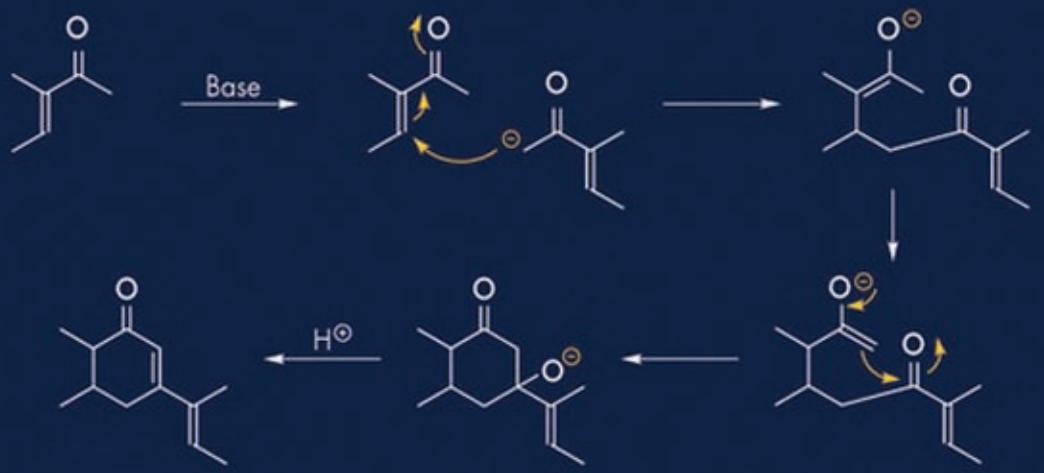
ARROW PUSHING IN ORGANIC CHEMISTRY

AN *EASY* APPROACH TO *UNDERSTANDING* REACTION MECHANISMS



DANIEL E. LEVY

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An Easy Approach to Understanding Reaction Mechanisms

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A JOHN WILEY & SONS, INC., PUBLICATION

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Dedicated to the memory of Henry Rapoport (1918–2002)
Professor of Chemistry, Emeritus
University of California — Berkeley
A true teacher and mentor

Contents

Preface

Organic chemistry is a general requirement for most students pursuing degrees in the fields of biology, physiology, medicine, chemical engineering, biochemistry, and chemistry. Consequently, many of the students studying organic chemistry initially do so out of obligations to required curriculum rather than out of genuine interest in the subject. This is, in fact, expected as almost all college students find themselves enrolling in classes in which they either have no interest or cannot foresee application of the subject to their future vocation. Alternatively, there are students who are intrigued with the potential application of organic chemistry to fields including pharmaceuticals, polymers, pesticides, food science, and energy. However, whichever group represents the individual students, there is always a common subset of each that tenuously approaches the study of organic chemistry due to rumors or preconceived notions that the subject is extremely difficult and requires extensive memorization. Having personally studied organic chemistry, and tutored many students in the subject, I assure you that this is not the case.

When first presented with organic chemistry course material, one can easily be caught up in the size of the book, the encyclopedic presentation of reactions, and the self-questioning of how one can ever decipher the subject. These students frequently compile endless sets of flash cards listing specific chemical reactions and their associated names. Like many of my classmates, I began to approach the subject in this manner. However, this strategy did not work for me as I quickly realized that memorization of reactions did not provide any deductive or predictive insight into the progression of starting materials to products and by what mechanisms the transformations occurred. In fact, the fundamental fault in the "memorization strategy" is that in order to be effective, the student must not only memorize all chemical reactions and associated reaction names, but also all associated reaction mechanisms and potential competing processes. It was not until I abandoned the memorization strategy that I began to do well in organic chemistry and develop a true appreciation for the subject and how the science benefits society.

The presumption that introductory organic chemistry entails very little memorization is valid and simplifies the subject provided the student adheres to the philosophy that the study

of organic chemistry can be reduced to the study of interactions between organic acids and bases. From this perspective, organic chemistry students can learn to determine the most acidic proton in a given molecule, determine the most reactive site (for nucleophilic attack), determine the best reactants (nucleophiles and electrophiles), and how to predict reaction products. In learning to predict these components of organic reactions, the beginning organic chemist will be able to deduce reasonable routes from starting materials to products using the basic mechanistic types involved in introductory organic chemistry. Furthermore, through an understanding of how electrons move, extrapolations from ionic or heterolytic mechanisms can be used to explain free radical and electrocyclic processes. Finally, by utilizing the principles discussed in this book, the student will gain a better understanding of how to approach the more advanced reaction types discussed as the introductory organic chemistry course progresses.

The goal of this book is not to present a comprehensive treatment of organic chemistry. Furthermore, this book is not intended to be a replacement for organic chemistry texts or to serve as a stand-alone presentation of the subject. This book is intended to supplement organic chemistry textbooks by presenting a simplified strategy to the study of the subject in the absence of extensive lists of organic reactions. Through application of the principles presented herein, it is my hope that this book, when used as intended, will aid the beginning student in approaching organic chemistry as I did—with little memorization and much understanding.

DANIEL E. LEVY, PH.D.

Acknowledgments

I would like to express my deepest appreciation to my wife, Jennifer, and to my children, Aaron, Joshua, and Dahlia, for their patience and support while writing this book. I would also like to express a special thanks to Dr. Lane Clizbe for his editorial contributions.

