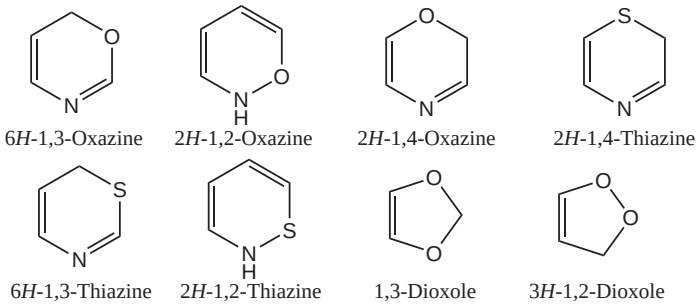


There are several important five-membered aromatic systems that contain both nitrogen and oxygen. There are two molecules with one nitrogen and one oxygen, isoxazole and oxazole. There are also two molecules with one nitrogen and one sulfur, isothiazole and thiazole. There are four isomeric molecules that have two nitrogen atoms and one oxygen, 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxidiazoles that are found in many biologically active compounds. The oxadiazoles are also known as furazans. *Valdecoxib* (sold as Bextra) is a nonsteroidal anti-inflammatory arthritis drug.



Reactions of 5-Membered Ring Heterocycles

Ditazole is a non-steroidal anti-inflammatory agent with analgesic and antipyretic activity. It is also a platelet aggregation inhibitor. 5-*Amino-3-methyl-4-isothiazolecarboxylic acid* exhibits antiviral, anti-inflammatory and immunotropic action.[7] The epothilones are a class of potential cancer drugs that prevent cancer cells from dividing by interfering with tubulin. *Epothilone A* is an antineoplastic agent, a tubulin modulator, a metabolite and a microtubule-stabilizing agent. *Raltegravir,* sold under the brand name Isentress is an antiretroviral medication used in combination with other drugs to treat HIV/AIDS.



There are many heterocycles that contain nitrogen and oxygen or nitrogen and sulfur in a six-membered ring. The oxazines and thiazines ae examples. The dioxoles are shown to illustrate that two oxygen atoms can be incorporated. There are molecules with two sulfur atoms in a five-membered ring (dithioles), two oxygens in a six-membered ring (dioxines) or two sulfur atoms in a six membered ring (dithiines), an oxygen and a sulfur in a five-membered ring (oxathioles) or a six membered ring (oxathiines).

23.2 SUBSTITUTION REACTIONS IN MONOCYCLIC HETEROCYCLIC AROMATIC COMPOUNDS

Aromatic heterocycles undergo electrophilic aromatic substitution reactions similar to reactions of aromatic hydrocarbons (Section 19.3). Five-membered heterocycles such as pyrrole, furan and thiophene are activated aromatic rings and undergo S_EAr reactions faster than benzene. Six-membered aromatic rings such as pyridine are deactivated and react slower than benzene in S_EAr reactions. The fundamental principles of reactivity and regioselectivity discussed for benzene derivatives in Section 19.3 apply to heterocyclic ring systems. The major site of substitution in this reaction is the one that yields the more stable arenium ion intermediate. There are two sites for substitution when an electrophile reacts with pyrrole, C2 and C3. If the pyrrole ring attacks the nitronium ion, NO_2^+ attaches to C2 to yield intermediate **8** as shown in Figure 23.1.

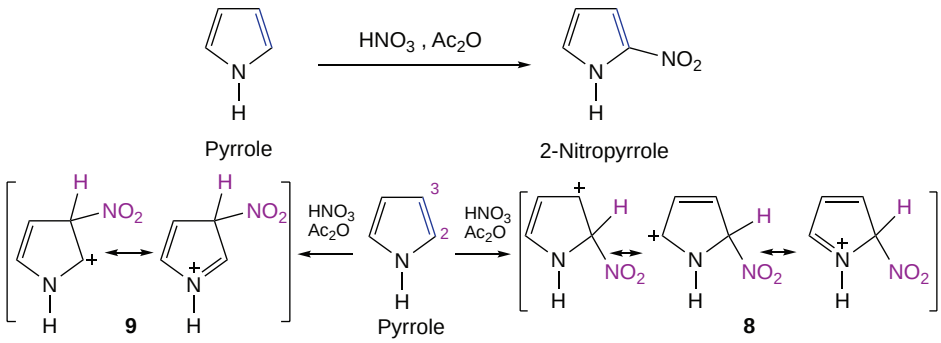
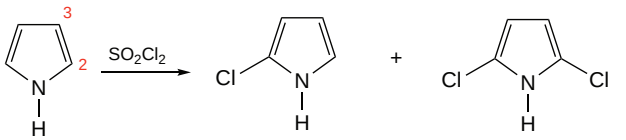


FIGURE 23.1 Mechanism of pyrrole nitration.

[7] (a) Regiec, A.; Machon, Z.; Miedzybrodzki, R.; Szymaniec, S. *Archives of Pharmacy* 2006, 339, 401–403; (b)Machon, Z. *Drugs Future* 1988, *13*, 426–428; (c) Alam, Md.A.; Shimada1, K.; Khan, Md.W.; Hossain, Md.H. *Medicinal and Analytical Chemistry International Journal* 2019, 3, 000137.



Pyrrole 2-Chloropyrrole 2,5-Dichloropyrrole

Intermediate **9** is formed by reaction at C3. Reaction at C2 can generate three resonance forms, but reaction at C2 generates only two. Since reaction at C2 leads to the more stable intermediate, the activation energy for that reaction is lower, and nitration gives 2-nitropyrrole as the major product. Indeed, five-membered ring heterocycles give C2 substitution in S_EAr reactions. Pyrrole is more reactive than benzene and milder reaction conditions can be used. Pyrrole reacts with nitric acid and acetic anhydride rather than nitric acid/sulfuric acid and gives 2-nitropyrrole by the S_EAr mechanism. Other S_EAr reactions are known, including the reaction of pyrrole with sulfuryl chloride (SO_2Cl_2) to give 2-chloropyrrole as the major product without the need for a Lewis acid. 2,5-Dichloropyrrole is also formed in this reaction since pyrrole is very activated. Bromination of pyrrole uses *N*-bromosuccinimide (NBS) as a brominating agent to yield 2-bromopyrrole.

23.8 Draw the product of the reaction between pyrrole with sulfur trioxide (SO_3) using pyridine as a solvent at 100°C.

Both furan and thiophene give primarily the C2 substitution product. Furan has less aromatic character than pyrrole and is less activated so it reacts slower in S_EAr reactions and more of the C3-substituted product is observed. Although *less* reactive than pyrrole, furan is ~ 10^5 times *more* reactive than benzene. Concentrated acid or aluminum chloride catalysts are not used since they induce polymerization with furan. Treatment of furan with nitrosonium tetrafluoroborate (NO_2^+ BF_4^-) leads to 2-nitrofuran. Furan reacts with SO_3 and pyridine to yield 2-furansulfonic acid and with a bromine-dioxane complex at -5 °C to give 2-bromofuran. The reaction of furan with acetyl chloride and tin tetrachloride ($SnCl_4$) gives the Friedel–Crafts type product 2-acetylfuran [1-(furan-2-yl)ethenone].

Furan 2-Nitrofuran Furan 1-(Furan-2-yl)ethanone (2-acetylfuran)

Thiophene has more aromatic character than furan and undergoes substitution readily. It is 10^3–10^5 times *more* reactive than benzene. However, thiophene is *less* reactive than furan in S_EAr reactions. Thiophene is a weaker base than furan. The reaction conditions used for thiophene are very similar to those used for furan, however. Treatment with nitric acid and acetic anhydride, for example, yields 2-nitrothiophene. The reaction with HCl and formaldehyde gives 2-chloromethylthiophene.

23.9 Determine the mechanism of bromination of furan at C2, assuming it proceeds via Br^+.

23.10 Draw the product formed in the reaction of thiophene with sulfuryl chloride; with NBS; with acetyl chloride and tin tetrachloride ($SnCl_4$).

Pyridine is a tertiary amine and a good base, and it is used in many organic reactions. Pyridine and pyrimidines are deactivated so S_EAr reactions are slow. In addition, pyridine reacts as a Lewis base with the Lewis acids used for S_EAr reactions. Nonetheless, electrophilic

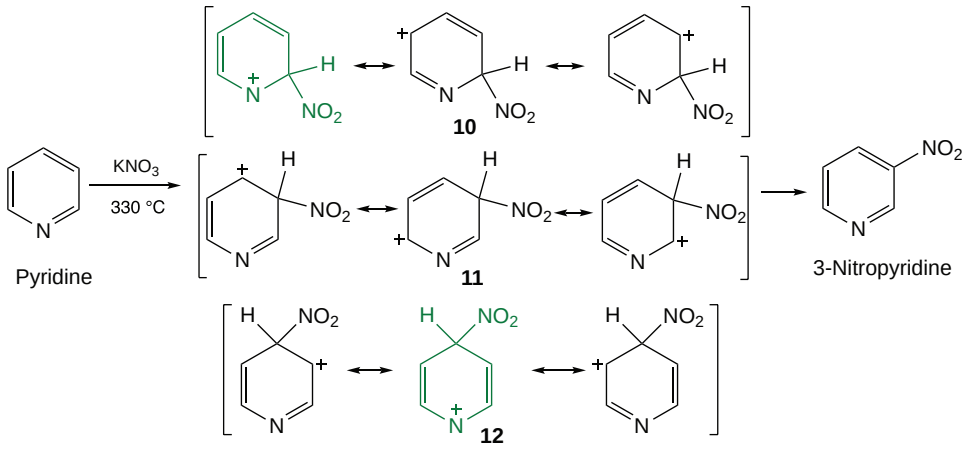
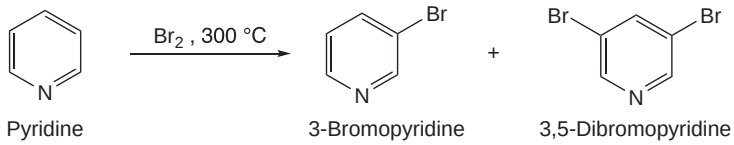


FIGURE 23.2 Electrophilic aromatic substitution of pyridine.

aromatic substitution does occur with pyridine without the use of Lewis acids, but the reaction is slow and harsh reaction conditions are required. In general, pyridine reacts with electrophilic reagents to yield the 3-substituted derivative. Pyridine reacts with potassium nitrate at 330 °C, for example, to give 3-nitropyridine. Relative to nitrogen, C3 and C5 have the greatest π-electron density and those are the major sites for reaction. The arenium ions generated from pyridine in electrophilic aromatic substitution reactions have a high activation energy for formation. As shown in Figure 23.2 reaction at C2 leads to intermediate **10**, reaction at C3 leads to **11** and reaction at C4 leads to **12**. Reaction at C2 and C4 give resonance contributors **10** or **12** with a positive charge directly on the nitrogen, which is very unstable. The three resonance forms for **10** and **12** are particularly destabilized so the rate of formation is very slow. Reaction at C3 (**11**) gives a relatively unstable arenium ion but the positive charge is never on nitrogen, so it is less destabilized than **10** or **12**. Therefore, the rate of formation of **11** is faster and leads to the major product, 3-nitropyridine. In addition to nitration, pyridine reacts with bromine (at a temperature near 300 °C) to yield a mixture of 3-bromopyridine and 3,5-dibromopyridine.

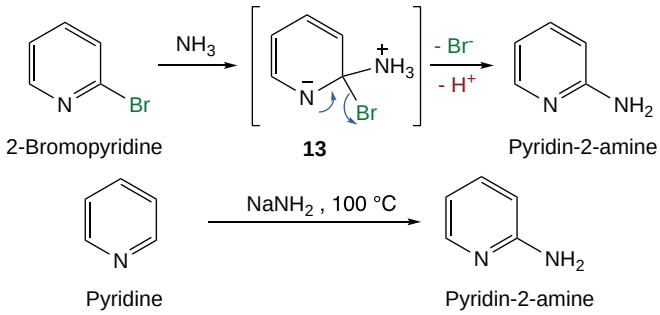
Reactions of 6-Membered Rings



23.11 Draw and name the acid-base product formed when pyridine is treated with HBr.

23.12 Draw the product of the reaction of pyridine with sulfur trioxide in sulfuric acid (in the presence of mercuric sulfate ($HgSO_4$).

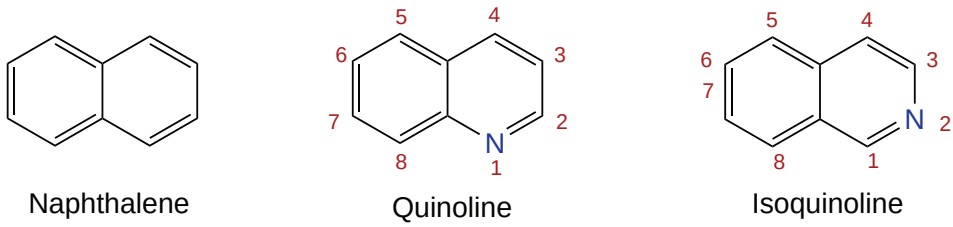
Although pyridine is a poor substrate in S_EAr reactions, it is susceptible to nucleophilic aromatic substitution (S_NAr reactions). The reaction of 2-bromopyridine with ammonia, for example, leads to 2-aminopyridine. Ammonia reacts at the ipso carbon to generate a carbanionic intermediate (**13**) by a S_NAr reaction (Section 19.10), which loses a bromide ion to give pyridin-2-amine. Pyridine also reacts directly with sodium amide ($NaNH_2$) at 100 °C to yield pyridin-2-amine in what is known as the *Chichibabin reaction*, named after Alexei E. Chichibabin (Russia; 1871–1945). Other bases can be used in this reaction. Pyridine reacts with phenyllithium at 100 °C, for example, to yield 2-phenylpyridine. This reaction is limited in scope since strong nucleophiles are required and the reaction conditions can be harsh. Five-membered ring heterocycles are less prone to nucleophilic aromatic substitution, in part because the preparation of the requisite halogen-substituted derivatives can be difficult.



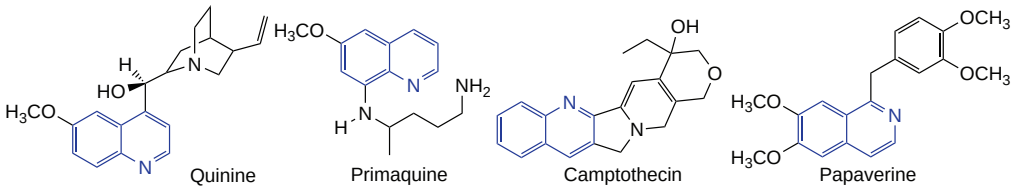
23.13 Draw the reaction and product formed when pyridine is heated with phenyllithium.

23.3 HETEROAROMATIC COMPOUNDS WITH MORE THAN ONE RING

Polycyclic Aromatic Heterocycles

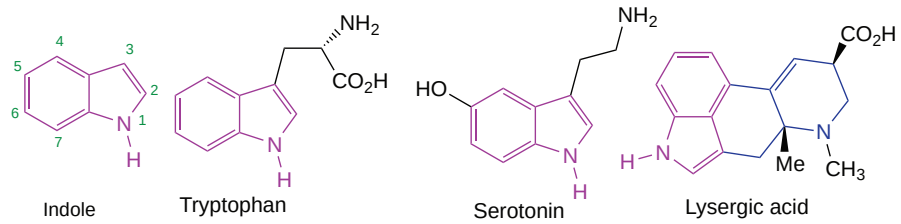


Polycyclic aromatic hydrocarbons such as naphthalene were discussed in Section 19.8.1. There are important polycyclic systems that contain heteroatom atoms, and many are found in biological systems and in medicines. The bicyclic aromatic amine with a nitrogen at position "1" is *quinoline*.



When the nitrogen is in position "2" the compound the amine is *isoquinoline*. Both quinoline and isoquinoline were first isolated from coal tar, and they are used to prepare dyes, insecticides, anti-malarial compounds. A large number of *alkaloids* (natural products containing nitrogen discussed in Section 23.6) have significant biological activity and contain either the quinoline, or isoquinoline ring systems, or hydrogenated forms of these rings. Quinoline is mentioned briefly in Section 17.4.1 as a poison in the *Lindlar hydrogenation* of alkynes to yield cis-alkenes. *Quinine* is a common quinoline derivative and an important antimalarial isolated from *Cinchona* bark (Section 1.1). Another antimalarial compound is *Primaquine*. *Camptothecin* is an important anticancer drug that contains the quinoline unit. An isoquinoline derivative isolated from the opium poppy is *papaverine*, which is related to morphine. Papapverine relaxes smooth muscle tissue in blood vessels.

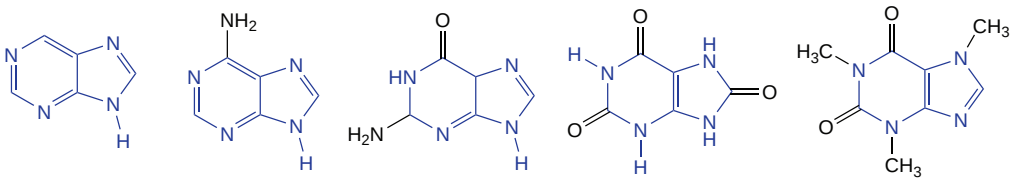
23.14 Draw 3-bromo-8-methylquinoline and 4,8-diethylisoquinoline.



Indole is an important bicyclic heterocycle with a six-membered ring fused to a five-membered ring. Indole is widely distributed in nature. It occurs naturally in human feces and has an intense fecal odor. At very low concentrations it has a flowery smell and is used as a constituent of many perfumes. A common indole derivative is the important amino acid *tryptophan* (Section 24.3). The closely related compound *serotonin* is a neurotransmitter that causes smooth muscle effects in the cardiovascular and gastrointestinal systems. Some indole-containing compounds have hallucinogenic effects, as seen with *lysergic acid*, which is found in a fungal parasite common to rye and wheat. Lysergic acid in combination with several related compounds found in this fungus are responsible for "ergot poisoning," which killed > 40,000 people in Europe in the 10th and 12th centuries.

23.15 Draw 5-bromo-1-methy-1H-indole.

There are aromatic derivatives that have one or two nitrogen atoms at different positions in bicyclic six–six, six–five, or five–five fused aromatic rings. It is also possible to incorporate three, four, or even five nitrogen atoms into these rings.

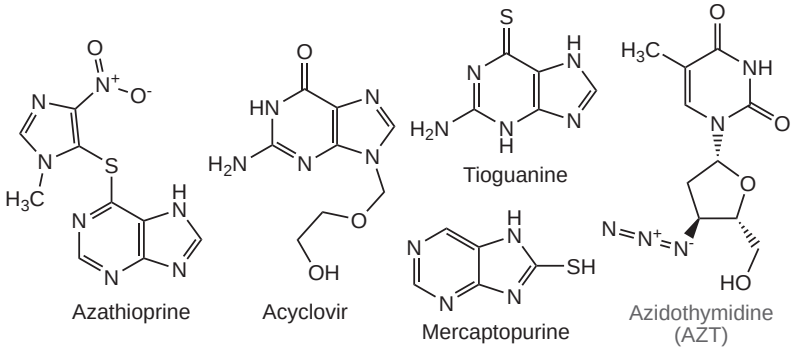


Purine is an important six-five heterocyclic ring system that contains four nitrogen atoms and derivatives of this heterocycle include *adenine* and *guanine*, which are components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA, Section 25.6). Both *uric acid* (a component of urine) and *caffeine* (found in coffee and tea) have a purine skeleton. A buildup of uric acid in the blood leads to gout, which is an inflammatory form of arthritis. Caffeine is a central nervous system stimulant, and it is found in many plants.

Gertrude Elion

Many important drugs with a purine component were developed by Nobel laureate Gertrude Elion (USA; 1918–1999), who worked at Burroughs and Wellcome and later was an adjunct professor at Duke University. Important drugs she developed were allopurinol (prevents gout) and nelarabine (an anti- cancer drug), *azathioprine*, the first immunosuppressive

drug used to fight rejection in organ transplants, and *acyclovir*, the first successful antiviral drug used to treat herpes infection.

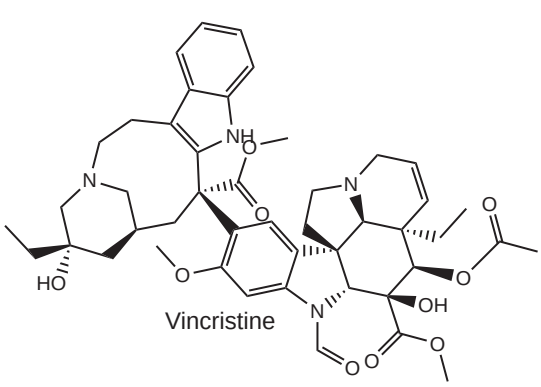


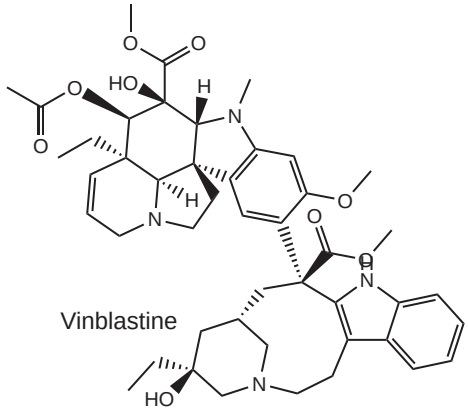
Professor Elion synthesized anti-metabolites of purines and developed *tioguanine* and *mercaptopurine*. She helped develop rational drug design, which uses the differences in biochemistry and metabolism to design drugs that could kill or inhibit the reproduction of particular pathogens without harming human cells. She also helped develop *azidothymidine* (AZT), the first drug approved for the treatment of HIV in the United States.

Atta-ur-Rahman

Professor Atta-ur-Rahman (Pakistan), Fellow of the Royal Society (London) is an organic chemist at the H.E.J. Research Institute of Chemistry, University of Karachi, in Karachi, Pakistan. He is currently serving as the Chairman of the Task Force of the Prime Minister of Pakistan on Science and Technology. Atta-ur-Rahman is an expert in the field of natural product chemistry in South Asia. His research on molecular structure and synthesis has led to the synthesis of numerous compounds of biological interest. He has also conducted important analytical studies of organic compounds using circular dichroism (Section 9.4) Alongside his work on synthesis, Atta-ur-Rahman has also conducted important analytical studies on bioactive natural products. His efforts at the national level in his capacity as the Federal Minister of Science and Technology (2000–2002) and later as Chairman of Higher Education Commission (2002–2008) has enabled a true transformation in the country's approach towards science, technology, engineering and medicine. He developed procedures for the large scale extraction and helped to synthesize derivatives and analogues of important cancer-fighting alkaloids obtained from the rosy periwinkle, *Catharanthus roseus*. *Catharanthus roseus* is a species of flowering plant in the family *Apocynaceae* and the source of the drugs vincristine and vinblastine. Vincristine is a chemotherapy drug used to treat acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin's disease, neuroblastoma, and small cell lung cancer among others. Vinblastine is a vinca alkaloid used to treat breast cancer, testicular cancer, neuroblastoma, Hodgkin's and non-Hodgkin's lymphoma, mycosis fungoides, histiocytosis, and Kaposi's sarcoma. Professor Atta-ur-Rahman has

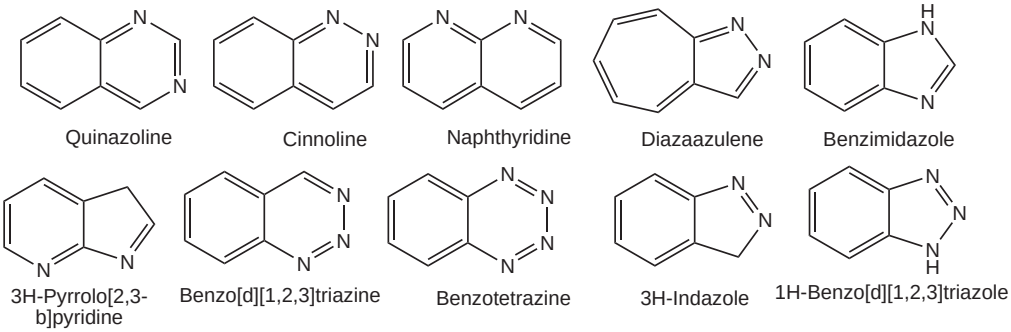
reported novel approaches to the synthesis of these important alkaloids, as well as analogs and derivatives.[8]



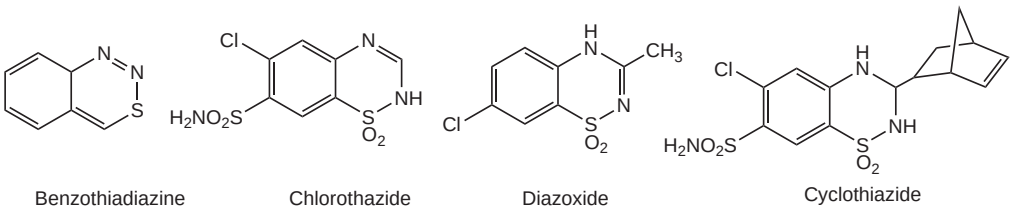


There are myriad bicyclic and polycyclic compounds that contain nitrogen, oxygen, and sulfur. A listing of all the known compounds is beyond the scope of this chapter or even this book. A brief list of important compounds that contain two or more heteroatoms is presented, however, to introduce some of the structural variety of these compounds. Quinazoline, cinnoline and naphthyridine have two nitrogen atoms in the two-ring system whereas benzo[1,2,3]triazine has three nitrogen atoms and benzotetrazine have four nitrogen atoms. Benzimidazole, 3*H*-indazole and 3*H*-pyrrolo[2,3]pyridine have two nitrogen atoms in the six-five ring system and 1*H*-benzo[1,2,3]-triazole has three nitrogen atoms. Diazaazulene is an example of a five-seven ring system with two nitrogen atoms.

Bicyclic Heterocycles-Alkaloids

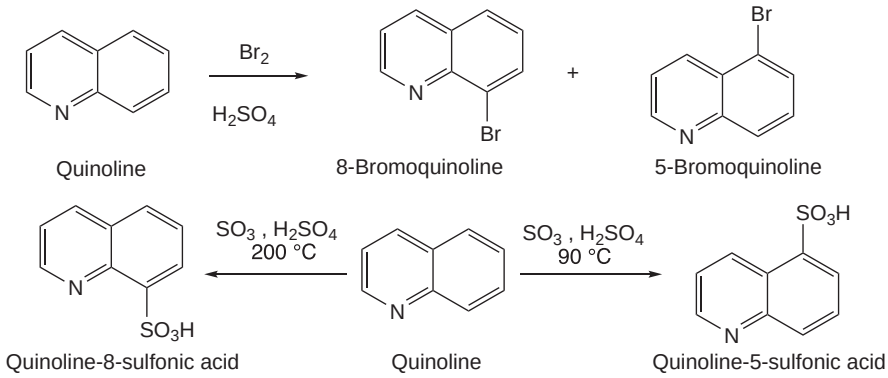


Thiazides are commonly used as diuretics. Examples are benzothiadiazine as well as the first approved drug of this class, chlorothiazide. Diazoxide is used to treat low blood sugar due to islet cell tumors and leucine sensitivity. Cyclothiazide is a benzothiadiazide diuretic and hypertensive.



[8] (a) Atta-ur-Rahman, *Journal of the Chemical Society of Pakistan* 1979, 1, 81–86; (b) *Stereoselective Synthesis: Studies in Natural Products Chemistry*, Atta-ur-Rahman (Ed.). Volume 14, Part I, 1994, pp. 805–887.

23.4 AROMATIC SUBSTITUTION REACTIONS OF POLYCYCLIC HETEROCYCLES



Both quinoline and isoquinoline contain a pyridine unit as well as a benzene ring unit. The benzene ring is expected to be activated for S_EAr reactions, whereas the pyridine ring is *deactivated*. Therefore, electrophilic aromatic substitution will occur exclusively in the benzene ring unit. The indole system contains an activated pyrrole unit and a benzene ring unit, which reacts more slowly in S_EAr reactions.

Therefore, indole reacts at the activated pyrrole unit rather than the benzene ring unit. Because the pyridine ring of quinoline is much less reactive only C5, C6, C7, and C8 in the benzene ring are potential sites for electrophilic substitution, and C5 and C8 are the most reactive sites.[9] The reaction with bromine and aluminum chloride gives two products, 5-bromoquinoline and 8-bromoquinoline. The bridgehead carbon atoms in quinoline are *not* available for substitution. Since the bromination reaction generates Br^+, reaction with quinoline at C8 gives intermediate **14**, as shown in Figure 23.3. Similar reaction at C7 yields **16**, reaction at C6

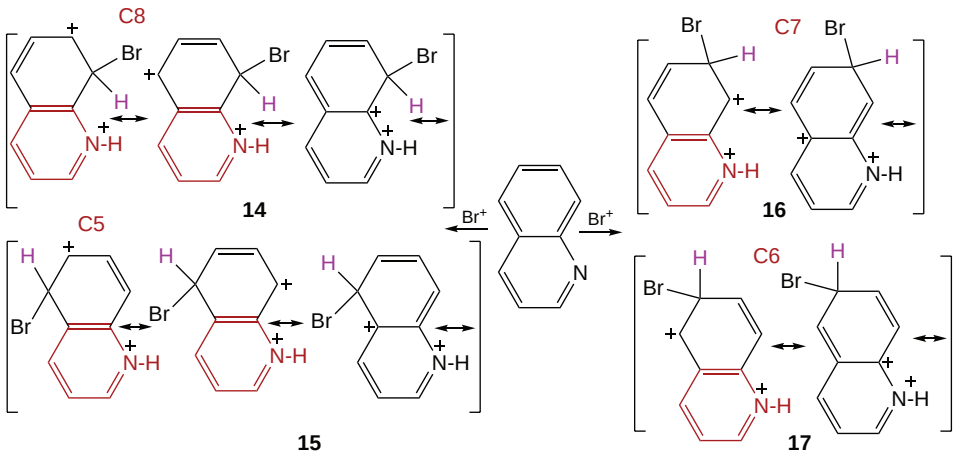
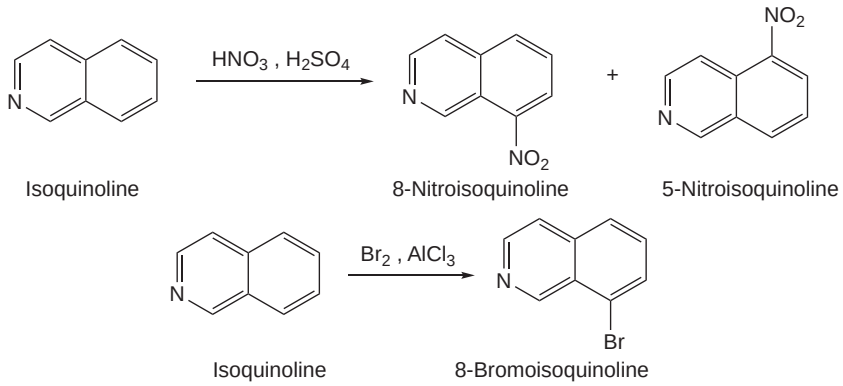


FIGURE 23.3 Electrophilic bromination of quinoline.

yields **17**, and reaction at C5 yields **15**. Attack at C5 and C8 is preferred because more intact rings (more Kekulé structures) are possible. There are more resonance structures, so reaction gives primarily 5- and 8-substituted quinoline derivatives. Another example is the reaction of quinoline at 90 °C with SO_3/H_2SO_4, which gives quinoline-8-sulfonic acid as the major product is, but when the reaction is heated to 220 °C, quinoline-5-sulfonic acid is also formed.

23.16 Draw the intermediate for attack of Br^+ at C2 of quinoline.
23.17 Draw all the resonance structures for **14** and **15**.

[9] Gilchrist, T.L. *Heterocyclic Chemistry*, 2nd ed., Longman Scientific & Technical, Essex, England, 1992, p. 160.



Isoquinoline reacts similarly to quinoline. Reaction of isoquinoline with nitric acid/sulfuric acid yields a mixture of 5-nitroisoquinoline and 8-nitroisoquinoline. The reaction of isoquinoline with bromine and aluminum chloride gives a high yield of 5-bromoisoquinoline. The rationale for this selectivity is the same as that for quinoline in that a substitution at C5 and C8 yields more stable intermediates.

Indoles are good reaction partners in electrophilic aromatic substitution. Since pyrrole is more reactive than benzene in electrophilic aromatic substitution it is reasonable to assume that the pyrrole ring of indole is more reactive than the benzene ring. When indole is treated with NBS, the major product is 3-bromoindole, as shown in Figure 23.4. The reaction of

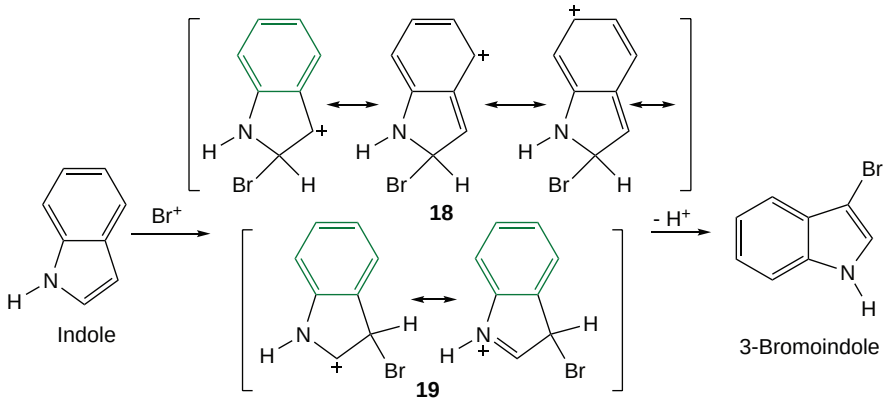


FIGURE 23.4 Electrophilic aromatic bromination of indole.

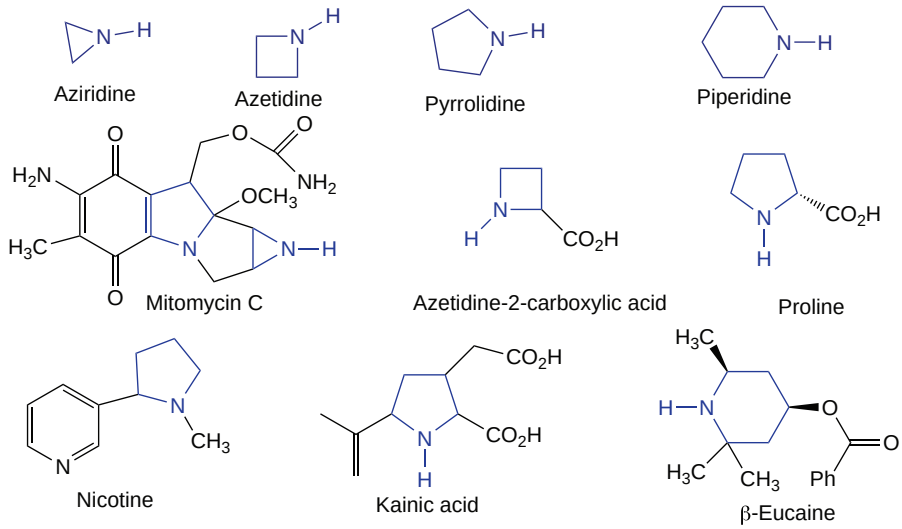
indole with Br^+ at C2 generates intermediate **18** and attack at C3 generates **19**. Attack at C3 allows only two resonance structures whereas reaction at C2 will delocalize the charge into the benzene ring. Therefore, reaction at C3 is preferred and the major product of electrophilic aromatic substitution is 3-bromoindole. This is a general observation, and another example is the reaction of indole with acetic anhydride to afford 3-acetylindole. Note that NBS is a source of Br^+ in this reaction.

23.18 Draw all resonance contributors for the intermediate formed when isoquinoline reacts with Cl^+ at C8.
23.19 Draw the product formed by the reaction of indole with SO_3/pyridine; with *N*-chlorosuccinimide; with benzenediazonium chloride ($PhN_2^+ Cl^-$).

23.5 REDUCED HETEROCYCLES

There are many important heteroatom-containing compounds that result from reduction of heterocycles. For a monocyclic system with one nitrogen, the three-membered ring

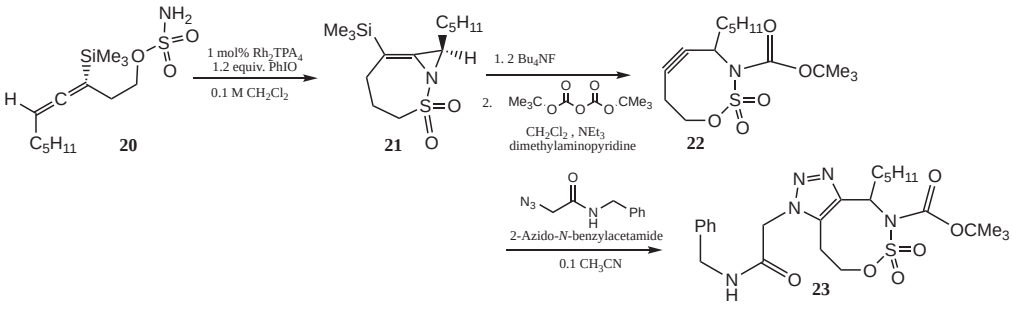
derivative is called aziridine, the four-membered ring is azetidine, the five-membered ring is pyrrolidine, and the six-membered ring is named piperidine. Pyrrolidine is prepared by catalytic hydrogenation of pyrrole and is formally named tetrahydropyrrole. Similarly, catalytic hydrogenation of pyridine leads to piperidine, which is formally named hexahydropyridine. All four of these cyclic amines are secondary amines and react as bases. These compounds are key units in important pharmaceuticals. *Mitomycin C* is used to treat cancer and the structure contains two fused pyrrolidine rings. *Azetidine-2-carboxylic acid* shows growth inhibitory activity on cultures of *Escherichia coli*. Many important compounds contain a pyrrolidine ring, including *proline*, which is a common amino acid (see Chapter 24). *Nicotine* is found in tobacco, and the carboxylate salt of *kainic acid* is a neurotoxin. A piperidine derivative, *β-eucaine*, is used as a local anesthetic.



Jennifer Schomaker

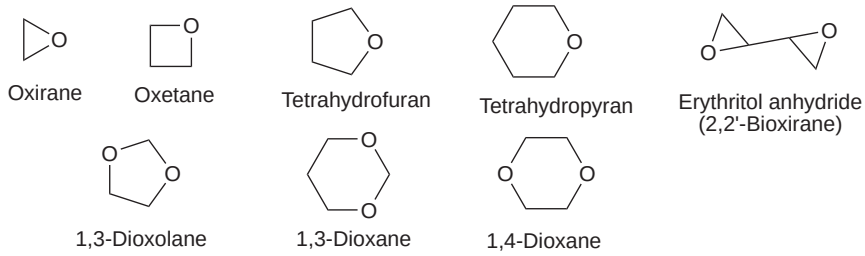
Professor Jennifer Schomaker (USA) is an organic chemist at the University of Wisconsin, Madison. Professor Schomaker and her group develop new methods that employ allenes as convenient three-carbon synthons for the preparation of densely substituted carbocycles and heterocycles. These methods rely on chemo-, site- and stereoselective intramolecular allene aziridinations that yield synthetically useful bicyclic methylene aziridines. These

intermediates have been utilized to prepare analogs of jogyamycin, a new antiprotozoal aminocyclopentitol antibiotic, to determine which structural features contribute to toxicity and tune selectivity for binding to pathogen over human ribosomes. Professor Schomaker has applied the methylene aziridine work to the development of useful biorthogonal chemistry protocols. She found that highly reactive cycloalkynes that are hyperconjugatively stabilized react faster with 1,3-dipoles, allowing the development of highly chemoselective, bioorthogonal methods. Note that hyperconjugation is the stabilizing interaction resulting from the interaction of the electrons in a σ-bond that has an adjacent empty or partially filled p-orbital or a π-orbital.



Hyperconjugation results in an extended molecular orbital that increases the stability of the system. The reaction of an allene such as **20** with $Rh_2(TPA)_4$ and PhIO leads to diastereoselective epoxidation, followed by rapid rearrangement to the azetidin-3-one **21**. Note that TPA is tetraphenylacetate and PhIO is iodosylbenzene. Subsequent treatment with tetrabutylammonium fluoride (TBAF) triggered elimination of the silyl group, followed by ring-opening of the aziridine to give a strained alkyne.[10] Protection of the amide unit as the Boc derivative (O_2CMe_3) by reaction with di-*tert*-butylcarbonate ($Me_3COCO_2CO_2CMe_3$) gives **22**. A [3+2]-cycloaddition reaction with 2-azido-*N*-benzylacetamide gives triazole **23**.[11] This approach was used to couple the cyclooctyne-sulfamate with 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)propanoyl chloride, which allowed coupling with human ribonuclease 1 (RNase 1) to generate a thiol-maleimide conjugation product, which was then reacted with an azide-PEG3-biotin to yield the biotin-RNase 1 conjugate. Note that PEG3 (Paternally Expressed Gene 3) is a protein coding gene. This work enhances the possibility of further method development in the context of chemoselective, bioorthogonal labeling.

23.20 Draw the products formed when azetidine reacts with HCl. When pyrrolidine reacts with sulfuric acid. When piperidine reacts with BF_3.

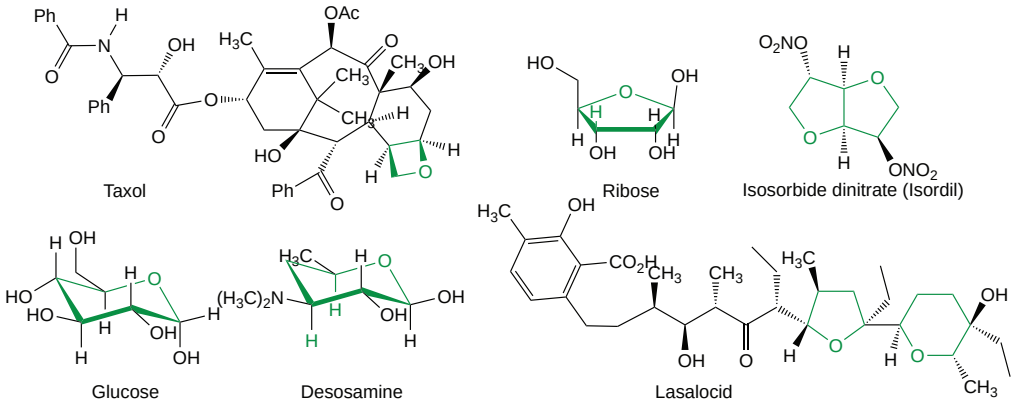


Oxygen-containing ring systems are cyclic ethers. The three-membered ring ether is oxirane, and this is the "parent" of the epoxides discussed Sections 11.7.2,3 and 15.3.2. The

[10] Burke, E.G.; Schomaker, J.M. *Angewandte Chemie International Edition* 2015, 54, 12097–12101.
[11] (a) Burke, E.G.; Gold, B.; Hoang, T.T.; Raines, R.T.; Schomaker, J.M. *Journal of the American Chemical Society*= 2017, 139, 8029–8037; (b) Burke, E.G.; Schomaker, J.M. *Journal of Organic Chemistry* 2017, 82, 9038–9046.

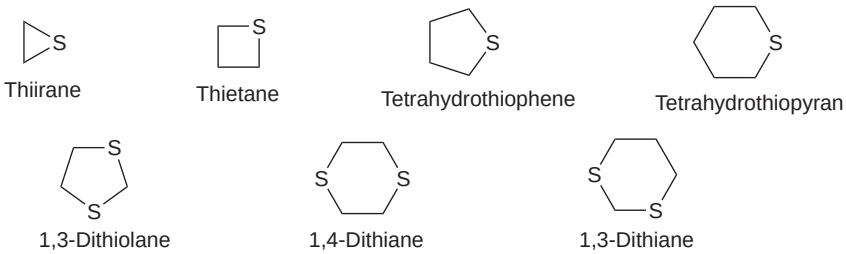
four-membered ring ether is oxetane, and the five-membered ring ether is oxolane, or tetrahydrofuran (THF). Tetrahydrofuran is an important cyclic ether prepared by catalytic hydrogenation of furan and used many times in this book as a polar, aprotic solvent. The six-membered ring ether is called oxane, or tetrahydropyran, obtained by catalytic hydrogenation of pyran. Oxygen-containing molecules that have two oxygen atoms include the five-membered ring compound 1,3-dioxolane. There are two six-membered ring derivatives, 1,3-dioxane and 1,4-dioxane.

23.21 Draw 3-bromotetrahydrofuran and *cis*-2,5-diethyltetrahydro-2*H*-pyran.



Cyclic ethers are components of many natural products as well as synthetic compounds. A simple example is *erythritol anhydride* (2,2'-bioxirane), which contains the epoxide unit, and is used to prevent microbial spoilage. The important anticancer drug *taxol* contains an oxetane unit. The THF unit is a component of the important carbohydrate ribose that is the "sugar" portion of RNA (Sections 25.5,6). A THF unit is found in *isosorbide dinitrate* (Isordil), which is a vasodilator used in the prevention and treatment of angina. The tetrahydropyran unit is found in common sugars (e.g., *ribose, glucose*) and in *desosamine*, which is the sugar component of many macrolide antibiotics. Both the THF and tetrahydropyran units are found in the antibiotic *Lasalocid*.

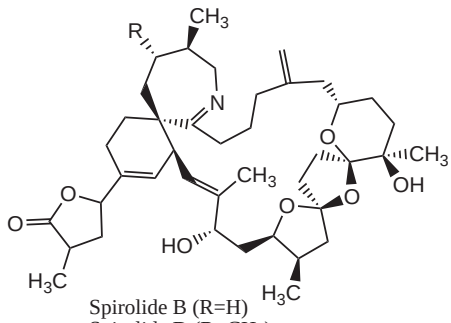
There are cyclic thioethers and the three-membered ring thioether is called thiirane, the four-membered ring thioether is called thietane, and the five-membered ring thioether is called thiolane (tetrahydrothiophene). Finally, the six-membered ring thioether is named thiane (tetrahydrothiopyran). A five-membered ring with two sulfur atoms is named 1,3-dithiolane. The six-membered ring compound with two sulfur atoms in a 1,3-relationship of the oxygen atoms is named 1,3-dithiane, whereas the isomer with a 1,4-relationship of the oxygen atoms is 1,4-dithiane.



23.22 Draw a series of reactions that prepare 2-benzyl-1,3-dithiane from benzene

Margaret Anne Brimble

Dame Margaret Anne Brimble (New Zealand) is a professor of organic chemist at the University of Auckland. Her research has focused on making and modifying naturally occurring bioactive compounds that have been isolated from plants, animal tissue, microbes, or marine and soil organisms. Her research includes the study of marine toxins, including the spirolides. The spirolides are a family of marine toxins isolated from mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*) from the eastern coast of Nova Scotia, Canada.



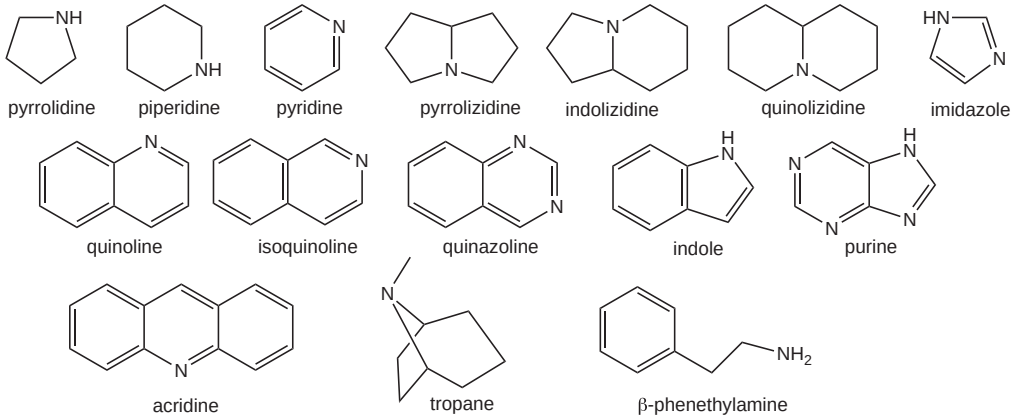
Spirolide B (R=H)
Spirolide D (R=CH_3)

The spirolides are metabolites of the marine dinoflagellate *Alexandrium ostenfeldii* that induce characteristic symptoms in the mouse bioassay and are weak activators of L-type transmembrane Ca^{2+} channels. Professor Brimble has reported the synthesis of key complex fragments of spirolides B and D.[12]

23.6 ALKALOIDS

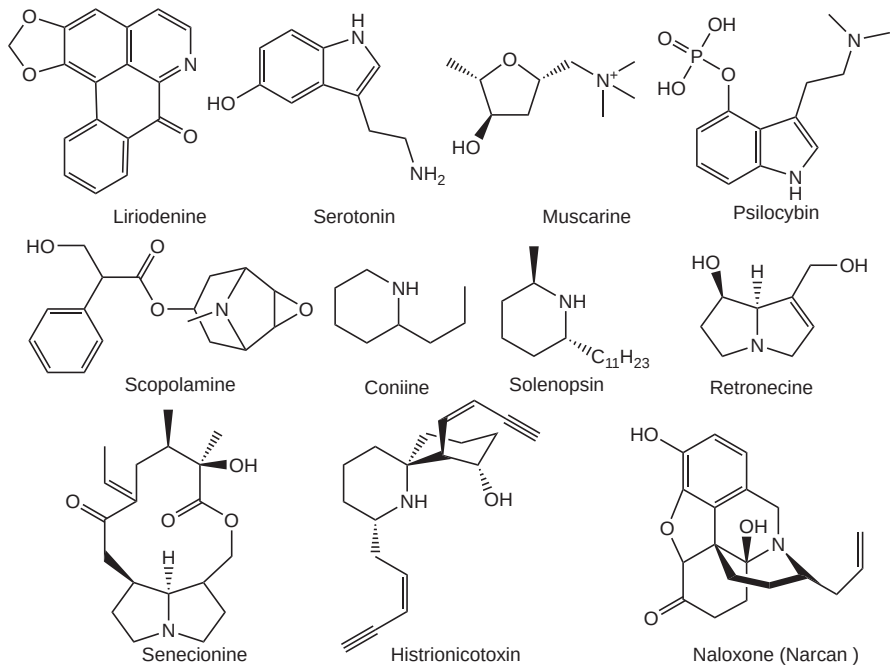
Alkaloids are a class of naturally occurring organic compounds produced by plants, fungi and animals that have at least one nitrogen and generally react as bases in acid-base reactions. However, some molecules related to alkaloids are neutral or even weakly acidic. Some compounds called alkaloids are prepared synthetically. Alkaloids have a wide range of pharmacological activities, and many are used in traditional or modern medicine. Alkaloids are also important leads for the development of new drugs. Many alkaloids possess psychotropic or stimulant activity or use as recreational drugs, and many are toxic. Several alkaloid structures were shown in preceding sections, including quinone, camptothecin, papaverine, lysergic acid, vincristine, vinblastine, and mitomycin C.

[12] Meilert, K.; Brimble, M.A. *Organic Letters* 2005, 7, 3497–3500.



Alkaloids can be divided into the several major groups. True alkaloids contain nitrogen in the heterocycle. Protoalkaloids contain nitrogen but not a nitrogen heterocycle. Polyamine alkaloids are long chain compound with several nitrogen atoms. Peptide and cyclopeptide alkaloids and pseudoalkaloids, which are alkaloid-like compounds that do not originate from amino acids. There are several types of alkaloids, categorized by the fundamental skeleton found in each class of alkaloids: pyrrolidine, piperidine, pyridine, pyrrolizidine, indolizidine, quinolizidine, imidazole, quinoline, isoquinoline, quinazoline, indole, purine, acridine, tropane, β-phenethylamine.

Most of the known functions of alkaloids are related to protection. For example, the aporphine alkaloid *liriodenine* protects tulip trees from parasitic mushrooms. The presence of alkaloids in the plant prevents insects and animals of the phylum *Chordata* from eating it. Many poison mushrooms contain toxic alkaloids such as *muscarine*, agaricine, or phalline. The main alkaloids in mushrooms with hallucinogenic properties are *psilocybin* and psilocin. *Atropa belladonna*, commonly known as belladonna or deadly nightshade, is a poisonous herbaceous plant that contains tropane alkaloids such as atropine, *scopolamine* and hyoscyamine. *Datura stramonium*, known by the common name jimson weed is a species of flowering plant in nightshade family Solanaceae also contains these tropane alkaloids. *Conium maculatum*, poison hemlock, is a highly poisonous herbaceous flowering plant in the carrot family *Apiaceae* that contains *coniine* and related poisonous alkaloids. A fire ant venom alkaloid called *solenopsin* protects the queen during the founding of new nests. The poison dart frogs are in the family *Dendrobatidae*, native to tropical Central and South America. These species often have brightly colored bodies that correlates with the toxicity of the species. The toxicity derives from their diet of ants, mites, and termites.



Many poison dart frogs secrete lipophilic alkaloid toxins such as allopumiliotoxin 267A, batrachotoxin, epibatidine *histrionicotoxin* and pumiliotoxin 251D through their skin that serve as a chemical defense against predation. North American populations of the monarch butterfly, *Danaus plexippus*, have been found to contain pyrrolizidine alkaloids and their N-oxides. Monarchs lay their eggs on milkweed and as the caterpillars eat the milkweed leaves, they ingest cardiac glycosides and then store the plant's toxic alkaloids such as *retronecine* (toxic to most animals) in their tissues. These alkaloids make the caterpillars and the adult monarch butterflies unpalatable to predators such as birds. The monarchs also contain senecionine, integerrimine, and seneciphylline, echinatine, and lycopsamine. Naloxone, sold as Narcan, is used to rapidly reverse an opioid overdose. Some animals use alkaloids in their own metabolism, such as *serotonin*, dopamine and histamine.

23.7 BIOLOGICAL RELEVANCE

Throughout this chapter, the presence of heterocyclic rings in medicines and other biologically relevant molecules such as alkaloids have been highlighted. Many biologically relevant heterocyclic compounds are discussed in Chapters 24 and 25. The biosynthesis of heterocyclic rings in biologically important molecules is widespread. *Thiamin* is an example, and it contains a thiazole ring as well as a pyrimidine ring and it is an essential component of the human diet. Thiamin is a water-soluble vitamin of the B complex (vitamin B_1). While humans cannot synthesize thiamin, many bacteria synthesize it and use it in the form thiamin pyrophosphate. *Bacillus subtilis* produces thiamin by a biosynthetic route, and it synthesizes the thiazole unit found in thiamin from the amino acid glycine (Section 24.3) and 1-deoxy-D-xylulose-5-phosophate.[13] (Section 25.1 for an introduction to sugars, e.g., xylulose).

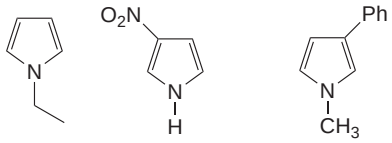
CORRELATION OF HOMEWORK WITH CONCEPTS

- Pyrrole is the five-membered ring heterocycle containing one nitrogen. There are two five-membered ring molecules with two nitrogen atoms, imidazole, and pyrazole. Furan is the five-membered ring heterocycle containing one oxygen. Thiophene is the five-membered ring heterocycle containing one sulfur. Pyran and thiopyran are the six-membered ring derivatives. Triazoles contain three nitrogen atoms: 1, 2, 6, 23, 24, 33.
- Pyridine is the six-membered ring heterocycle containing one nitrogen. Three six-membered ring molecules contain two nitrogen atoms, pyrazine, pyrimidine, and pyradazine. Triazines contain three nitrogen atoms and tetrazine contain four nitrogen atoms: 3, 4, 5, 7, 23, 24.
- Five-membered ring heterocycles containing one heteroatom are more reactive in S_EAr reactions and give substitution at C2: 8, 9, 10, 25, 30.
- Six-membered ring heterocycles containing one heteroatom are much less reactive than benzene (deactivated) in S_EAr reactions and give substitution at C3: 11, 12, 26, 34.
- Pyridine derivatives undergo S_NAr reactions: 16, 26.
- There are bicyclic aromatic and polycyclic compounds that contain one nitrogen: quinoline, isoquinoline and indole. Many other derivatives are known: 14, 15, 28.
- Quinoline and isoquinoline show electrophilic aromatic substitution reactions are the more reactive benzene ring since the "pyridine" ring is less reactive. Indole undergoes electrophilic aromatic substitution primarily in the pyrrole ring since it is much more reactive than the benzene ring: 16, 17, 18, 19, 29.
- There are many reduced heterocyclic compounds: 20, 21, 22, 27, 31, 32.
- Spectroscopy can be used to determine the structure of a particular molecule (Chapter 13): 35, 36, 37.

[13] Begley, T.P.; Downs, D.M.; Ealick, S.E.; McLafferty, F.W.; Van Loon, A.G.M.; Taylor, S.; Campobasso, N.; Chiu, H.-J.; Kinsland, C.; Reddick, J.J.; Xi, J. *Archives of Microbiology* **1999**, *171*, 293–300.

ANSWERS TO IN-CHAPTER QUESTIONS

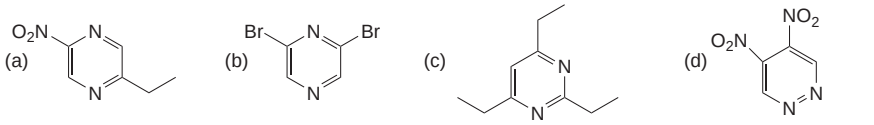
23.1



23.2

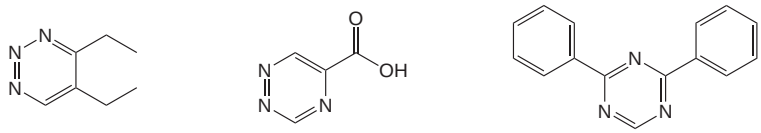
1,3-Dimethyl-(1H)-pyrazole 4-Bromo-2-ethyl-(1H)-imidazole

23.3



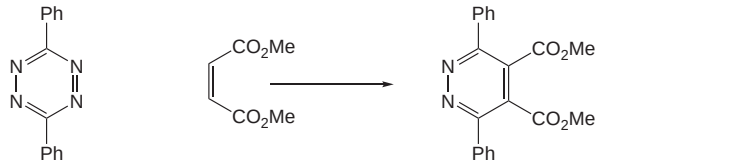
2-Ethyl-5-nitropyrazine 2,6-Dibromopyrazine 2,4,6-Triethylpyrimidine 4,5-Dinitropyridazine

23.4



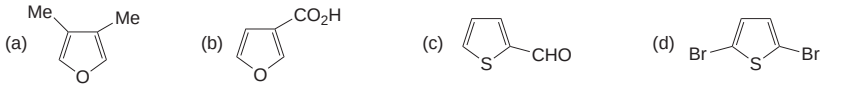
4,5-diethyl-1,2,3-triazine **1,2,4-triazine-5-carboxylic acid,** **2,4-diphenyl-1,3,5-triazine**

23.5



3,6-diphenyl-1,2,4,5-tetrazine dimethyl maleate dimethyl 3,6-diphenylpyridazine-4,5-dicarboxylate

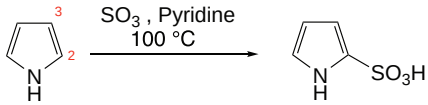
23.6



3,4-Dimethylfuran Furan-3-carboxylic acid Thiophene-2-carbaldehyde 2,5-Dibromothiophenene

23.7

23.8



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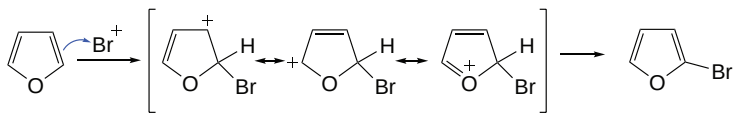

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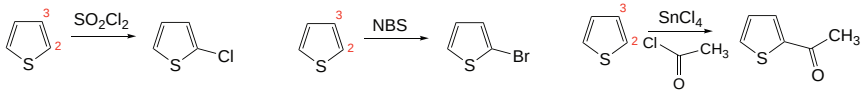

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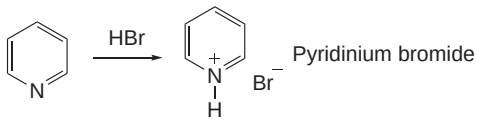
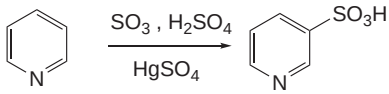
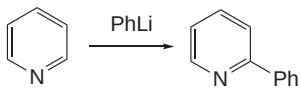


Pyridinium bromide

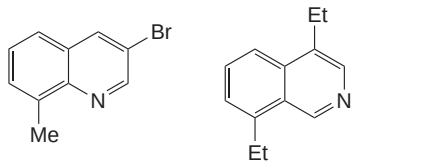
23.12



23.13

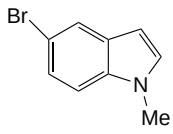


23.14



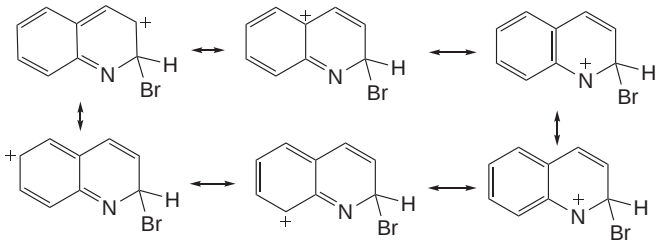
3-Bromo-8-methylquinoline 4,8-Diethylisoquinoline

23.15



5-Bromo-1-methyl-1H-indole

23.16



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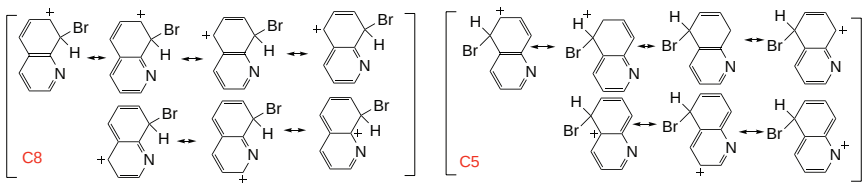

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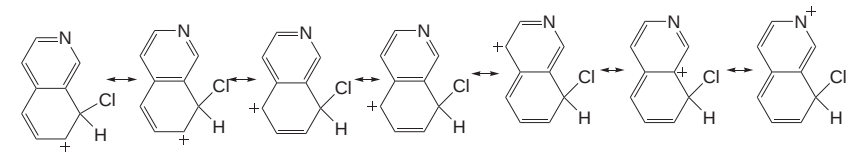

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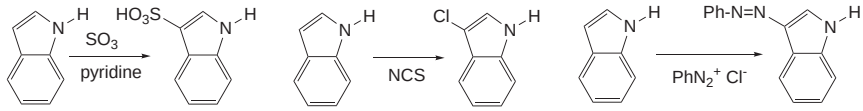

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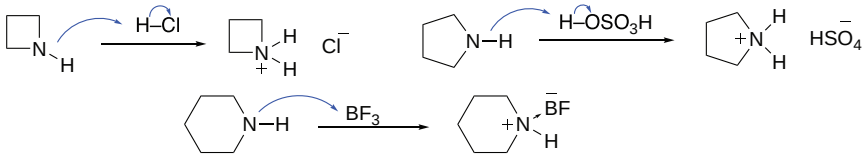
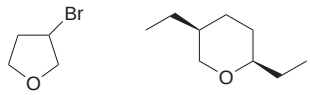


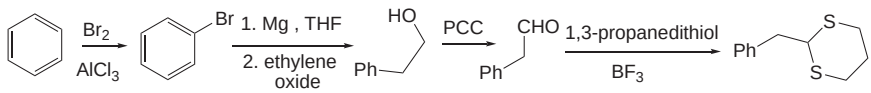
23.21

3-Bromotetrahydrofuran



2,5-Diethyltetrahydro-(2H)-pyran

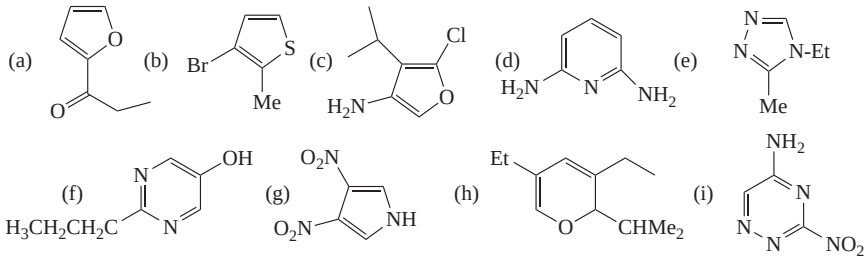
23.22



HOMEWORK

23. Draw the structures of each of the following molecules:
    (a) *N*,3-Dimethylpyrrole (b) 3,4-Diacetylpyrrole (c) 2,4-Dichloropyrazole
    (d) 1-Methyl-4-chloroimidazole (e) 2,4,6-Trimethylpyridine
    (f) 5-Aminopyrimidine
    (g) 3-Nitropyrazine (h) 3,5-Dibromopyradazine
    (i) 2-Amino-5-methylpyrimidine

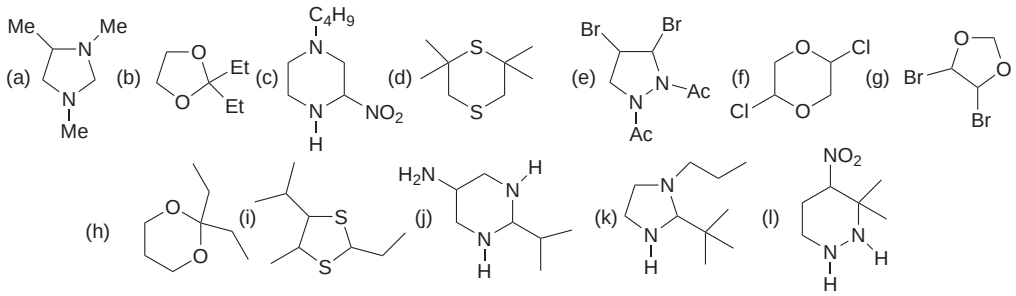
24. Give the IUPAC name for each of the following molecules:



25. Give the major product expected from each of the following reactions:
    (a) *N*-Methylpyrrole + HNO_3/acetic anhydride
    (b) 2-Methylimidazole + $SOCl_2$
    (c) *N*,5-Dimethylpyrazole + HNO_3/Ac_2O
    (d) Furan + 1. butanoyl chloride/$SnCl_4$ 2. $NaBH_4$ 3. hydrolysis
    (e) 3-Nitrofuran + SO_3/pyridine
    (f) Furan + 1. $NO_2^+BF_4^-$ 2. H_2/Pd–C
    (g) Furan + 1. dioxane-Br_2 2. Mg, THF 3. cyclohexanone 4. hydrolysis
    (h) 3-Ethylthiophene + SO_3/pyridine
    (i) Imidazole + 1. BuLi 2. benzyl bromide, THF 3. HNO_3/acetic anhydride

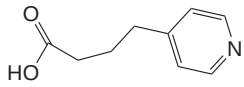
26. Give the major product for each of the following:
    (a) Pyrimidine + 1. Br_2/300 °C 2. PhLi, heat
    (b) Pyridine + 1. KNO_3/330 °C 2. H_2, Pd–C 3. propanoyl chloride, NEt_3
    (c) Pyridine + 1. Br_2/300 °C 2. $MeNH_2$, heat

27. Draw the structure for each of the following:
    (a) *N*-Acetyl-3-ethylimidazoline (b) 1,2,4,5-Tetramethylpiperazine
    (c) 3,5-Dibromotetrahydrofuran
    (d) *trans*-2,3-Dimethyl-1,4-dioxane (e) 1-Ethyl-4-nitropyrazolidine
    (f) *cis*-3,5-Dinitropiperidine
    (g) *N*-Propylaziridine (h) 2,3-Diethyloxirane (i) *N*,2-Diethylazetidine
    (j) 3-Chlorothiane (k) 2-Phenylthiirane (l) *cis*-2,3-Diphenyloxetane
28. Draw the structure for each of the following.
    (a) 4,6-Dibromoquinoline (b) 6-Methyl-7-nitroisoquinoline (c) 6-Ethylindole
    (d) 3-Butyl-5-nitroisoquinoline (e) 8-Chloroquinoline
    (f) 1-Methyl-7-cyanoindole
29. Give the major product for each of the following.
    (a) Quinoline + $Br_2/AlCl_3$ (b) 8-Methoxyquinoline + $Br_2/AlCl_3$
    (c) Isoquinoline + acetyl chloride/$AlCl_3$ (d) 5-Methylisoquinoline + SO_3/H_2SO_4
    (e) Indole + HNO_3/H_2SO_4 (f) 3-Methylindole + $Br_2/AlCl_3$
30. Suggest a reason why it is difficult to form 3-substituted furan derivatives.
31. Draw a structure for tetrahydrothiazole.
32. Give the correct IUPAC name for each of the following molecules:



33. Suggest a reason why the four-membered ring molecule shown is unknown.

34. Explain why an intramolecular Friedel–Crafts reaction based on the molecule shown is probably not a good way to make an isoquinoline derivative.



Spectroscopic problems. Do not attempt these problems until Chapter 13 is read and understood.

35. Describe differences in the ^{1}H NMR spectrum between pyrazine and pyrimidine.
36. Give the structure of this molecule given the following spectral data:
    MS: M (107) 100% M+1 (108) 8.14% M+2 (109) 0.3%. IR: 3096-2870, 1603, 1571, 1492, 1453, 1380, 1032, 817, 727, 647, 641, 485 cm^{-1}. ^{1}H NMR: 8.31 (d, 1H), 7.35 (d, 1H), 7.02 (d, 1H), 2.5 (s, 3H), 2.26 (s, 3H) ppm.
37. Give the structure of this molecule given the following spectral data: The formula is C_6H_8O.
    IR: 3116, 2975-2850, 1697, 1509, 1454, 1089, 1006, 729 cm^{-1}. ^{1}H NMR: 7.28 (d, 1H), 6.26 (m, 1H), 5.96 (d, 1H), 2.63 (q, 2H), 1.22 (t, 3H) ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-24.php

24

Multifunctional Compounds

Amines, Amino Acids and Peptides

The structure and nomenclature of amines was introduced in Section 5.5.3. Amines have been used as bases in many portions of this text, but there has been little discussion for the preparation of amines. Some molecules contain both an amine and a carboxyl group, the amino acids. Poly(amino acids) are linked by amide bonds. Amide bonds are known as peptide bonds in peptides and enzymes.

To begin this chapter, you should know the following topics:

- Amines (Section 5.3).
- Aldehydes and ketones (Sections 5.6.2 and 16.1–16.4).
- Carboxylic acids (Sections 5.6.3, 18.1, and 18.2).
- Carboxylic acid derivatives (Sections 18.2–18.9).
- Heterocyclic compounds (Sections 23.2–23.4).
- Rotamers and conformations (Sections 8.1–8.3 and 8.5).
- Transition states and reaction energetics (Sections 7.4–7.6).
- Acyl addition reactions (Sections 16.2–16.4).
- Acyl substitution reactions (Sections 18.4–18.6 and 18.11)
- Substitution reactions (Sections 11.2–11.3, 11.5–11.6).
- Acid-base reactions (Section 6.2–6.7).
- Isomers (Section 4.2.2).
- Absolute configuration (Sections 9.1–9.3).
- (*E*) and (*Z*)-isomers (Section 9.8).
- Oxidation reactions (Sections 15.1–15.5).
- Reduction reactions (Sections 17.2–17.5).

24.1 REACTIONS THAT FORM AMINES

The fundamental structure and nomenclature of amines was introduced in Section 5.5.3. The nitrogen atom of an amine may have one, two, or three carbon groups attached to give primary amines, secondary amines, and tertiary amines, respectively. There are three important methods for making amines. Ammonia and amines react with an alkyl halide via a S_N2 process. An amine reacts with an aldehyde or ketone under reducing conditions to give a different amine via an acyl addition-reduction process. Amines are formed by the formal reduction of nitrogen-containing functional groups. Aromatic amines were discussed in Sections 19.4.4, 19.10, and 19.11 and the reactions of aniline and derivatives are not repeated here.

When 1-bromobutane is heated with ammonia, an initial S_N2 reaction gives butan-1-ammonium bromide (Section 22.2.3 and 11.3). This ammonium salt is a weak acid and reacts further with the basic ammonia to give butan-1-amine. After one half-life both ammonia and butan-1-amine are present, and butan-1-amine reacts with bromobutane faster than does ammonia to give *N*-butylbutan-1-ammonium bromide and then *N*-butylbutan-1-amine. *N*-Butylbutan-1-amine reacts further so secondary and tertiary amine products are often observed as minor constituents. This *overalkylation* process is particularly difficult to stop when reactive halides iodomethane are used. With iodomethane, overalkylation is called

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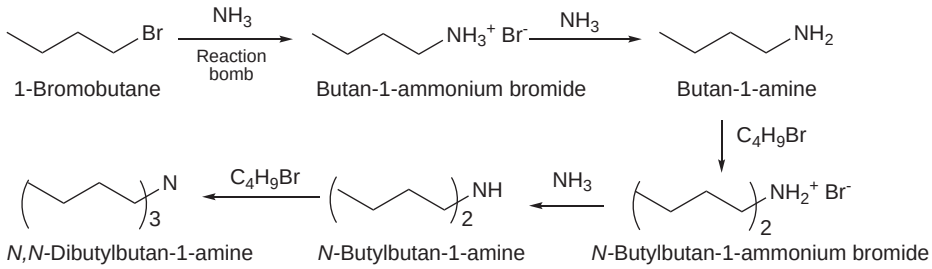
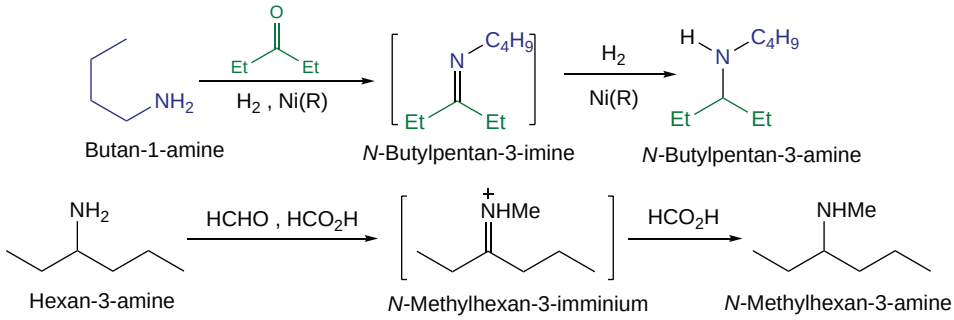
Amines With Alkyl Halides

exhaustive methylation. Overalkylation is not as much of a problem in reactions with more substituted alkyl halides.



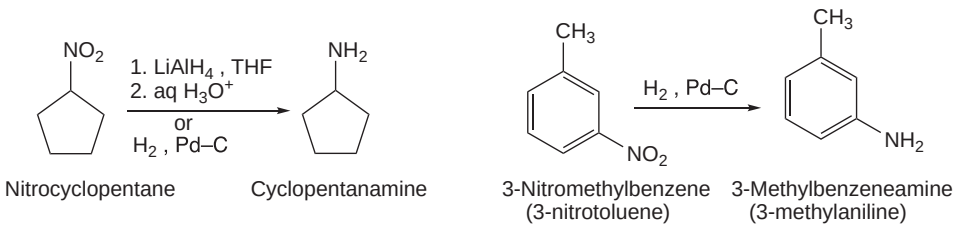
24.1 Draw and name the product formed when pyridine is treated with an excess of iodomethane; when butan-1-amine is similarly treated.

The reaction of butan-1-amine reacts and pentan-3-one in the presence of Raney nickel [Ni(R)] and hydrogen gas gives *N*-butylpentan-3-amine. The initial product is an imine (Section 16.4.3) and in situ hydrogenation gives the amine in a process called *reductive amination*. The reaction of an aldehyde or ketone with a primary amine on the presence of zinc metal (Zn°) and HCl also gives reductive amination. A variation of reductive amination gives *N*-methyl amines by heating formic acid with an amine and formaldehyde. Hexan-3-amine reacts with formaldehyde and formic acid to gives the iminium salt in situ. Formic acid converts the iminium salt to *N*-methylhexan-3-amine. This latter sequence is called the *Eschweiler-Clarke reaction*, named after Wilhelm Eschweiler (Germany; 1860–1936) and Hans Thacher Clarke (England; 1887–1972).



24.2 Draw the product of a reaction between butan-2-amine and phenylacetaldehyde, in the presence of hydrogen gas and Ni(R).
24.3 Draw the product of a reaction between 3-phenylbutan-2-amine and a mixture of formaldehyde/formic acid.

Amine Surrogates



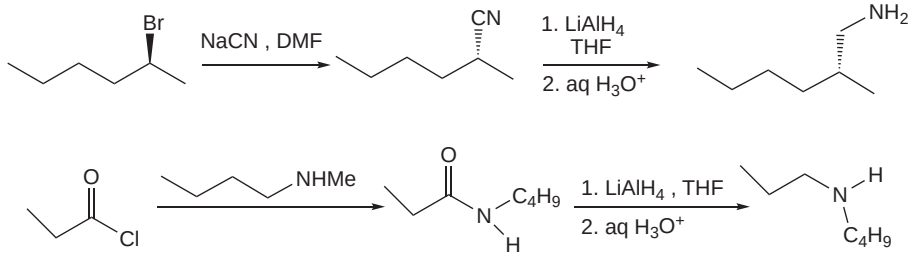
There are several nitrogen-containing functional groups known as amine surrogates that can be reduced to give amines. A nitroalkane can be formed a by direct substitution of

hydrocarbons with nitric acid, by displacement reactions with nitrite ions, or by oxidation of primary amines. Aromatic nitro groups are best incorporated by a S_EAr reaction using nitric acid/sulfuric acid (Section 19.3.1). The nitro group of a nitroalkane is reduced to an amine by catalytic hydrogenation or by reaction with lithium aluminum hydride ($LiAlH_4$, Section 17.2). Nitrocyclopentane, for example. reacts with $LiAlH_4$ or with H_2/Pd–C to give cyclopentanamine. Aromatic nitro compounds are *not* reduced to an amine with $LiAlH_4$ but rather to a diazo compound, Ar–N=N–Ar. Catalytic hydrogenation of 3-nitrotoluene gives 3-methylaniline (3-methylbenzeneamine).

24.4 Write out a preparation of *N*,4-dimethylaniline from toluene.

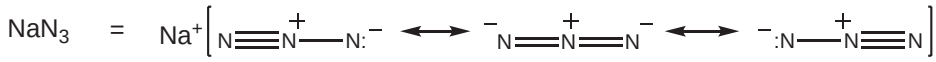
The cyanide ion, $N{\equiv}C^-$, is the conjugate base of hydrocyanic acid (HCN, pK_a, 9.31). In Section 11.3, sodium cyanide or potassium cyanide were shown to react via a S_N2 reaction with alkyl halides to give a nitrile. Reduction of the –C≡N unit in a nitrile will give a $–CH_2NH_2$ unit, a primary amine. The S_N2 reaction of (2*S*)-bromohexane with NaCN in DMF, for example, affords (2*R*)-methylhexanenitrile. Subsequent reduction with $LiAlH_4$ gives a primary amine, (2*R*)-methylhexan-1-amine.

More Amine Surrogates



Carboxylic acids are readily converted to an amide by reaction of the corresponding acid chloride or ester with ammonia or an amine (Section 18.8). Reduction of the amide with $LiAlH_4$ removes the carbonyl oxygen to give an amine. 3-Ethylpropanoyl chloride, for example, reacts with *N*-methylbutan-1-amine to give *N*-butyl-3-ethylpropanamide. Reduction with $LiAlH_4$ gives *N*-propylbutan-1-amine after neuralization of the reaction. This approach is flexible relative to other methods since primary, secondary or tertiary amines can be prepared depending on the substitution pattern of the amide nitrogen.

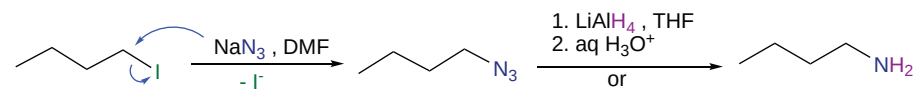
24.5 Draw a synthesis of 2-phenethylhexan-1-amine from hexan-2-one.



Sodium azide

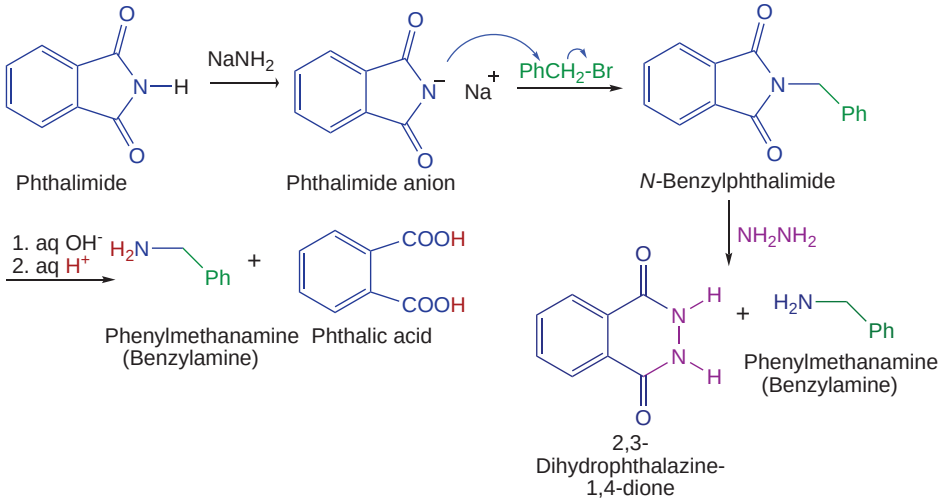
The azide ion in sodium azide (NaN_3) is a resonance stabilized nucleophilic species as shown. A S_N2 reaction with an alkyl halide (RX) affords an alkyl azide, RN_3. Azides are reduced to the corresponding primary amine. Sodium azide reacts with 1-iodobutane, for example, to give 1-azidobutane. Reduction with either $LiAlH_4$ or with hydrogen gas and a palladium catalyst gives butan-1-amine. Care should be exercised any time an azide is involved because many alkyl azides are unstable.

24.6 Write out a synthesis of *N*-benzoylpentan-(2*R*)-amine from (2*S*)-bromopentane.



1-Iodobutane 1-Azidobutane Butan-1-amine

Phthalimide (isoindoline-1,3-dione) is an imide derived from phthalic acid (Section 18.10). The N–H unit of phthalimide is a weak acid so reaction with a strong base (e.g., butyllithium or sodium amide) generates the phthalimide anion as the conjugate base. The phthalimide anion is a good nucleophile in S_N2 reactions with alkyl halides. Reaction with benzyl bromide gives *N*-benzylphthalimide via a straightforward S_N2 displacement.