About the Author

Daniel E. Levy received his Bachelor of Science in 1987 from the University of California at Berkeley where, under the direction of Professor Henry Rapoport, he studied the preparation of 4-amino-4-deoxy sugars and novel analogs of pilocarpine. Following his undergraduate studies, Dr. Levy pursued his Ph.D. at the Massachusetts Institute of Technology. Under the direction of Professor Satoru Masamune, he studied sugar modifications of amphotericin B, the total synthesis of calyculin A and the use of chiral isoxazolidines as chiral auxiliaries. In 1992, Dr. Levy completed his Ph.D. and has since worked on various projects involving the design and synthesis of novel organic compounds. These compounds include glycomimetic inhibitors of fucosyl transferases and cell adhesion molecules, peptidomimetic matrix metalloproteinase inhibitors, carbocyclic AMP analogs as inhibitors of type V adenylyl cyclase, heterocyclic ADP receptor antagonists, and inhibitors of calmodulin-dependent kinase. Dr. Levy is currently the director of synthetic chemistry at Intradigm Corporation in Palo Alto, California.

Arrow Pushing in Organic Chemistry is Dr. Levy's third book. In 1995, Dr. Levy co-authored a book entitled *The Chemistry of C-Glycosides* (1995, Elsevier Sciences). Collaborating with Dr. Péter Fügedi, Dr. Levy developed and presented short courses entitled "Modern Synthetic Carbohydrate Chemistry" and "The Organic Chemistry of Sugars," which were offered by the American Chemical Society Continuing Education Department. With Dr. Fügedi, Dr. Levy co-edited his second book entitled *The Organic Chemistry of Sugars* (2005, CRC Press).

Chapter 1

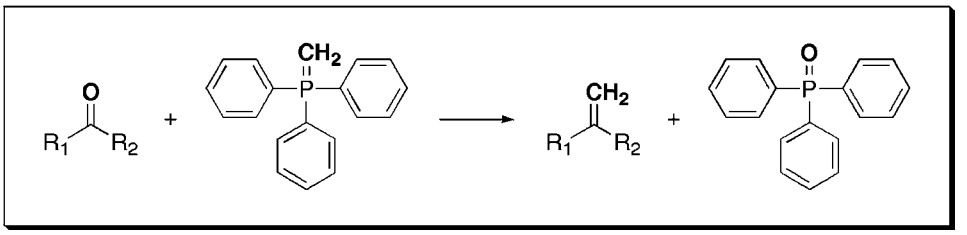
Introduction

The study of **organic chemistry** focuses on the chemistry of materials essential for life. Specifically, organic chemistry defines the science surrounding the chemistry of elements essential for life to exist. In addition to carbon, the most common elements present in organic molecules are hydrogen, oxygen, nitrogen, sulfur, and various halogens. Through the study of organic chemistry, our understanding of the forces binding these elements to one another and how these bonds can be manipulated are explored. In general, our ability to manipulate organic molecules is influenced by several factors that include the nature of functional groups near sites of reaction, the nature of reagents utilized in reactions, and the nature of potential leaving groups. Additionally, these three factors impart further variables that influence the course of organic reactions. For example, the nature of the reagents used in given reactions can influence the reaction mechanisms and ultimately the reaction products. By recognizing the interplay between these factors and by applying principles of arrow pushing, which really represents bookkeeping of electrons, reasonable predictions of organic mechanisms and products can be realized without the burden of committing to memory the wealth of organic reactions studied in introductory courses. In this chapter, the concept of arrow pushing is defined in context with various reaction types, functional groups, mechanism types, reagents/nucleophiles, and leaving groups.

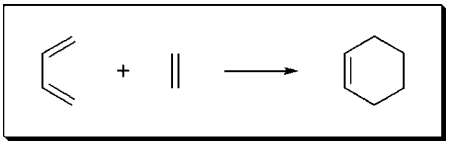
1.1 DEFINITION OF ARROW PUSHING

Organic chemistry is generally presented through a treatment of how organic chemicals are converted from starting materials to products. For example, the **Wittig reaction** (Scheme 1.1) is used for the conversion of **aldehydes** and **ketones** to **olefins**, the

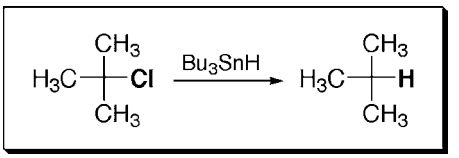
Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 1.1 *Example of the Wittig reaction.*



Scheme 1.2 *Example of the Diels–Alder reaction.*



Scheme 1.3 *Example of a tin hydride dehalogenation.*

Diels–Alder reaction (Scheme 1.2) is used for the formation of six-membered ring systems, and treatment of alkyl halides with reagents such as tributyltin hydride (Scheme 1.3) results in removal of the associated halides. However, by presenting these reactions as illustrated in Schemes 1.1, 1.2, and 1.3, no explanation is provided as to how the starting materials end up as their respective products.

By definition, the outcome of any chemical reaction is the result of a process resulting in the breaking and formation of chemical bonds. Referring to material covered in most general chemistry courses, bonds between atoms are defined by sets of two electrons. Specifically, a single bond between two atoms is made of two electrons, a double bond between atoms is made of two sets of two electrons, and a triple bond between atoms is made of three sets of two electrons. These types of bonds can generally be represented by **Lewis structures** using pairs of dots to illustrate the presence of an electron pair. In organic chemistry, these dots are most commonly replaced with lines. Figure 1.1 illustrates several types of chemical bonds in both electron dot notation and line notation. The list of bond types shown in Figure 1.1 is not intended to be inclusive with respect to functional groups or potential combinations of atoms.

While chemical bonds are represented by lines connecting atoms, electron dot notation is commonly used to represent **lone pairs** (nonbonding pairs) of electrons. Lone pairs are found on **heteroatoms** (atoms other than carbon or hydrogen) that do not require bonds with additional atoms to fill their valence shell of eight electrons. For example, atomic

Single Bonds		Double Bonds		Triple Bonds	
Electron Dots	Lines	Electron Dots	Lines	Electron Dots	Lines
$H_3C:CH_3$	H_3C-CH_3	O::O	O=O	N:::N	N≡N
$H_3C:Cl$	H_3C-Cl	$H_2C::CH_2$	$H_2C=CH_2$	HC:::CH	HC≡CH
$H_3C:NH_2$	H_3C-NH_2	$H_2C::NH$	$H_2C=NH$	HC:::N	HC≡N
$H_3C:OH$	H_3C-OH	$H_2C::O$	$H_2C=O$		
$H_3C:SH$	H_3C-SH	$H_2C::S$	$H_2C=S$		

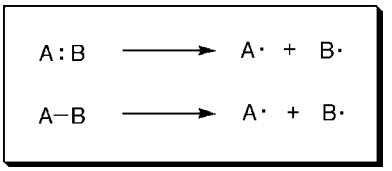
Figure 1.1 *Examples of chemical bonds.*

carbon possesses four valence electrons. In order for carbon to achieve a full complement of eight valence electrons, it must form four chemical bonds leaving no electrons as lone pairs. Atomic **nitrogen**, on the other hand, possesses five valence electrons. In order for nitrogen to achieve a full complement of eight valence electrons, it must form three chemical bonds leaving two electrons as a lone pair. Similarly, atomic **oxygen** possesses six valence electrons. In order for oxygen to achieve a full complement of eight valence electrons, it must form two chemical bonds leaving four electrons as two sets of lone pairs. In the examples of chemical bonds shown in Figure 1.1, lone pairs were not represented in order to focus on the bonds themselves. In Figure 1.2 the missing lone pairs are added where appropriate. Lone pairs are extremely important in understanding organic mechanisms because they frequently provide the sources of **electron density** necessary to drive reactions, as will be discussed later in this book.

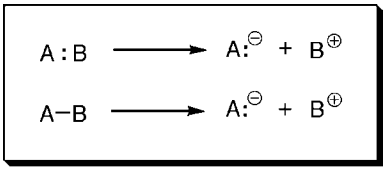
As organic reactions proceed through the breaking and subsequent formation of chemical bonds, it is now important to understand the various ways in which atomic

Single Bonds		Double Bonds		Triple Bonds	
Electron Dots	Lines	Electron Dots	Lines	Electron Dots	Lines
$H_3C:CH_3$	H_3C-CH_3	:Ö::Ö:	:Ö=Ö:	:N:::N:	:N≡N:
$H_3C:\ddot{C}l:$	$H_3C-\ddot{C}l:$	$H_2C::CH_2$	$H_2C=CH_2$	HC:::CH	HC≡CH
$H_3C:\ddot{N}H_2$	$H_3C-\ddot{N}H_2$	$H_2C::\ddot{N}H$	$H_2C=\ddot{N}H$	HC:::N:	HC≡N:
$H_3C:\ddot{O}H$	$H_3C-\ddot{O}H$	$H_2C::\ddot{O}:$	$H_2C=\ddot{O}:$		
$H_3C:\ddot{S}H$	$H_3C-\ddot{S}H$	$H_2C::\ddot{S}:$	$H_2C=\ddot{S}:$		

Figure 1.2 *Examples of chemical bonds and lone pairs.*



Scheme 1.4 *Illustration of homolytic cleavage.*

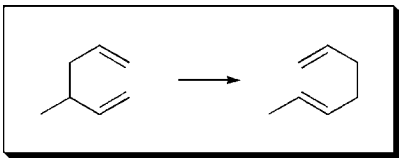


Scheme 1.5 *Illustration of heterolytic cleavage.*

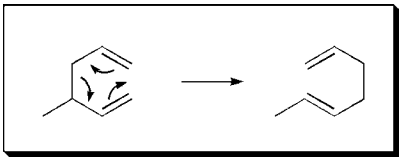
bonds can be broken. In general, there are three ways in which this process can be initiated. As shown in Scheme 1.4, the first is simple separation of a single bond where one electron from the bond resides on one atom and the other electron resides on the other atom. This type of bond cleavage is known as **homolytic cleavage** because the electron density is equally shared between the separate fragments and no charged species are generated. It is this process that leads to **free radical** mediated reactions.

Unlike homolytic cleavage, **heterolytic cleavage** (Scheme 1.5) of a chemical bond results in one species retaining both electrons from the bond and one species retaining no electrons from the bond. Generally, this also results in the formation of **ionic** species where the fragment retaining the electrons from the bond becomes **negatively charged** while the other fragment becomes **positively charged**. These charged species then become available to participate in ion-based transformations governed by the electronic nature of reactants or adjacent functional groups.

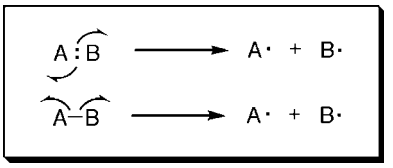
Having introduced homolytic cleavage and heterolytic cleavage as the first two ways in which bonds are broken at the initiation of organic reactions, attention must be drawn to the



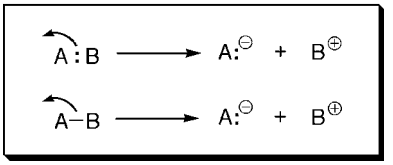
Scheme 1.6 *Illustration of a concerted reaction (Cope rearrangement).*



Scheme 1.7 *Illustration of arrow pushing applied to the Cope rearrangement.*



Scheme 1.8 *Application of arrow pushing to homolytic cleavage using single-barbed arrows.*



Scheme 1.9 *Application of arrow pushing to heterolytic cleavage using double-barbed arrows.*

possibility that bonds can rearrange into lower energy configurations through **concerted** mechanisms where bonds are simultaneously broken and formed. This third process, associated with **pericyclic reactions**, is illustrated in Scheme 1.6 using the **Cope rearrangement** and does not involve free radicals or **ions**. Instead, it relies on the overlap of atomic orbitals, thus allowing the transfer of electron density that drives the conversion from starting material to product. Regardless, whether reactions rely on free radicals, ions, or concerted mechanisms, all can be explained and/or predicted using the principles of arrow pushing.