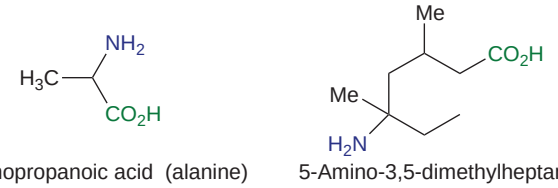
Hydrolysis of the imide by reaction with aqueous base followed by aqueous acid affords phenylmethanamine (benzylamine) and phthalic acid after neutralization. A *better* procedure treats *N*-benzylphthalimide with hydrazine (NH_2NH_2) to give benzylamine and 2,3-dihydrophthalazine-1,4-dione. This latter product is called a *hydrazide* and it is easily separated from the amine. Hydrazides will not be discussed further.

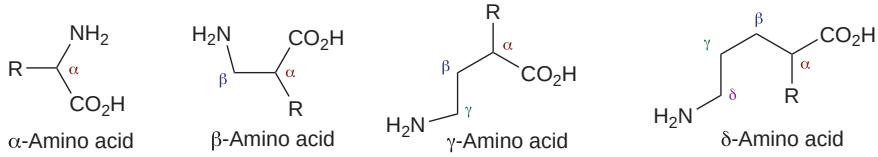
Amino Acids

24.7 Draw a reaction sequence that prepares pentan-(2*S*)-amine from (2*R*)-bromopentane.

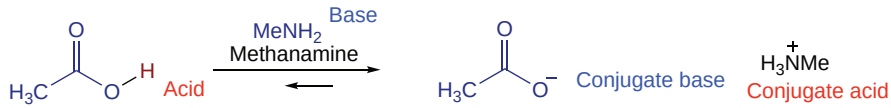
24.2 AMINO ACIDS

Amino acids are difunctional compounds as the name implies with an amine unit ($-NR_2$) and a carboxyl group, COOH in the same molecule. The nomenclature uses the parent acid as the base name and treats the NR_2 unit as a substituent. Two examples are 2-aminopropanoic acid (known as alanine) and 5-amino-3,5-dimethylheptanoic acid. Structural variations for amino acids focus on the carbon bearing the amino group relative to the carbonyl carbon. If the amine unit is attached to C2 of the carboxylic acid chain, the α-carbon, it is an *α-amino acid*. If the amine group is on C3, the β-carbon, it is a *β-amino acid*. Similarly, there are *γ-amino acids*, *δ- amino acids*, and so on. To distinguish α-amino acids from other amino acids, the term *non-α-amino acids* is used. 5-Amino-3,5-dimethylheptanoic acid is an example of a non-α-amino acid.





24.8 Draw the structure of (a) 2-aminomethyl-2-phenylpentanoic acid, (b) 1-amino-3, 3-diethylcyclobutane-1-carboxylic acid, (c) 1-aminocyclohexane-1-carboxylic acid, and (d) *cis*-3-aminocyclohexane-1-carboxylic acid.



Both an amine and a carboxylic acid are mono-functional compounds. An amine reacts as both a base and a nucleophile. The carboxyl group in a carboxyl acid reacts as a Brønsted-Lowry acid. If methanamine and acetic acid are mixed together, for example. the product is methylammonium acetate in a normal acid-base reaction. An amino acid has both functional groups, and the acid-base reaction is intramolecular. In an amino acid such as alanine, the amine reacts with the carboxylic acid unit under neutral conditions to give a *zwitterion* product, 2-ammoniopropanoate.

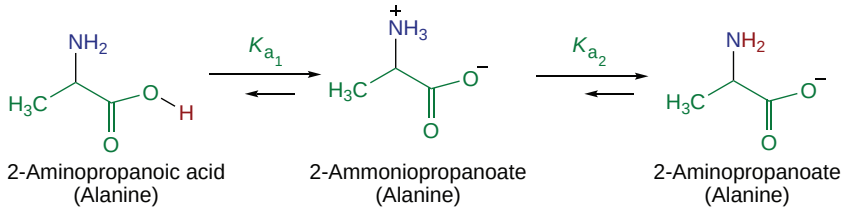
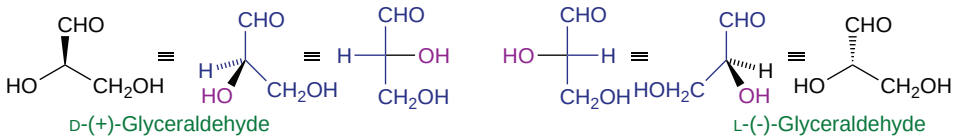


FIGURE 24.1 Internal acid–base reaction of an amino acid.

The equilibrium constant for this internal acid-base reaction is labeled *K*a1, as shown in Figure 24.1. 2-Ammoniopropanoate is an ammonium salt and therefore a weak acid. A second acid-base reaction labeled K_{a2} is possible to convert the ammonium carboxylate to the amine carboxylate (2-ammoniopropanoate). As with other acid-base reactions, p*K* values are used to evaluate acidity in amino acids rather than the values of K_{a1} or K_{a2}. The value of pK_{a1} and pK_{a2} depends on the nature of the substituents attached to the α-carbon of the amino acid.

All acid-base reactions of an amino acid are equilibrium reactions. One of the species in that equilibrium is the *neutral* zwitterion. The point in the equilibrium when this *neutral* species is formed is the *isoelectric point, pI*, defined as the pH at which the compound carries no net electrical charge. The isoelectric point is $pI = \frac{pK_{a_1} + pK_{a_2}}{2}$. Once pK_{a1} and pK_{a2} are experimentally determined for any amino acid the isoelectric point can be determined. Figure 24.2 shows the change in pH for an amino acid as base is added and the isoelectric point, pK_{a1} and pK_{a2} are marked. Different amino acids have different groups on the α-carbon of an amino acid, so each amino acid may have a *different* pK_{a1} value and a different isoelectric point. In principle, there are an infinite number of α-amino acids that vary as the groups attached to the α-carbon change, but only about 20 α-amino acids are important in proteins and enzymes. Most of these α-amino acids are chiral molecules inasmuch as the α-carbon is a stereogenic center.



Emil Fischer (Germany; 1862–1919) devised a system based on the chiral molecule glyceraldehyde to identify the absolute configuration of enantiomeric amino acids. The Fischer projection (Section 9.1) of (+)-glyceraldehyde, which is (2*R*),3-dihydroxypropanal, is drawn as with the CHO unit on "top" and the OH unit on the "right." In this view, the OH unit is on the right (dextera in *Latin*) and Fischer called this a D-configuration. Therefore, (2*R*),3-dihydroxypropanal is D-(+)-glyceraldehyde. The Fischer projection of (2*S*),3-dihydroxypropanal has the OH unit on the left (sinister or sinistram in Latin), so it is an

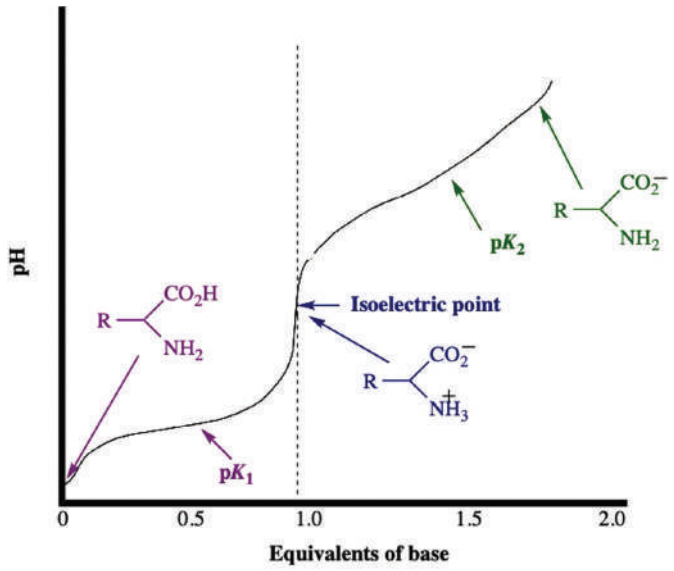
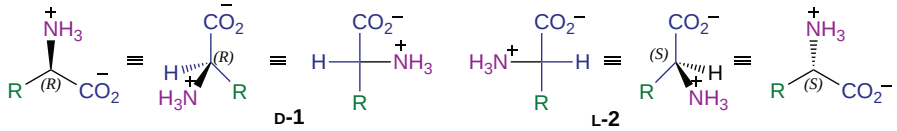


FIGURE 24.2 The position of p*K* and isoelectric points for a generic amino acid.

L-configuration. (2*S*),3-Dihydroxypropanal is L-(-)-glyceraldehyde. In 1951 Johannes Martin Bijvoet (Netherlands; 1892–1980) showed by X-ray analysis that Fischer's assignments are correct. The absolute configuration of α-amino acids is identified using D- or L-glyceraldehyde as reference compounds. The Fischer projection of the (*R*)- and (*S* enantiomers are **D-1** and **L-2**, respectively, where the COOH unit is on the "top" just as the CHO unit is on top in glyceraldehyde. If the NH_3 unit is drawn on the "right" in the Fischer projection it is a D-amino acid (**D-1**), whereas an L-amino acid has the NH_3 unit on the left (**L-2**). Virtually all of 20 amino acids found most often in proteins and enzymes are L-amino acids with structure **L-2**.



Twenty α–Amino Acids

24.9 Draw both D- and L-2-aminohexanoic acid in Fischer projection.

Table 24.1 shows the structure of 20 protein amino acids based on **L-2** and the name of the amino acid. Both a *three-letter code* and *a one-letter code* are listed in the table. These codes are used to abbreviate each amino acid. There are three categories of substituent in **L-2**: R is neutral, R has an acidic group or R has a basic group. The R in one category of neutral amino acids is a simple alkyl fragment. This group includes *glycine* (R = H), *alanine* (R = Me), *valine* (R = isopropyl; $CHMe_2$), *leucine* (R = isobutyl), *isoleucine* (R = *sec*-butyl), and *phenylalanine* (R = benzyl; CH_2Ph). Amino acids with a neutral substituent also include *serine* (R = CH_2OH), *threonine* (R = CH[OH]Me) and *tyrosine* (R = CH_2-[4-OH]phenyl). *Cysteine* (R = CH_2SH) bears a thiol unit and *methionine* (R = CH_2CH_2SMe) bears a methylthio unit. Note that the presence of the SH in cysteine leads to an (*R*)-absolute configuration in **L-2**. Two neutral amino acids have an amide unit as part of the side chain: *asparagine* (R = CH_2CONH_2) and *glutamine* (R = $CH_2CH_2CONH_2$).

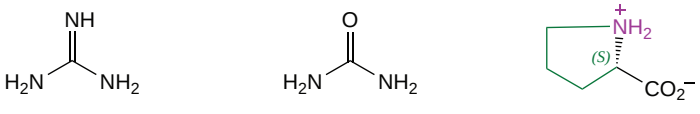


TABLE 24.1 Structures and Names of the 20 Amino Acids Found in Proteins Based on Structure L-2

C2 Substituent	Name	Three-Letter Code	One-Letter Code
H	Glycine	gly	G
Me	Alanine	ala	A
$CHMe_2$	Valine	val	V
$CHMe_2$	Leucine	leu	L
CH(Me)Et	Isoleucine	ile	I
CH_2Ph	Phenylalanine	phe	F
CH_2OH	Serine	ser	S
CH(OH)Me	Threonine	thr	T
CH_2(4-hydroxy-C_6H_4)	Tyrosine	tyr	Y
CH_2SH	Cysteine	cys	C
CH_2CH_2SMe	Methionine	met	M
CH_2CONH_2	Asparagine	asn	N
$CH_2CH_2CONH_2$	Glutamine	gln	Q
CH_2COOH	Aspartic acid	asp	D
CH_2CH_2COOH	Glutamic acid	glu	E
$CH_2CH_2CH_2CH_2NH_2$	Lysine	lys	K
CH_2(2-indolyl)	Tryptophan	trp	W
CH_2(4-imidazolyl)	Histidine	his	H
$CH_2NHC(=NH)NH_2$	Arginine	arg	R
2-Pyrrolidinyl	Proline	pro	P

Acidic amino acids have a carboxyl group (COOH) as part of the side chain. These include *aspartic acid* (R = CH_2COOH) and *glutamic acid* (R = CH_2CH_2COOH). Note that asparagine is the amide derivative of aspartic acid, and that glutamine is the amide derivative of glutamic acid. There are several amino acids with basic side chains where the R group in **L-2** has an amine unit. *Lysine* [R = $(CH_2)_4NH_2$] has a primary amine substituent, *tryptophan* (R = CH_2-indole) has the indole unit, and *histidine* (R = CH_2-imidazoyl) has an imidazoyl unit. *Arginine* [R = $(CH_2)NHC(=NH)NH_2$] has a guanidinyl unit. The *guanidinyl* unit is the imine derivative of *urea*. *Proline* is unique because it has a pyrrolidine ring and it is the only α-amino acid with a secondary amine unit.

Each of the 20 amino acids has unique pK_a values and different isoelectric points. Table 24.2 shows the name of the amino acid, pK_{a1}, pK_{a2} and each isoelectric point.[1] For amino

TABLE 24.2 The p*K* Values of Amino Acid at the Isoelectric Point in Water at 25 °C

Amino Acid	pK_{a_1}	pK_{a_2}	Isoelectric Point	pK_{a_3}
Glycine	2.34	9.60	5.97	
Alanine	2.34	9.69	6.00	
Valine	2.32	9.62	5.96	
Leucine	2.36	9.60	5.98	
Isoleucine	2.36	9.60	6.02	
Phenylalanine	1.83	9.13	5.48	
Serine	2.21	9.15	5.68	
Threonine	2.09	9.10	5.60	
Tyrosine	2.20	9.11	5.66	10.07
Cysteine	1.96	10.28	5.07	8.18
Methionine	2.28	9.21	5.74	
Asparagine	2.02	8.80	5.41	
Glutamine	2.17	9.13	5.65	
Aspartic acid	1.88	9.60	2.77	3.65
Glutamic acid	2.19	9.67	3.22	4.25
Lysine	2.18	8.95	9.74	10.53[a]
Tryptophan	2.83	9.39	5.89	
Histidine	1.82	9.17	7.59	6.00[a]
Arginine	2.17	9.04	10.76	12.48[a]
Proline	1.99	10.60	6.30	

a This pK_{a_3} value is for the ammonium salt of the amine side chain.

[1] *CRC Handbook of Chemistry and Physics*, 94th ed., CRC Press, Boca Raton, FL, 2014, pp. 7–1 to 7–2.

acids with acidic and with basic side "R" groups, another acid-base reaction is possible in the equilibrium. Those amino acids have a third p*K* value, pK_{a3}. For glutamic acid, pK_{a3} is for the reaction of the COOH side chain shown in Figure 24.3. For tyrosine pK_{a3} is for the reaction of

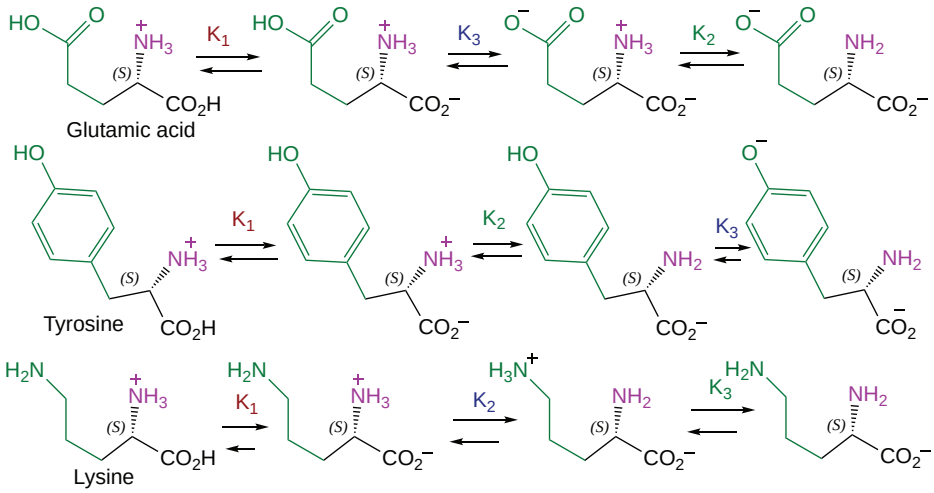


FIGURE 24.3 The K_a equilibria for glutamic acid, tyrosine and lysine.

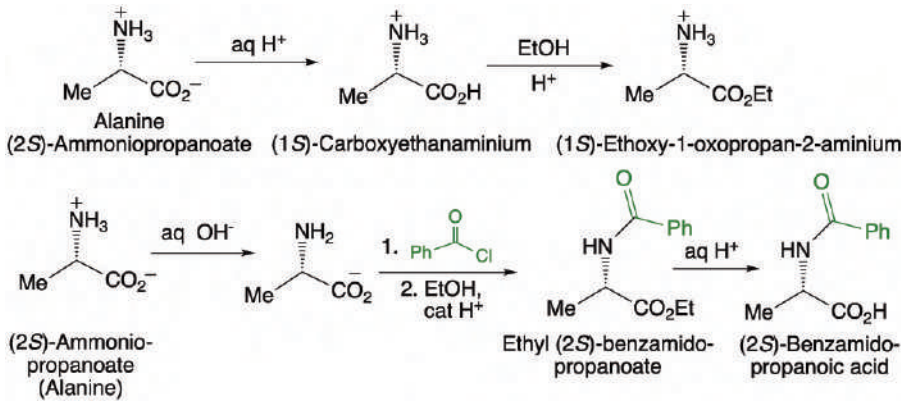
the acidic OH unit. When there is a basic side chain, as in lysine, pK_{a3} is for the ammonium salt of the amine unit on the side chain.

Reactions of Amino Acids

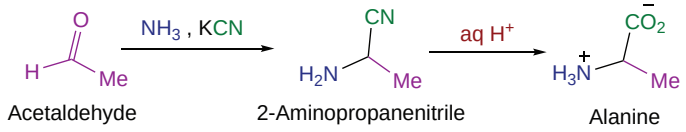
24.10 Write out the complete p*K* equilibrium for histidine, as was done for lysine.

24.3 REACTIONS AND SYNTHESIS OF α-AMINO ACIDS

Both the amine and the carboxyl of an amino acid undergo chemical reactions that are expected for each group. The conversion of a simple carboxylic acid to an ester, for example is straightforward. Protonation of alanine generates the protonated form, (1*S*)-carboxyethanaminium. Subsequent reaction with aqueous ethanol and an acid catalyst affords alanine ethyl ester [(1*S*)-ethoxy-1-oxopropan-2-aminium]. Alternatively, conversion of the acid to an acid chloride and subsequent reaction with an alcohol gives the ester. Conversion of an amino acid to an amine carboxylate, allows reaction with an acid chloride (e.g., benzoyl chloride) to give the amide. Subsequent reaction with an acidic solution of ethanol will afford the amide-ester, *N*-benzyl alanine ethyl ester [ethyl (2*S*)-benzamidopropanoate]. Aqueous acid hydrolysis of the ester group yields the amide–acid, *N*-benzyl alanine [(2*S*)-benzamidopropanoic acid].

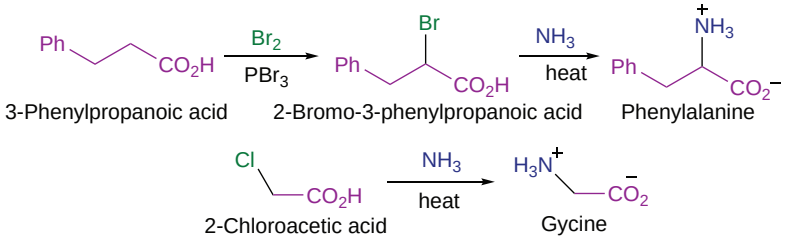


24.11 Write out a sequence that converts valine to its benzyl ester.

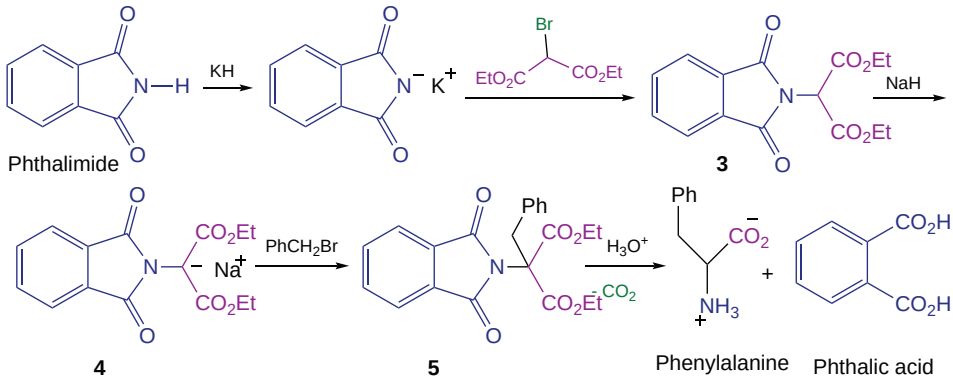


Amino acids are synthesized by several methods to give *racemic* amino acids. Methods are known that produce amino acids highly enriched in one enantiomer, but they use reactions not discussed in this book. Adolph Strecker (Germany; 1822–1871) reported one of the first syntheses of an amino acid and the method bears his name, the *Strecker synthesis*. Heating an aldehyde with ammonia and KCN gives an amino nitrile. Acid hydrolysis of the nitrile unit affords an amino acid. In a specific example, acetaldehyde is heated with ammonia and KCN to yield 2-aminopropanenitrile. Treatment with aqueous acid gives alanine. Many different amino acids can be prepared by this method, but they are racemic.

The reaction of bromine and phosphorus tribromide with a carboxylic acid that has an α-hydrogen gives an α-bromo acid in a reaction known as the *Hell-Volhard-Zelenskii reaction*. This reaction was named for the work of C. Hell, Nikolai D. Zelinskii (Russia; 1861–1953), and J. Volhard. The reaction of 3-phenylpropanoic acid with these reagents gives 2-bromo-3-phenylpropanoic acid. Subsequent heating with ammonia, followed by neutralization of the product yields the amino acid, phenylalanine. This route was used as early as 1858 to prepare glycine by the reaction of chloroacetic acid and ammonia. Amine surrogates such as azides can similarly be used in the synthesis of amino acids.



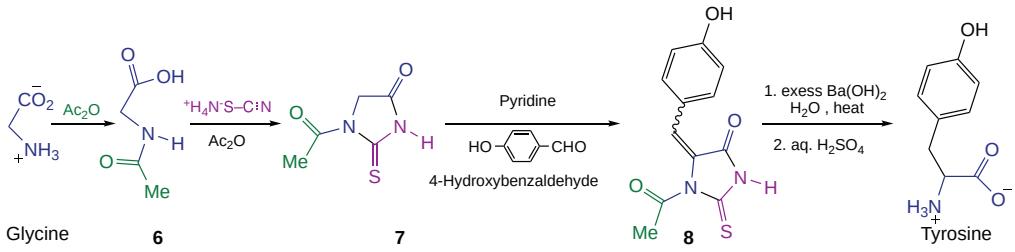
24.12 Prepare 2-amino-2-methyl-3-phenylpropanoic acid from 1-phenylpropan-2-ol.
24.13 Prepare 2-amino-2-cyclopentylethanoic acid from 1-(bromomethyl) cyclopentane.



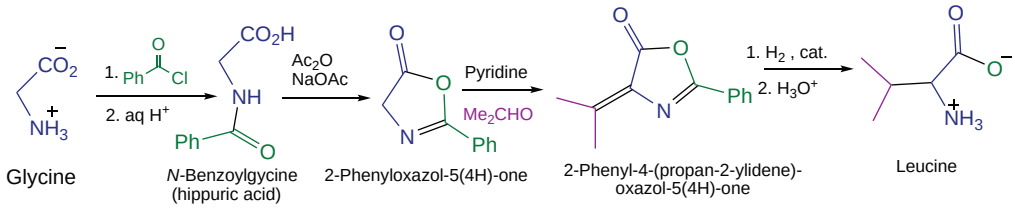
An amine surrogate such as phthalimide can be used in the synthesis of amino acids. If diethyl malonate is treated with bromine/PBr_3, diethyl 2-bromomalonate is readily formed. Reaction of this α-bromo ester with the phthalimide anion affords **3**. The

reaction of **3** with a base gives enolate anion **4**, which reacts with a benzyl bromide to yield **5**. Heating **5** with aqueous NaOH followed by aqueous HCl gives phthalic acid and racemic phenylalanine.

24.14 Write out a complete synthesis of tyrosine using this approach with the appropriate alkyl halide and show a synthesis of the requisite halide from phenol.



One amino acid can be converted to another by conversion to a heterocyclic compound via alkylation at the α-carbon. If glycine is treated with acetic anhydride, the product is *N*-acetyl glycine, **6**. Subsequent reaction with ammonium thiocyanate and acetic anhydride gives an imidazolidinone, otherwise known as a *thiohydantoin* (1-acetyl-2-thioxoimidazolidin-4-one), **7**. The methylene unit in **7** is converted to an enolate anion by reaction with base, allowing condensation reactions with aromatic aldehydes. The reaction of 4-hydroxybenzaldehyde with the enolate anion of 3-acetyl-2-aminothiazolidin-5-one gives a new thiohydantoin (**8**). Heating **8** with barium hydroxide in water and neutralization with aqueous sulfuric acid gives the racemic amino acid, tyrosine.



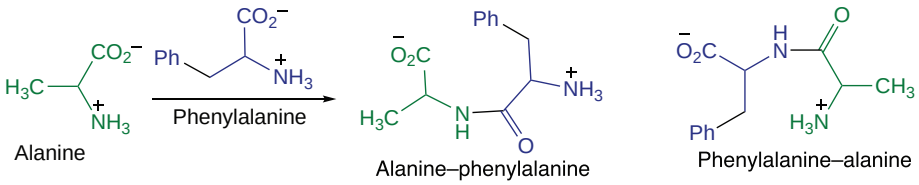
The *azlactone synthesis* is another amino acid synthesis. Glycine is converted to *N*-benzoyl glycine (*hippuric acid*) by reaction with benzoyl chloride. Subsequent treatment with acetic anhydride (Ac_2O) gives 2-phenyloxazol-5(4*H*)-one, an azlactone. This oxazolone has the common name of *hippuric acid azlactone*. The methylene unit in 2-phenyloxazol-5(4*H*)-one is converted to an enolate anion that will react with aldehydes. Therefore, reaction of 2-methylpropanal with pyridine yields a new azlactone, 2-phenyl-4-(propan-2-ylidene)oxazol-5(4*H*)-one. Catalytic hydrogenation of the alkene unit and acid hydrolysis of the lactone unit give the amino acid leucine.

24.15 Write out the synthesis of tryptophan from the appropriate indole aldehyde using the thiohydantoin method.
24.16 Write out an azlactone synthesis of phenylalanine using the appropriate aldehyde.

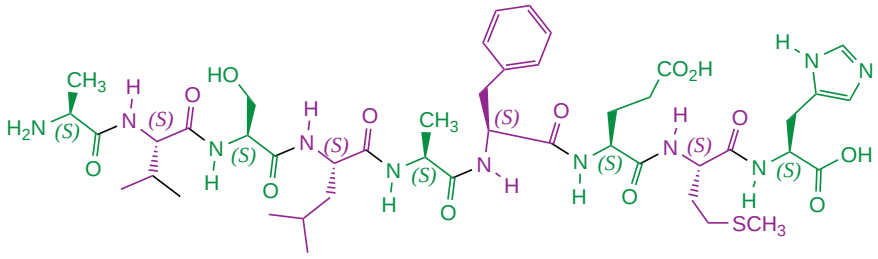
Peptides and Proteins

24.4 BIOLOGICAL RELEVANCE: PEPTIDES

Two amino acids may be coupled together to form an amide, but there are two possible products. An example is the reaction of alanine with phenylalanine where coupling may generate either the alaninyl-phenylalanine or phenylalaninyl-alanine. Compounds that contain several amide bonds are known as polyamides.



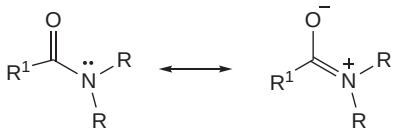
Long chain polyamides found in biological systems are called *peptides*. The amide bonds within the peptide are called *peptide bonds*. The amino acid components of a peptide are known as *amino acid residues*, so ala-phe and phe-ala are dipeptides with two amino acid residues. A peptide with three amino acid residues is a tripeptide and a peptide with 15 amino acid residues is called a pentadecapeptide. Large peptides (hundreds or thousands of amino acid residues) are known.



Alanine–valine–serine–leucine–alanine–phenylalanine–glutamic acid–methionine–histidine

As more amino acids are coupled together, drawing and naming the polypeptide becomes increasingly difficult. An example is the nonapeptide alanine-valine-serine-leucine-alani ne-phenylalanine-glutamic acid-methionine-histidine reading from left to right, all (*S*)-amino acids. To facilitate communicating the structure of this and all peptides, a shorthand notation assigns the three-letter code or the one-letter code to each amino acid residue (see Table 24.1). Using the three-letter code, this nonapeptide is ala-val-ser-leu-ala-phe-glu-met-his, and it is A-V-S-L-A-F-E-M-H using the one-letter code. Closer examination of ala-val-ser-leu-ala-phe-glu-met-his shows that the carboxyl group is on the right side in histidine, *the carboxyl terminus or C-terminus*. There is an amino group at the left side in alanine, *the amino terminus or N-terminus*) By convention, in peptides the *N*-terminus is written and drawn on the left and the *C*-terminus is drawn on the right.

24.17 Write the primary structure of a peptide in three-letter code if the one-letter code is S-S-L-N-C-D-G-A-F-W-H.



The connectivity of the amino acids in a peptide is called the *primary structure*. The amide bond that connects two amino acid residues is called a peptide bond. This amide bond is essentially planar inasmuch it has two resonance structures. One resonance contributor is a carboxamide unit and the other is an alkoxy-iminium salt unit as shown. These structures are observed in the IR spectrum of amides as the amide I and amide II bands at 1640 cm^{-1} (C—O stretch) and 1650–1515 cm^{-1} (imine N—H bend). The peptide bond therefore has partial double bond character and there is no rotation about the O=C—N bond. Only the alpha carbons in a peptide backbone can potentially rotate around their bond axes. In a peptide, the rotational angle ψ is the angle defined by rotation about the C^{α}—C=O bond. The rotational angle Φ is for rotation about the C^{α}—N bond. The alkyl groups on the α-carbon in each amino acid residue have a significant influence on the magnitude of angles ψ and Φ, which define the conformation for that portion of the peptide.

The groups attached to the α-carbon of adjacent amino acid residues typically have a trans relationship since it is lower in energy. Therefore, the amide unit of one amino acid residue is anti to the amide unit of the adjacent amino acid residue. The carbonyl of the alanine residue

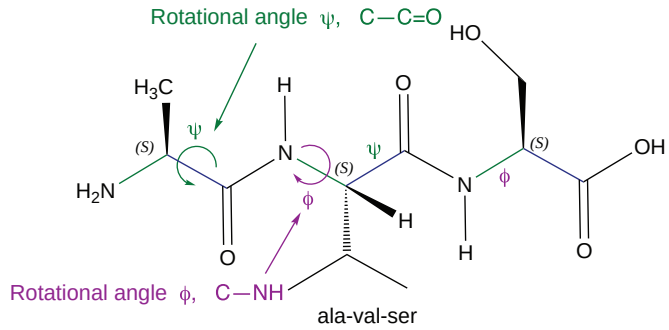
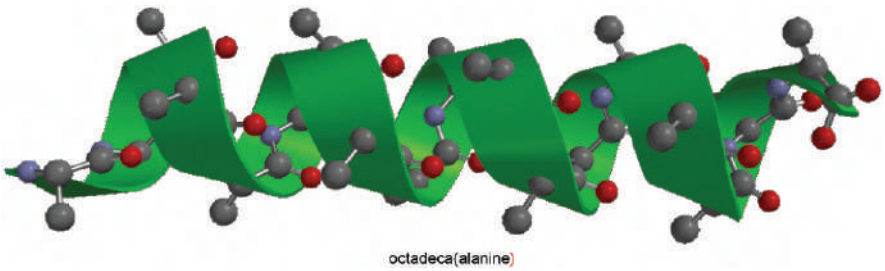


FIGURE 24.4 Rotational angles associated with the tripeptide ala-val-ser.

in Figure 24.4 is also anti to the carbonyl of the valine residue, which is anti to the carbonyl of the serine residue. If this preference is extended to a peptide chain, an alternating or anti pattern is the preferred conformation.

Several conformations are available to a long-chain peptide composed of L-amino acid residues and these conformations constitute the secondary structure of a peptide. Formally, the *secondary structure* is the three dimensional form of local segments of proteins resulting from internal hydrogen bonding. One conformation is called an α-helix, where the hydrogen atom on the amide nitrogen is hydrogen-bonded to the oxygen of the carbonyl on the fourth amino acid residue. The α-helix structure was proposed by Nobel laureate Linus Pauling (USA; 1901–1995) and Robert Brainard Corey (USA; 1897–1971) in 1951. An α-helix is superimposed on the structure of octadeca(alanine) to illustrate the secondary structure.



Internal hydrogen bonds stabilize the α-helix structure. The hydrogen atoms have been omitted from the structure, so the focus is on the helical structure. One *turn* of an α-helix represents 3.6 amino acid residues. There are 13 atoms involved in the turn, starting with a carbonyl oxygen, and ending with an amide proton. The *pitch* of the α-helix is defined as the "rise" in the amino acid residue in the helix for each turn. The rise per amino acid is ~ 1.5 Å (150 pm) and the pitch of each turn is ~ 5.4 Å (540 pm). These values are influenced by the steric hindrance of the side chains on the amino acid residues. The percentage of an α-helix varies and is largely determined by the nature of the side-chain groups of the amino acid residues. Some amino acid residues can destabilize the α-helix, namely glutamate, aspartate, lysine, arginine, glycine serine, isoleucine, and threonine. The presence of a proline residue will create a bend in the α-helix. Note that a left-handed helix can be formed when D-amino acids are used to make a peptide.

Two other secondary structures are observed with peptides. One is a *β-pleated sheet,* and the other is called a *random coil*. A random coil, as its name implies, does not feature a regular structure such as an α-helix because the intramolecular hydrogen bonds are not present. Turns in a random coil generally occur when the protein chain must change direction to connect two other elements with a secondary structure. Poly(aspartic acid) forms a random

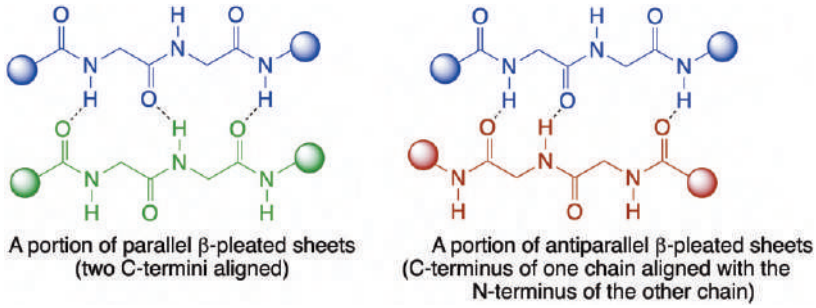


FIGURE 24.5 A portion of parallel and antiparallel β-pleated sheets.

coil structure. The *β-pleated sheet*, on the other hand, involves intermolecular hydrogen bonding between two different peptide chains rather than intramolecular hydrogen bonding within a single peptide chain. There are parallel[2] or antiparallel β-pleated sheets (Figure 24.5). These variations are defined by having the two *C*-termini aligned or the *C*-terminus of one chain aligned with the *N*-terminus of the other chain.[2]

24.18 Draw a two amino-acid strand of a parallel β-pleated sheet for ser-ala.

Jane S. Richardson (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

The folds and coils of a peptide chain generate a complex, globular structure that is known as its *tertiary structure*. A *ribbon diagram* is a shorthand method for drawing complex peptide structures in which β-strands are shown as "thick" arrows, an α-helix is a spiral ribbon, and nonrepetitive structures are shown as ropes. These shorthand structures are also known as *Richardson diagrams*, after Jane S. Richardson (USA).[3] Ribonuclease A, is shown in Figure 24.6,[4] along with the helical ribbon and "tube" used to represent a helix.

[2] Smith, C.K.; Regan, L. *Accounts of Chemical Research* 1997, 30, 153–161.

[3] (a) Richardson, J.S. *Advances in Protein Chemistry* 1981, 34, 167–339; (b) Richardson, J.S. *Methods in Enzymology: Macromolecular Crystallography Part B* 1985, 115, 359–380; (c) Richardson, J.S. *Nature. Structural and Molecular Biology* 2000, 7, 624–625.

[4] Richardson, J.S. *Methods in Enzymology: Macromolecular Crystallography Part B* 1985, 115, 359–380. Figure 13 on p. 374.

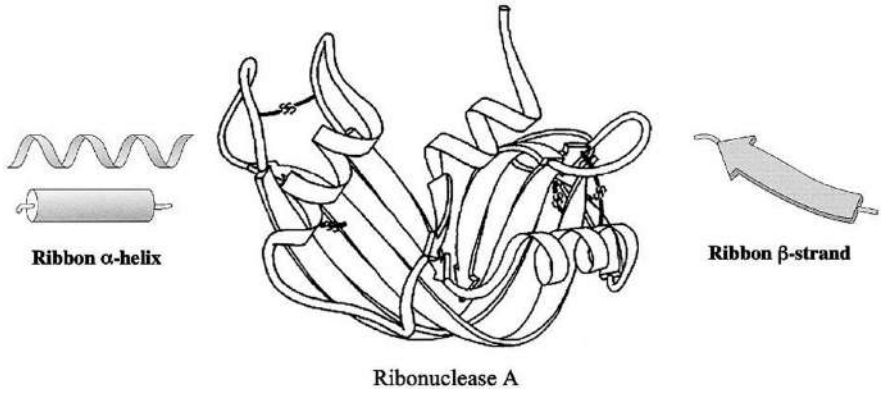
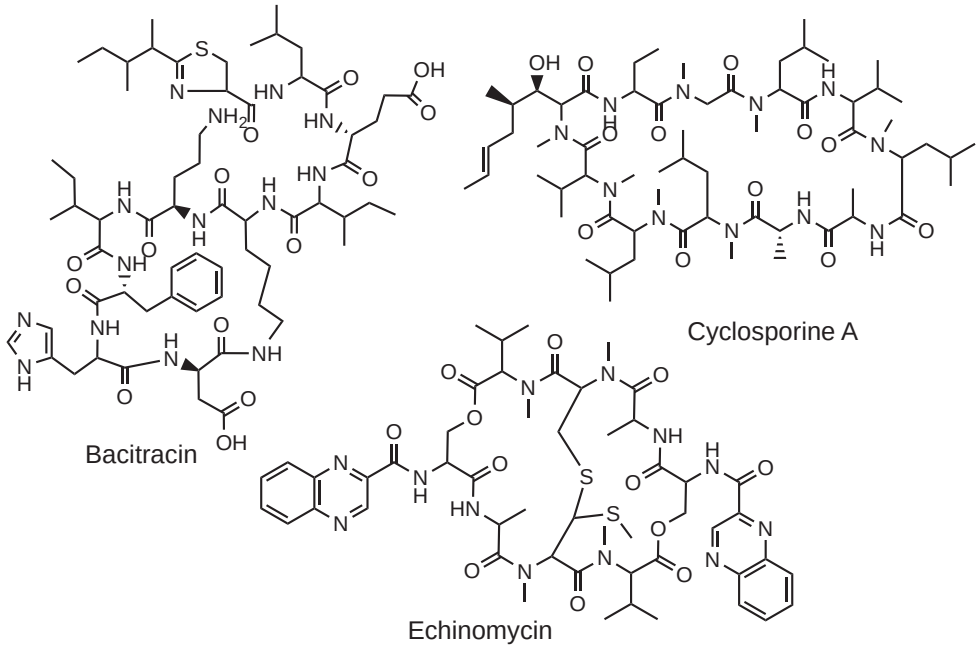


FIGURE 24.6 Richardson drawings. Ribonuclease A, illustrating a variety of junctions between loops and helices and between loops and β–strand arrows. [Reprinted from Richardson, J.S. *Methods in Enzymology: Macromolecular Crystallography Part B*, 1985, 115, 359–380. Figure 13 on p. 374, with permission from Elsevier].

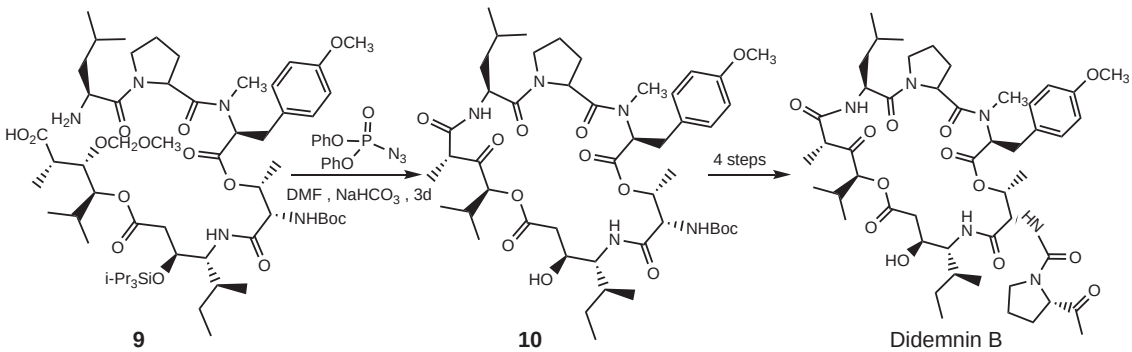
Cyclic Peptides

Cyclic peptides are polypeptide chains that contain a sequence of peptide bonds in a ring. Many cyclic peptides have been discovered in nature and they are frequently antimicrobial or toxic. Others have been synthesized in the laboratory. *Cyclic peptides* can be classified according to the types of bonds that comprise the ring. *Homodetic cyclic peptides*, such as *cyclosporine A*, are those in which the ring is composed exclusively of normal peptide bonds. A *heterodetic cyclic peptide* has at least one link between amino acids that is other than a normal peptide an isopeptide, a disulfide or an ester, etc. *Cyclic isopeptides* contain at least one non-alpha amide linkage, such as a linkage between the side chain of one residue to the alpha carboxyl group of another residue, as in microcystin and *bacitracin*. Cyclic depsipeptides have at least one lactone (ester) linkage in place of one of the amides as in *didemnin B*. Bicyclics such as *echinomycin* contain a bridging group, generally between two of the side chains.