Arrow pushing is a term used to define the process of using **arrows** to conceptually move **electrons** in order to describe the mechanistic steps involved in the transition of **starting materials** to **products**. An example of arrow pushing is illustrated in Scheme 1.7 as applied to the Cope rearrangement introduced in Scheme 1.6. As the Cope rearrangement proceeds through a concerted mechanism, the movement of electrons is shown in a single step. As will become apparent, arrow pushing is broadly useful to explain even very complex and multistep mechanisms. However, while arrow pushing is useful to explain and describe diverse mechanistic types, it is important to note that different types of arrows are used depending on the type of bond cleavage involved in a given reaction. Specifically, when homolytic cleavage is involved in the reaction mechanism, **single-barbed arrows** are used to signify movement of **single electrons**. Alternatively, when heterolytic cleavage or concerted steps are involved in the reaction mechanism, **double-barbed arrows** are used to signify movement of **electron pairs**. Schemes 1.8 and 1.9 illustrate the use of appropriate arrows applied to homolytic cleavage and heterolytic cleavage.

1.2 FUNCTIONAL GROUPS

Having presented the concept of arrow pushing in context of the steps that initiate chemical reactions, some factors impacting the flow of electrons leading from starting materials to products can now be explored.

As a rule, electrons will flow from atomic centers **high in electron density** to atomic centers **low in electron density**. This dependence on **polarity** is similar to the way that

electricity flows in an electrical circuit. If there is no difference in **electrical potential** between the ends of a wire, electricity will not flow. However, if a **charge** is applied to one end of the wire, then the wire becomes **polarized** and electricity flows. If we imagine a simple **hydrocarbon** such as ethane, we can analogously relate this system to a **nonpolarized wire**. Both carbon atoms possess the same density of electrons and thus ethane has no polarity. However, if functionality is added to ethane through introduction of groups bearing heteroatoms, the polarity changes and electron flow can be used to induce chemical reactions. These heteroatom-bearing groups are known as **functional groups** and serve to donate or withdraw electron density.

While functional groups can be either **electron donating** or **electron withdrawing**, these properties rely upon the specific heteroatoms the functional group is composed of as well as the configuration of these heteroatoms relative to one another. With respect to

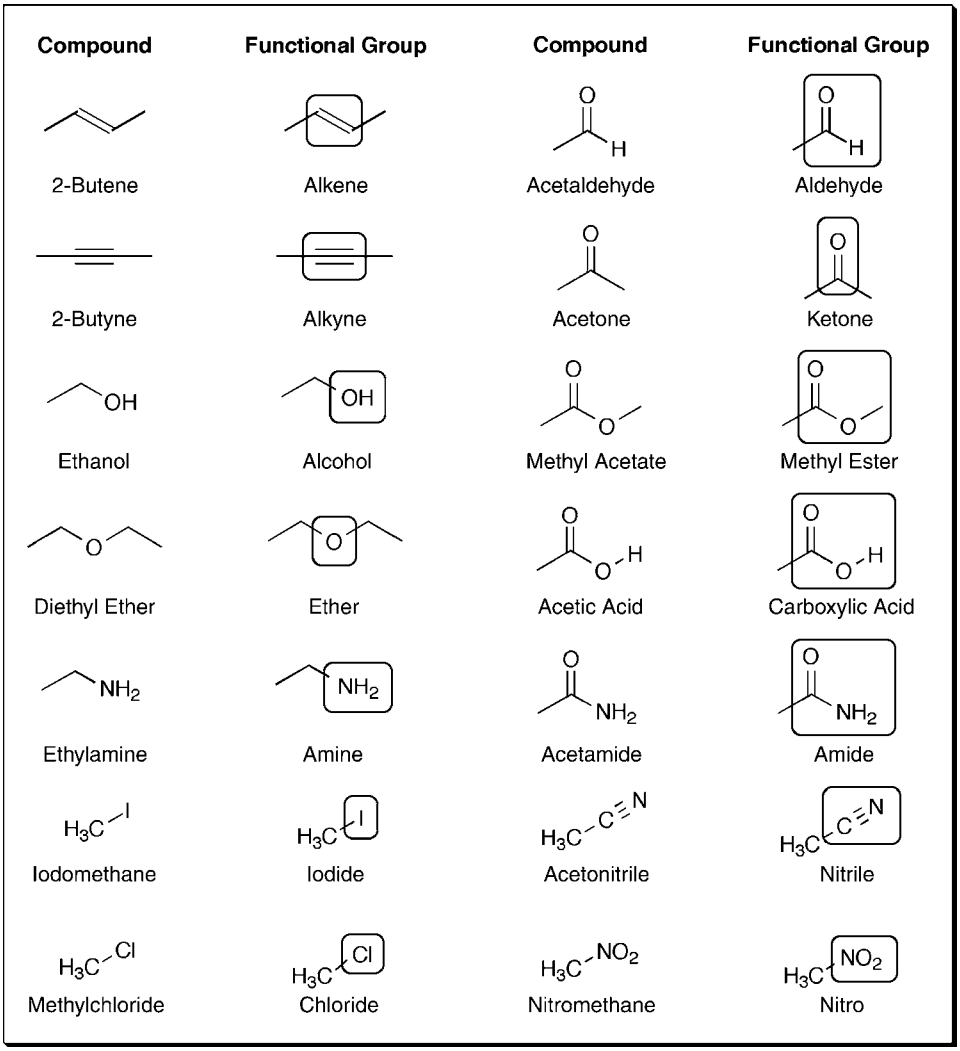


Figure 1.3 *Common organic functional groups.*

the specific heteroatoms, **electronegativity** of the heteroatoms is the driving force influencing polarity. Thus, the more electronegative the atom, the greater the affinity of electrons for this atom. As a calibration for electronegativity, the **periodic table of the elements** serves as an excellent resource. Specifically, moving from left to right and from bottom to top, electronegativity increases. For example, nitrogen is more electronegative than carbon, and oxygen is more electronegative than nitrogen. Likewise, fluorine is more electronegative than chlorine, and chlorine is more electronegative than bromine. It is important to note that the influence of electronegativity on polarity is so strong that simply replacing a carbon atom with a heteroatom is enough to impart strong changes in polarity compared to the parent structure. Figure 1.3 illustrates common organic functional groups as components of common organic molecules.

Polarity in organic molecules is generally represented as **partial positive** (δ^+) **charges** and **partial negative** (δ^-) **charges**. These **partial charges** are induced based upon the presence of heteroatoms either by themselves or in groups. These heteroatoms, as described in the previous paragraph and in Figure 1.3, define the various functional groups. Returning to the example of ethane as a nonpolar parent, Figure 1.4 illustrates how polarity changes are influenced by the introduction of heteroatoms and functional groups. As shown, heteroatoms such as nitrogen, oxygen, and halogens, due to their increased electronegativities compared to carbon, adopt partial negative charges. This causes **adjacent carbon atoms** to take on partial positive characteristics.

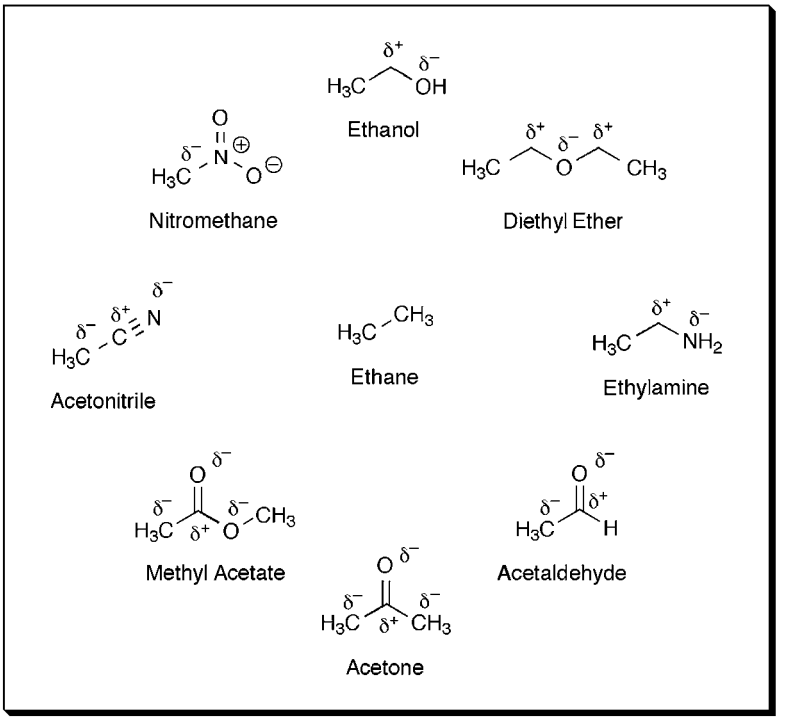


Figure 1.4 *How functional groups influence polarity.*

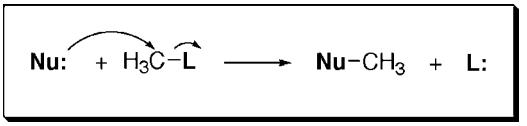
As illustrated in Figure 1.4, charges on carbon atoms are not limited to positive. In fact, when a carbon atom is adjacent to a positive or partial positive center, it can adopt partial negative characteristics. As will be discussed in later chapters, this ability to control the charge characteristics of carbon atoms leads to the ability to create reactive centers with a diverse array of properties. By taking advantage of this phenomenon of **induced polarity**, we are able to employ a multitude of chemical transformations allowing for the creation of exotic and useful substances relevant to fields ranging from material science to food science to agriculture to pharmaceuticals.

1.3 NUCLEOPHILES AND LEAVING GROUPS

As discussed in the previous section, polarity is key to the ability to initiate most **chemical reactions**. However, this is not the only factor influencing the ability to initiate reactions. In fact, the type of reaction on a given molecule is often dependent upon the nature of the **solvent** and the **reagents** used. For example, solvent polarity can influence the **reaction rate** and the **reaction mechanism**. Furthermore, the nature of the chemical **reagents** used can affect the **reaction mechanism** and the identity of the final product. The following definitions will be key to understanding the terminology used in the following chapters.

Nucleophiles are reagents that have an affinity for **positively charged species** or **electrophiles**. In organic reactions, **nucleophiles** form **chemical bonds** at sites of partial positive charge through donation of their electrons. This generally results in the need for the starting compound to release a leaving group. An example of a nucleophilic reaction is shown in Scheme 1.10 where Nu: represents the nucleophile and L: represents the leaving group. Arrow pushing is used to illustrate the movement of the electron pairs.

Leaving groups are the components of chemical reactions that detach from the starting material. Referring to Scheme 1.10, the leaving group, L:, ends up separate from the product while the nucleophile, Nu:, becomes incorporated into the product. Furthermore, while an initial evaluation of the material covered in an introductory organic chemistry course may seem overwhelming, the majority of the material covered can be reduced to the principles illustrated in the single reaction shown in Scheme 1.10.