Madeleine M. Joullié (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

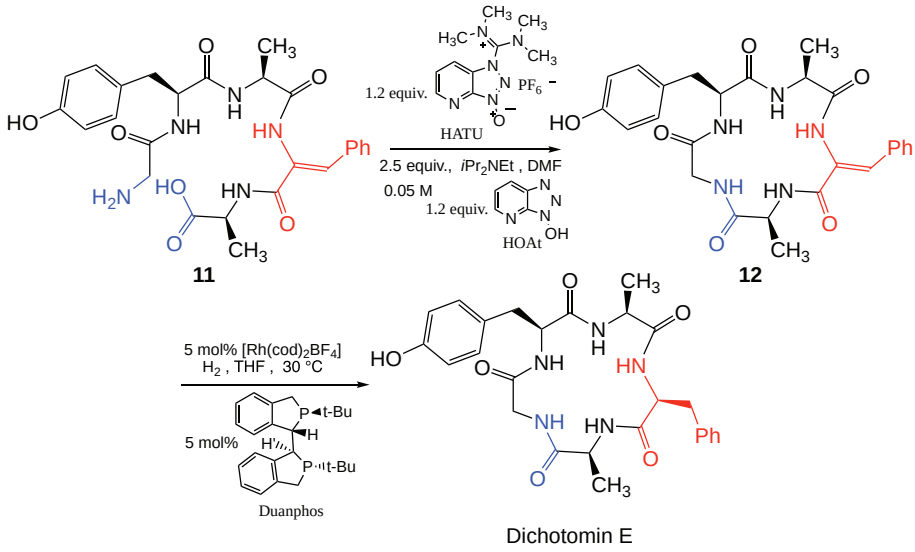
Professor Madeleine M. Joullié (USA) is an organic chemist at the University of Pennsylvania and was the first woman to join that faculty. She was the first woman organic chemist to be appointed to a tenure track position in a major American university. Much of professor Joullié's research has focused on the synthesis of natural products. She helped to develop methodologies for aromatic substitution and introduced the term *chirality transfer*. A major area of her research involved the synthesis of the cyclic depsipeptide didemnins,[5] isolated from a marine tunicate of the family *Didemnidae*. The didemnins are a family of marine cyclic depsipeptides (a peptide where one or more of its amide groups are replaced by the corresponding ester) isolated from tunicates (marine invertebrates such as sea squirts). There are several didemnins (A, B, C) that exhibit antiviral, antitumor and immunosuppressive activity. The cyclic structure of the didemnins has a series of ester and amide linkages in the ring, a lactone-lactam structure as shown in the structure for Didemnin B. Didemnin B has the most potent in vitro cytotoxicity and in vivo antitumor activity. It was the first marine natural product to be used in clinical trials against cancer. Professor Joullié's multistep synthesis included a cyclization reaction of pentapeptide **9**, featuring the reaction with diphenyl phosphoryl azide and sodium bicarbonate in DMF for 3 days to afford **10** in 40% yield. Note that –N-Boc is –N-CO_2t-Bu and the –O-CH_2OCH_3 unit is a protecting group for the alcohol. Protected macrocycle **10** was converted to Didemnin B in several steps, including removal of the N and O protecting groups.[5b]



[5] (a) Xiao, D.; Vera, M.D.; Liang, B.N.; Joullié, M.M. *Journal of Organic Chemistry* 2001, 66, 2734–2742; (b) Li, W.R.; Ewing, W.R.; Harris, B.D.; Joullié, M.M. *Journal of the American Chemical Society* 1990, 112, 7659–7672; (c) Lee, J.l.; Currano, J.N.; Carroll, P.J.; Joullié, M.M. *Natural Product Reports* 2012, 29, 404–424.

Vy Maria Dong (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Vy Maria Dong (USA) is a professor of chemistry at the University of California, Irvine. Professor Dong develops better tools for organic synthesis, including new reagents, catalysts, and strategies. Her research examines methodology that directly converts carbon-hydrogen bonds into other functional groups and that uses carbon dioxide as a raw material. This methodology targets biologically active heterocycles using the power of transition metal catalysis to transform simple reagents into valuable products. Her interest in new organometallic pathways is guided by a practical need for more efficient and environmentally friendly technologies. She works on enantioselective catalysis and natural product synthesis and has developed a rhodium-catalyzed approach to cyclic peptides, In addition, she has worked on catalytic hydroacylation and the activation of aldehyde C—H bonds. In her work with cyclic peptides, professor Dong and her co-workers Diane Le and Jan Riedel reported a synthesis of dichotomin E, a cyclic peptide containing five amino acids with cell growth inhibitory activity against leukemia cells isolated from the chickweed plant, *Stellaria dichotoma*.[6] The synthetic strategy features the first use of dehydrophenylalanine as a traceless turn-inducer. Peptide **11** was prepared and incorporation of the dehydrophenylalanine unit (in red) induced a left-handed α-turn as the lowest energy structure, which is preorganized toward macrocyclization. The steric interactions of the group at the β-carbon of the dehydroamino acid are correlated to its ability to induce a turn. The preorganization allowed macrocyclization by reaction with a mixture of HATU and HOAt to give **12** in 81% yield.



[6] Le, D.N.; Riedel, J.; Kozlyuk, N.; Martin, R.W.; Dong, V.M. *Organic Letters* 2017, 19, 114–117.

Catalytic hydrogenation was used to install the final stereocenters. This reaction featured 5 mol% $Rh(cod)_2BF_4$ and 5 mol% of the chiral ligand. Duanphos in THF solution under 30 atm of hydrogen gas, to provide dichotomin E in 96% yield with >95:5 dr. Professor Dong's synthesis allows relatively a high concentration of substrates to be used for the macrocyclization (0.1 M vs. 0.001 M from other synthetic work), so there is less solvent waste. Note that HATU is *O-(*7-azabenzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate, HOAt is 1-hydroxy-7-azabenzotriazole and COD is 1,5-cyclooctadiene.

24.5 BIOLOGICAL RELEVANCE: PROTEINS

Proteins

A *protein* contains at least one long polypeptide, which is a linear chain of amino acid residues. Proteins differ from one another primarily in their sequence of amino acids. Polypeptides that contain fewer than 20–30 residues are commonly called peptides or sometimes oligopeptides rather than proteins. Proteins have many functions within organisms. Many proteins are enzymes that act as biocatalysts for reactions that are important to metabolism. Once formed, proteins only exist for a completion of a certain function and are then degraded and recycled by the cell's machinery (*protein turnover*).

Secondary, Tertiary and Quaternary Structures

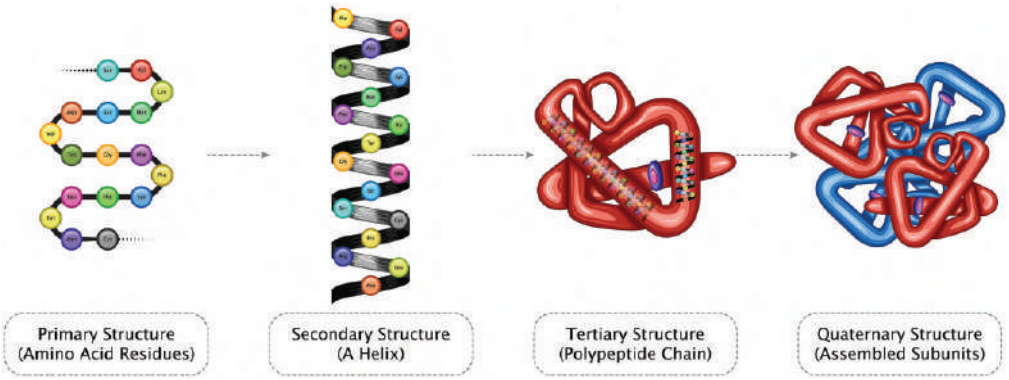


FIGURE 24.7 Protein Structure Primary Secondary Tertiary Quaternary Amino Acid residues Helix Polypeptide Chain Assembled Sub units. Reprinted from Shutterstock vector ID: 1474657079.

In Section 24.7, the four components of protein structure were introduced. The *primary structure* is the amino acid sequence. The *secondary structure* is the regular repeating local units such as an α-helix, β-sheets and β-turns that are stabilized by hydrogen bonds. Because secondary structures are local, many regions of different secondary structure can be present in the same protein molecule. The *tertiary structure* is the overall folding that leads to the shape of a single protein in water solution, which is usually stabilized by nonlocal features, including hydrogen bonds and disulfide bonds. The tertiary structure is essentially the lowest energy state that provides maximum stability to the protein due to the stabilizing bonding interactions of the amino acid side chains. The tertiary structure is what controls the basic function of the protein. The *quaternary structure* is formed by several protein molecules called protein subunits that associate into a close-packed arrangement called a protein complex. Each of the subunits will have a primary, secondary, and tertiary structure and the subunits are held together by hydrogen bonds and van der Waals forces between nonpolar side chains. Different subunits are comprised of more than one poly(peptide) chain. If the subunits are the same, the subunit is called a homodimer, whereas if the subunit are different, it is called a heterodimer. Figure 24.7 shows simplified examples of each of the four structural components of a protein.

Helen Miriam Berman (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

A proper discussion of proteins and their functions would occupy more than one complete course so this section is only a brief introduction. There are regulatory proteins that control the ability of other proteins to carry out their functions. Insulin is a peptide hormone (Section 24.12) composed of 51 amino acid residues produced by beta cells of the pancreatic islets that regulates glucose metabolism in animals. Hemoglobin is the iron-containing oxygen-transport metalloprotein in the red blood cells of almost all vertebrates. It is an example of a transport protein, which transports specific substances from one place to another. Specifically, hemoglobin transports oxygen from the lungs to tissues. Hemoglobin has four multi-subunit globular proteins that constitute the quaternary structure in roughly a tetrahedral arrangement. Most of the amino acids in hemoglobin form alpha helices and hydrogen bonds stabilize the helical sections inside this protein. Some nutrients are stored in special proteins called storage proteins. Examples are casein, which is composed of phosphoproteins αS1, αS2, β, κ and commonly constitute about 80% of cow's milk. Casein contains a high number of proline amino acid residues and no disulfide bridges so there is little tertiary structure. Another example is ferritin, which stores iron in animal tissues. Ferritin is an intracellular protein that keeps iron in a soluble and non-toxic form. Ferritin is a globular protein complex that consists of 24 protein subunits. The very structure of cells and tissues is due to structural proteins (e.g., the α-keratins, collagen, elastin, and fibroin). The α-keratins are an example of fibrous structural proteins that make up hair, horn, and fingernails. Keratins contain a central ~310 residue domain with four segments in α-helical conformation that are separated by three short linker segments in beta-turn conformation. Collagen is found in bone, tendons, and cartilage and it is the main structural protein in the extracellular matrix in the body's connective tissues. Collagens have a triple-helix structure that associates into a right-handed super-super-coil referred to as the collagen microfibril. Helen Miriam Berman is a Board of Governors Professor Emerita of Chemistry and Chemical Biology a Rutgers University and a former director of the RCSB Protein Data Bank (one of the member organizations of the Worldwide Protein Data Bank). A structural biologist, her work includes structural analysis of protein-nucleic acid complexes, and the role of water in molecular interactions. She is also the founder and director of the Nucleic Acid Database and led the Protein Structure Initiative Structural Genomics Knowledgebase. Professor Berman along with other scientists co-founded the Nucleic Acid Database (NDB) at Rutgers to collect and disseminate information about nucleic acid structure. As of July, 2018, the NDB held over 9600 nucleic acid structures and the PDB holds more than 142,000 macromolecular structures. At Rutgers, she continued to study nucleic acids, their interactions with proteins and researched and solved the structure of collagen in collaboration with Barbara Brodsky and Jordi Bella.[7] The structure of a protein triple helix was determined

[7] Bella, J.; Eaton, M.; Brodsky, B.; Berman H.M. *Science* 1994, 266, 75–81.

at 1.9 angstrom resolution by x-ray crystallographic studies of a collagen-like peptide containing a single substitution of the consensus sequence. This peptide adopts a triple-helical structure that confirms the basic features determined from fiber diffraction studies on collagen.

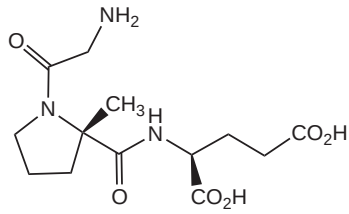
Elastin is highly elastic and is present in connective tissues in the body such as ligaments so they can resume their shape after stretching or contracting. Fibroin is an insoluble protein that is a major component of the silk used to make cocoons, and it is a major component of spider webs. The fibroin protein consists of layers of antiparallel beta sheets and the primary structure is mainly the recurring amino acid sequence $(Gly\text{-}Ser\text{-}Gly\text{-}Ala\text{-}Gly\text{-}Ala)_n$. There is tight packing of the sheets due to a high glycine content, and this contributes to silk's rigid structure and tensile strength. Some proteins are important for cell protection. The immunoglobulins (antibodies) are large, Y-shaped proteins used by the immune system identify and neutralize foreign objects such as pathogenic bacteria and viruses. Immunoglobulins are produced by lymphocytes and defend the body against bacteria, viruses, and so on. Thrombin is a serine protease enzyme that is proteolytically cleaved to form thrombin in the clotting process. Thrombin in turn acts as a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions. Fibrinogen is a glycoprotein complex made in the liver. There are glycoproteins that contain carbohydrates (Sections 25.1–3), lipoproteins that contain lipids, and nucleoproteins that are important for storage and transmission of genetic information. Proteins are critical to life process in plants, insects, and animals and as a group may well be the most important organic chemicals known.

Margaret Anne Brimble (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Dame Margaret Anne Brimble (New Zealand) is an organic chemist at the University of Auckland. Her research has focused on natural products, which provide a rich source of lead compounds to develop front-line drugs. Her research focused on the modification of naturally occurring bioactive compounds isolated from plants, animal tissue, microbes, or marine and soil organisms. This work includes the synthesis of shellfish toxins (Section 23.5). Professor Brimble has developed a national peptide, peptidomimetic and glycopeptide chemistry facility and the peptide synthesis therein supports growth in the burgeoning area of peptide therapeutics. An example is the development of NNZ2566, which is currently in phase 3 trials for Rett Syndrome and has been given the name *trofinetide*, (*S*)-1-glycyl-2-me thylpyrrolidine-2-carbonyl)-L-glutamic acid, by the World Health Organization. Trofinetide, developed by a team of medicinal chemists led by Professor Brimble, acts as an analog of the neuropeptide IGF-1, which is a simple tripeptide Gly-Pro-Glu, formed by enzymatic cleavage of the human insulin-like growth factor-1 (IGF-1)in the brain.[8] NNZ-2566 results from

[8] (a) Harris, P.W.R.; Brimble, M.A.; Muir, V.J.; Lai, M.Y.H.; Trotter, N.S.; Callis, D.J. *Tetrahedron* 2005, 61, 10018–10035; (b) Bickerdike, M.J.; Thomas, G.B.; Batchelor, D.C.; Brimble, M.A.; Harris, P.W.; Gluckman, P.D. *Journal of the Neurological Sciences* 2009, 278, 85–90.

α-methylation of the proline ring, and features improved elimination half-life and oral bioavailability over the parent peptide



Trofinetide

Enzymes

24.6 BIOLOGICAL RELEVANCE: ENZYMES

Catalysts used in biological systems are called *enzymes*, and they speed up particular biochemical reactions. Enzymes are proteins that can exist in particular conformations such that they form a reactive complex with a reactant (the *substrate*) that is converted to the product. The site on the enzyme where substrate binding and subsequent reaction occurs is called the "*active site*" or the "*binding site*." The binding of a substrate into a reactive complex weakens key substrate bonds to facilitate a particular chemical reaction. The active site of an enzyme features the amino acid residues that participate in making and breaking chemical bonds. Each enzyme is optimized for a particular reaction, or more precisely the transition state for that reaction. Once the reaction occurs, the original substrate binding is sufficiently weakened that the product can dissociate from the enzyme, allowing another reaction to occur. For such specificity, there is usually an equilibrium between the free substrate and the enzyme complex. To be specific for a particular reaction or a small subset of related reactions, the active site should react with only a specific substrate or a small subset of substrates. It is known that some enzyme reactions promote a biological process by forming a covalent bond between the enzyme and the substrate. Once formed, the covalently bound enzyme can participate in various enzymatic reactions.

The catalytic activities of many enzymes are blocked by molecules known as *inhibitors*, which mimic the substrate for binding to the active site. *Competitive inhibitors* are usually structural analogs of the substrate, and they compete for the same enzymatic binding sites. The inhibitor occupies the active site by forming a tight complex with the enzyme. Therefore, the enzyme cannot react until the inhibitor dissociates. Many pharmaceutical drugs are designed to operate as inhibitors. A *noncompetitive inhibitor* is a molecule that binds to the enzyme, but away from the active site. Typically, both the inhibitor and the substrate can bind to the enzyme. Such binding alters the shape of the enzyme such that binding of the substrate may be less efficient and the enzyme activity is less effective. An example is heavy metal poisoning, such as lead poisoning.

24.19 Ethanol binds to the enzyme alcohol dehydrogenase in the liver when present in large amounts and it is sometimes used as a means to treat or prevent toxicity following accidental ingestion of methanol. Is ethanol likely to be competitive or a non-completive inhibitor?

Enzymes facilitate myriad chemical transformations. Once the activity in a specific transformation has been confirmed, the enzyme is assigned an *EC number*: *Enzyme Commission Number*.[9] The EC number is a numerical classification scheme based on the chemical reactions that are catalyzed. The name of an enzyme often refers to the chemical reaction it

[9] (a) Webb, E.C. *Enzyme Nomenclature 1992: Recommendation of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology on the Nomenclature and Classification of Enzymes*, San Diego, CA, 1992; (b) Also see Nath, N.; Mitchel, J.B.O. *BMC Bioinformatics*, 2012, 13, 60.

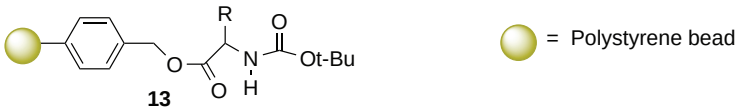
catalyzes: oxidases, reductases, aldolases, decarboxylases, etc. Two or more different enzymes that catalyze the same chemical reaction are called *isozymes*. There are six "top-level" (main) categories of enzymes, EC 1-EC 6.[10] *Oxidoreductases* that catalyze oxidation/reduction reactions (*EC 1*). *Transferases* catalyze the transfer of a specific group from one molecule to another [donor to acceptor] (*EC 2*). *Hydrolases* catalyzed the hydrolysis of a chemical bond (*EC 3*). *Lyases* cleave chemical bonds by mechanisms other than hydrolysis or oxidation (*EC 4*). *Isomerases* catalyze the isomerization of one molecule to another (*EC 5*). *Ligases* catalyze the formation of a covalent bond between two molecules (*EC* 6). The actual EC number for a specific enzyme has four numbers that take the form 1.X.X.X, all beginning with the "top level" categories 1–6. The second level subclass and third level sub-subclass indicate the specific bonds or functional groups involved in the reaction, and the fourth level serial number defines the specific chemical reaction. The third number indicates the type of acceptor involved, except in subclasses EC 1.11, EC 1.13, EC 1.14 and EC 1.15. A seventh category has been added to the list, the *translocases*.[11] The translocase enzymes (EC 7) catalyze the movement of ions or molecules across membranes or their separation within membranes.

24.7 COMBINATORIAL METHODS

Combinatorial Chemistry

Combinatorial chemistry is a term used to describe various microscale methods of solid-state synthesis and testing. It involves the synthesis of large numbers of compounds (called libraries), by conducting reactions in a manner that produces large combinations of products, usually as mixtures.[12] Combinatorial chemistry is the preparation of a large number (tens to thousands or even millions) of compounds in a single process. Combinatorial chemistry has been useful for the synthesis of small molecules and for peptides. This approach has been called *irrational drug design*, since early approaches involved making a large vat of all possible chemical combinations of several reactants. In a *parallel synthesis* a compound library is constructed by synthesizing many compounds in parallel, keeping each compound in a separate reaction vessel. When the final compounds are kept separate in this manner, methods are available to confirm their identity.

In 1963 Nobel laureate Robert Bruce Merrifield (USA; 1921–2006) introduced solid-state synthesis for the synthesis of peptides.[13] This technique involves chemical functionalization of a polystyrene bead (or another polymeric bead) that reacts with the carboxylic acid portion of a *N*-protected amino acid to give a polymer-bound amino ester such as **13**. When **13** is treated with a reagent to deprotect the amine, it can then react with another N-protected amino acid, activated at the carbonyl, to give a dipeptide. This procedure can be repeated to generate a desired polypeptide. When the target has been attained, a reagent is added to cleave the polypeptide from the bead (usually by hydrolysis). This solid-state synthesis method has been applied to other types of chemical transformations.[14]



13

[10] Table 6.2 in Thomas, G. *Medicinal Chemistry, An Introduction,* John Wiley, Chichester, 2000, p. 218.
[11] *Enzyme Nomenclature News*, August 2018. www.enzyme-database.org/news.php; ExplorEnz: McDonald, A.G., Boyce, S.; Tipton, K.F. *Nucleic Acids Research*, 2009, 37, D593–D597.
[12] (a) Issue of *Chemical Reviews* about combinatorial chemistry: *Chemical Reviews* 1997, 97, 347–510; (b) Czarnik, A.W.; DeWitt, S.H. (Eds.). *A Practical Guide to Combinatorial Chemistry* American Chemical Society, Washington, DC, 1997; (c) Chaiken, I.N.; Janda, K.D. (Eds.). *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery* American Chemical Society, Washington, DC, 1996.
[13] Merrifield, R.B. *Journal of the American Chemistry Society* 1963, 85, 2149–2154.
[14] (a) Crowley, J.I.; Rapoport, H. *Accounts of Chemical Research* 1976, 9, 135–144; (b) Leznoff, C.C. *Accounts of Chemical Research* 1978, 11, 327–333.

24.20 Draw the product formed when **13** reacts with (1) aqueous acid (2) serine methyl ester.

The fundamental idea of the Merrifield solid-state synthesis can be extended to use several beads, where each is attached to a different amino acid (V, I, S, etc. in Figure 24.8). Subsequent reaction can generate a "pool" of peptides. If this mixture of beads is treated with three activated amino acids (V, I, S or valine, isoleucine, serine; see Table 24.1), a total of nine products would be generated, each one attached to a bead, as shown in Figure 24.8.

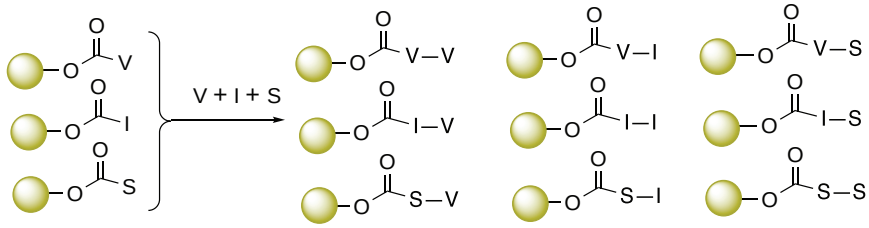


FIGURE 24.8 Generation of a nine-component dipeptide library.

This approach can be expanded to generate a large number of peptides. If the bead containing V were made to react with 20 different amino acids, a mixture of 20 dipeptides would be generated. If each of these 20 dipeptides were to subsequently react with 20 different amino acids, 20 x 20 or 400 tripeptides would be generated as a mixture. If this 400-member tripeptide library were to react subsequently with 20 amino acids, a mixture of 20 x 20 x 20, or 8000 tetrapeptides, would be generated. If this process is continued, 20^4 (160,000) pentapeptides, 20^5 (3,200,00) hexapeptides, 20^6 (1,280,000,000) heptapeptides, and 20^7 (25,600,000,000) octapeptides would be generated. Clearly, these are libraries of compounds mixed together.

Variations allow the construction of other libraries. A mixture of the three amino acids shown in Figure 24.8, for example, could be mixed with 20 amino acids to generate 60 dipeptides. If this new library of dipeptides were reacted with 20 amino acids, 60^{20} different tetrapeptides (3.656×10^{35}) compounds would be generated, which is a new library. In a pharmaceutical industry, researchers attempting to optimize the activity profile of a compound create a library of many different but related compounds. In order to handle the vast number of structural possibilities, researchers often create a "virtual library," a computational enumeration of all possible structures of a given pharmacophore. Subsequent selection of a subset of the "virtual library" is the target for actual synthesis.

Once a library is generated, the target(s) is(are) cleaved from the solid support. A method known as *deconvolution* is used to identify molecules that may be interest. Millions of different compounds may be in the library. The strategies used to identify important targets are based on the synthesis and testing of partial libraries. One method is recursive deconvolution.[15] Another method involved Encoded combinatorial libraries.[16] This method attaches tags to the beads, in parallel with the synthesis of the library, that encode the structure of the compound formed in the bead.

[15] (a) Furka, Á. https://mersz.hu/mod/object.php?objazonosito=matud202006_f42772_i2; (b) Furka, Á. *Drug Discovery Today* 2002, 7, 1–4; (c) Erb, E.; Janda, K.D.; Brenner, S. *Proceeding of the National Academy of Science USA* 1994, 91, 11422–11426.

[16] For examples, see (a) Ohlmeyer, M.H.J.; Swanson, R.N.; Dillard, L.W.; Reader, J.C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W.C. *Proceeding of the National Academy of Science USA* 1993, 90, 10922–10926; (b) Sarkar, M.; Pascal, B.D.; Steckler, C.; Aquino, C.; Micalizio, G.C.; Kodadek, T.; Chalmers, M.J. *Journal of the American Society for Mass Spectrometry* 1993, 24, 1026–1036; (c) Gartner, Z.J.; Tse, B.N.; Grubina, R.B.; Doyon, J.B.; Snyder, T.M.; Liu, D.R. *Science* 2004, *305,* 1601–1605.

Lisa A. Marcaurelle (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Lisa A. Marcaurelle (USA) is an organic chemist who has served as a senior executive at multiple biotechnology companies. Dr. Marcaurelle has worked on high-throughput chemistry, diversity-oriented chemical synthesis, chemical biology, and medicinal chemistry projects. She led the development of a diversity-oriented synthesis platform at the Broad Institute based on newly evolving chemotypes such as spirocycles and macrocycles. In 2018, she became Senior Director of the DNA Encoded Library Technology Chemistry group at GlaxoSmithKline in Cambridge, MA

24.8 AMINO ACID RESIDUE IDENTIFICATION IN PROTEINS

Determining the Primary Structure

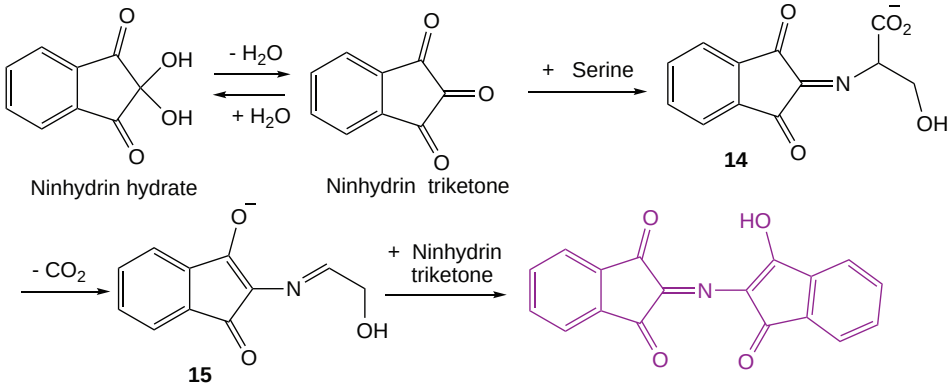
Hsien Wu (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

When a protein is isolated from an animal or a plant, it is possible to determine which amino acids are present, and in what order those amino acids are connected in the polypeptide. The process of identifying the chemical structure of a protein (or any other peptide) usually begins by heating it in 6 N HCl at 105 °C for 24 h. These conditions completely hydrolyze the peptide into its constituent amino acids, which are then separated. This procedure is

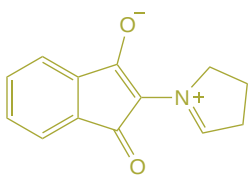
called *denaturation*, which is a process in which proteins lose their quaternary, tertiary, and secondary structures by exposure to strong acid or base, an organic solvent, heat, or radiation. Hsien Wu (China/USA; 1893–1959) was a biochemist and geneticist at Peking Union Medical College and later he was Professor of Molecular Genetics and Biology at Cornell University. He was the first to propose that protein denaturation was a purely conformational change such as protein unfolding rather than some chemical alteration of the protein.

There are problems with the denaturation procedure. Tryptophan has an indole unit which is acid sensitive, and it is partially destroyed by harsh acidic conditions. Glutamine, asparagine, glutamic acid, and aspartic acid decompose with loss of ammonia when heated in 6 N HCl. When the amino acid residue has a sterically hindered side chain, as in valine or isoleucine, hydrolysis may be incomplete and heating for a longer period of time may be necessary. Therefore, after the 24 h hydrolysis 100% of the amino acid residues in the original peptide or protein may *not* be available. Once all the amino acids have been obtained, however, there are several techniques that can be used to give structural information.

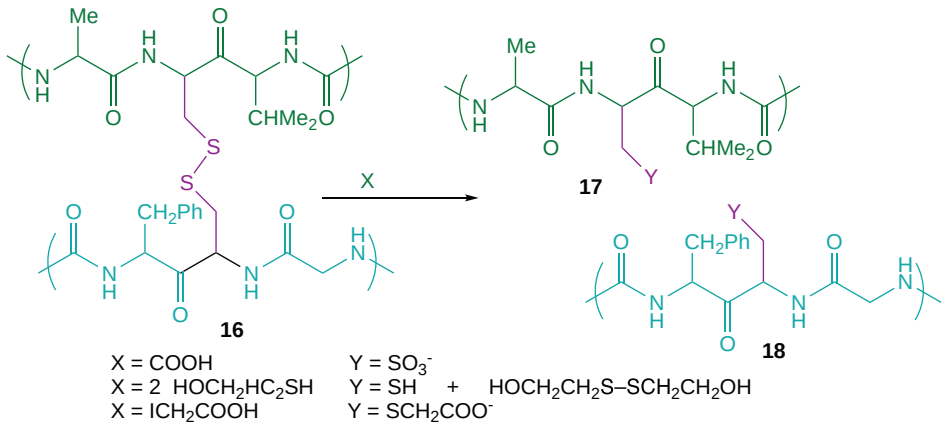
The first task is to identify the amino acids and calculate a percentage of each residue in the protein. For example, if the protein consists of 21% alanine and 5% methionine, this knowledge is essential for determining the primary structure. There are chromatography columns that will separate individual amino acids and as these separated amino acids are isolated. One method for their identification relies on heating them to 100 °C in the presence of ninhydrin.



Ninhydrin can exist in the hydrate or tri-ketone forms as the amount of water in the medium is changed. When an amino acid (e.g., serine) reacts with ninhydrin, the initial reaction between a ketone unit and the amine unit produces imine **14** along with water. Under the reaction conditions decarboxylation occurs to yield **15**, which reacts with a second molecule of ninhydrin to yield 2-(3-hydroxy-1-oxo-1*H*-inden-2-ylimino)-1*H*-indene-1,3(2*H*)-dione, which has a characteristic *purple color* (λ_{max} = 570 nm) that is easily detected by UV spectroscopy. All amino acids behave similarly except for proline, which reacts with ninhydrin to yield (2-(3,4-dihydro-2*H*-pyrrolium-1-yl)-1-oxo-1*H*-inden-3-olate) with a distinctive *yellow color* (λ_{max} = 440 nm).



24.21 Why can ninhydrin spray be used to detect fingerprints?



Part of the analysis determines the presence of absence of a disulfide bond. When two cysteine residues are in close proximity, they form a disulfide bond as in **16**. These bonds may be formed intramolecularly to create coils of the tertiary protein structure, or they may occur intermolecularly to help bind two peptides together in a β-sheet type structure. Disulfide bonds are cleaved if the peptide is treated with peroxyformic acid (**16**, X = COOH) to give cysteic acid residues in **17** and **18** (Y = SO_3^-). When **16** reacts with two equivalents of 2-mercaptoethanol cleavage leads to products with two free cysteine units in **17** and **18** (Y = SH) as well as the disulfide, 2,2'-disulfandiyldiethanol. To prevent the cysteine residues **17** and **18** (Y = SH) from recombining to form a new disulfide linkage, they are quickly treated with iodoacetic acid to yield **17** and **18** (Y = SCH_2COO^-). Once the disulfide bridges (if any) are removed, the process of identifying the termini of the peptide can begin, which is called *end group analysis* (Section 24.9).

Nowadays, the primary method used to find the amino acid sequences of proteins is mass spectrometry. Mass spectrometry is used to identify proteins and their post-translational modification. Protein complexes, their subunits and functional interactions can also be analyzed. The main mass spectral methods used for the ionization of protein in mass spectrometry are electrospray (ESI)[17] and matrix-assisted laser desorption/ionization (MALDI).[18] Used in conjunction with tandem mass spectrometry, proteins are analyzed either in a "top-down" approach in which proteins are analyzed intact. Alternatively, a "bottom-up" approach digests the protein into fragments, which are then analyzed. In another approach, larger peptide fragments are analyzed. Tandem mass spectrometry, also known as MS/MS, uses two or more mass analyzers that are coupled together. An additional reaction step is used to increase the ability to an analyze chemical samples.

Proteomics, Peptides and Proteins

Non-destructive methods are available for determining the structure of proteins. *Proteomics* generally refers to the large-scale experimental analysis of proteins and proteomes, but this term is often used to describe protein purification and mass spectrometry. Proteins may be detected by using either antibiotics (immunoassays) or mass spectrometry. Either a very specific antibody needs to be used in quantitative dot blot analysis, or a biochemical separation needs to be used before the detection step. Modified proteins may be studied by developing an antibody specific to that modification. Analysis using antibiotics are among the most common tools used by molecular biologists today, including the enzyme-linked immunosorbent (*ELISA*) method, or the *western blot* method that is used for detection and quantification of individual proteins, where a complex protein mixture is purified by using SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) and then the protein of interest is identified by using an antibody. SDS-PAGE is a discontinuous electrophoretic system that is commonly used as a method to separate proteins with molecular masses between 5 and 250 kilo Daltons (kDa). Note that the *dalton* or *unified atomic mass unit* is a unit of mass defined as 1/12 of the mass of an unbound neutral atom of carbon-12 in its nuclear and electronic ground state and at rest. The lower limit of detection with conventional immunoassay technology is the upper femtomolar range (10^{-13} M).

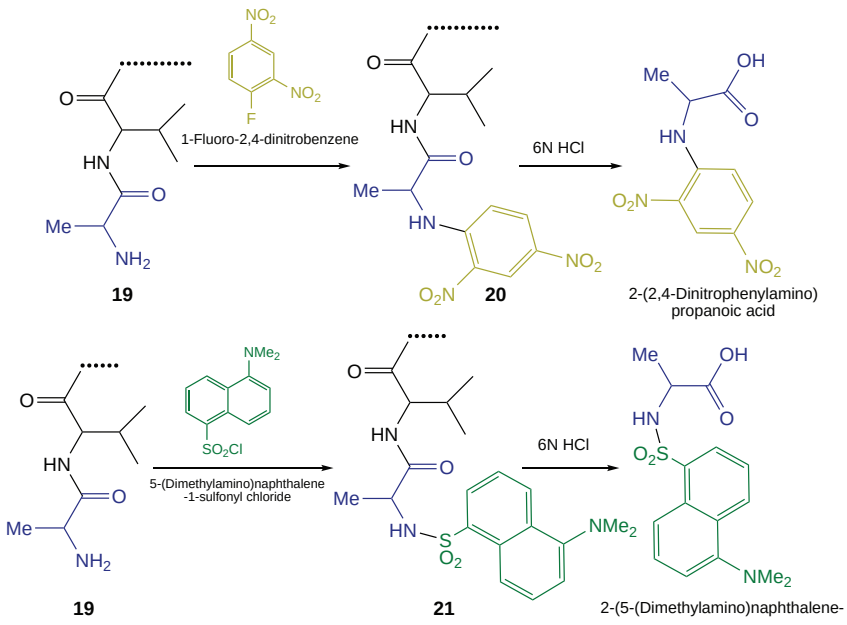
[17] Yamashita, M.; Fenn, J.B. *The Journal of Physical Chemistry* 1984, 88, 4451–4459.
[18] (a) Hillenkamp, F.; Karas, M.; Beavis, R.C.; Chait, B.T. *Analytical Chemistry* 1991, 63, 1193A–1203A; (b) Karas, M.; Krüger, R. *Chemical Reviews* 2003, 103, 427–440.

Recent methods use two mass spectrometry-based techniques for protein profiling. The more established and widespread method uses high resolution, two-dimensional electrophoresis to separate proteins from different samples in parallel, followed by selection and staining of differentially expressed proteins to be identified by mass spectrometry. The second quantitative approach uses stable isotope tags to differentially label proteins from two different complex mixtures. Here, the proteins within a complex mixture are first labeled isotopically and then digested to give labeled peptides. The mixtures of labeled peptides are combined, the peptides separated by multidimensional liquid chromatography and then analyzed by tandem mass spectrometry. Mass spectrometry cleavage occurs mainly at peptide bonds, and charge is retained in one product, so the entire protein is ionized, trapped in the spectrometer and the *m/z* are measured. One *m/z* peak is selected, and a fragment of the protein is fragmented so the *m/z* values of the new fragments can be evaluated A database is used to match the peaks to known sequences. There are programs currently available for protein identification that take the peptide sequences output from mass spectrometry and microarray and return information about matching or similar proteins.

The relative number of amino acids in a protein is determined. An unknown nonadecapeptide, for example, is shown to contain a total of 19 amino acid residues after acid hydrolysis. Analysis shows there are 3 lys, 4 gly, 2 val, 3 ile, and 2 phe, along with one each of arg, his, trp, ser, and met. Before the primary structure of the peptide can be determined, the connectivity of these amino acid residues must be known. To begin, the *N*- and *C*-terminal amino acid residues must be identified. The protein is treated with specialized reagents before denaturation that cleave the peptide chain at known amino acid residues. A subsequent assay can identify the terminus of each fragment.

24.9 END GROUP ANALYSIS

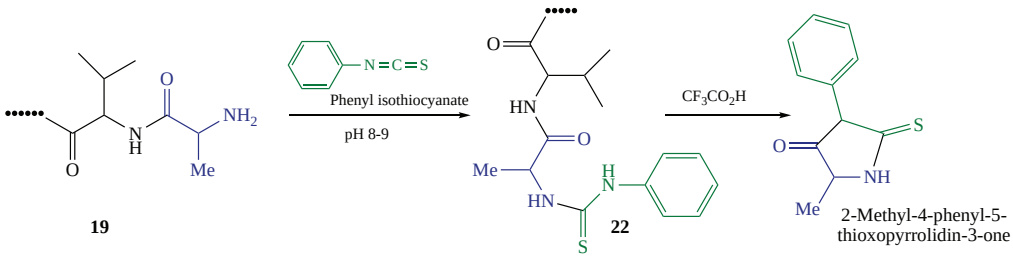
Several procedures to determine the amino acid residues on either end of a peptide, called *end group analyses*, rely on reagents that react with the C-terminal residues or N-terminal residues. The N-terminal amino acid of a peptide will react with *1-fluoro-2,4-dinitrobenzene* (*FDNB*) to yield an *N*-aryl derivative. Reagent FDNB is known as *Sanger's reagent,* named after Frederick Sanger (England; 1918–2013). If there is a peptide that terminates in an alanine residue (see **19**), it reacts with FDNB in aqueous ethanol that is buffered with sodium bicarbonate to yield **20** by a S_NAr reaction (Section 19.10). After heating with 6 N HCl, there are myriad individual amino acids but there is one and only one *N*-(2,4-dinitrophenyl)alanine. This compound is yellow and is easily separated and identified. There are complications, however. The FDNB reacts with the amine unit on the side chain of lysine, the imidazole nitrogen on the side chain of histidine, and with the sulfur unit on the side chain of cysteine.



Another method for determining the identity of the *N*-terminal amino acid reacts the peptide with *dimethylaminonaphthalenesulfonyl chloride* [5-(dimethylamino)naphthalene-1-sulfonyl chloride], known as *dansyl chloride*. When dansyl chloride reacts with a peptide (e.g., **19**), the amine unit reacts with the sulfonyl chloride to yield sulfonamide **21**. Heating this *N*-dansyl peptide with 6N HCl leads to release of the N-terminal amino acid, *N*-dansyl alanine, 2-(5-(dimethylamino)naphthalene-1-sulfonamido)propanoic acid. It is easily isolated because the presence of the dansyl group makes this sulfonamide highly *fluorescent* (Section 21.2). The ability to detect the product by fluorescence means that lower concentrations can be detected than is possible using Sanger's reagent.

24.22 Draw the product formed when valine ethyl ester is treated with Sanger's reagent.
24.23 Draw the product formed when dansyl chloride reacts with serine *tert*-butyl ester.

A problem with Sanger's reagent or dansyl chloride is that the peptide must be destroyed by heating with 6N acid after tagging the *N*-terminal amino acid residue. Therefore, only the amino acid at the *N*-terminus position of the peptide can be identified. Another reagent identifies the *N*-terminus, but it also allows sequencing of the remainder of the peptide. This reagent is *phenyl isothiocyanate*, which is known as *Edman's reagent* after Pehr Victor Edman (Sweden; 1914–1977).