Scheme 1.10 *Example of a nucleophilic reaction.*

1.4 SUMMARY

In this chapter, the basic principle of arrow pushing was introduced in the context of organic reactions driven by homolytic cleavage, heterolytic cleavage, or concerted mechanisms. Furthermore, the concept of polarity was introduced using heteroatoms and common organic functional groups. This discussion led to the definitions of nucleophiles and

leaving groups in the context of simple nucleophilic reactions. Finally, by pulling these ideas together, the concept of approaching the study of mechanistic organic chemistry from a simplified perspective of understanding the principles of arrow pushing was introduced.

While characteristics such as homolytic cleavage, heterolytic cleavage, and concerted mechanisms were discussed, the principles of arrow pushing apply equally to all. However, with respect to heterolytic cleavage, an understanding of the properties of organic acids and bases is essential in order to understand underlying organic mechanisms. Therefore, moving forward, this book primarily focuses on arrow pushing as applied to heterolytic reaction mechanisms.

PROBLEMS

1. Use arrow pushing to explain the following reactions:

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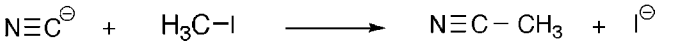

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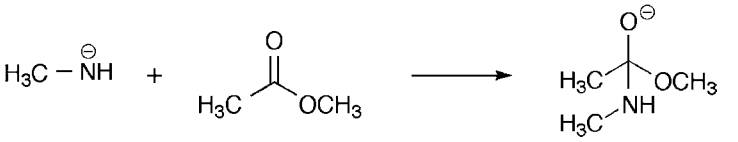

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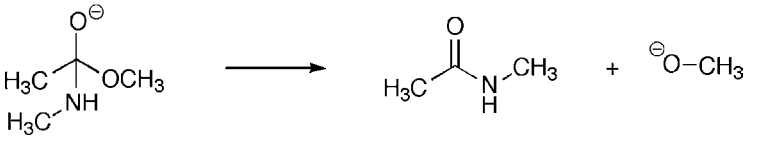

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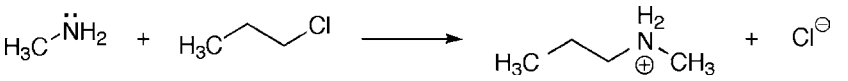

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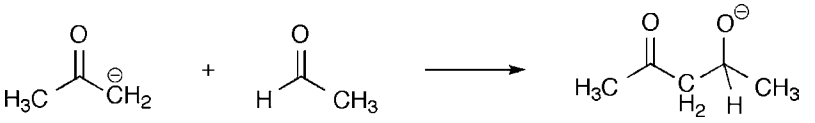

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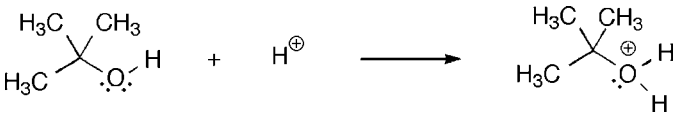
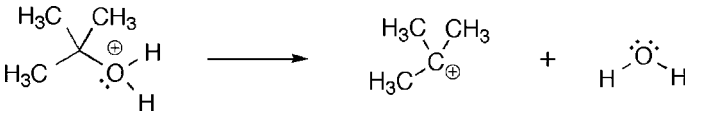


g.



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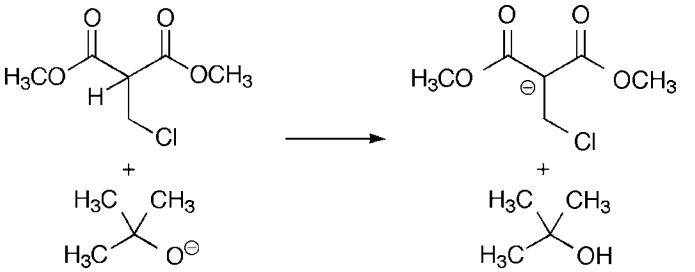

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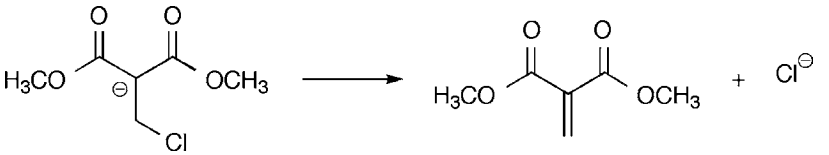

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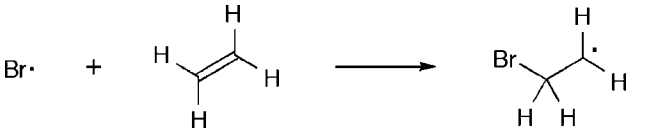
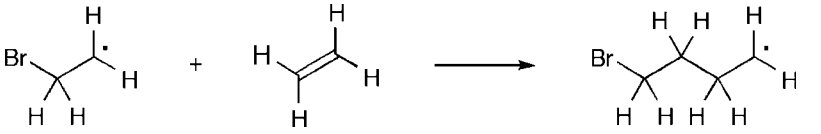
k. 

l. 

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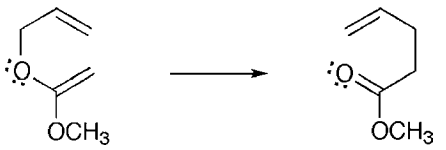

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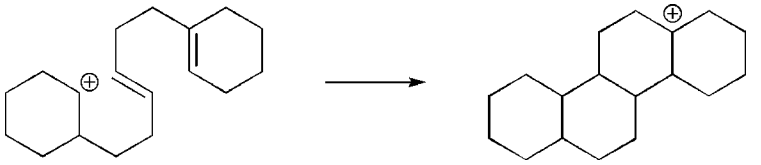

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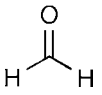
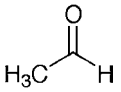
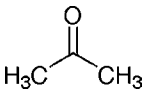
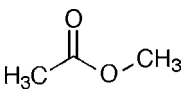
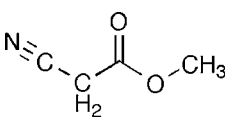


b. 

c. 

d. 

e. 

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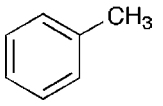
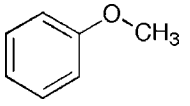
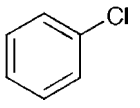
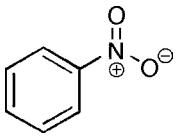
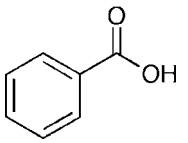
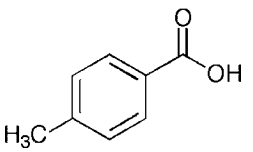
g. 

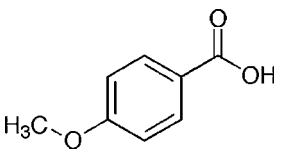
h. 

i. 

j. 

k. 

l. 

m. 

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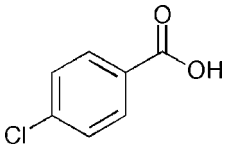

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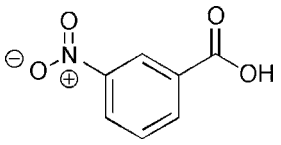

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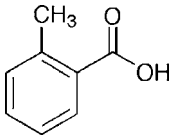

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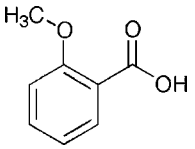

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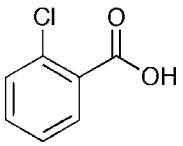


Chapter 2

Acids

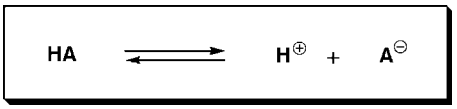
As mentioned at the end of Chapter 1, an understanding of heterolytic reaction mechanisms must be accompanied by an understanding of the properties of organic acids and bases. Through this understanding, an ability to predict the reactive species in organic reactions and the reactive sites in organic molecules will evolve. Therefore, this chapter focuses on the properties of acids, dissociation constants, and the relative acidities observed for protons in different environments.

2.1 WHAT ARE ACIDS?

The most general description of an **acid** is a molecule that liberates **hydrogen ions**. Therefore, if we consider a molecule, HA, this molecule is said to be an acid if it dissociates as shown in Scheme 2.1. It is important to note that any **acid dissociation** is an **equilibrium process**. Through this equilibrium process, two species, a **proton** (hydrogen **cation**) and an **anion**, are liberated. Furthermore, because this dissociation results in the formation of two ionic (charged) species, it is important to consider why this would be favorable as compared to the neutral state of undissociated HA. The answer to this question lies in the stability of the anion, A^-, itself.

Regarding **anionic stability**, there are many relevant factors. Among these are external influences such as **solvent effects** (Fig. 2.1). Specifically, a **polar solvent** has the ability to **stabilize** ionic species through **charge–charge interactions** or **charge–heteroatom interactions**. Conversely, a **nonpolar solvent** generally **inhibits** formation of charged species because it cannot interact with the ions. Figure 2.2 lists common polar and nonpolar organic solvents. While solvent polarity is an important factor in the progression and rate of reactions, its role applied to arrow pushing relates more to mechanistic determination

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 2.1 *General representation of acid dissociation.*

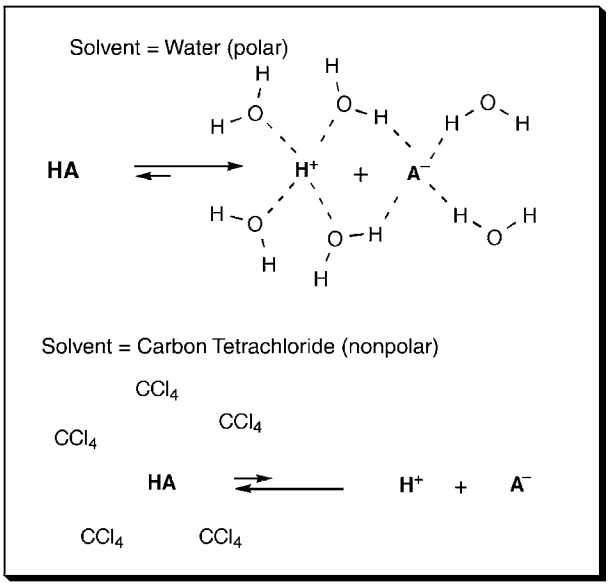


Figure 2.1 *Solvent effects on acid dissociation.*

than to how electrons move. Therefore, solvent polarity will not be addressed further in this chapter and will be revisited in the context of various mechanistic types.

In addition to external factors such as solvent effects, there are internal factors that influence anionic stability. Among these are **inductive effects** (how do electron-donating or electron-withdrawing substituents affect a molecule?), and **resonance effects** (is the charge localized or delocalized?). As inductive effects generally work in concert with resonance effects, our primary focus will be on the resonance effects themselves.