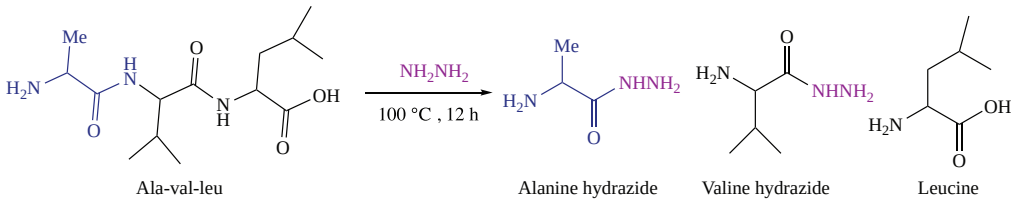


This method of identification is known as the *Edman degradation*.[19] When the amino unit of peptide **19** reacts with the C=S unit of phenyl isothiocyanate at pH 8 to 9, a thioamide derivative **22** is formed. When treated with trifluoroacetic acid **22** is converted to the phenylthiohydantoin derivative of alanine (2-methyl-4-phenyl-5-thioxopyrrolidin-3-one). The thiohydantoin is cleaved from the peptide chain to expose the amino unit of the next amino acid. This new *N*-terminus can be subjected to further analysis with more phenyl isothiocyanate and then cleaved to identify that amino acid residue. Therefore, the next amino acid can be examined, and so on. The phenylthiohydantoin is soluble in organic solvents, so it is easily removed from the peptide by extraction with ethyl acetate, allowing identification by various techniques. Edman degradation using a protein sequenator is an important method to determine the amino acids in a protein. The method is most useful to characterize the N-terminus of a protein

24.24 Draw the product formed when phenylalanine ethyl ester reacts with phenyl isothiocyanate and is then treated with trifluoroacetic acid.
24.25 Draw the phenylthiohydantoin formed after the alanine group in **19** is cleaved by use of phenyl isothiocyanate and then the new peptide is treated with phenyl isothiocyanate followed by trifluoroacetic acid.

Fewer methods are available to identify the *C*-terminal amino acid residue of a peptide. Heating a peptide to 100 °C (for ~ 12 h) with hydrazine (NH_2NH_2) leads to cleavage of the amide bond of each residue. The products are amino amide known as *amino hydrazides*. If tripeptide ala-val-leu is heated with hydrazine, for example, there are two amide products are alanine hydrazide, valine hydrazide, and the C-terminus amino acid leucine. Leucine is *not* converted to the hydrazide because hydrazine reacts with the amide carbonyl, not the carboxylate, so leucine is the *C*-terminal amino acid residue.

[19] Edman, P. *Acta Chemica Scandinavica* 1950, 4, 283–293.



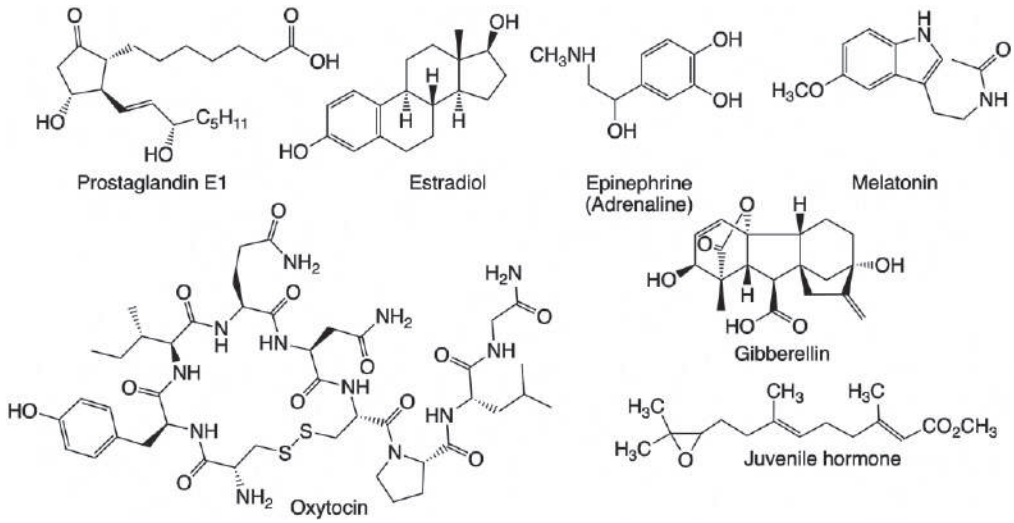
Ala-val-leu | Alanine hydrazide | Valine hydrazide | Leucine

An enzymatic procedure can be used to identify the *C*-terminal amino acid residue. Four common enzymes cleave the *C*-terminal amino acid residue from a peptide. They are *carboxypeptidase A* (from bovine pancreas), *carboxypeptidase B* (from hog pancreas), *carboxypeptidase C* (from citrus leaves), and *carboxypeptidase Y* (from yeast). *Carboxypeptidase A* cleaves all *C*-terminal amino acid residues *except* proline, arginine, and lysine. *Carboxypeptidase B* cleaves *only* an arginine or a lysine. *Carboxypeptidase C* cleaves *all* amino acid residues from the *C*-terminus, as does *carboxypeptidase Y*. In principle, a combination of these enzymes can be used to gain information about the *C*-terminus. The enzyme trypsin, which is a digestive enzyme, cleaves peptide bonds, but only when the amino acid residue has a carbonyl unit that is part of arginine or lysine. *Chymotrypsin* cleaves amino acid residues that have a carbonyl that is part of an aromatic amino acid such as phenylalanine, tyrosine, or tryptophan. *Staphylococcal protease* cleaves acidic amino acid residues (e.g., aspartic acid and glutamic acid). A chemical method fragments peptides using *cyanogen bromide* (BrC≡N), which reacts specifically with methionine residues.

Hormones

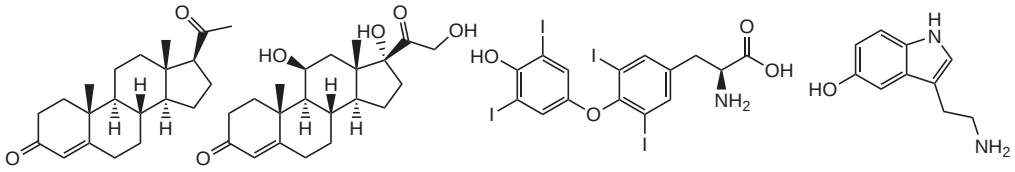
24.10 BIOLOGICAL RELEVANCE: HORMONES

A hormone is any member of a class of signaling molecules in multicellular organisms that are transported to various organs to regulate physiology and/or behavior. Hormones are used to communicate between organs and tissues. Most hormones initiate a cellular response by binding to either cell membranes or intracellular receptors. The interaction of hormone and receptor typically triggers a cascade of secondary effects within the cytoplasm of the cell, described as *signal transduction*.



Among invertebrate hormones there are eicosanoids (*prostaglandin E1* and thromboxane A2), steroids (*estradiol* and testosterone), amino acid derivatives (norepinephrine, *epinephrine* [also called adrenaline], *melatonin* and thyroxane), protein/peptides (insulin, a protein composed of two chains, and *oxytocin*) and gases (ethylene and nitrous oxide). A hormone that is important in invertebrates such as insects and crustaceans is *juvenile hormone*. In plants, hormones modulate almost all aspects of development. Plant hormones include abscisic acid, auxin, cytokinin, ethylene and *gibberellin*.

In vertebrates, adrenaline (epinephrine) and norepinephrine regulate heart rate and blood pumping from the heart, modulate blood pressure, and helps break down fat and increase blood sugar levels to provide more energy to the body. The linear peptide hormone gastrin in the stomach and the linear peptide hormone secretin (composed of 27 amino acids) in the small intestine, regulate digestion along with other hormones. Metabolism is regulated by the 167 amino acid peptide known as leptin and also by insulin. Insulin is a protein composed of two chains, a 21 amino acids A-chain and a B chain 30 amino acid B-chain linked together by sulfur atoms. *Progesterone* and thyroxine are important for respiration. Thyroid hormones such as *thyroxine* regulate sensory perception; and *melatonin* regulates sleep. *Cortisol* is important as a stress hormone and insulin, glucagon, cortisol, epinephrine, testosterone, and human growth hormone (a polypeptide chain produced by the pituitary gland containing about 190 amino acid residues) are important for movement. Estrogens such as estradiol and testosterone are important hormones for reproduction and serotonin, adrenalin, dopamine are important for mood manipulation.

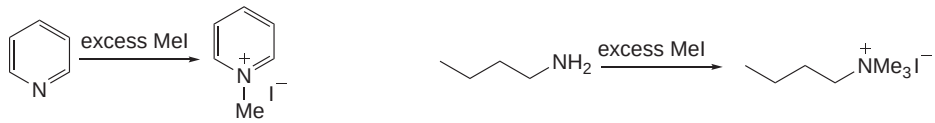


CORRELATION OF HOMEWORK WITH CONCEPTS

- Several methods are available for the preparation of amines: 1, 2, 3, 4, 5, 6, 7, 26, 28, 33.
- Amino acids are difunctional molecules that have a carboxylic acid unit and an amine unit in the same molecule: 8, 9, 27, 29.
- A zwitterionic amino acid gains a proton at the carboxyl unit with an acid or loses a proton from the ammonium unit with a base to generate two acid–base equilibria, K_1 and K_2: 10, 30, 31.
- Reactions of amino acids involves either the carboxyl or the amine unit: 11, 34.
- Several methods are available for the preparation of amino acids: 12, 13, 14, 15, 16, 32, 42, 43, 44, 45.
- Peptides are composed of two or more amino acid units joined together by peptide (amide) bonds. Peptides have primary, secondary, tertiary and quaternary structures: 17, 18, 19, 20, 21, 40, 41.
- End group analysis identifies constituent amino acid residues: 22, 23, 24, 25, 35, 36, 37, 38, 39.
- Spectroscopy can be used to determine the structure of a particular molecule (see Chapter 13): 46, 47.

ANSWERS IN IN-CHAPTER QUESTIONS

24.1



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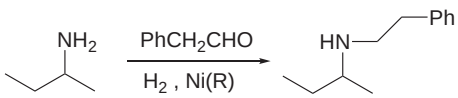

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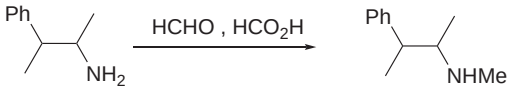

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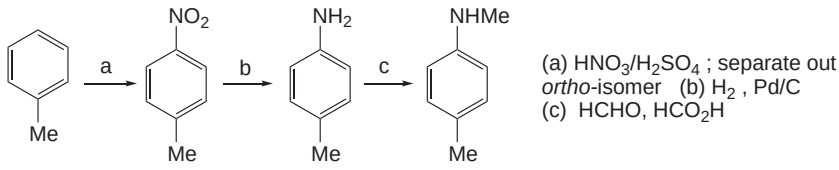

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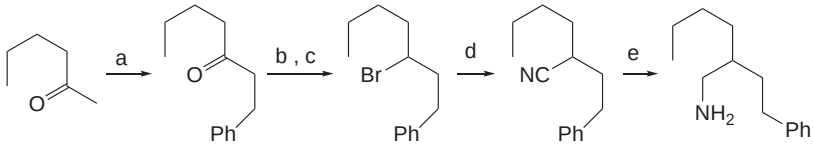

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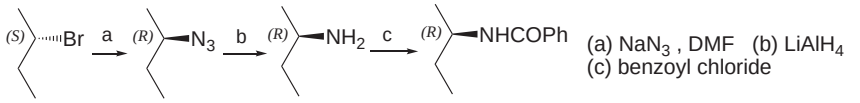

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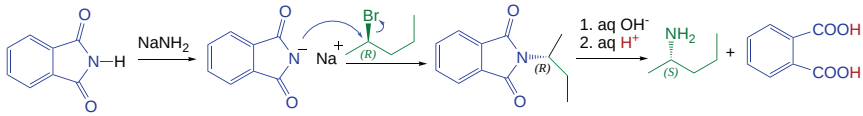

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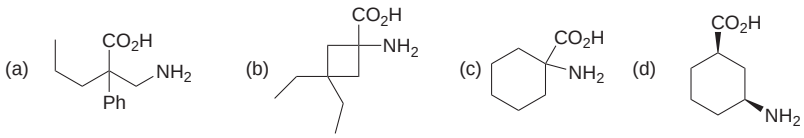

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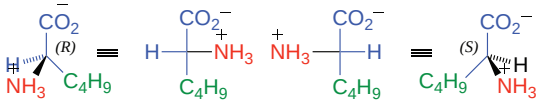

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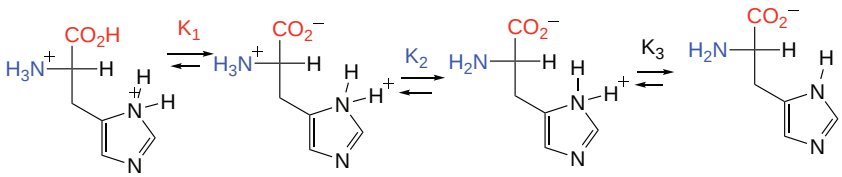

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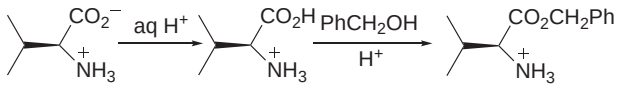

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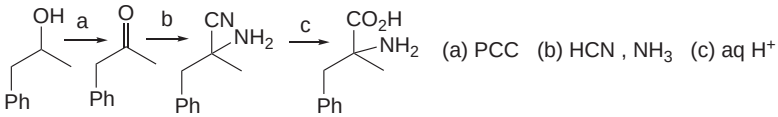

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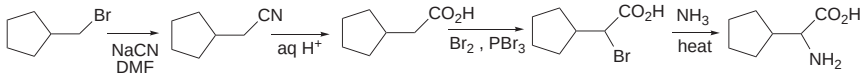

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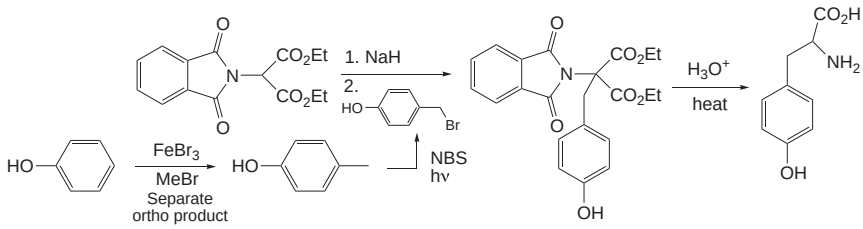
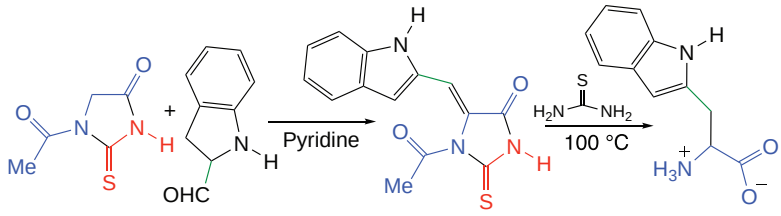


Note that phenol is so reactive that mono-methylation is difficult since poly-methylation can be a serious problem. For this answer, and for simplicity, it is assumed that the mono-methylation reaction proceeds without a problem.

24.15



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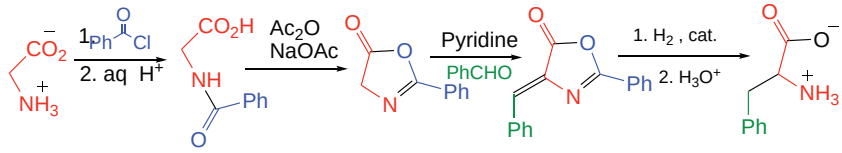
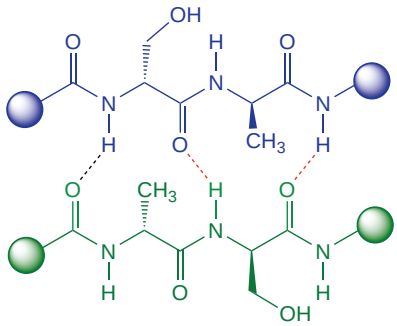


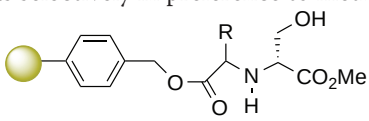
24.17 The primary structure is ser-ser-leu-asn-cys-asp-gly-ala-phe-trp-his.

24.18



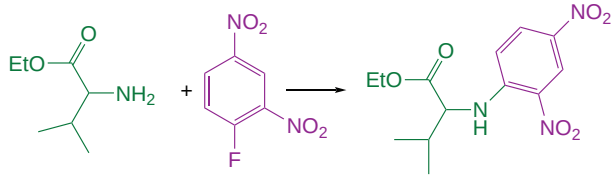
24.19 Ethanol is a competitive inhibitor for *alcohol dehydrogenase* when administered for methanol poisoning to stop the conversion of methanol to its toxic metabolite, formate. Ethanol binds selectively in preference to methanol.

24.20



24.21 Ninhydrin reacts with the peptides left behind on a fingerprint to form a purple product that can be visualized.

24.22



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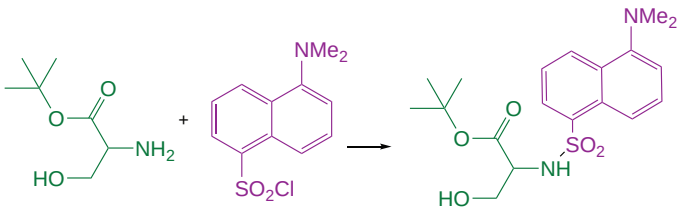

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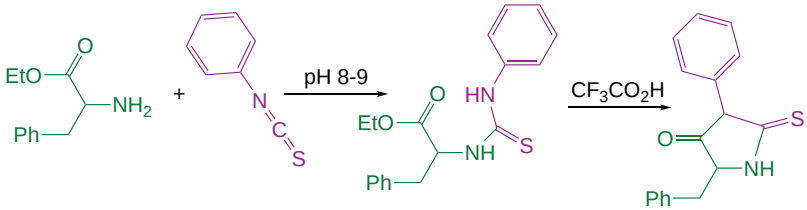

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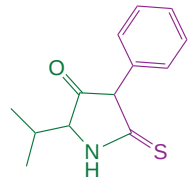
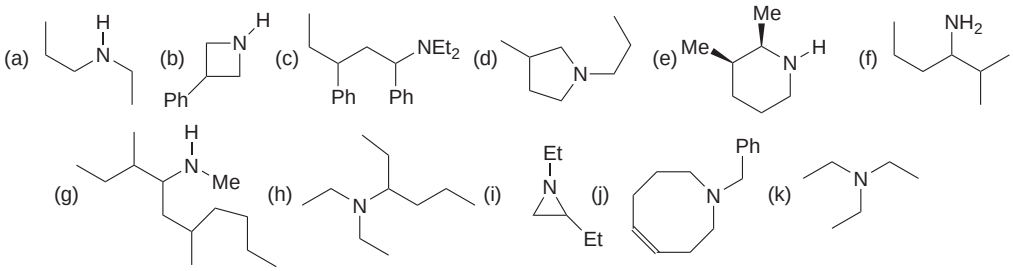
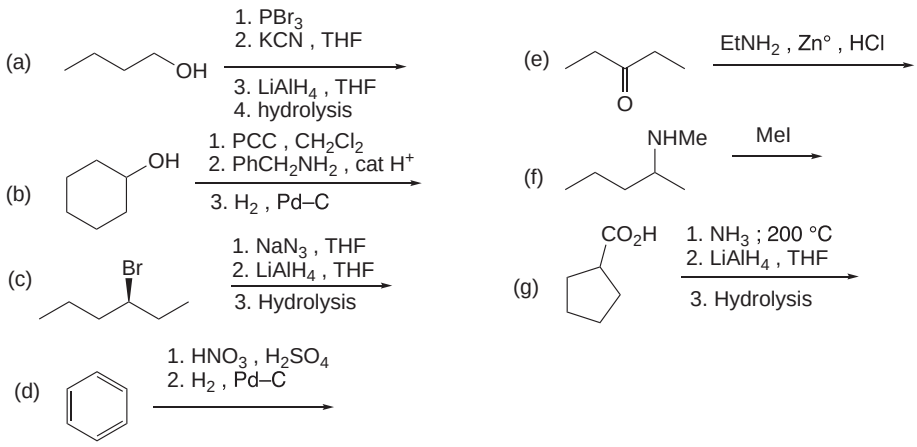


HOMEWORK

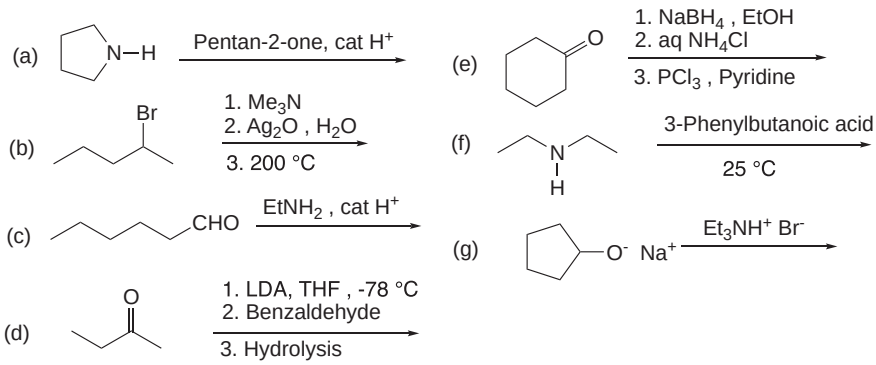
26. Give the IUPAC name for each of the following:



27. Give the major product of each of the following reactions. In each case, hydrolysis indicates a hydrolytic workup.



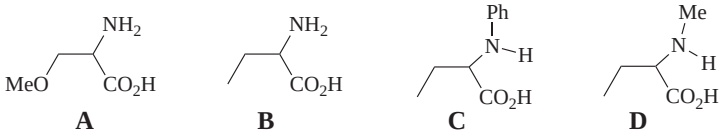
28. Give the major product for each of the following reactions. In each case, hydrolysis indicates a hydrolytic workup.



29. Draw the structure for each of the following, using line notation:
(a) 3,4-Diphenyl-5-aminohexanoic acid (b) 4-Aminohex-5-enoic acid
(c) Aziridine-2-carboxylic acid (d) *N*-Methylpiperidine-4-carboxylic acid

(f) 3-Aminobenzoic acid (f) (2*R*)-Amino-(3*R*,4*S*)-dihydroxyhexanoic acid
(g) *N*-Ethyl-3-amino-1,5-pentanedioic acid (h) (2*S*)-Amino-3-phenylpropanoic acid
(i) Pyrrolidine-(2*S*)-carboxylic acid (j) *N*,3-Dimethyl-(2*S*)-aminobutanoic acid

30. (a) Which of the following should have the smallest pK_1, **A** or **B**? Explain. (b) Which of the following should have the largest pK_2, **C** or **D**? Explain.



A **B** **C** **D**

31. Both pK_1 and pK_2 are lower for phenylalanine than for isoleucine. Explain.
32. Phenylalanine has been synthesized by the following sequence. Ethyl 2-phenyl acetate is brominated at the α-position, and then treated with ammonia. Treatment with aq NaOH and then acidification to pH 4 is followed by extraction with hexane. Phenylalanine is *not* obtained in the hexane. Why not?
33. Briefly explain why an amide is not as basic as an amine.
34. Draw the product formed when ninhydrin reacts with each of the following:
(a) gly (b) met (c) ser (d) val (e) his (f) arg
35. Draw the product formed when Sanger's reagent reacts with each of the following:
(a) gly-ala-met-asn-ile (b) gln-gln-val-ser (c) his-trp-phe-trp
36. Draw the product formed when dansyl chloride reacts with each of the following:
(a) arg-tyr-thr-gln (b) glu-glu-ser-thr (c) phe-ile-lys
37. Show the products for the Edman degradation of each of the following:
(a) arg-tyr-thr-gln (b) glu-glu-ser-thr (c) phe-ile-lys
38. Show the products formed when each of the following reacts with hydrazine at 100 °C:
(a) arg-tyr-thr-gln (b) glu-glu-ser-thr (c) phe-ile-lys
39. Show the product formed when each of the following reacts with 1. $LiAlH_4$ and 2. Hydrolytic workup:
(a) ser-ile (b) ala-val (c) cys-leu
40. Draw both the syn and anti-conformations for the dipeptide phe-ala.
41. Draw the product formed when EtO-ile-ser-phe-NH_2 reacts with MeO_2CCl.
42. Explain why an amino acid cannot be prepared from phthalimide and the ethyl ester of 2-bromo-2-methylbutanoic acid.
43. Draw the amino acid formed by reductive amination of 3-phenylhexanal and the ethyl ester of glycine.
44. Write out the structures of the thiohydantoin derivatives of phenylalanine, serine, and histidine.
45. Use the azlactone of glycine to prepare the allyl, benzyl and 4,4-diphenylbutyl derivatives. Convert each to the appropriate amino acid.

Spectroscopic problems. Do not attempt these problems until Chapter 13 is read and understood.

46. Describe spectroscopic differences that would allow *N*-methylbutan-1-amine to be distinguished from pentan-2-amine.
47. Give the structure for the molecule with a formula of $C_8H_{17}NO_2$ and the following spectral data:
IR: 3198, 3092 and 3076, 2950-2860, 1681, 1632, 1463, 805 cm^{-1}. ^1H NMR: 5.11 (broad s, 2H; this peak is diminished when treated with D_2O), 4.25 (d, 1H), 4.21 (q, 2H), 2.14 (m, 1H), 1.55 (m, 2H), 1.29 (t, 3H), 1.11 (d, 3H), 0.90 (t, 3H) ppm. ^{13}C NMR: 171.5, 61.3, 56.9, 36.3, 25.1, 15.0, 14.1, 11.3 ppm.

The video clips for this chapter are available at:
https://routledgetextbooks.com/textbooks/9780367768706/chapter-25.php

25

Multifunctional Compounds

Carbohydrates

Carbohydrates (hydrates of carbon) are multifunctional compounds that contain several hydroxyl units as well as a ketone, aldehyde, or a carboxyl unit. Carbohydrates are commonly known as *sugars* and they have the generic formula $(CH_2O)_n$. Carbohydrates are important in mammalian biology, as well as in the biology of plants and insects. Glycosides are molecules in which a sugar is bound to another substructure via a glycosidic bond. Nucleosides are the structural subunit of nucleic acids such as DNA and RNA. Nucleosides have a ribose unit and a pyrimidine or a purine nucleobase.

To begin this chapter, you should know the following points:

- Aldehydes and ketones (Sections 5.6.2 and 16.1).
- Alcohols (Section 5.5.1).
- Carboxylic acids (Sections 5.6.3 and 18.1).
- Carboxylic derivatives (Section 18.2).
- Amines (Section 5.5.3).
- Acetals and ketals (Section 16.4.2).
- Acid-base equilibria (Section 6.1).
- Conformations of cyclic compounds (Section 8.5).
- Stereogenic centers and (*R/S*) configuration (Sections 9.1 and 9.2).
- Diastereomers (Section 9.5).
- S_N2 and S_N1 reactions (Sections 11.2, 11.3, and 11.4).
- Reactions of amines (Sections 24.1 and 24.2).
- Acyl addition reactions (Section 16.4)
- Acyl substitution reactions (Sections 18.4–18.6 and 18.8).
- Oxidation reactions (Sections 15.2–15.5).
- Reduction reactions (Section 17.2–17.5).

25.1 POLYHYDROXY CARBONYL COMPOUNDS

Carbohydrates are polyhydroxylated derivatives, $X^1\text{-}(CH_2OH)_n\text{-}X^2$. Carbohydrates can be classified by the functional groups X^1 and/or X^2, which are CH_2OH, CHO, COR (a ketone), or COOH. A *glycose* has a CH_2OH and an aldehyde or ketone unit and a *glycitol* has two CH_2OH units (sometimes called an *alditol*). When one group is a carboxylic acid, and the other is CH_2OH it is a *glyconic acid* (sometimes called an *aldonic acid*). A *glycaric acid* is a hydroxy-dioic acid with two carboxyl units (sometimes called an *aldaric acid*), and a *uronic acid* has a carboxyl group and an aldehyde group. A second classification is based on the number of repeating CHOH units that make up the carbohydrate, defined by the integer "*n*," in $X^1\text{-}(CH_2OH)_n\text{-}X^2$ where n=3, 5, or 6, and so on. The glycose with three carbon atoms (n=1) is called a *triose* and a glycose with four carbon atoms (n=2) is a *tetrose*. A *pentose* has five carbon atoms (n=3), and a *hexose* has six carbon atoms (n=4). *Aldoses* are glycoses with an aldehyde carbonyl unit and *ketoses* are glycoses with a ketone carbonyl unit. Using the glycoses as examples, the three-carbon aldose is an *aldotriose* and a six-carbon aldose is an *aldohexose,* the four-carbon ketone is a *ketotetrose*, and a six-carbon ketone is a *ketohexose*.

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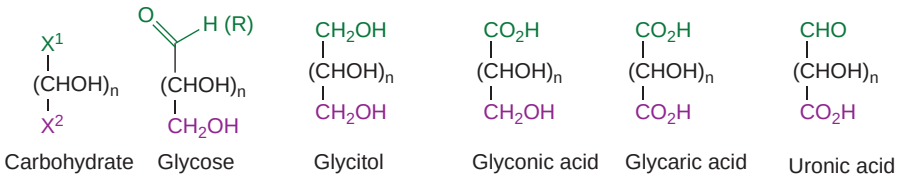


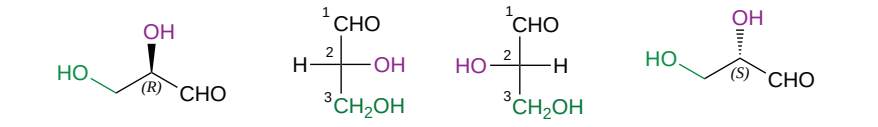
Carbohydrates or *saccharides* are also categorized by the number of sugar units. A *monosaccharide* is one carbohydrate unit (one sugar) X^1-$(CH_2OH)_n$-X^2 where n=1. If two monosaccharides are coupled together, the resulting molecule is a *disaccharide* and a molecule with three monosaccharide units is a *trisaccharide*. Linking 5-15 monosaccharides generates an *oligosaccharide*. A *polysaccharide* has > 15 monosaccharides linked together. In both disaccharides, trisaccharides and polysaccharides the units are linked together by an acetal linkage.

Monosaccharides

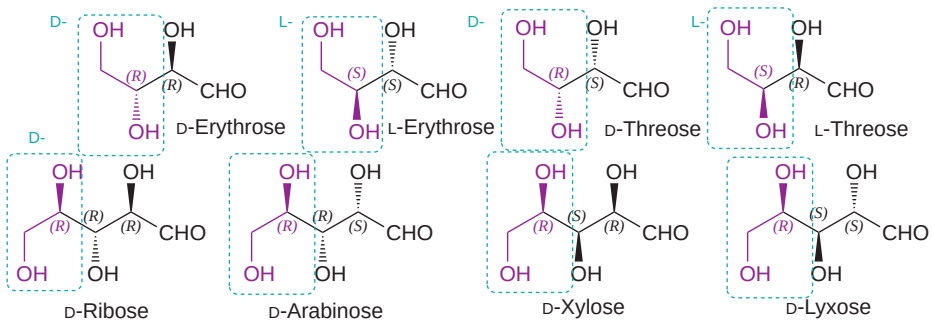
25.1.1 MONOSACCHARIDES

Glycoses are chiral aldehyde-alcohol or chiral ketone-alcohol carbohydrates that are usually monosaccharides. The carbon of each hydroxymethyl (CHOH) unit in X^1-$(CH_2OH)_n$-X^2 is a stereogenic center, so there is the possibility of several diastereomers based on the number of carbons. Except for meso compounds, each diastereomer will have an enantiomer. When n=1 there is one stereogenic center and there are two stereoisomers (the two enantiomers). When n=2, there are 4 possible stereoisomers; when n=3 there are 8 possible stereoisomers; and when n=4 there are 16 possible stereoisomers. All monosaccharides have a terminal –CH(OH)CH_2OH unit with a stereogenic center. A nomenclature system has been developed based on the stereochemistry of this terminal stereogenic center.

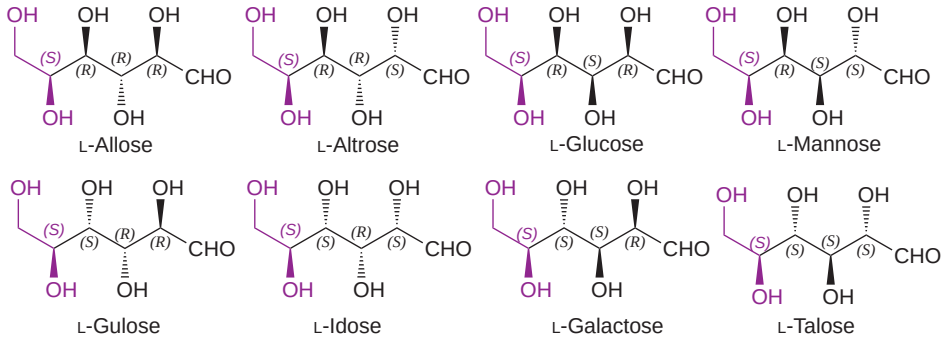
25.1 Draw the structure of a ketopentose and an aldotetrose.



Emil Fischer used glyceraldehyde as the basis for the D,L nomenclature system used to classify the stereochemistry of amino acids (Section 24.3). Glyceraldehyde is a carbohydrate, so this D,L nomenclature is also used for carbohydrates. *Glyceraldehyde* is an aldotriose with one stereogenic center and two enantiomers. Both enantiomers are shown as line drawings and in Fischer projection. The CHO unit is on the top and the CH_2OH unit is on the bottom in the Fischer projection. The terminal —CHOH—CH_2OH unit is correlated with C2 and C3 of glyceraldehyde. If the OH unit at C2 is on the right as in Fischer projection **1** it is a (*R*)-stereocenter and it is D. If the OH unit is on the left as in Fischer projection **2**, it is a (*S*)-stereocenter and it is L. The absolute configuration of D-(+)-glyceraldehyde is *(R)*-2,3-dihydroxypropanal and that of L-(-)-glyceraldehyde is *(S)*-2,3-dihydroxypropanal. This correlation to glyceraldehyde is shown in the boxed portion of aldotetroses and aldopentoses.



There are two aldotetroses, D- and L-erythrose and D- and L-threose and the four D-aldopentoses are shown, D-ribose, D-arabinose, D-xylose, and D-lyxose. All of the D-sugars have the (*R*) absolute configuration at C5. The enantiomeric (mirror image) L-aldopentoses are not shown. There are eight diastereomeric aldohexoses, each with an enantiomer, but only the L-enantiomers are shown: L-allose, L-altrose, L-glucose, L-mannose, L-gulose, L-idose, L-galactose, and L-talose. For all of the L-sugars shown, C5 has the (*S*) absolute configuration. All of the L-sugars have the (*R*)-configuration at C5. The enantiomeric (mirror image) D-aldohexoses are not shown



25.2 Determine the number of diastereomers and the total number stereoisomers for an aldoheptose.

25.1.2 HEMI-ACETALS

Anomeric Centers

All of the aldotetrose, aldopentose, and aldohexose compounds shown in Section 25.1.1 are hydroxy-aldehydes. From Section 16.2, it is known that an aldehyde and an alcohol react to form an acetal. In the glycose derivatives discussed, formation of acetals is not possible via an intramolecular reaction of two hydroxyl units although intermolecular acetal units are observed in disaccharides, trisaccharides, etc. One hydroxyl unit can react intramolecularly to form a stable cyclic hemiacetal, however. D-Glyceraldehyde does *not* easily form a cyclic hemiacetal. Cyclization would dictate formation of a four-membered ring, which has significant strain energy (Section 8.5.2). Aldoglycoses of four carbon atoms or greater form stable five- and six-membered ring *hemiacetals* as shown in Figure 25.1. The terminal

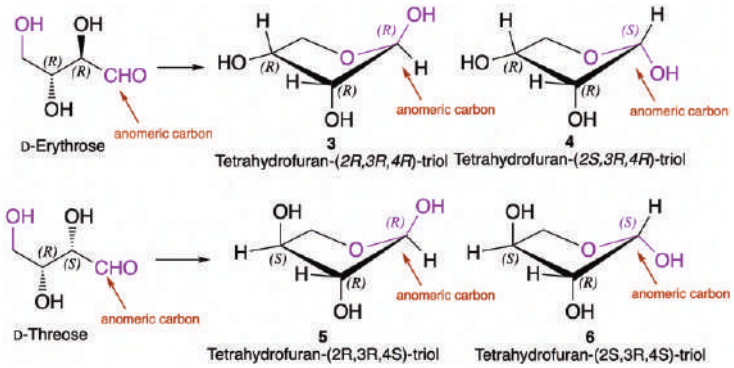


FIGURE 25.1 Hemiacetal furanose forms of D-erythrose and D-threose.

CH_2OH group is used to form the oxygen-containing ring and cyclization favors formation of five- and six-membered rings. The C2 carbon bears the hemiacetal–OH unit, derived from the acyl carbon of the aldehyde unit. This carbon is called the *anomeric carbon* or an *anomeric center*.

Furanoses and Pyranoses

A hemiacetal can be formed to generate either a (*R*) or a (*S*) configuration, and both diastereomers of D-erythrose (**3** and **4**) and D-threose (**5** and **6**) are shown. Isomers that differ only in the configuration at the anomeric carbon are called *anomers*. The suffix "*ose*" is used for the cyclized hemiacetals. They are formally derived from tetrahydrofuran, which is derived from furan so their name is *furanose*. Therefore, D-erythrose forms D-erythrofuranose derivatives and D-threose forms D-threofuranose derivatives. Inspection of **3** and **4** reveals that the OH units at the anomeric carbon are on opposite faces of the ring. Likewise, the OH units at the anomeric carbon are on opposite faces of the ring in of **5** and **6**. Two hemiacetals form because the hydroxyl group can approach the planar carbonyl carbon from the "top" or the "bottom" face. The furanose rings are drawn in an envelope conformation to show a normal conformation for the five-membered rings.

25.3 Write out the mechanism of formation and the hemiacetal product when 4-nitrobenzaldehyde reacts with methanol in the presence of an acid catalyst.
25.4 Draw the structure of D-xylofuranose.

A structure representation has been developed to identify the position of the OH unit on the anomeric carbon. The anomeric carbon is drawn on the right side of a planar ring with the oxygen drawn away from the viewer (to the rear). The ring carbons are drawn as a **bold** line to the front. In this view, the *β-anomer has the* OH on the "top" and the *α-anomer* has the OH on the "bottom". Therefore, α means *down* and β means *up* for the D-series but *only* when the ring is drawn as in Figure 25.2. This protocol is used for both furanose and pyranose derivatives. Both β-furanose

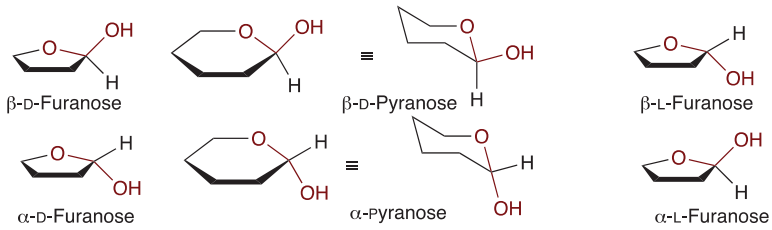
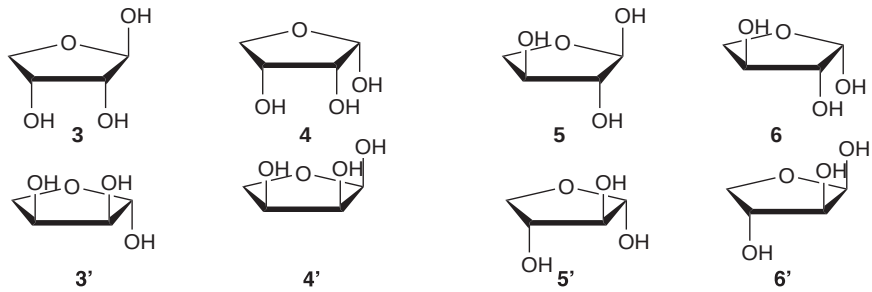


FIGURE 25.2 Convention for assigning α and β configurations for D-sugars.

and α-furanose anomers are labeled as well as the β-pyranose and α-pyranose anomers. In the L-series, the definitions of α and β are reversed as shown.

25.5 Draw L-α-furanose and L-β-furanose.

Another structural representation of furanose and pyranose derivatives also uses planar five- and six-membered rings. The oxygen atom is projected to the rear. The OH substituents are drawn "straight up" to represent a (S) stereocenter or "straight down" to represent a (R) stereocenter on the flat ring. This representation is known as a *Haworth formula*, named after Walter Norman Haworth (England; 1883–1950). D-Erythrofuranose diastereomers **3** and **4** and D-threofuranose diastereomers **5** and **6** are drawn as Haworth formulas where **3** is α-D-erythrofuranose, **4** is β-D-erythrofuranose, **5** is α-D-threofuranose, and **6** is β-D-threofuranose. The L-stereoisomers are also shown as Haworth formulas for comparison, where **3'** is α-L-erythrofuranose, **4'** is β-L-erythrofuranose, **5'** is α-L-threofuranose, and **6'** is β-L-threofuranose.



Pentose and hexose derivatives form cyclic hemiacaetals. An example is cyclization of the C4 OH unit to the anomeric carbon in the pentose D-ribose. D-Ribose exists in the cyclic or furanose form as α-*D*-ribofuranose and β-D-ribofuranose. Both are drawn as Haworth formulas. There is an equilibrium between the two hemiacetal forms and the open chain aldehyde, as shown in Figure 25.3. There is free rotation around the C1—C2 bond in the open chain aldehyde of D-ribose. The OH may add to the anomeric carbon from either face, *path A* or *path B*. Cyclization via *path A* from the "top" forms the OH unit "down" to give the α-anomer, α-D-ribofuranose. Cyclization via *path B* from the "bottom" forms the OH unit "up" to give the β-anomer, β-D-ribofuranose. Changing the C4 OH unit in D-ribose to a C4 alkoxy group in the ribofuranose changes the absolute configuration of C3 from (*R*) to (*S*) in the ribofuranose anomers.

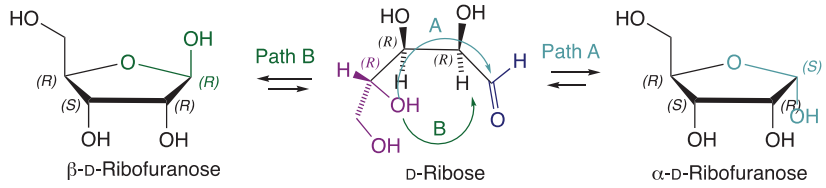
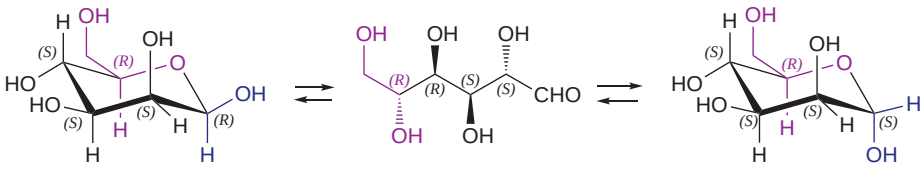


FIGURE 25.3 Formation of anomers in equilibrium with the open-chain form of D-ribose.

25.6 Draw the furanose structures for β-D-arabinose and α-D-xylose, in Haworth projection.

Just as an aldohexose can cyclize to a *furanose*, a six-membered ring carbohydrate can cyclize to a *pyranose*, a *pyran* derivative. By analogy to the conformation of cyclohexane, a pyranose should assume a low energy chair conformation. Cyclization of mannopyranose can form the OH unit 'down' to form the α-anomer, α-D-mannopyranose or "up" to form the β-anomer, β-D-mannopyranose. Hemiacetal formation leads to an equilibrium with α-D-mannopyranose and β-D-mannopyranose. The anomeric OH is axial in α-mannopyranose and equatorial in β-mannopyranose. The position of this equilibrium can be measured, so it is possible to determine the relative percentage of these three species. This discussion must begin with an *assumption*, however. The open-chain aldehyde form accounts for < 1% of the equilibrium where the furanose or pyranose forms of the carbohydrate are the major contributors. This is easily verified by NMR analysis.



25.7 Using chair representations, write the structure of α-D-allopyranose, β-D-altropyranose, α-D-gulopyranose, β-D-idopyranose, and α-D-talopyranose.

Mutarotation

Since these are chiral non-racemic compounds, one way to measure the equilibrium is to measure the specific rotation (Section 9.3). When either enantiopure α-D-mannopyranose or β-D-mannopyranose is in solution, an equilibrium is established with both anomers and the open-chain aldehyde form of D-mannose. The optical rotation of each anomer is observed to change in this equilibrium and this change is called *mutarotation*. The specific rotation of each pure enantiomer and that of the equilibrium mixture after mutarotation is measured. With this information, the relative percentage of α- and β-D-mannose can be determined. The percentage of aldehyde is assumed to be very small. The specific rotation of pure α-D-mannopyranose is +29.3° and β-D-mannopyranose is -16.3°. When either pure α-D-mannopyranose or β-D-mannopyranose is allowed to stand in aqueous solution, however, mutarotation leads to a specific rotation of +14.5°. Once this value is known, the percentage of each anomer can be calculated.

% α-D-mannopyranose (+29.3) + % β-D-mannopyranose (-16.3) = +14.5, and
since % α-D-mannopyranose + % β-D-mannopyranose = 1,
the % α-D-mannopyranose = 1-% β-D-mannopyranose.
Therefore, (1-% β-D-mannopyranose)(+29.3) + % β-D-mannopyranose (-16.3) = +14.5
= 29.3 -29.3% β-D-mannopyranose -16.3% β-D-mannopyranose = +14.5,
% β-D-mannopyranose (-29.3-16.3) = 14.5-29.3,

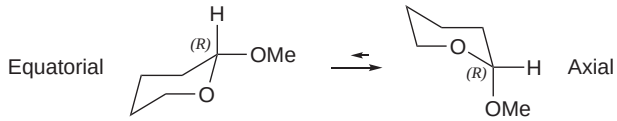
% β-D-mannopyranose (-45.6) = -14.8, so % β-D-mannopyranose = $\frac{-14.8}{-45.6} = 0.32_5$.
Therefore,
β-D-mannopyranose = 32.5% and α-D-mannopyranose = 67.5%.

25.8 Calculate the equilibrium mixture for D-mannopyranose if the specific rotation of the final solution is -3.2°.

25.1.3 THE ANOMERIC EFFECT

In the mutarotation example for D-mannose, the sign of specific rotation is positive so there is more of the α-D-mannopyranose than the β-D-mannopyranose. This means there is more of the axial anomer than the equatorial anomer. Remember from Section 8.5.3 that a substituent on a cyclohexane ring in the equatorial position has less $A^{1,3}$-strain than when that substituent is in the axial position. In α-D-mannopyranose the hydroxyl group at the anomeric carbon is in the axial position. There must be another factor that influences this equilibrium.

The *anomeric effect* is the tendency for an electronegative hydroxy or alkoxy substituent attached to an anomeric carbon in a pyran ring to prefer an axial orientation. In a pyran ring, when a hydroxy or alkoxy substituent assumes an axial configuration the dipoles of both oxygen atom are opposed. In an equatorial configuration, the dipoles of both oxygen atoms are partially aligned, and they repel. The axial configuration is lower in energy. An example is (*R*)-2-methoxytetrahydropoyran. Therefore, the anomer with an axial OH group at the anomeric carbon is usually preferred in a pyranose-aldehyde equilibrium.



(*R*)-2-Methoxytetrahydro-2H-pyran

The anomeric effect is apparent in the D-mannose mutarotation equilibrium, where the axial anomer α-D-mannopyranose is preferred, 68% α:32% β. The anomeric effect can be small and have little effect in carbohydrates if there are compensating structural features. In glucose the anomeric effect is small. Glucopyranose has all-equatorial substituents and there is a preference for β-D-glucopyranose (36% α:64% β). In water, the dipole effect is minimal, and solvation plays an important role.

Eusebio Juaristi (An online version of this photo can be found at
https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Professor Eusebio Juaristi (Mexico) is an organic chemist at the Centro de Investigacion y de Estudios Avanzados in Mexico City, Mexico. He does research on stereochemistry, conformational analysis, asymmetric synthesis and green chemistry. Professor Juaristi has developed new methods for the enantioselective synthesis of β-amino acids, designed new chiral organocatalysts for use in asymmetric synthesis, developed "green" chemistry methodology and does research in computational chemistry.

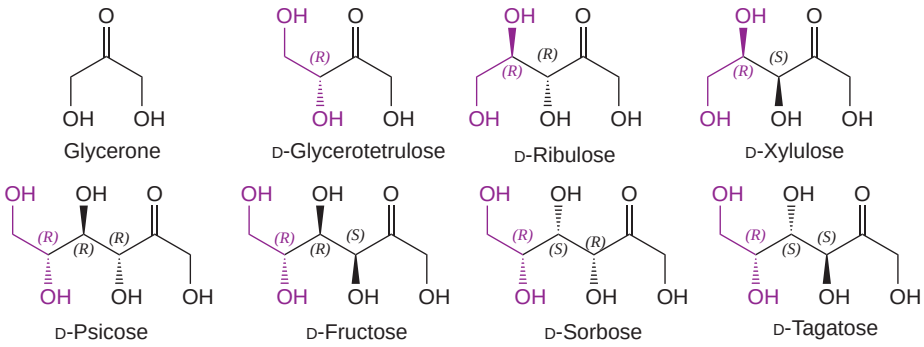
He is a world leader in the study of the anomeric effect.[1] Professor Juaristi has examined the increased reactivity of nucleophilic sites with a lone pair at an adjacent atom, which is known as the *α-effect*.[2] This effect has also been described as "a positive deviation from Brønsted-type nucleophilicity plots in comparison with a reference nucleophile of the same basicity".[3] This effect varies for different reactions and will sometimes disappear. Professor Juaristi has shown that the effect of an adjacent lone pair on the donor ability of another lone pair depends on several factors, including the electronegativity effects on hybridization and energy of lone pairs.[4] The α-effect also depends on the number of stereoelectronically active lone pairs present at the α-heteroatom. The effect is strikingly different for nitrogen and oxygen. Increasing the electronic "push" by making the α-position negatively charged led to a small to moderate increase in anomeric stabilization, suggesting activation of the α-effect. However, the overall stabilization is weaker than expected from a large increase in the stereoelectronic component, indicating that in the anionic systems the electrostatic components mask the role of stabilizing orbital interactions.

25.9 If α-D-galactopyranose has a specific rotation of +150.7, α-D-galactopyranose has a specific rotation of +52.8, and the mutarotation value is +80.2°, draw all three equilibrium structures and calculate the relative percentages of the two galactopyranose structures.

Ketone Monosaccharides

25.1.4 KETOSE MONOSACCHARIDES

Just as there are many aldose monosaccharides there are many ketose monosaccharides. This section will focus only on the D-diastereomers as with the aldoses. The triose is 1,3-dihydroxypropan-2-one (also called *glycerone*) and the tetrose is *D-glycerotetrulose*. There are two pentoses named *D-ribulose* and *D-xylulose*. There are four hexoses named *D-psicose, D-fructose, D-sorbose,* and *D-tagatose*. D-Diglycerotetrulose is a ketotetrose, D-ribulose is a ketopentose, and D-psicose is a ketohexose. Technically, ketoses generate hemi-ketals. However, the ketal nomenclature is not used and in modern nomenclature, so they are acetals (Section 16.4.2). In other words, ketoses generate hemi-acetals.



[1] Juaristi, E.; Cuevas, G. *The Anomeric Effect* CRC Press, Boca Raton, FL, 1995.
[2] Edwards, J.O.; Pearson, R.G. *Journal of the American Chemical Society* 1962, 84, 16–24.
[3] (a) Gold, V. *Pure and Applied Chemistry* 1979, 51, 1731–1753; (b) Hoz, S.; Buncel, E. Israel *Journal of Chemistry* 1985, 26, 313–319.
[4] Juaristi, E.; Gomes, G.d.P.; Terent'ev, A.O.; Notario, R.; Alabugin, I.V. *Journal of the American Chemical Society* 2017, 139, 10799–10813.

Cyclization via the OH unit at C5 will lead to furanose derivatives as the preferred structure but furanose can also cyclize via the C6 OH unit to give pyranose anomers. α-D-Fructofuranose:β-D-fructofuranose in Figure 25.4 are in equilibrium with α-D-fructopyranose:β-D-fructopyranose. Similarly, β-D-sorbofuranose:α-D-sorbofuranose are in equilibrium with α-D-sorbopyranose:β-D-sorbopyranose. The relative percentages for fructose, for example, are 2.5% of α-D-fructopyranose, 65% of α-D-fructopyranose, 6.5% of

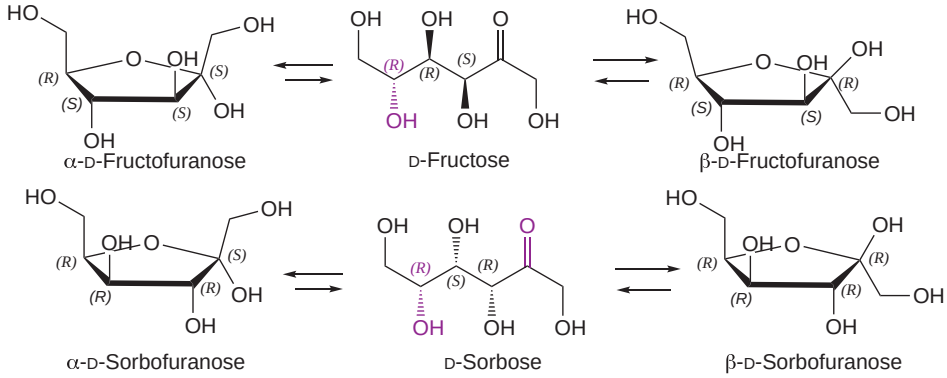


FIGURE 25.4 D-Sorbofuranose and D-fructofuranose.

β-D-fructofuranose, and 25% of β-D-fructofuranose.[5] Not all keto derivatives yield significant amounts of both furanose and pyranose derivatives. D-Xylose, for example, forms 36.5% of α-D-xylopyranose and 63% of β-D-xylopyranose, but <1% of xylofuranose derivatives (Figure 25.5).

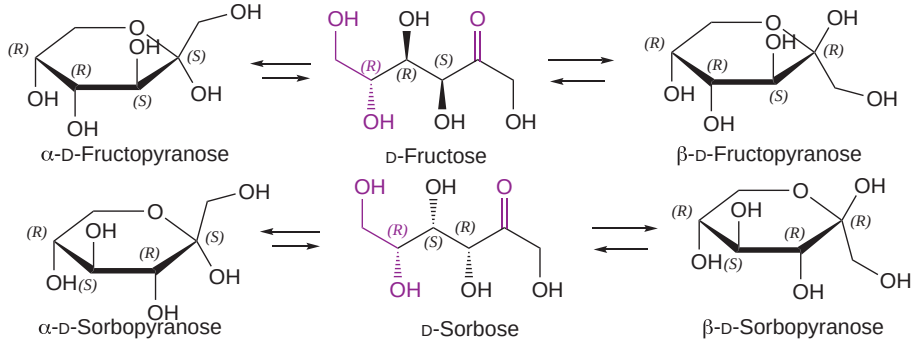


FIGURE 25.5 D-Sorbopyranose and D-fructopyranose.

25.10 Draw L-glycerotetrulose and L-xylulose.
25.11 Draw the structure of α-D-tagatofuranose, β-D-psicopyranose, and β-D-psicofuranose.

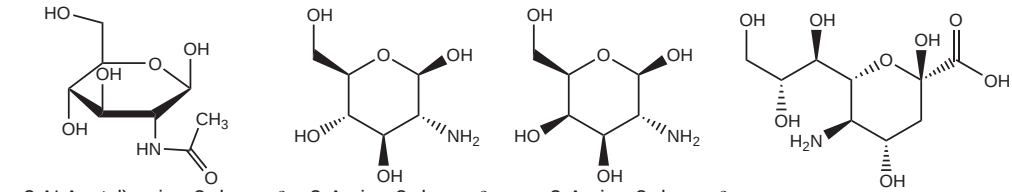
Amino Sugars

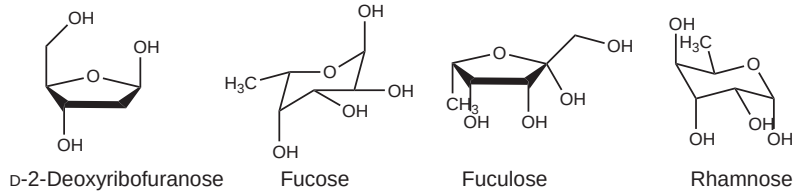
25.1.5 AMINO SUGARS

An amino sugar is a molecule in which a hydroxyl group has been replaced with an amine group. More than 60 amino sugars are known. An important amino sugar is *glucosamine*, a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids. Glucosamine is part of the structure of chitosan and chitin, and it is one of the most abundant monosaccharides. Perhaps the most abundant amino sugars is *N*-acetyl-D-glucosamine (*GlcNAc*), which is 2-(*N*-acetylamino)-2-deoxy-β-D-glucopyranose. GlcNAc is part of the

[5] Binkley, R.W. *Modern Carbohydrate Chemistry* Marcel Dekker, NY, 1988, p. 80.

bacterial cell wall, and it is the monomeric unit of chitin, which forms the exoskeletons of insects and crustaceans. Another important amino sugar is *galactosamine*, a constituent of some glycoprotein hormones such as follicle-stimulating hormone and luteinizing hormone. Although *neuraminic acid* does not occur naturally, derivatives are widely distributed in the glycoproteins and gangliosides of animal tissues and in bacteria. The *N*- or *O*-substituted derivatives of neuraminic acid are collectively known as sialic acids, and *N*-acetylneuraminic acid is the predominant form in mammalian cells. Deoxy sugars are important; the best known is *2-deoxyribose* which is a constituent of DNA (25.6). Other important deoxy sugars are *fucose* (5-deoxy-L-galactose), which is a major component of fucoidan found in brown algae and in N-linked glycans. *Fuculose* (6-deoxy-L-tagatose) is found in avian influenza virus and *rhamnose* (6-deoxy-L-manose is found in plant glycosides.





Carolyn Bertozzi (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Disaccharides and Trisaccharides

Carolyn Bertozzi (USA) is professor of chemistry at Stanford University; she is the Baker Family Director of Stanford ChEM-H. Professor Bertozzi's research interests span the disciplines of chemistry and biology with an emphasis on studies of cell surface sugars important to human health and disease. The Bertozzi group develops chemical tools to study the glycobiology underlying diseases such as cancer, inflammation, tuberculosis and most recently COVID-19. Her research group profiles changes in cell surface glycosylation associated with cancer, inflammation and bacterial infection, She uses this information to develop new diagnostic and therapeutic approaches, most recently in the area of immuno-oncology. Professor Bertozzi has developed antibody-sialidase conjugates that enhance tumor cell susceptibility to antibody-dependent cell-mediated cytotoxicity (ADCC) by selective desialylation of the tumor cell glycocalyx. This work focuses on cancerous tumors that can evade the immune system by the presentation of sugars, called sialic acids to the cell surface's sugar coating, or

glycocalyx. As noted, the *N*- or *O*-substituted derivatives of neuraminic acid are collectively known as sialic acid. The amino group bears either an acetyl or a glycolyl group. The Bertozzi group has designed biotherapeutic molecules, termed "antibody-enzyme conjugates" that selectively remove sialic acids from tumor cells. Chemical fusion of a recombinant sialidase to the human epidermal growth factor receptor 2 (HER2)-specific antibody *trastuzumab* through a C-terminal aldehyde tag, as shown in Figure 25.6,[6] led to selective desialylation of the tumor cell glycocalyx. The antibody directs the enzyme to the cancer cells, the enzyme cleaves the sugars, and then the antibody directs immune cells to kill the desialylated cancer cells. This approach is based on the observation that cell surface sialosides constitute a

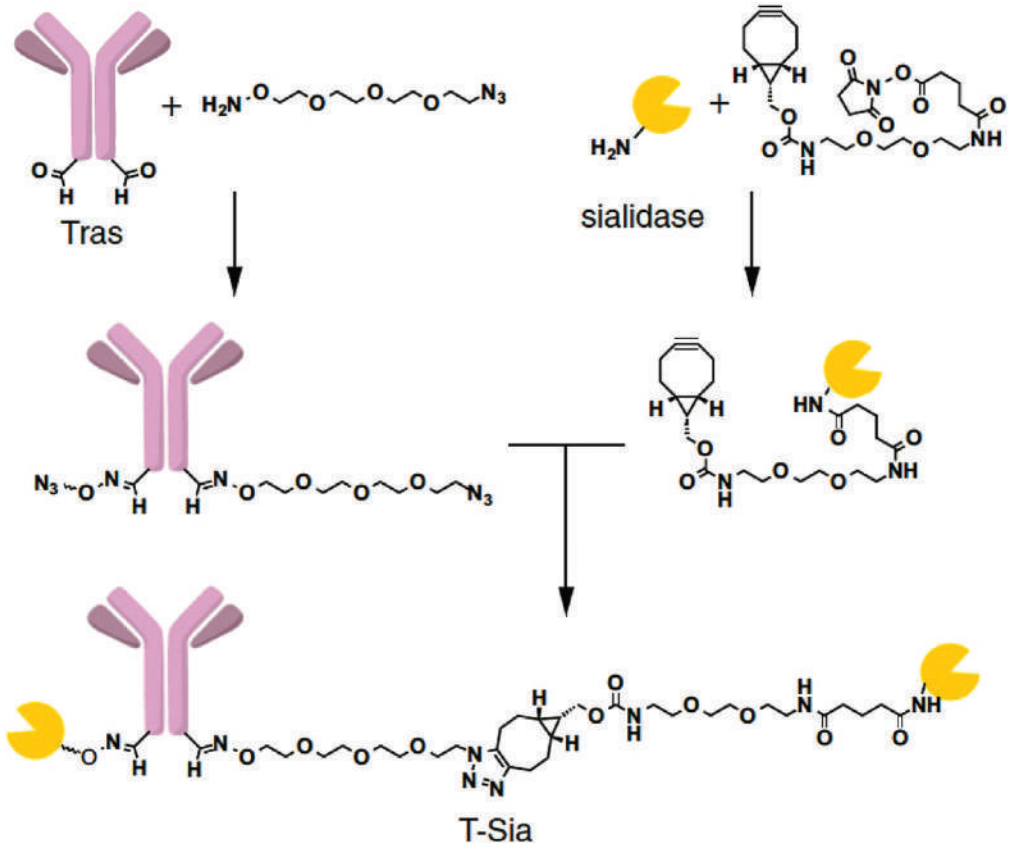


FIGURE 25.6 Preparation of antibody-sialidase conjugate. Xiao, H.; Woods, E.C.; Vukojicic, P.; Bertozzi, C.R. Permission from the *Proceedings of the National Academy of Science*, 2016, 113, 10304-10309, Figure 3A therein. P 10306

central axis of immune modulation that is exploited by tumors to evade both innate and adaptive immune destruction. Note that *Tras* is human epidermal growth factor receptor 2 (HER2)-targeting therapeutic monoclonal antibody *trastuzumab*. *Sialidase* (*neuraminidase*) enzyme is a glycoside hydrolase enzymes that cleaves the glycosidic linkages of neuraminic acids. Figure 25.6 shows the coupling of the antibody Tras bearing a C-terminal aldehyde tag to aminooxy-tetraethyleneglycol-azide (aminooxy- TEG-N3). Separately, *V. cholerae sialidase* was non-selectively functionalized on lysine residues with bicyclononyne-*N*-hydroxysuccinimide ester, and then conjugated to Tras adorned with the azide-functionalized

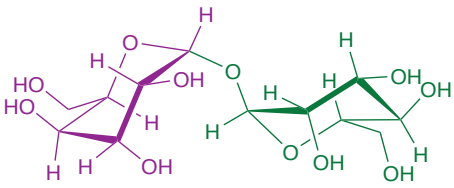
[6] Xiao, H.; Woods, E.C.; Vukojicic, P.; Bertozzi, C.R. *Proceedings of the National Academy of Science* 2016, 113, 10304–10309, Figure 3A therein. P 10306. Also see Woods, E.C.; Kai, F.; Barnes, J.M.; Pedram, K.; Pickup, M.W.; Hollander, M.J.; Weaver, V.M.; Bertozzi, C.R. *eLife* 2017, 6, e25752, pp. 1–15.

linker via copper-free click chemistry[7] (Section 23.1). More than 85% of the enzymatic activity remained after the chemical conjugation process.

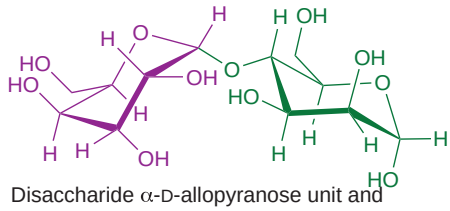
25.2 DISACCHARIDES, TRISACCHARIDES, OLIGOSACCHARIDES, AND POLYSACCHARIDES

A *disaccharide* is a molecule containing two sugar units, formed when two monosaccharides are coupled together by reaction of a hydroxyl unit of one saccharide with a carbonyl of the second saccharide to yield a *mixed acetal linkage*. The *anomeric partner* is usually the "glycosyl donor" and the *non-anomeric partner* is the "acceptor". The sugar units can exist in either the pyranose or furanose form and the reaction of two monosaccharides can, in principle, couple via any of the OH units. Many disaccharides are characterized by coupling at C1 of one saccharide to C1 of the second saccharide, or C1 to C4. In one example, the OH at C1 in α-D-allopyranose (from allose) was coupled to C1 (the anomeric carbon) of α-D-idopyranose (idose) to form the disaccharide. This coupling is said to be a (1→1) linkage where the first number is for the anomeric partner and the second number is for the non-anomeric partner. If C1 in α-D-allopyranose couples to the C4 hydroxyl of α-D-idopyranose, the disaccharide has a so-called (1→4) linkage. In the 1→4 linkage the anomeric (donor) partner is "1" and the non-anomeric (acceptor) partner is "4," so β-D-idopyranose is the anomeric partner.

In both disaccharides shown, the acetal oxygen is α- for both the allopyranose unit and the idopyranose unit. The (1→1) disaccharide is named *O*-α-D-allopyranosyl-(1→1)-α-D-idopyranose. The *allopyranose unit* is treated as a substituent so the *-ose* ending is dropped and replaced by *-osyl.*



Disaccharide α-D-allopyranose unit and α-D-idopyranose unit (1→1)



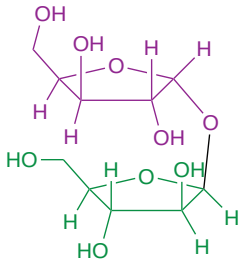
Disaccharide α-D-allopyranose unit and α-D-idopyranose unit (1→4),

In other words, an allopyranose is a allopyranosyl substituent and an idopyranose unit is an idopyranosyl substituent. The two monosaccharide units are linked together via an oxygen, as indicated by *O*- in the name. The carbon atoms of each monosaccharide that contribute to the ketal linkage are indicated by numbers reading from left to right (1→1). In this case it means that the C1 hydroxyl of the altropyranosyl unit is attached to the C1 hydroxyl of the mannopyranose unit via an acetal linkage. The (1→4) disaccharide is named *O*-α-D-allopyranosyl-(1→4)-α-D-idopyranose. It is also possible to couple a furanose unit to another furanose, or a furanose to a pyranose. When α-D-ribofuranose is coupled 1→1 to β-D-xylofuranose, the disaccharide is *O*-α-D-ribofuranosyl-(1→1)-β-D-xylofuranose. There are several possibilities for coupling, including ketofuranose and ketopyranose derivatives. Common table sugar is a ketopyranose disaccharide known as sucrose [α-D-glucopyranosyl-(1→2)-β-D-fructofuranoside], with fructose and glucose components.

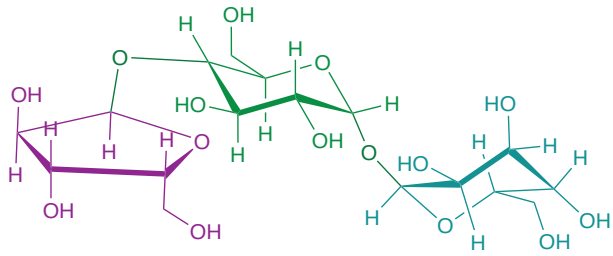
25.12 Draw the disaccharide formed by coupling the C2 hydroxyl of β-D-allopyranose with the C6 hydroxyl of α-D-idopyranose.

25.13 Draw the structures of O-β-D-altropyranosyl-(1→1)-α-D-mannopyranose and of O-β-D-altropyranosyl-(1→4)-α-D-mannopyranose.

[7] Hudak, J.E.; Barfield, R.M.; de Hart, G.W.; Grob, P.; Nogales, E.; Bertozzi, C.R.; Rabuka, F. *Angewandte Chemie International Edition* 2012, 51, 4161–4165.

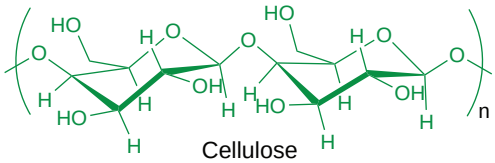


O-α-D-Ribofuranosyl-(1→1)-β-D-xylofuranose

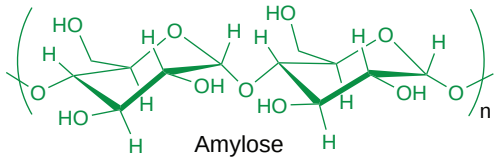


O-β-D-Ribofuranosyl-(1→4)-α-D-gulopyranosyl-(1→1)-α-D-allopyranose

Trisaccharides are named in the same way as the disaccharides. The trisaccharide shown is *O*-β-D-ribofuranosyl-(1→4)-α-D-gulopyranosyl-(1→1)-α-D-allopyranose and it is composed of ribofuranose, gulopyranose, and allopyranose. This nomenclature system applies to large oligosaccharides and polysaccharides, but the names can be quite long and clumsy. Carbohydrates are usually assigned a *three-letter code* (see Table 25.1)[8] that is used in conjunction with the letters *p (a pyranose) or f (a furanose)* to generate a shorthand name. Using this system, *O*-β-D-ribofuranosyl-(1→4)-α-D-gulopyranosyl-(1→1)-α-D-allopyranose becomes *O*-β-D-Rib*f*-(1→4)-α-D-Gul*p*-(1→1)-α-D-All*p*.



Cellulose

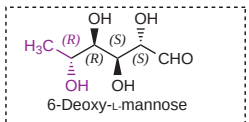


Amylose

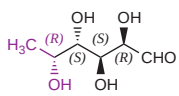
For polysaccharides, even the shorthand notation is unwieldy. Most of these compounds are given common names, and since they are usually polymeric only the repeating monosaccharide or disaccharide units are shown. Many of these saccharides are *homopolymers*, which means that the poly(saccharide) is formed by using only one monosaccharide unit. *Cellulose*, for example, a linear poly(glucopyranose), coupled in a (1→4)-β-D- manner and it is a major constituent of plant cell walls. *Amylose* (a constituent of starch) is a linear poly(glucopyranose) coupled (1→4)-α-D-Inulin (found in dandelions) is a linear fructofuranose coupled (2→1)-β-D-. There are branched poly(saccharides) as well as linear poly(saccharides). In other words, there is a linear chain with other polymeric chains branching from the main one.

TABLE 25.1 Three-Letter Codes Used to Represent Common Monosaccharides

Monosaccharide		Three-Letter Code
Allose		All
Altrose		Alt
Arabinose		Ara
Fructose		Fru
Fucose	(6-Deoxygalactose)	Fuc
Galactose		Gal
Glucose		Glc
Gulose		Gul
Idose		Ido
Lyxose		Lyx
Mannose		Man
Rhamnose	(6-Deoxy-L-mannose)	Rha
Talose		Tal
Xylose		Xyl



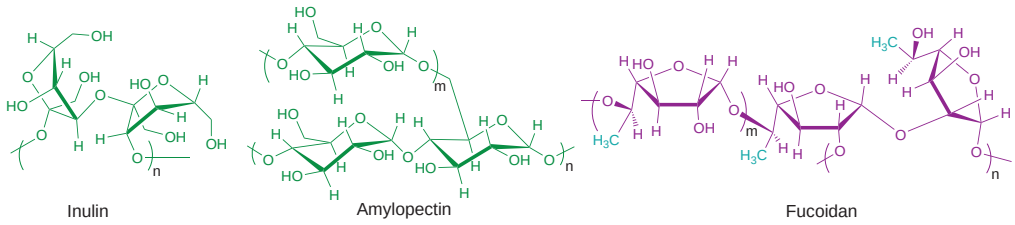
6-Deoxy-L-mannose



6-Deoxygalactose

[8] Kennedy, J.F.; White, C.A. *Bioactive Carbohydrates*, Ellis Horwood Ltd., Chichester, UK, 1983, p. 41.

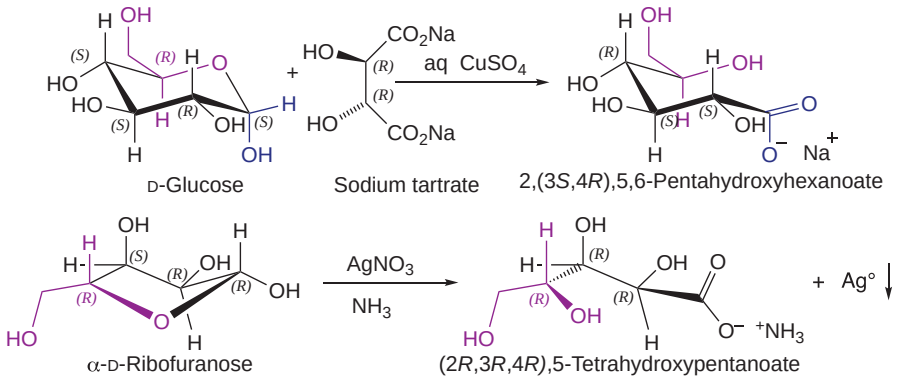
An example is amylopectin, another constituent of starch, which has a linear (1→4)-α-D-glucopyranosyl chain with (1→6)-α-D-glucopyranosyl branches. Similarly, *fucoidan* [found in brown seaweed (e.g. *Fucus distichus*)] has a (1→2)-α-L-fucosofuranosyl chain with (1→4)-α-L-fucosofuranosyl branches. Recall that α and β are reversed for the L series relative to the D series (Figure 25.2). The sugar fucose is 6-deoxygalactose. Therefore, fucofuranose has a methyl group at C6, as shown (in *cyan*). In addition to homopolymeric poly(saccharides), there are poly(saccharides) composed of more than one monosaccharide unit. For example, coniferous woods contain a poly(saccharide) that is a linear chain of D-glucopyranosyl and D-mannopyranosyl units. Plant cell walls also contain a poly(saccharide) that is a branched structure contains L-arabinofuranosyl and D-xylofuranosyl units.



25.3 REACTIONS OF CARBOHYDRATES

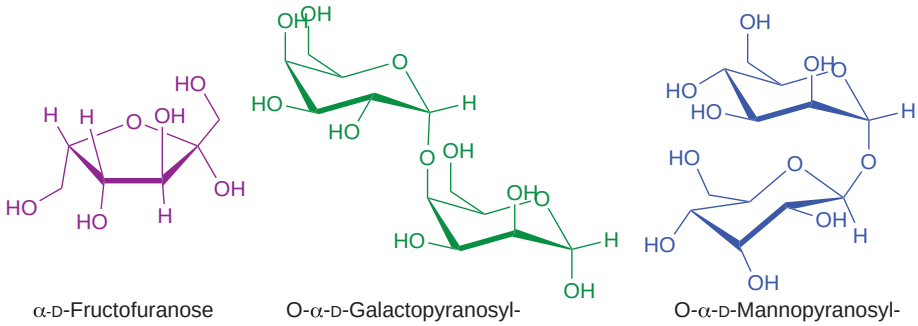
Carbohydrate Reactions

Carbohydrates are subject to many of the reactions of alcohols, aldehydes and ketones seen in previous chapters. The presence of multiple functional groups must be taken into consideration because one group may influence the reactivity of another. It may also be difficult to selectively do a reaction at one group without reaction at the others.



This discussion begins with the introduction of another classification scheme for carbohydrates. There are *reducing sugars* and *nonreducing sugars*. Sugars that react with *Fehling's solution* [heating in aqueous copper (II) sulfate and sodium tartrate] or with *Tollens's solution* (silver nitrate in ammonia) are reducing sugars. Fehling's solution reacts with the α-hydroxy aldehyde, α-hydroxyketone or α-ketoaldehyde units of carbohydrates to give the corresponding carboxylate salt along with the reduction of Cu(II) to Cu(I) oxide. The latter is a red-brown solid and is easily detected. Tollens's solution oxidizes a carbohydrate to a carboxylate salt and forms silver metal, which precipitates to produce an easily detected *silver mirror.* A silver mirror is a thin film of metallic silver deposits on the inner surface of a test tube. These reagents are named after Hermann von Fehling (Germany; 1812–1885) and Bernhard Tollens (Germany; 1841–1918). Carbohydrates that do not react with Fehling's or Tollens' reagent are known as nonreducing sugars. α-D-Fructofuranose is a nonreducing sugar. A disaccharide that is coupled 1→4 may have an aldehyde unit and be a reducing sugar.

A disaccharide coupled 1→1 cannot have an aldehyde unit available, and it is not a reducing sugar.



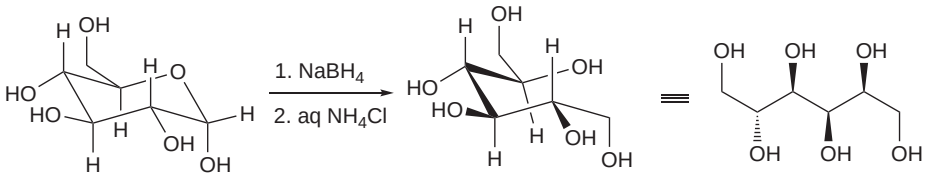
α-D-Fructofuranose

O-α-D-Galactopyranosyl-(1→4) α-D-talopyranose

O-α-D-Mannopyranosyl-(1→1)-β-D-altropyranose

Benedict's reagent is a mixture of sodium carbonate, sodium citrate and copper(II) sulfate pentahydrate and it is often used in place of Fehling's solution. A positive test with Benedict's reagent is shown by oxidation of the reducing sugar by the cupric (Cu^{2+}) complex of the reagent to produce a cuprous (Cu^{+}) salt. Benedict's test will detect the presence of an aldehyde, α-hydroxyl aldehydes and hemiacetals, including those found in some ketoses. In the disaccharide *O*-α-D-glucopyranosyl-(1→4)-α-D-talopyranose, the talopyranose unit can undergo mutarotation, which means there is an aldehyde unit available, so it is a reducing sugar. In *O*-α-D-mannopyranosyl-(1→1)-β-D-altropyranose, both anomeric carbons are tied up in the ketal linkage and mutarotation cannot occur, so no aldehyde unit is available to react, and it is not a reducing sugar.

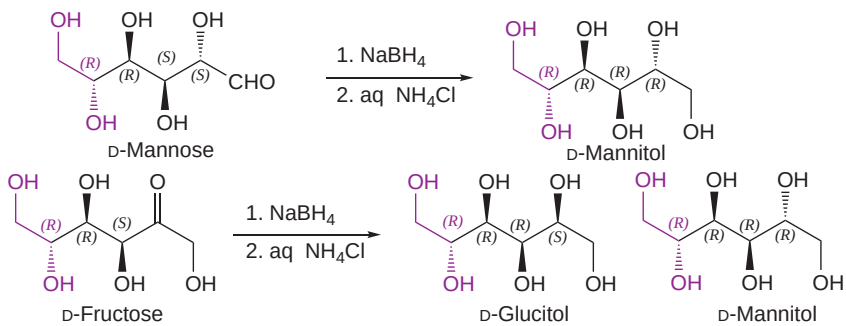
25.14 Draw the products of a reaction between erythrose and Tollens' reagent.
25.15 Categorize each as a reducing sugar or a nonreducing sugar: (a) O-α-D-Arap-(1→4)-α-D-Glcp; (b) O-α-D-Gulp-(1→1)-α-D-Manp; (c) O-α-D-Fruf-(1→3)-α-D-idop; (d) O-α-D-Araf-(1→1)-α-D-Glcp; and (e) O-α-D-Gulp-(1→1)-α-D-Glcp.



D-Glucopyranose

Hexane-1,(2*R*,3*R*,4*R*,5*S*),6-hexaol
(D-Glucitol; Sorbitol)

The carbonyl units of carbohydrates are easily reduced using traditional reducing agents. When D-glucopyranose is reduced with sodium borohydride, the product is a glycitol, hexane-1,(2*R*,3*R*,4*R*,5*S*),6-hexaol, known as D-glucitol or sorbitol. Most aldoses are similarly reduced, and the name of the poly-hydroxyl product is generated by dropping *-ose* and adding *-itol.* Sorbitol is a naturally occurring sweetening agent found in many berries, plums, apples, and in seaweed and algae.



D-Mannose

D-Mannitol

D-Fructose

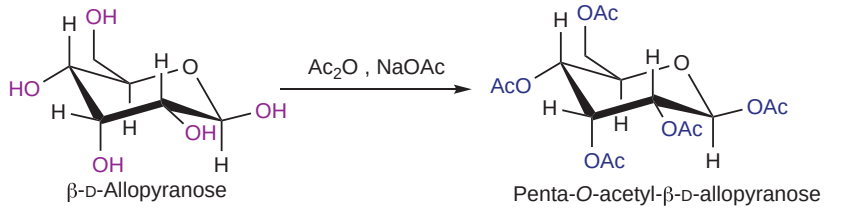
D-Glucitol

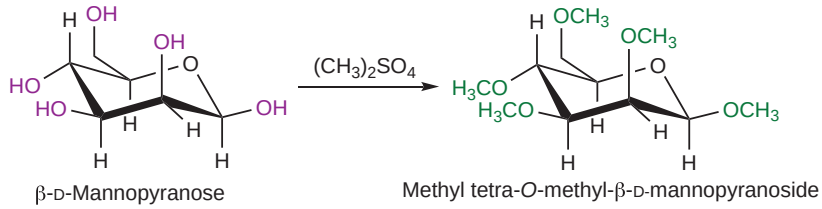
D-Mannitol

It is sold commercially and added to many foods, particularly candy, as a natural sweetening agent. Reduction of D-mannose gives D-mannitol, which is found in many plants, including seaweed, and is used to make artificial resins and plasticizers. The aldehyde unit of an aldose is reduced with sodium amalgam (Na/Hg), with Ni(R) in ethanol at reflux, or by catalytic hydrogenation. Reduction of a ketose leads to a diastereomeric mixture. Hydrogenation of D-fructose, for example, affords both the (*R*) and the (*S*) configuration at C2 when the carbonyl is reduced, a mixture of D-glucitol and D-mannitol.

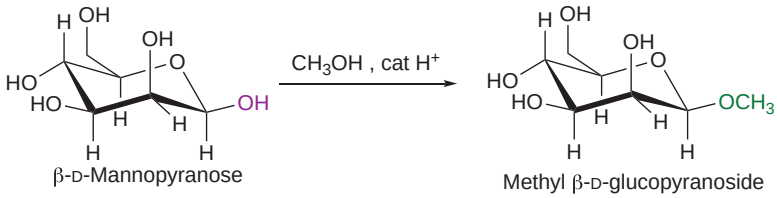
25.16 Draw the product formed when L-arabinose is reduced.
25.17 Draw and name the product formed by the catalytic hydrogenation of D-threose.

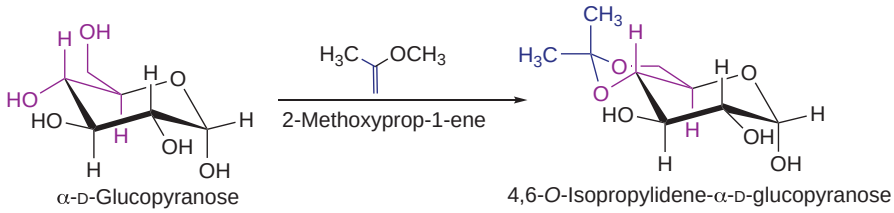
There are many hydroxyl sites in a carbohydrate and generally reagents react with all available hydroxyl units. When β-D-allopyranose reacts with acetic anhydride and sodium acetate, the product is the pentaacetate (penta-*O*-acetyl-β-D-allopyranose). Similar results are obtained when benzoyl chloride and pyridine are used.





When β-D-mannopyranose reacts with dimethyl sulfate [$(CH_3)_2SO_4$ is Me_2SO_4], the product is the pentaether (methyl tetra-*O*-methyl-β-D-mannopyranoside). Dimethyl sulfate is the dimethyl ester of sulfuric acid, and it is a common reagent for converting an OH unit to an OCH_3 unit. The suffix *-ide* is used rather than *-ose* for the ether. In some cases, the proper techniques allow one hydroxyl unit to react, leaving the others untouched.



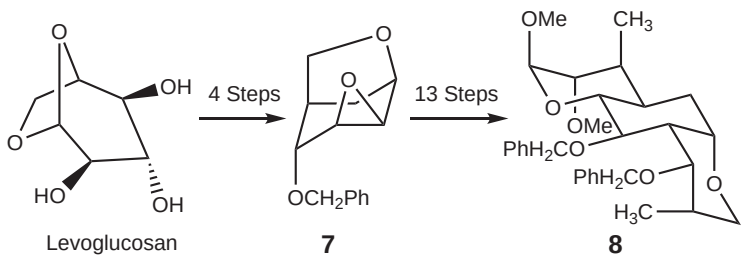


The reaction of β-D-mannopyranose and methanol with an acidic catalyst, affords methyl β-D-glucopyranoside. When a carbohydrate reacts with a vinyl ether (e.g., 2-methoxyprop-1-ene), the product is a ketal. The reaction of α-D-glucopyranose with this vinyl ether, in the presence of an acid catalyst, leads to a ketal, 4,6-*O*-isopropylidene-α-D-glucopyranose. This reaction essentially "protects" the C4- and C6-hydroxyl units as a 1,3-dioxane. The isopropylidene group is the $C(CH_3)_2$ unit, and the *O*-isopropylidene name refers to the presence of the acetone ketal unit.

25.18 Draw the structure of the pentabenzoyl derivative of α-D-glucopyranose.
25.19 Draw the product of a reaction between benzaldehyde and 4,6-O-benzylidene-α-D-glucopyranose.

Bertram Oliver "Bert" Fraser-Reid (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Bertram Oliver "Bert" Fraser-Reid (Jamaica-USA; 1934–2020) was a synthetic organic chemist at the University of Waterloo, Waterloo, Ontario and then at Duke University. He utilized chiral sugars as starting material that could be transformed into chiral natural products. Professor Fraser-Reid explored the role of oligosaccharides in immune responses,[9] and particularly on the effect of molecules on human diseases like malaria and AIDS. He established the Natural Products & Glycotechnology Research Institute in Pittsboro, North Carolina, a nonprofit, to study the carbohydrate chemistry/biology of tropical parasitic disease in developing countries and to develop a carbohydrate-based malaria vaccine. Professor Fraser-Reid developed the so-called *pyranosidic homologation* strategy for synthetic targets with multiple contiguous chiral centers. An application of this strategy was applied to the *ansa chain* of rifamycin S, with a tricyclic construct **8** as the target.[10] The starting material for this work was the known oxirane **7**,[11] which can be prepared from levoglucosan in four steps in 80% yield. Levoglucosan is obtained by vacuum pyrolysis of starch.[12] Compound **7** was converted to **8** in 13 steps, and further work was required to convert **8** to the ansa chain of rifamycin S. Rifamycin S is an ansamycin (from the Latin *ansa*, handle), which are lipophilic macrocyclic antibiotics comprised of two aromatic rings that are connected by a long chain. The chain confers a rigid character to the entire molecule. The pyranosidic homologation generates seven centers with complete stereoselectivity and/or regioselectivity, so no separation of isomers is required. Oxirane moiety **7** can be a synthon for pyranosidic homologation of other ansamycins.



Levoglucosan **7** **8**

[9] See Anilkumar, G.; Nair, L.G.; Fraser-Reid, B. *Organic Letters* 2000, 17, 2587–2589.
[10] Fraser-Reid, B.; Magdzinski, L.; Molino, B. *Journal of the American Chemical Society* 1984, 106, 731–734.
[11] Trana, T.; Cerny, M. *Collection of Czechoslovak Chemical Communications* 1971, 36, 2216–2225.
[12] Ward, R.B. *Methods of Carbohydrate Chemistry* 1963, 2, 394–396.

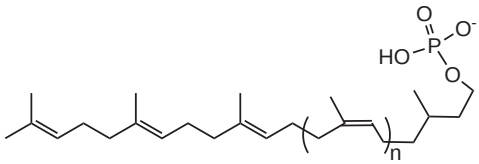
25.4 GLYCANS AND GLYCOSIDES

Glycans and Glycosides

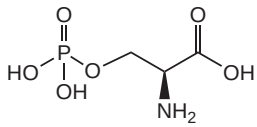
A *glycoside* is a molecule in which a carbohydrate is bonded to another group by a *glycosidic bond*. A glycosidic bond joins a functional group with the anomeric OH unit of a carbohydrate. Glycosides can be linked by a C- (a *C-glycoside*) an O- (an *O-glycoside*), N- (a *glycosylamine*), S- (a *thioglycoside*), P- (a *phosphoglycoside*) glycosidic bond. The carbohydrate group in a glycoside is known as the *glycon* and the non-sugar group as the *aglycon* or *genin* part of the glycoside. The glycon can consist of a single carbohydrate or several sugar groups.

Glycosylation is the reaction in which a carbohydrate (a glycosyl donor) is attached to a hydroxyl or other functional group of a protein, lipid, or another molecule (a glycosyl acceptor). The biological donor molecule is often an activated nucleotide sugar. While this process can be non-enzymatic glycosylation also refers to the enzymatic process that attaches glycans to proteins or other organic molecules. *Glycation* is the covalent attachment of a sugar to a protein or lipid and this non-enzymatic process is responsible for many complications in diabetes and is implicated in some diseases and in aging. Glycosylation is a form of co-translational and post-translational modification. Some proteins do not fold correctly unless they are glycosylated.

Glycans are chain-like structures that are composed of monosaccharides linked together by chemical bonds. Glycans are often polysaccharides, which are carbohydrate-based polymers made by all living organisms. They are essential biomolecules that are important in structure, energy storage and system regulation. *N*-linked glycosylation is the attachment of an oligosaccharide, a glycan, to a nitrogen atom such as the amide unit of an asparagine residue of a protein. The anomeric carbon of the sugar binds to a free hydroxyl group.



Dolichol phosphate



Phosphoserine

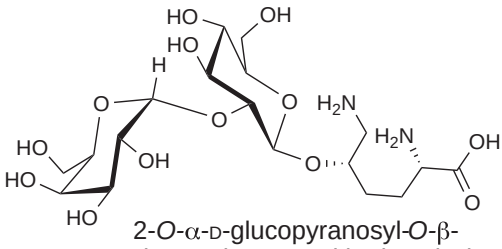
The structure of these saccharides varies depending on the structure of the molecules to which they bind. *N*-Glycosylation requires participation of a special lipid called *dolichol phosphate*. More than half of all human proteins are glycoproteins, and *N*-glycans constitute a major portion of glycoproteins.[13] *N*-Glycans are delivered to a (poly)peptide chain as a lipid-linked oligosaccharide. *O*-linked glycans are attached to the hydroxyl oxygen of a serine, threonine, tyrosine residue in a protein or a lipid (e.g., ceramide). Phosphoglycans are linked through the phosphate of a *phosphoserine*. *C*-Linked glycans have a sugar added to a carbon on a tryptophan side-chain.

Glycolipids are lipids with a carbohydrate attached by a glycosidic bond. They maintain the stability of the cell membrane and facilitate cellular recognition, which is important to form tissue. The essential feature of a glycolipid is the presence of a monosaccharide or oligosaccharide bound to a lipid moiety such as a glycerolipid or a sphingolipid. The saccharides that are attached to the polar head groups on the outside of the cell are the ligand components of glycolipids. They are polar and soluble in the aqueous environment surrounding the cell.

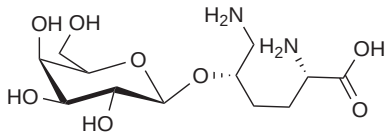
Cervical spinal cord injury alters the collagen metabolism of the affected patients,[14] which can be monitored by measuring the urinary excretion of collagen metabolites.[15] Two collagen metabolites are the *O*-glycosides glucosylgalactosyl hydroxylysine and galactosyl hydroxylysine. The former metabolite is prevalent in skin collagen. An increased presence in urine is associated with patients that have erythema multiforme (a hypersensitivity reaction

[13] Apweiler, R.; Hermjakob, H.; Sharon, N. *Biochimica et Biophysica Acta* 1999, 1473, 4–8.
[14] Claus-Walker, J. *International Journal of Rehabilitation Research* 1980, 3, 540–541.
[15] Rodriguez, G.P.; Claus-Walker, J. *Journal of Chromatography* 1984, 308, 65–73.

associated with certain infections as an acute and sometimes recurring skin condition) or burns. The latter metabolite is prevalent in bone collagen and increased presence in patients is associated with bone disease such as osteomalacia or Paget's disease.

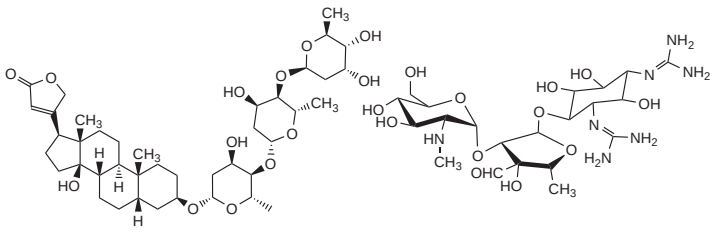


2-*O*-α-D-glucopyranosyl-*O*-β-D-galactosylpyranosyl hydroxylysine



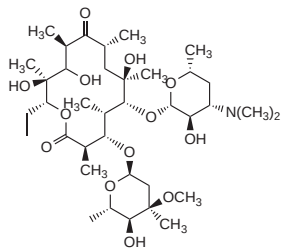
O-β-D-galactosylpyranosyl-hydroxylysine

Many antibiotics and other medicines are glycosides, and the carbohydrate portion of the drug is often essential for full potency. The drug without the pendant carbohydrate is called the aglycon. An example is the cardiac glycoside *digitoxin*, isolated from foxglove (*Digitalis purpurea*). *Streptomycin* is an aminoglycoside antibacterial antibiotic produced by the soil actinomycete *Streptomyces griseus*. It acts by binding to the 30S ribosomal subunit of susceptible organisms, which disrupts the initiation and elongation steps in protein synthesis. *Erythromycin* is a broad-spectrum, macrolide antibacterial that diffuses through the bacterial cell membrane to reversibly bind to the 50S subunit of the bacterial ribosome. This binding prevents bacterial protein synthesis.



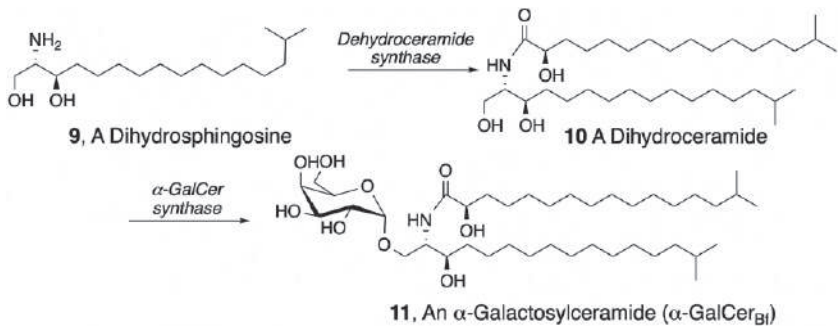
Digitoxin

Stryptomycin



Erythromycin

The enzymatic coupling of carbohydrates to other large molecules gives glycosides that are biologically important. Examples are glycolipids, glycopeptides, glycoproteins, and glyconucleotides. Relatively simple examples of a glycolipid are the sphingolipids. Galactosylceramide (GalCer) is the principal glycosphingolipid in brain tissue with the trivial name "cerebroside".



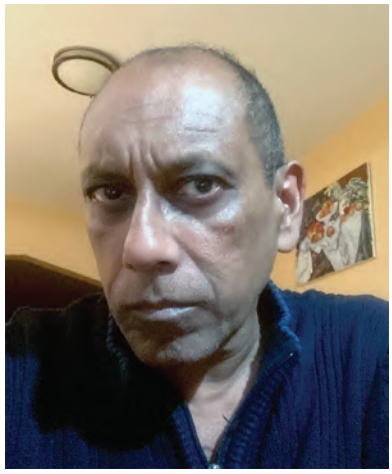
9, A Dihydrosphingosine

10 A Dihydroceramide

11, An α-Galactosylceramide (α-GalCer$_{BI}$)

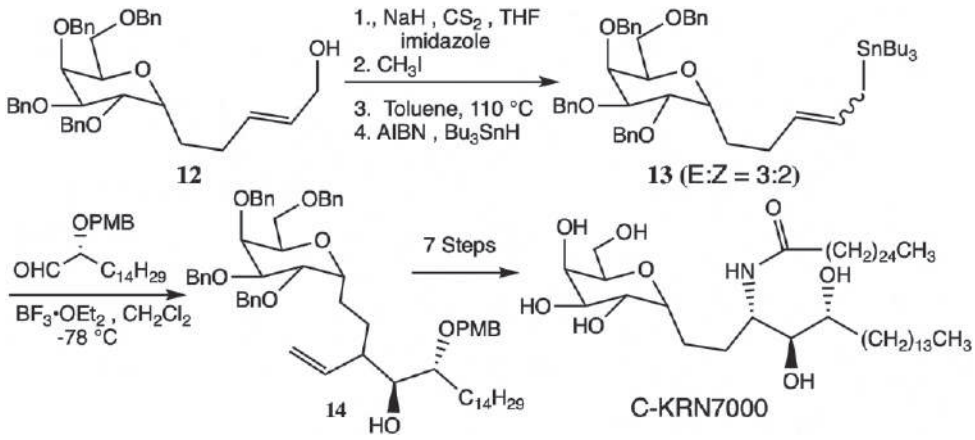
The β-D-galactosylceramides are found in all nervous tissues and they are major constituents of oligodendrocytes in brain tissue. Typically, sphingosine is the main long-chain base in cerebrosides of animal tissues. *Bacteroides fragilis,* an anaerobic, Gram-negative, rod-shaped bacterium, produces an isoform of a galactosylceramide, which is a sponge-derived

sphingolipid. *Bacteroides fragilis* biosynthesize a dihydrosphingosine, **9**, which is converted by *dihydroceramide synthase* to dihydroceramide, **10**. The glycosylation step uses α-*GalCer synthase* to form α-GalCer$_{Bf}$, the α-galactosylceramide, **11**. [16]



David Mootoo (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

David Mootoo (USA) is a professor of chemistry at Hunter College. Professor Mootoo's research centers on the design and synthesis of molecular probes for biological pathways, with the ultimate goal of elucidating disease processes and devising new therapeutic strategies. His interests span two broad categories of molecules, unnatural analogues of disease-related carbohydrates and natural products with unique biological activity. Representative projects are synthetic methods for tailored glycomimetics, and applications of immunoactive glycolipids, carbohydrate-based antiviral agents and tumor targeting cytotoxic agents.



The glycolipid KRN7000 (α-galactosylceramide) is isolated from a marine sponge, and it has a novel α-galactosylceramide (α-GalCer) structure that was found to exhibit potent antitumor activity in a variety of experimental and spontaneous tumor metastasis models. The antitumor effects were shown to be attributable to natural killer (NK) cell activation and the antigen presentation function of dendritic cells. NKT cells have a range of characteristics

[16] Brown, L.C.W.; Penaranda, C.; Kashyap, P.C.; Williams, B.B.; Clardy, J.; Kronenberg, M.; Sonnenburg, J.L.; Comstock, L.E.; Bluestone, J.A.; Fischbach, M.A. *PLOS Biology* 2013, 11, e1001610.

that distinguish them from conventional T and NK cells, including their remarkable capacity to produce immunoregulatory cytokines upon stimulation. Presentation to invariant natural killer T (iNKT) cells stimulates the production of cytokines that lead to differentiation of T helper cells into Th1 or Th2 cells.[17] Professor Mootoo proposed a synthesis of KRN7000 analogs that centered on the reaction of carbohydrate derived crotylstannanes with relatively simple aldehydes, followed by elaboration of the crotylation products.[18] Galactose derivative **12** was first converted to the xanthate derivative by reaction with NaH, carbon disulfide and then iodomethane. Thermal rearrangement and in situ treatment of the resulting secondary dithiocarbonate with Bu_3SnH in the presence of AIBN gave crotyltin **13** with an E:Z ratio of 3:2, in 57% overall yield from **12**. Addition of the *E:Z* mixture of **13** to a preincubated mixture of (*R*)-2-((4-methoxybenzyl)oxy)hexadecanal and $BF_3{\bullet}OEt_2$ in dichloromethane solution at -78°C gave diastereomeric mixtures from which **14** was isolated in 38% yield. This alcohol was converted in 7 steps to C-KRN7000, a hydrolytically stable analog of KRN7000 in which the glycosidic "O" is replaced by "CH_2". Note that OBn is $-OCH_2Ph$ and OPMB is *p*-methoxybenzyl.

Laura Lee Kiessling (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Laura Lee Kiessling (USA) is the Novartis Professor of Chemistry at the Massachusetts Institute of Technology. Professor Kiessling's research focuses on the elucidation and exploitation of interactions on the cell surface, particularly those mediated by proteins binding to carbohydrates. Understanding and manipulating multivalent protein-carbohydrate interactions allows the study biological processes and the design therapeutic treatments. Her research combines organic synthesis, polymer chemistry, structural biology, and molecular and cell biology. She has synthesized and studied many biologically active molecules, including glycosyl peptides glycopolymers and modified peptides.

Mycobacteria, including the pathogen *Mycobacterium tuberculosis*, possess a mycolic acid membrane that is a barrier to antibiotics. Control and manipulation of bacterial populations requires an understanding of the factors that govern growth, division, and antibiotic action. Fluorescent and chemically reactive small molecule probes of cell envelope components can help to visualize these processes and advance our knowledge of peptidoglycan production. Professor Kiessling has synthesized a fluorogenic analog of *trehalose monomycolate*, the building block used by *mycolyltransferase* enzymes to construct the mycolic acid membrane.[19] This probe, quencher-trehalose-fluorophore (QTF), is an analog of the natural *mycolyltransferase* substrate. When the QTF is processed in cells by *mycolyltransferases*, fluorescence monitoring allows mycolic acid membrane biosynthesis to be followed in real time over several generations. The QTF probe therefore reports

[17] (a) Pei, B.; Vela, J.L.; Zajonc, D.; Kronenberg, M. *Annals of the New York Academy of Sciences* 2012, 1253, 68–79 (b) Rossjohn, J.; Pellicci, D.G.; Patel, O.; Gapin, L.; Godfrey, D.I. *Nature Reviews Immunology* 2012, 12, 845–857.
[18] Altiti, A.S.; Bachan, S.; Mootoo, D.R. *Organic Letters* 2016, 18, 4654–4657.
[19] Hodges, H.L.; Brown, R.A.; Crooks, J.A.; Weibel, D.B.; Kiessling, L.L. *Proceedings of the National Academy of Science* 2018, 115, 5271–5276. See Figure 1, p. 5272.

on the *mycolyltransferases* that assemble the mycolic acid membrane. This peptidoglycan-anchored bilayer-like assembly functions to protect these cells from antibiotics and host defenses. A robust increase in fluorescence occurred upon QTF exposure to Ag85A, Ag85B, or Ag8C, the three catalytically active *mycolyltransferases* of *M. tuberculosis*. The features of QTF are shown in Figure 25.7.[19] Assembly A shows components of the mycobacterial cell envelope that include the peptidoglycan-anchored mycolyl-arabinogalactan (mAG) complex. The *mycolyltransferases*, including the antigen 85 complex (Ag85) of *M. tuberculosis*, construct the mycolic acid membrane by processing endogenous trehalose monomycolate (TMM) to afford trehalose dimycolate (TDM) or mycolyl-arabinogalactan (mAG). Shown in Figure 25.7(*B*) QTF is a TMM mimic bearing a fluorophore and quencher. When *mycolyltransferases* process QTF a fluorescent signal is generated. In Figure 25.7 (*C*) the chemical structure of TMM and QTF are shown, and exposure of QTF to Ag85 leads to cleavage products Q-Tre and lipid-FL.

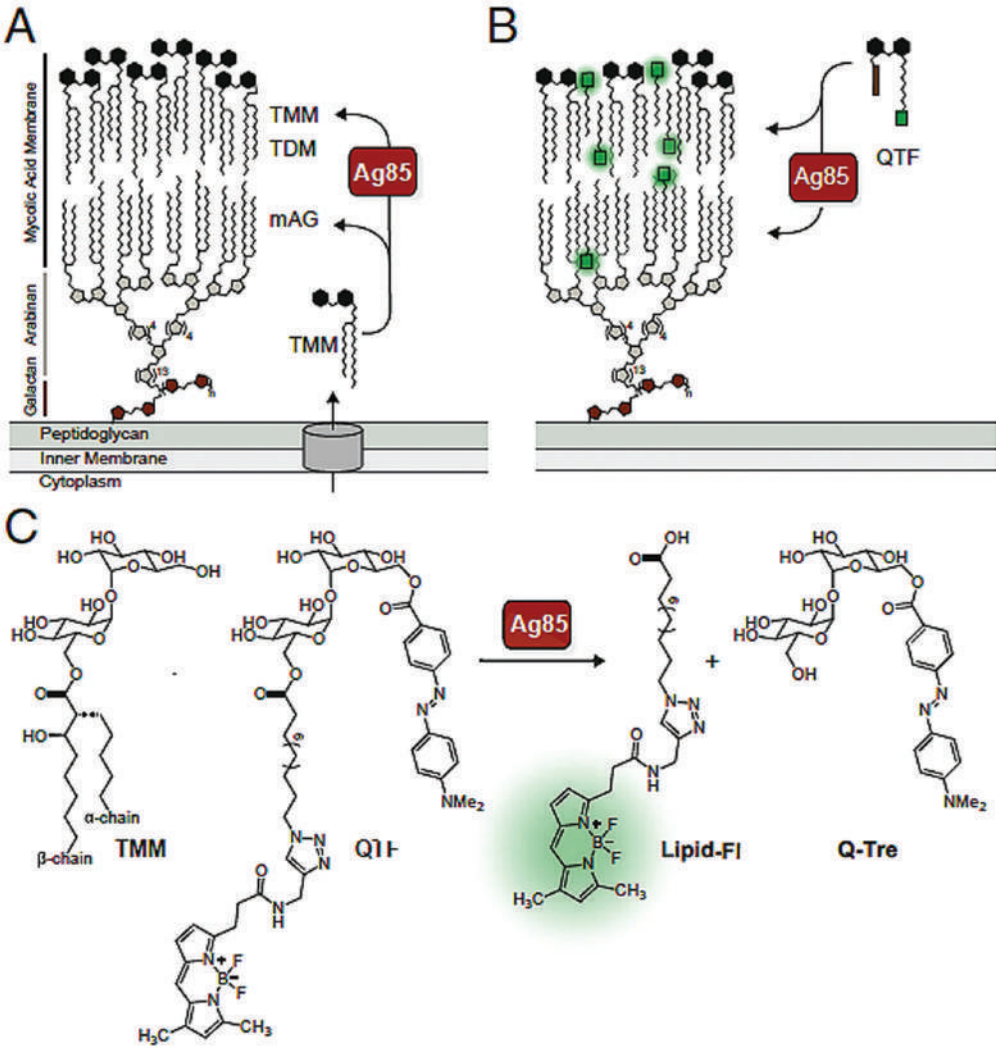


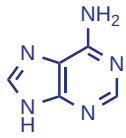
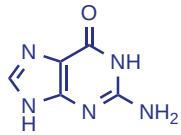
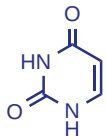
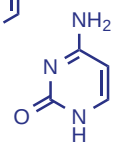
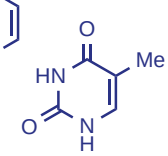
FIGURE 25.7 Features of QTF, a fluorogenic probe of Ag85-mediated cell wall biogenesis. Permission from Hodges, H.L.; Brown, R.A.; Crooks, J.A.; Weibel, D.B.; Kiessling, L.L. *Proceedings of the National Academy of Science*, 2018, 115, 5271-5276. See Figure 1, p 5272

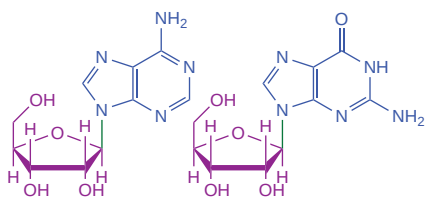
Nucleotides and Nucleosides

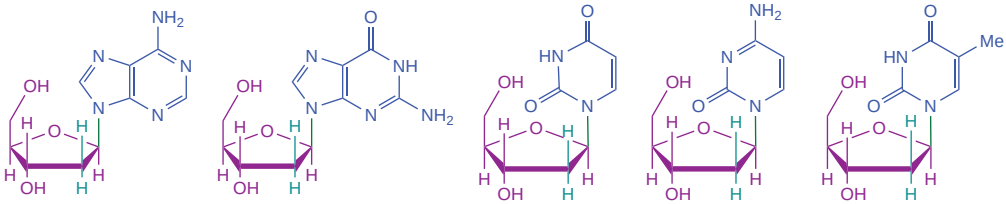
25.5 BIOLOGICAL RELEVANCE: NUCLEOSIDES AND NUCLEOTIDES

Ribose-purine and ribose-pyrimidine components make up ribonucleic acids (RNA) and deoxyribose-purines and deoxyribose-pyrimidines make up deoxyribonucleic acids (DNA). Ribonucleic acids and deoxyribonucleic acids are biopolymers made up of repeating deoxyribofuranose or ribofuranose units. A ribofuranose with a purine or pyrimidine attached at the anomeric carbon (C1) is called a *ribonucleoside*, or simply a *nucleoside*. There are five particularly important heterocycles attached to D-ribofuranose or D-deoxyribofuranose: two purine derivatives and three pyrimidine derivatives. The purines are *adenine* and *guanine* and the pyrimidines are *uracil, cytosine* and *thymine* (Table 25.2). The heterocycles bound to the ribofuranose unit are known as *nucleobases*.

TABLE 25.2 One-Letter Codes for Heterocyclic Amines

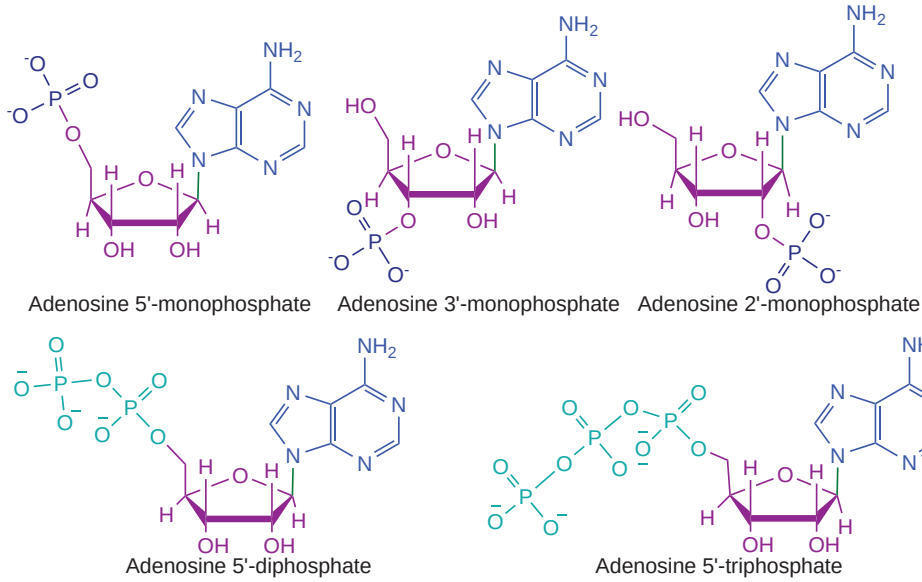
Heterocycles (Bases, B)	Structure	One-Letter Code
Adenine		A
Guanine		G
Uracil		U
Cytosine		C
Thymine		T





25.20 Draw (a) the arabinofuranose formed when it is coupled to cytosine and (b) the xylofuranose formed when it is coupled with guanine.

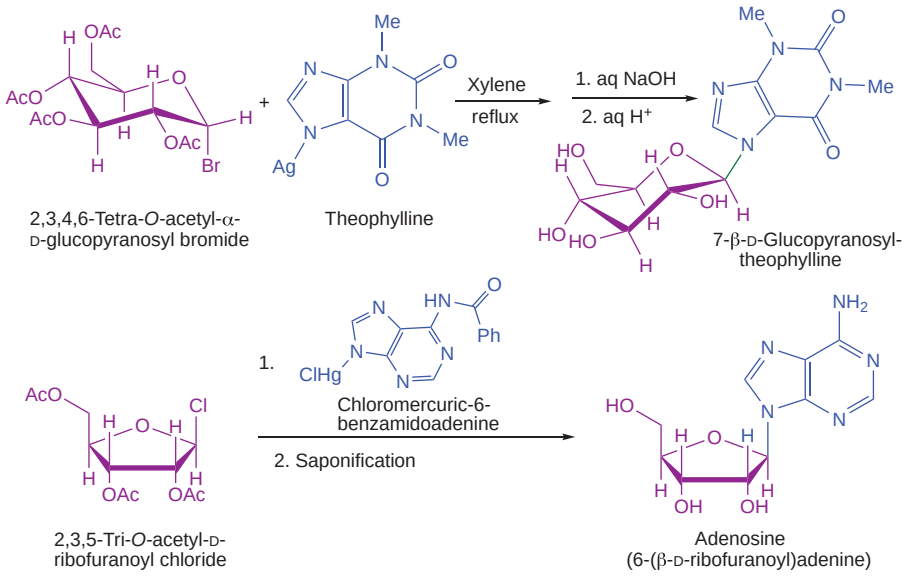
Each nucleoside can be converted to a phosphate ester. *The phosphate ester of a nucleoside is called a ribonucleotide or simply a nucleotide*. Using adenosine derivatives as an example, there are three possible monophosphate esters, adenosine 5'-monophosphate, adenosine 3'-monophosphate, and adenosine 2'-monophosphate. A nucleotide with a second attached phosphate unit is a diphosphate (e.g. adenosine 5'-diphosphate), and a third phosphate unit is seen in adenosine 5'-triphosphate. The monophosphate is abbreviated AMP, the diphosphate is ADP, and the triphosphate is ATP. These abbreviations derive from the one-letter code A for adenine (see Table 25.2).



Four nucleobases bound to a ribose unit are of particular importance for RNA, namely purine derivatives adenosine and guanosine and pyrimidine derivatives uridine and cytidine. Five nucleobases bound to a 2'-deoxyribose unit are important in DNA, purine derivatives 2'deoxyadenosine and 2-deoxyguanosine and pyrimidine derivatives 2'deoxyuridine, 2'deoxycytidine and thymidine. It is also possible to attach other nucleobases to ribofuranose molecules or even other furanose or pyranose units. The chemical synthesis of nucleosides and nucleotides is obvious of great interest.

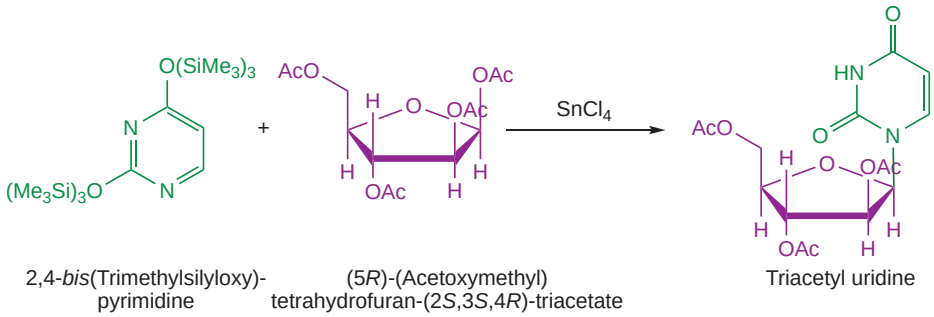
25.21 Draw the structure of (a) 5'-GMP, (b) 5'-UTP, and (c) 5'-TDP.

The first reported synthesis of this type of compound involved the reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with the silver salt of a purine called theophylline, heated together at reflux in xylene solution. Subsequent removal of the acetate groups by saponification gave the coupled product, 7-β-D-glucopyranosyltheophylline. This compound was first synthesized by Emil Fischer and B. Helferich (Germany) in 1914.[20] This early work did not give good results in the reaction if pyrimidines were used because *O*-glycosides are formed rather than the desired *N*-glycosides.



[20] Fischer, E.; Helferich, B. *Berichte* 1914, 47, 210, 1377–1393.

A later improvement on this approach was the reaction of a chloromercury salt of the heterocyclic amine with a halo sugar. The reaction of chloromercuric-6-benzamidoadenine and 2,3,5-tri-*O*-acetyl-D-ribofuranoyl chloride, for example, gave to 6-(β-D-ribofuranoyl)adenine (adenosine) after removal of the acetyl groups and the *N*-benzyl protecting group. Pyrimidine derivatives can also be prepared, and other coupling methods are available.



2,4-*bis*(Trimethylsilyloxy)-pyrimidine

(5*R*)-(Acetoxymethyl) tetrahydrofuran-(2*S*,3*S*,4*R*)-triacetate

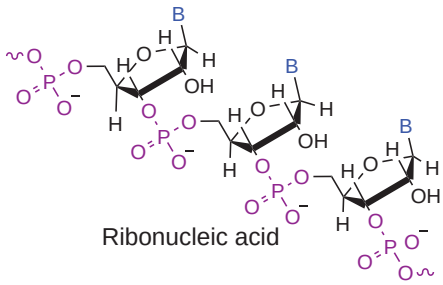
Triacetyl uridine

The *Vorbrüggen glycosylation* reaction[21] is an important reaction used by many nowadays to prepare many nucleosides. A silylated heterocycle such as 2,4-bis(trimethylsilyloxy) pyrimidine] is used. Reaction of this pyrimidine derivative and tetra-*O*-acetyl ribofuranose [(5*R*)-(acetoxymethyl) tetrahydrofuran-(2*S*,3*S*,4*R*)-triacetate] in the presence of a Lewis acid (e.g., $SnCl_4$ or $TiCl_4$) affords nucleoside derivative, triacetyluridine. Note that the silyl protecting groups are removed during a hydrolytic workup to reveal the uridine base. Other heterocyclic bases may be used in the reaction, but each base requires a unique set of protecting groups.

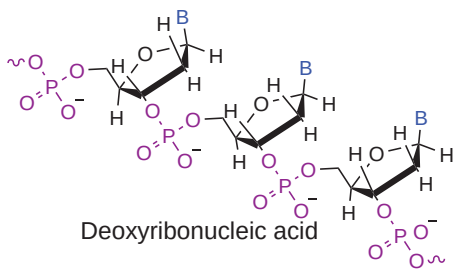
RNA and DNA

25.6 BIOLOGICAL RELEVANCE: POLYNUCLEOTIDES

Without question, the most important nucleotides are the purine and pyrimidine derivatives shown in Section 25.5. Nucleotides are long-chain nucleotides, or *polynucleotides,* such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). A purine or pyrimidine heterocycle is attached to the anomeric carbon of deoxyribose or ribose. Both DNA and RNA are linear polymers with a phosphodiester linkage between the 3' position of one nucleotide and it is linked to the 5'-position of the next nucleotide.



Ribonucleic acid



Deoxyribonucleic acid

This 3'→5' linkage continues as the polynucleotide chain is extended (nucleotides are added sequentially to the 3' end of the growing chain). In other words, both DNA and RNA

[21] (a) Niedballa, U.; Vorbrüggen, H. *Angewandte Chemie International Edition* 1970, 9, 461–462; (b) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chemische Berichte* 1981, 114, 1234–1255.

are oligo(sugar phosphates) with connective phosphorous units formed by linking nucleotides together by phosphodiester links at the 3' and 5' positions of the nucleotides. DNA and RNA are polymers with a phosphate backbone and a free 5' terminus at the "beginning" of the polymer and a free 3' terminus at the "end" of the polymer.

The fundamental difference between DNA and RNA is that DNA is missing a substituent at the C2' position of the ribofuranose unit. The structure of DNA usually consists of nucleotides containing the purines adenine (**A**) and guanine (**G**), as well as the pyrimidines cytosine (**C**) and thymine (**T**). Adenine, guanine and cytosine are incorporated into RNA, but uracil (**U**) is usually found rather than thymine (**T**). These differences affect the conformation for the two nucleic acids. Both DNA and RNA have a highly charged and polar sugar-phosphate "backbone" that is hydrophilic (solvated by water). The heterocyclic bases attached to the ribofuranose or deoxyribofuranose units are relatively hydrophobic (less solvated by water). These interactions lead to the secondary and tertiary structures of DNA and RNA.

Rosalind Franklin (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Dorothy Crowfoot Hodgkin (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Deoxyribonucleic acid is the repository of genetic information in cells. The major form of DNA under physiological conditions (those found in a normal cell) is the β-form, which consists of two anti-parallel stands. This *Watson-Crick double helix structure* was named after James D. Watson (USA) and Francis H.C. Crick (England; 1916–2004) who published the seminal paper on the double helix structure of DNA. The X-ray work of Nobel laureate Maurice Hugh Frederick Wilkins (New Zealand-England; 1916–2004) contributed to an understanding of the structure. In earlier work, Rosalind Franklin (England; 1920–1958) obtained X-ray crystallographic images of DNA with the goal of structure determination. She reportedly shared her images with Dorothy Crowfoot Hodgkin (Nobel laureate, England; 1910–1994), who assisted in the interpretation of the X-ray images. There is little doubt that X-ray crystallographic evidence such as this was critical for determining the structure of DNA, for which Watson and Crick shared the Nobel prize in 1962. Dorothy Hodgkin was awarded the Nobel prize in 1964 for her many contributions to understanding protein structure and the structure of important drugs such as penicillin. Rosalind Franklin died in 1958 of ovarian cancer and did not win a Nobel prize for her work, although her contributions to understanding the structure of DNA were recognized after her death.

The double helical structure is characterized by base pairs that feature intermolecular hydrogen bonds. An adenosine (**A**) nucleotide (called a *base* in DNA and RNA) can hydrogen bond with a thymine nucleotide (**T**) of the other strand (an **A-T** base pair) and a guanine nucleotide (**G**) base in one strand can hydrogen bond with a cytosine nucleotide (**C**) base in the other strand (a **G-C** base pair). The strands must be antiparallel (one strand extends 3'→5' while the other strand aligns 5'→3') to maximize hydrogen bonding. The inherent symmetry of the D-ribofuranose and the D-deoxyribofuranose compels the β-form of DNA to adopt a right-handed helix. Each base-pair plane is rotated ~ 36° relative to the one preceding it. This feature leads to a complete right-handed turn for every 10 contiguous base pairs and a helical pitch of ~ 34 Å (34 pm).[22] These hydrogen-bonding base pairs are called *Watson-Crick base pairs*. The **C–G** pair, as well as the **A-T** base pair are shown in Figure 25.8.[23]

The β-form leads to the presence of two helical grooves: the *major groove* and the *minor grove*, indicated in Figure 25.8. The major and minor groove arise because of the orientation

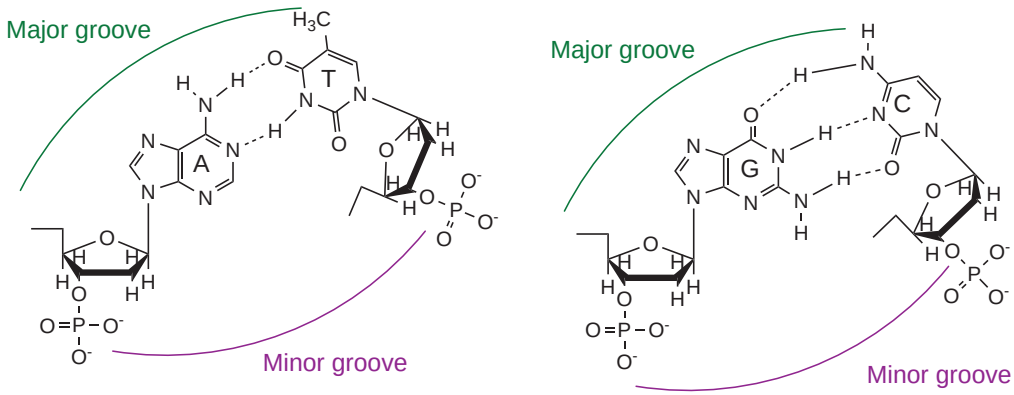


FIGURE 25.8 The C-G and T-A interactions. (Reprinted with permission and adapted from Figure 2 in Rajski, S.R.; Williams, R.M. *Chem Rev.*, 1998, 98, 2723–2796. Copyright 1998 American Chemical Society).

of the base pairs across the helix. The grooves separate the two sugar-phosphate backbones from each other, exposing the atoms in the grooves to the solvent and to interactions with proteins. The β-form is shown in Figure 25.9,[24] where the two stands are connected by hydrogen bonds between particular nucleotides on each strand (intermolecular hydrogen bonding).

[22] Hecht, S.M. (Ed.). *Bioorganic Chemistry: Nucleic Acids,* Oxford University Press, NY, 1996, p. 6.
[23] Adapted from Figure 2 in Rajski, S.R.; Williams, R.M. *Chemical Reviews* 1998, 98, 2723–2796.
[24] Adapted from Figure 6 in Liu, H.; Lynch, S.R.; Kool, E.T. *Journal of the American Chemical Society* 2004, 126, 6900–6905.

The minor groove is narrow, and the major grove is wide, but both are of about the same depth. When DNA interacts with small molecules or proteins, the major or minor groove provides a "microenvironment" for interactions with bound molecules, called ligands.[24] As the specific nucleotides in the stands of DNA change, the "floor" of each groove changes, leading to ligand sites specificity. There are two other forms of DNA, the A-form and the Z-form.[25] If the relative humidity of the β-form of DNA decreases to 75% and the sodium chloride concentration drops to < 10%, the β-form is transformed into the A-form helix.[25] The A-form is a right-handed helix; the Z-form of DNA adopts a left-handed helix, *but it is not simply the mirror image of the β-form or the A-form helices.*[25]

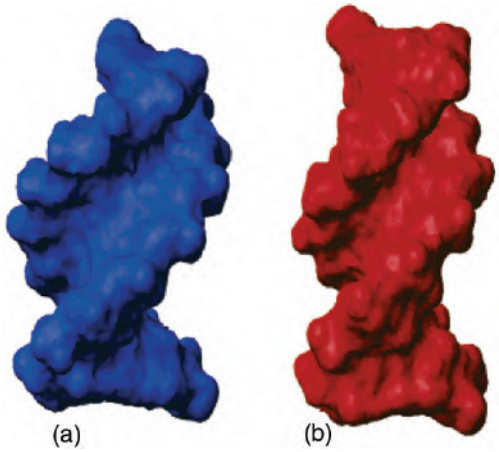


FIGURE 25.9 Space filling model of β-DNA: (a) major groove and (b) minor groove. [Reprinted with permission and adapted from Figure 6 in Liu, H.; Lynch, S.R.; Kool, E.T. *J. Am. Chem. Soc.*, 2004, 126, 6900. Copyright 2004 American Chemical Society].

DNA replication is the biological process that produces a second identical molecule of DNA from one original DNA molecule. DNA replication occurs in all living organisms and is essential for cell division during growth and repair of damaged tissues. DNA replication also ensures that each new cell receives its own copy of the DNA**,** which is essential since each cell can undergo division. DNA is made up of a double helix of two complementary strands. During replication, the two DNA-strands are separated. Each strand of the original DNA molecule serves as a template for production of its counterpart. This process is referred to as semi-conservative replication whereby the new helix is composed of an original DNA strand as well as a newly synthesized strand. Cellular mechanisms ensure nearly error-free DNA replication. In a cell, DNA replication begins at specific locations in the *genome*, which contains the genetic material of an organism. The genome includes both the genes and the noncoding DNA, as well as mitochondrial DNA and chloroplast DNA. The study of the genome is called *genomics*. An enzyme known as ***helicase*** unwinds DNA at the origin allowing the synthesis of new strands. Replication forks grow bi-directionally from the origin. Several proteins are associated with the replication fork to help in the initiation and continuation of DNA synthesis. An enzyme known as *DNA polymerase* directs the synthesis of the new strands by adding nucleotides that complement each (template) strand. DNA replication (DNA amplification) can also be performed artificially (outside of a cell) or in vitro. DNA polymerases isolated from cells and artificial DNA primers can be used to start DNA synthesis at known sequences in a template DNA molecule. A preliminary form of transport RNA is a necessary component of translation, which is the biological synthesis of new proteins in accordance with the genetic code.

In human cells, both normal metabolic activities and environmental factors such radiation or genotoxic chemicals can cause tens of thousands of individual molecular lesions per cell per day. Many of these lesions cause structural damage to the DNA molecule and can

[25] Hecht, S.M. (Ed. *Bioorganic Chemistry: Nucleic Acids,* Oxford University Press, NY, 1996, see Figure 1–9, pp. 10–11.

alter or eliminate the cell's ability to transcribe the gene that affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome and affect the survival of its daughter cells after it undergoes mitosis. If left unrepaired, this damage could result in harmful mutations within the cell genomic material.

DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. As a consequence, the DNA repair process is continually active as it responds to damage in the DNA structure. When normal repair processes fail, and when cellular *apoptosis*, a form of programmed cell death, does not occur. Irreparable DNA damage may result, including double-strand breaks and DNA crosslinks (interstrand crosslinks). This can eventually lead to malignant tumors or cancer.

Amanda Cordelia Bryant-Friedrich (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Amanda Cordelia Bryant-Friedrich (USA) is a chemist at the College of Pharmacy and Health Sciences at Wayne State University. She studies the mechanisms by which small molecules interact with nucleic acid. Her research features the synthesis of modified nucleosides and nucleotides, the study of the intercalation of small aromatic systems into DNA via the design of novel chromophores and the creation of nucleic acid probes of the events that occur around DNA. Professor Bryant-Friedrich has studied the protection of *small nuclear RNA (snRNA)* from oxidative damage. The snRNA is essential for the function of the *spliceosome*. A spliceosome is a large ribonucleoprotein complex found primarily within the nucleus of eukaryotic cells, assembled from snRNA and several proteins. The spliceosome removes *introns* from a transcribed pre-mRNA. An intron (for intragenic region) is any nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product.

Hydrogen atom abstraction events result from hydroxyl radicals that result formed by the indirect effect of ionizing radiation. This oxidative damage in DNA structures was probed by the design of model substrates encountered in DNA replication and repair. Hydroxyl radicals are also produced under conditions of oxidative stress. Five possible 2'-deoxyribose radicals are generated in DNA upon hydrogen atom abstraction by •OH, under hypoxic conditions. The C1', C3', and C4' radicals can be chemically "repaired" by cellular thiols from proteins or glutathione to deliver the original 2'-deoxyribose. Professor Bryant-Friedrich examined the anaerobic fate of the C3'-thymidinyl radical **16** by using the C3'-pivaloylthymidine precursor **15**, shown in Figure 25.10.[26] Earlier work in Professor Bryant-Friedrich laboratory demonstrated the utility of C3'-acetylthymidine-containing DNA oligomers as photolabile precursors for the site-specific generation of the C3'-thymidinyl radical in DNA under anaerobic conditions.[27] In this work, C3'-pivaloylthymidine was incorporated into single-stranded DNA

[26] Amato, N.J.; Bryant-Friedrich, A.C. *ChemBioChem* 2013, 14, 187–190.
[27] Bryant-Friedrich, A.C. *Organic Letters* 2004, 6, 2329–2332.

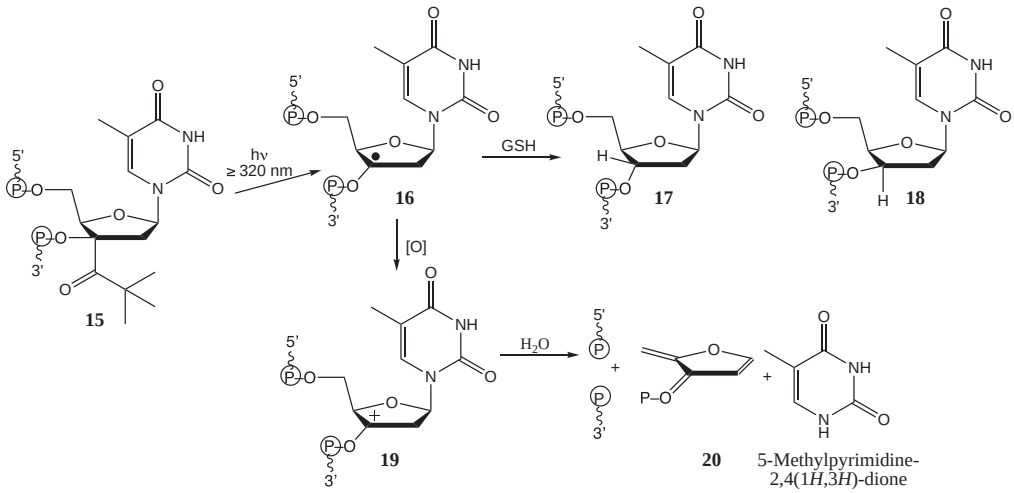


FIGURE 25.10 The anaerobic fate of the C3′-thymidinyl radical **16** using the C3′-pivaloylthymidine precursor **15**.

oligomers by using the H-phosphonate method, as previously reported.[28] Photochemical generation of radical **16** in the presence of 6 mM glutathione (GSH) in argon-purged aqueous buffer led to the formation of the expected reduction and strand-break products in all architectures. The reduction of this reactive intermediate by glutathione competes with strand breaks to deliver full-length oligomers (**17** and **18**) along with several modified strand-break products (~~P~~). Oxidation of the radical to the cation **19** lead to cleavage to form the strand break products as well as **20** and 5-methylpyrimidine-2,4(1*H*,3*H*)-dione. The distribution of products derived from the C3' radical was found to be dependent upon the structure of the 2'-deoxyoligonucleotide substrate. The deoxyribose sugar moiety can undergo inversion of configuration at the site of radical generation to deliver damage lesions and this inversion of configuration at the C3' carbon was shown to interfere with DNA synthesis.

Jacqueline K. Barton (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Jacqueline K. Barton (USA) is the Kirkwood-Noyes Professor of Chemistry at the California Institute of Technology. Professor Barton studies the chemical and physical properties of DNA and their roles in biological activities. The primary focus of her research is transverse electron transport along double-stranded DNA, its implications in the biology of DNA damage and repair, and its potential for materials applications such as targeted chemotherapeutic treatments for cancer. Iron-sulfur clusters are ubiquitous modular, tunable metal cofactors

[28] Lahoud, G.; Fancher, J.; Grosu, S.; Cavanaugh, B.; Bryant-Friedrich, A. *Bioorganic & Medicinal Chemistry* 2006, 14, 2581–2588.

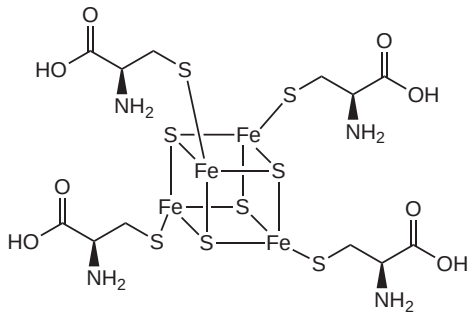


FIGURE 25.11 A cubane [$4Fe_4S$] cluster, with cysteine residues bound to iron.

that serve as one-electron carriers operating over a wide range of physiological potentials. There are many DNA-processing enzymes that contain a common redox cofactor in biology, a [$4Fe_4S$] cluster (Figure 25.11). DNA polymerases as well as the DNA repair proteins contain these $4Fe_4S$ clusters. Professor Barton describes a model where repair proteins may signal one another using DNA-mediated charge transport as a first step in their search for lesions.[29] As electrons travel through DNA, between repair proteins bound to the double helix, cells scan for mistakes that regularly arise in DNA. In this case, a redox switch of oxidation to $[4Fe_4S]^{3+}$ followed by reduction to a $[4Fe_4S]^{2+}$ cluster, which is activated from a distance using DNA charge transport (DNA CT) chemistry.

It is known that in these [$4Fe_4S$] systems, double-stranded DNA (dsDNA), can conduct charge via the π-stacked DNA bases (DNA CT) over long molecular distances with shallow distance dependence. However, DNA CT is sensitive to perturbations in π-stacking of the bases. A model developed by Professor Barton for DNA-redox signaling among a network of [$4Fe_4S$] repair proteins illustrates that this DNA-mediated CT chemistry is used for more efficient lesion detection. Enzymes with the cluster in the native $[4Fe_4S]^{2+}$ state first bind DNA, causing the cluster to become activated toward oxidative stress. Oxidation initiates the damage search that produces guanine radical cations that oxidize DNA-bound proteins in their vicinity to the $[4Fe_4S]^{3+}$ state, which leads to an increase in DNA-binding affinity. DNA-mediated CT effectively scans the intervening DNA for lesions. Another $[4Fe_4S]^{2+}$ protein bound at a distant site reduces the oxidized protein and the reduced protein binds less tightly to DNA and can diffuse away on damage-free DNA. By this process, long-range DNA-mediated redox signaling provides a means of rapid communication among DNA-processing proteins for coordination of replication and repair activity across the nucleus. Both enzyme association and dissociation with DNA is regulated in polymerase handoff, and in the oxidative stress response, which is integral to the DNA CT-driven lesion search in [$4Fe_4S$] repair proteins.

Deoxyribonucleic acid (DNA) stores genetic information, whereas RNA transcribes and translates this information for the cell. While DNA tends to form linear repeating structures, RNA forms diverse structures with a unique function. There are three main classes of RNA found in a cell: transfer RNA (tRNA), ribosomal RNA (rRNA), and messenger RNA (mRNA). tRNA tends to be single strands of nucleic acid with 60–96 nucleotides. The tRNA transports an amino acid, covalently attached to a specific proton of the polynucleotide chain, to a ribosome where it can be incorporated in its proper sequence in a protein. The primary and secondary structure of cysteine tRNA (the tRNA used to transport the amino acid cysteine) is shown as a "cloverleaf" structure (see Figure 25.12)[30] that contains double stranded stems connected to single stranded loops. This structure consists of one nucleotide strand is effectively held together by intramolecular hydrogen bonding, but base-pairing in self-complimentary regions of this strand leads to double-stranded loops. The 5′-terminus

[29] Barton, J.K.; Silva, R.M.B.; Elizabeth O'Brien, E. *Annual Review of Biochemistry* 2019, 88, 19.1–19.28.
[30] Hou, Y.-M.; Gamper, H.B. *Biochemistry* 1996, 35, 15340–15348.

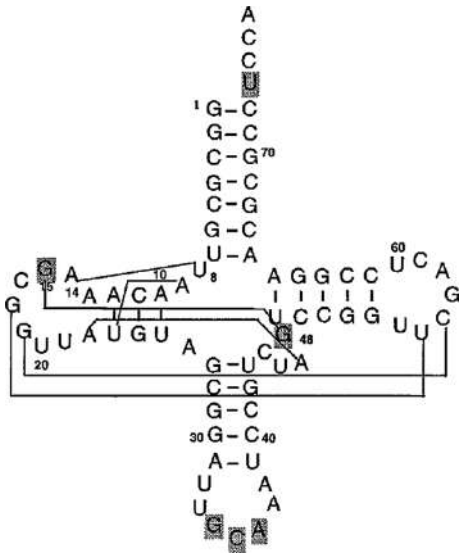


FIGURE 25.12 Sequence and cloverleaf structure of *E. coli* $tRNA^{Cys}$. U73, G15:G48, and the GCA anticodon are shaded to indicate that they are the major nucleotide determinants for recognition by cysteine tRNA synthetase. [Reprinted with permission from Hou, Y.-M.; Gamper, H.B. *Biochemistry*, 1996, 35, 15340–15348, Figure 1 therein. Copyright 1996 American Chemical Society].

is phosphorylated and the 3'-terminus of tRNA (featuring the sequence CCA-3' with a free OH group) is attached to the amino acid. Almost all tRNAs have a seven-base pair structure that is called the *acceptor stem* (the seven-base pairs prior to the CCA-3' terminus). In Figure 25.12, the acceptor stem is U-U-G-C-A-A-A. The loop of nucleotides at the bottom of the cloverleaf has the three base pairs that will bind this tRNA C-G-U on mRNA, which allows the amino acid, here *alanine*, to be transferred to the protein.

Ribosomal RNA (rRNA), the main component of the ribosome, has a complex structure. The ribosome is the organelle an organism uses to manufacture proteins. The ribosome binds mRNA, which then interacts with tRNA. The 70S ribosome for *Escherichia coli* (70S) has two rRNA subunits, the 50S and the 30S subunits. The 30S subunit has one large rRNA (16S RNA) and 21 individual proteins; the 50S subunit has two RNAs (5S and 23S) and 32 different proteins.[31] The secondary structure of the 16S rRNA is shown in Figure 25.13.[32]

Messenger RNA is a single-stranded nucleic acid with unique secondary structures and functions to carry the genetic code from DNA to the ribosome. This code is recognized by the hydrogen bonds to the three base pairs of tRNA mentioned above (the *triplet anticodon*). To ensure this genetic code is easily "read," mRNA is generally less structured than tRNA or rRNA. Each strand of mRNA may be categorized by a characteristic group of three base pairs, wherein each group is the genetic code for a specific amino acid. These base pair triplets (called *codons*) will match a complimentary set of three base pairs on a tRNA (an *anticodon*, see Figure 25.12).

The codon and anticodon are complimentary, which means that a G–C–C codon on mRNA will match a C–G–G anticodon on tRNA. The anticodon is at the bottom loop of tRNA in Figures 25.12 and 25.14. This feature is important because the C–G, G–C, G–C base pairs are capable of hydrogen bonding that allows the tRNA to attach itself to the mRNA at the proper place. The amino acid carried by the tRNA is then released to a growing peptide chain being synthesized on the ribosome.

[31] Hecht, S.M. (Ed.). *Bioorganic Chemistry: Nucleic Acids,* Oxford University Press, NY, 1996, pp. 15–17.
[32] Hoerter, J.A.H.; Lambert, M.N.; Pereira, M.J.B.; Walter, N.G. *Biochemistry* 2004, 43, 14624–14636.

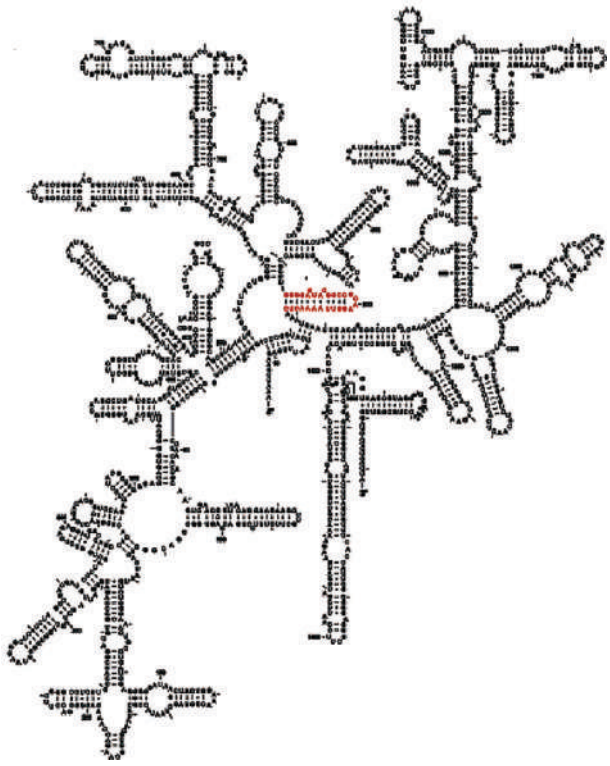


FIGURE 25.13 Secondary structure of the 16S RNA unit of *E. Coli*, for the 30S Subunit of the 70S subunit. (Reprinted with permission from Hoerter, J.A.H.; Lambert, M.N.; Pereira, MJ.B.; Walter, N.G. *Biochemistry*, 2004, 43, 14624, Figure 1B therein. Copyright 2004 American Chemical Society).

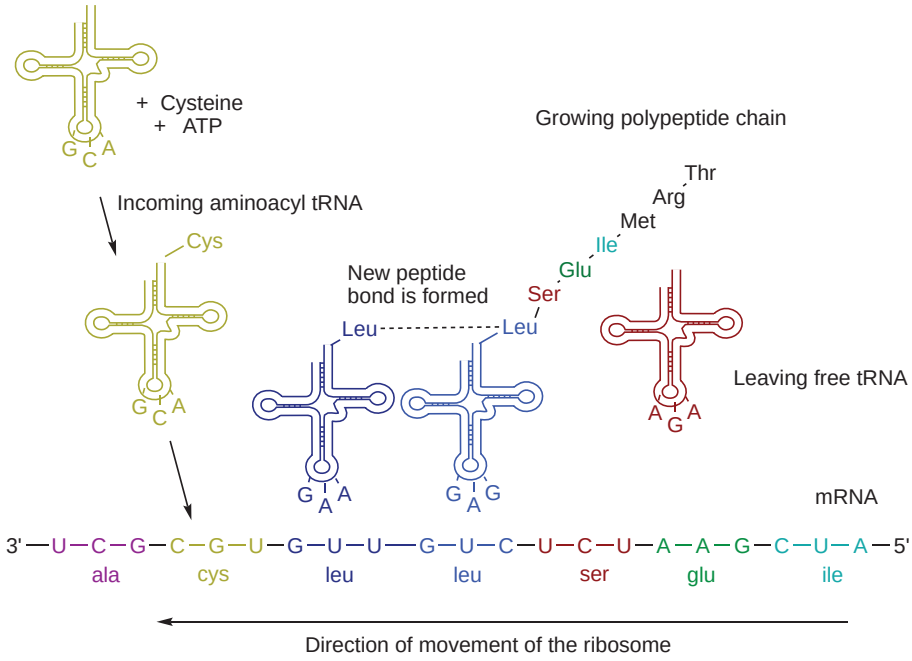


FIGURE 25.14 Protein synthesis.

Each amino acid has a tRNA with a unique anticodon, and that amino acid will attach itself only to that tRNA. The ribosome will bind a strand of mRNA to build a specific protein, which has a specific sequence of amino acids. The genetic code on the mRNA (the set of codons) matches the amino acid sequence of the protein. Therefore, the mRNA will bind

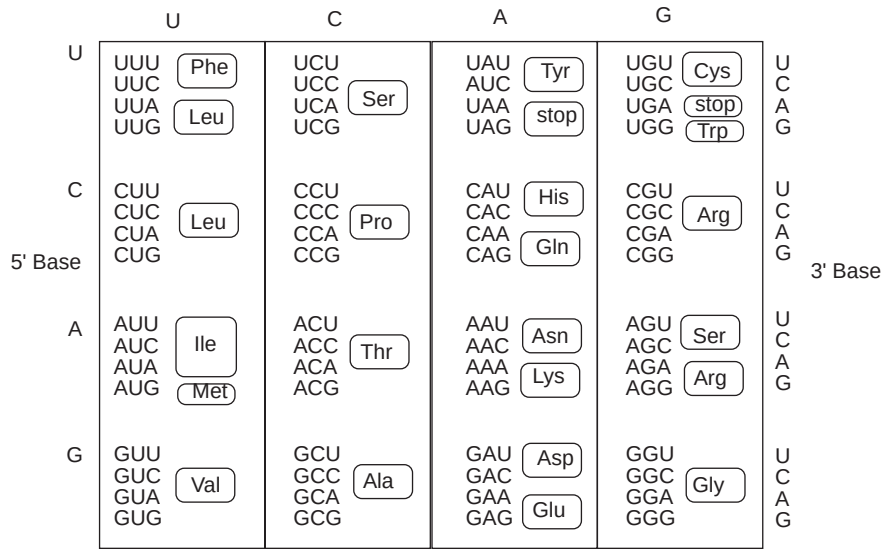


FIGURE 25.15 The genetic code composed of 64 codons. [Devlin, T.M. *Textbook of Biochemistry with Clinical Correlations, 2nd Ed.,* Wiley, p. 738, 1986. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.]

tRNA molecules in a particular sequence, allowing that amino acid to be released to the growing protein sequence associated with the ribosome. The genetic code for the amino acids used to make proteins is shown in Figure 25.15.[33] Although only five heterocyclic bases have been indicated thus far, several others are also known.

Har Gobind Khorana (An online version of this photo can be found at https://routledgetextbooks.com/textbooks/9780367768706/image-gallery.php)

Nobel laureate Har Gobind Khorana (India/USA; 1922-2011) was a biochemist at the University of Wisconsin-Madison. His research elucidated the order of nucleotides in nucleic acid, which carry the genetic code the cell and control synthesis of proteins. In addition, Professor Khorana was the first scientist to chemically synthesize oligonucleotides.

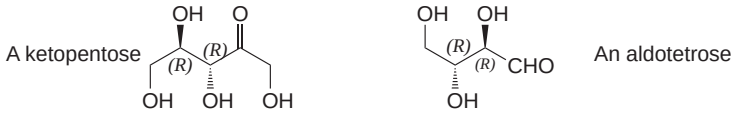
[33] Devlin, T.M. *Textbook of Biochemistry with Clinical Correlations*, 2nd ed. Wiley, NY, 1986, see Table 19.2, p. 738.

CORRELATION OF HOMEWORK WITH CONCEPTS

- Carbohydrates are polyhydroxy aldehydes and ketones known as sugars: 1, 2, 3, 4, 23, 24, 32.
- The OH unit derived from the carbonyl group, formed by cyclization to a furanose or a pyranose, is attached to the so-called anomeric carbon. Cyclization of an aldose or a ketose to a furanose or pyranose is accompanied by mutarotation at the anomeric carbon: 3, 5, 6, 7, 8, 9, 10, 11, 25, 26, 27, 28.
- The anomeric effect manifests in 1-alkoxy pyranose (pyranoside) derivatives: 41
- A reducing sugar reacts with Fehling's reagent, Tollen's reagent or Benedict's solution: 14, 15, 35, 36.
- The carbonyl of an aldose or a ketose can be reduced to the corresponding alcohol: 16, 17, 33, 42, 43.
- Chemical reactions of carbohydrates include reactions at the hydroxyl groups: 18, 19, 434, 35, 36, 37.
- Several heterocyclic compounds, including purines and pyrimidines, can be coupled to a ribofuranose at the anomeric carbon to form a ribonucleoside (or simply a nucleoside). The phosphate ester of a nucleoside is called a nucleotide: 20, 21, 38, 44, 47.
- Polynucleotides include RNA and DNA. Under physiological conditions, DNA normally exist in the β-form, which consists of two antiparallel strands: 22, 39, 40, 47.
- Spectroscopy can be used to determine the structure of a particular molecule (see Chapter 13): 48, 49.

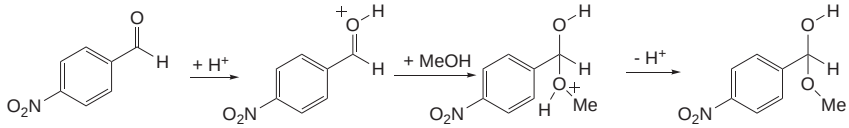
ANSWERS TO IN-CHAPTER QUESTIONS

25.1

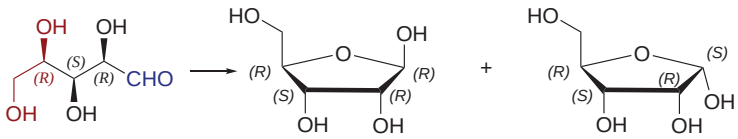


25.2 There are five stereogenic centers in a typical aldoheptose. Discounting the possibility of meso compounds, there should be $2^5 = 32$ total stereoisomers, which means there would be 16 diastereomers.

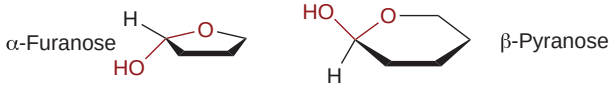
25.3



25.4



25.5



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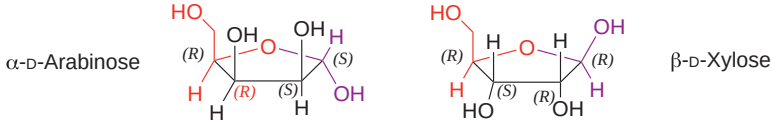
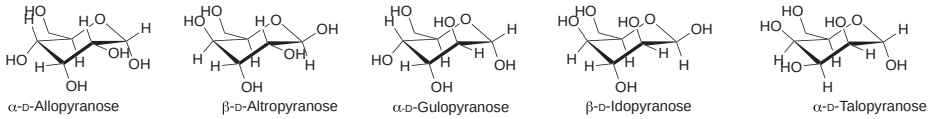


25.7



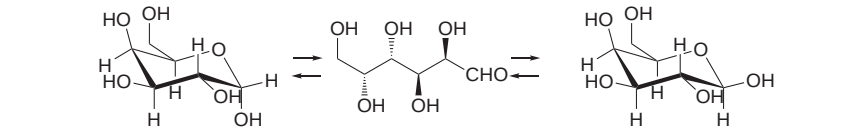
25.8 $x(+14.5) + y(-14.5) = -3.2$, where x = relative % of D and y = relative % of L.

$x+y = 1$, so $x = 1-y$, so $(1-y)(+14.5)-14.5y = -3.2$. so, $14.5 - 14.5y - 14.5y = -3.2$

$-29y = -17.7$, so $y = \dfrac{-17.7}{-29} = 0.61$, making $x = -0.39$.

Therefore, 61% of L and 39% of D.

25.9



α-D-Galactopyranose "x" "y" β-D-Galactopyranose

For this calculation, assume that the aldehyde form does not contribute to the equilibrium

x(+150.7) + y(+52.8) = +80.2 and x = y = 1

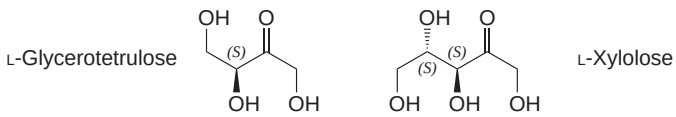
(1-y)(150.7) + y(52.8) = 80.2

150.7 - 150.7y + 52.8y = 80.2

-97.9y = -70.5

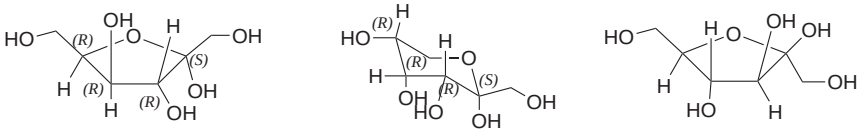
y = -70.5/-97.9 = 0.72 Therefore 72% of β-D and 28% of α-D

25.10



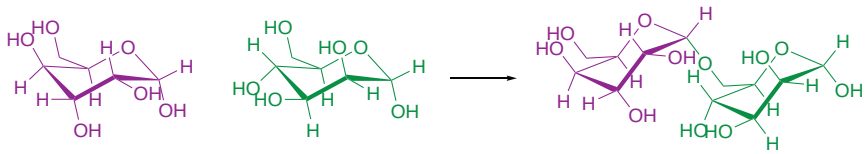
L-Glycerotetrulose L-Xylolose

25.11



α-D-Tagatofuranose β-D-Psicopyranose β-D-Psicofuranose

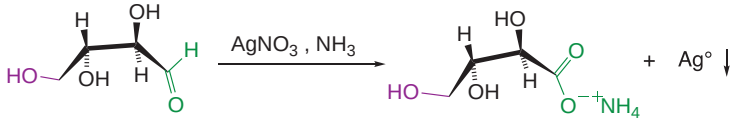
25.12



25.13

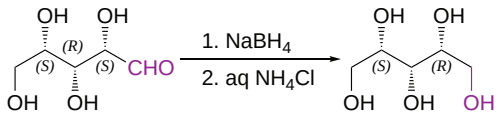
O-β-D-Altropyranosyl-(1→1)-α-D-mannopyranose *O*-β-D-Altropyranosyl-(1→4)-α-D-mannopyranose

25.14

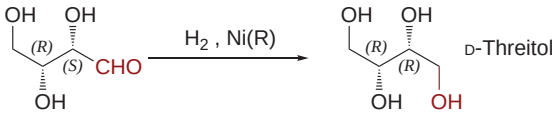


25.15 (a) reducing (b) not reducing (c) reducing (d) not reducing (e) reducing

25.16

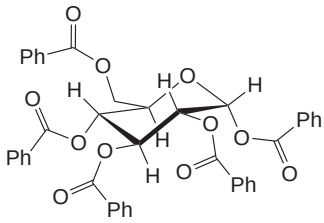


25.17



D-Threitol

25.18



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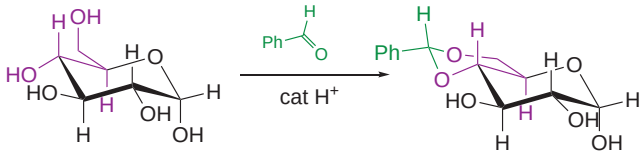

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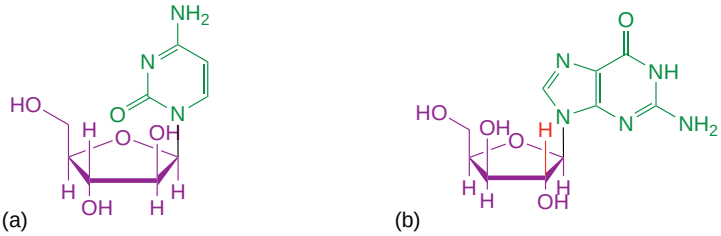
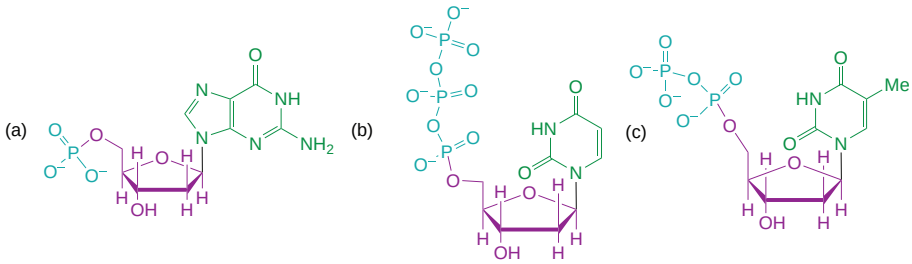


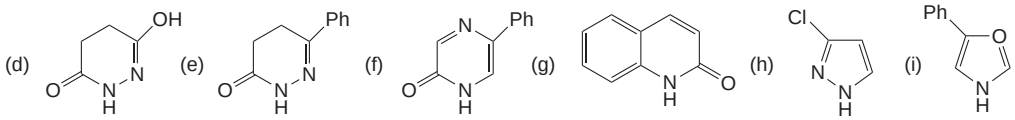
25.21



HOMEWORK

22. Draw the structure for
    (a) A four-carbon glycose (b) A three carbon glycitol
    (c) A six-carbon glyconic acid
    (d) A four-carbon glycaric acid (e) A seven-carbon uronic acid
23. Draw the structure of
    (a) An aldotetrose (b) A ketopentose (c) An aldopentose
    (d) An aldoheptose
    (e) A ketooctose (f) An aldotriose.
24. Draw the complete mechanism for conversion of pentanal to the hemiacetal under acid catalyzed conditions. Complete the mechanism by converting the hemiacetal to the acetal.
25. Draw the structure for
    (a) α-D-Arabinopyranose (b) α-L-Xylofuranose (c) β-D-Allofuranose
    (d) β-L-Mannopyranose (e) α-D-Idopyranose (f) β-L-Talofuranose
26. The α-form of a carbohydrate has a specific rotation of -38° and the β-form has a specific rotation of +90°. Mutarotation occurs to yield a mixture of α and β with a specific rotation of +18°. What is the percentage composition of this mixture, assuming < 0.1% of the open-chain form?
27. Draw the structure for each of the following:
    (a) the furanose form of α-L-ribulose (b) the pyranose form of α-D-psicose
    (c) the furanose form of β-L-fructose (d) the pyranose form of β-D-tagatose
28. Draw the structure for each of the following:
    (a) *O*-α-D-glucopyranosyl-(1→1)-β-D-allopyranose
    (b) *O*-β-D-altropyranosyl-(1→4)-β-D-galactopyranose
    (c) *O*-α-D-talopyranosyl-(1→1)-α-D-glucopyranose
    (d) *O*-β-D-idopyranosyl-(1→4)-α-D-mannopyranose
29. Draw the structure of each of the following:
    (a) *O*-α-D-Fuc*f*-(1→4)-α-D-Lyx*p*-(1→1)-α-D-Alt*p*
    (b) *O*-α-D-Rib*f*-(1→4)-α-D-Xyl*p*-(1→1)-α-D-Fru*p*
    (c) *O*-α-D-Alt*f*-(1→4)-α-D-All*p*-(1→1)-α-D-Ido*p*
30. Draw both hemiacetal forms of D-ribofuranose and both hemiacetal forms of D-xylofuranose.

31. Give one example of an aldotetrose, an aldopentose and an aldohexose. Give one example of a ketotetrose, a ketopentose and a ketohexose.
32. Why is *O*-α-D-mannopyranosyl (11)-α-D-gulopyranose not a reducing sugar. Draw this disaccharide.
33. Give the product of the following reactions: (a) α- D-allopyranose + excess acetic anhydride and NaOAc (b) α- D-talopyranose + excess dimethyl sulfate (c) β- D-gulopyranose + hydrogen gas and a platinum catalyst.
34. Give the major product of the following reactions:
    (a) *O*-α-D-Ara*f*-(1→4)-α-D-Gul*p* + $AgNO_3/NH_3$
    (b) *O*-α-D-Fuc*f*-(1→4)-α-D-Man*p* + aq $CuSO_4$/sodium tartrate
    (c) *O*-α-D-Gal*f*-(1→1)-α-D-Gal*p* + $AgNO_3/NH_3$ (d) α-D-Ara*f* + aq $CuSO_4$/sodium tartrate
    (e) α-D-Gal*p* + $AgNO_3/NH_3$ (f) α-D-Lyx*p* + aq $KMnO_4$
    (g) α-D-Rha*p* + 1. $NaBH_4$ and 2. aq NH_4Cl (h) α-D-Tal*f* + Na/Hg
    (i) α-D-All*p* + Br_2/pH 5 (j) α-D-Glc*p* + H_2, Ni(R) (k) α-D-Ido*p* + HNO_3
35. Which of the following are reducing sugars?
    (a) α-D-arabinopyranose (b) α-L-xylofuranose (c) β-D-allofuranose
36. Draw the major product for each of the following reactions.
    (a) α-D-Glc*p* + acetic anhydride/NaOAc (b) α-D-Alt*p* + Et_2SO_4
    (c) α-D-Tal*p* + EtOH, cat H^+
    (d) α-D-Ido*f* + acetone, cat H^+ (e) α-D-Ara*p* + benzaldehyde, cat H^+
37. Draw the structure of each of the following:
    (a) 9-(β-D-Ribofuranoyl)guanine (b) 1-(sym-D-Ribofuranoyl)thymine
    (c) 9-(β-D-Ribofuranoyl)adenine (d) 1-(β-D-Ribofuranoyl)uracil
38. Write out the structures of the following DNA sequences:
    (a) A-A-C (b) U-G-T (c) T-T-T
39. In the 1-*O*-methyl derivative of α-L-glucopyranose, is the methoxy group likely to be axial or equatorial in the major product? Explain.
40. Suggest two different reactions that will convert α-D-xylose to xylitol.
41. Suggest two different reactions that will convert sorbitol to glucoaldaric acid.
42. Draw the 2-deoxyribose nucleotide that will result if each of the following heterocycles are incorporated:
    (a) 3-fluorouracil (b) 3-cyclopropylcytosine (c) 6-amino-2-chloropurine



43. If α-D-glucopyranose has a specific rotation of +112° and β-D-glucopyranose has a specific rotation of +19°, what is the specific rotation of a mixture of 80% α and 20% β? If the specific rotation of the mixture is +53°, what is the percentage of α and β at equilibrium?
44. Adenosine triphosphate is utilized in an enzymatic reaction that produces AMP. Draw both of these compounds. Draw the structures of uracil diphosphate and uracil monophosphate.
45. Caffeine is 1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione. Draw the structure of this compound, and then draw the structure of a compound in which the N-methyl group of caffeine replaces deoxyribofuranosyl.

Spectroscopy Problems. Do not attempt these problems until the concepts in Chapter 13 have been mastered.

46. Give the structure of the molecule with the formula $C_6H_{14}O_6$ and the spectral data shown.
    IR: broad peak at 3550–3070, 2980-2930, 1419, 1309, 1265, 1098, 1064, 1048, 1000, 646 cm^{-1}.
    ^1H NMR: 4.56–4.12 (very broad s, 6H; this peak is diminished when treated with D_2O), 3.67 (m 1H), 3.58–3.37 (d, 2H), 3.55 (m, 1H), 3.48 (m 1H), 3.44-3.35 (d,

2H), 3.39 (m, 1H) ppm. Note: Most of these peaks overlap. ^{13}C NMR: 74.0, 72.3, 72.2, 70.8, 63.9, 63.6 ppm.

47. Give the structure of the molecule with the formula $C_5H_{10}O_5$ and the spectral data shown.
IR: broad peak 3400–3230, 2970–2900, 1041, 934 cm^{-1}. ^{1}H NMR: 5.2 (d, 1H), 4.6 (broad s, 4H; this peak is diminished when treated with D_2O); 3.69–3.63 (m, 4H), 3.52 (m 1H) ppm.

Index

A

B

C

D

E

F

G

H

I

J

K

N

O

P

Q

R

S

T

U

V

W

X

Y

Z