2.2 WHAT IS RESONANCE?

When a given molecule or ion can exist with multiple configurations of double/triple bonds or multiple sites bearing positive/negative charges, the molecule or ion is said to possess **resonance** forms. These resonance forms can be represented by drawings where the changes in electronic configuration are rationalized using arrow pushing. Furthermore, these changes in electronic configuration occur with no alterations to the connectivity of the individual atoms. For example, as shown in Scheme 2.2, a **carboxylic acid** dissociates into a **proton** and a **carboxylate anion**. As shown in Scheme 2.3, this carboxylate anion possesses two resonance structures. These resonance structures, illustrated using a

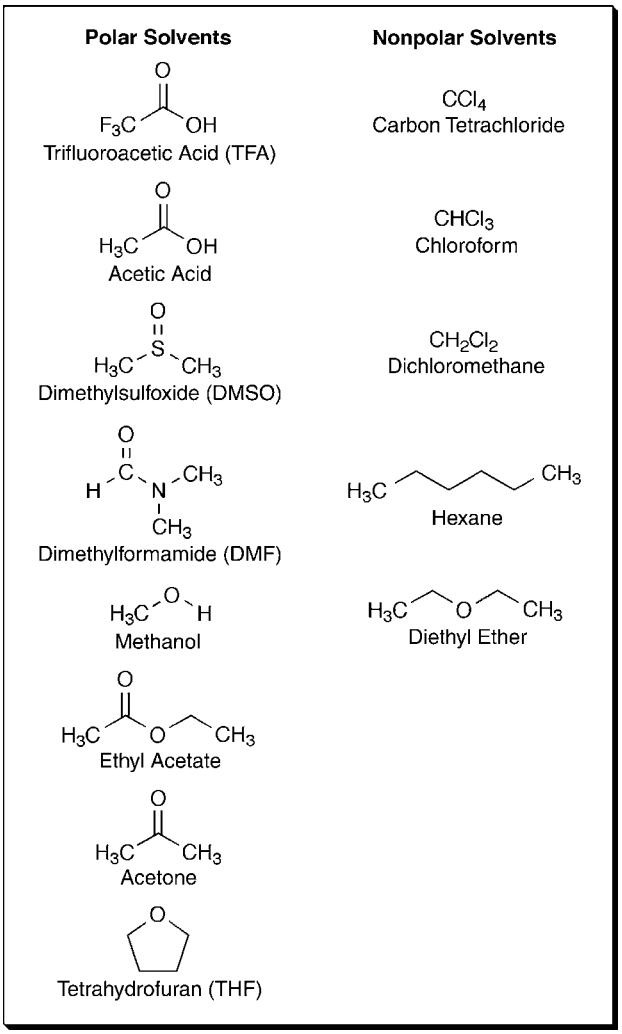
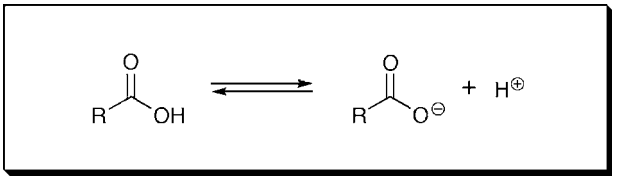


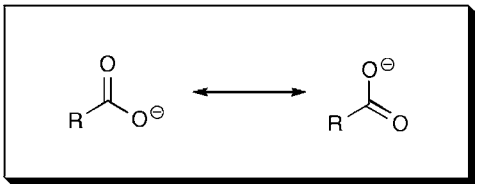
Figure 2.2 *Common polar and nonpolar organic solvents.*

double-headed arrow, are easily explained using arrow pushing to move the electrons associated with the negative charge from one oxygen atom to the other (Scheme 2.4).

Although carboxylic acids exist in **equilibrium** with their resonance-stabilized carboxylate anions, it is important to understand that resonance stabilization alone will

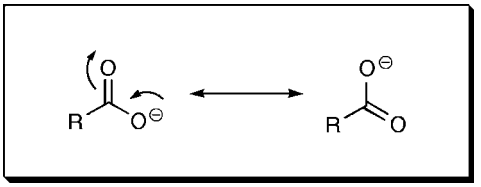


Scheme 2.2 *Dissociation of a carboxylic acid forming a proton and a carboxylate anion.*

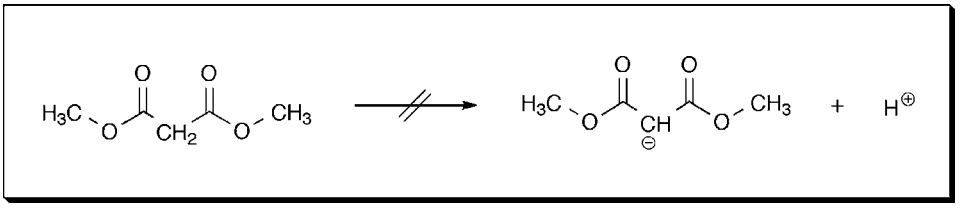


Scheme 2.3 *Resonance forms of the carboxylate anion.*

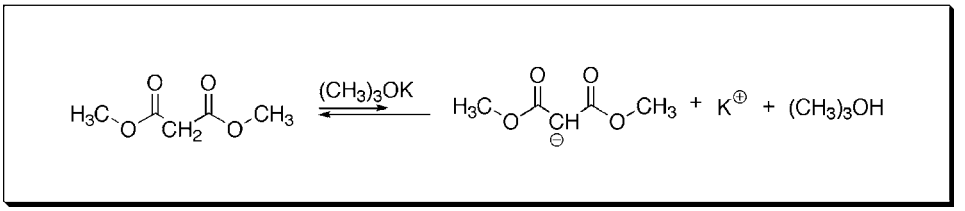
not induce carboxylate anions to form. In fact, when resonance stabilization is not enough to induce formation of a carboxylate anion, addition of a base generally will accomplish this task. For example, considering **dimethyl malonate**, there is no **dissociation** of any protons liberating **malonate anions** (Scheme 2.5). The equilibrium lies entirely in favor of neutral dimethyl malonate. However, with addition of a **base** such as **potassium *tert*-butoxide**, a proton is readily extracted, generating malonate anions, potassium cations, and *tert*-butyl alcohol (Scheme 2.6). The three resonance forms of the malonate anion, described using arrow pushing, are illustrated in Scheme 2.7. While **deprotonation** under these conditions does not proceed to completion, the equilibrium is such that malonate anions are available in sufficient quantities to react as required.



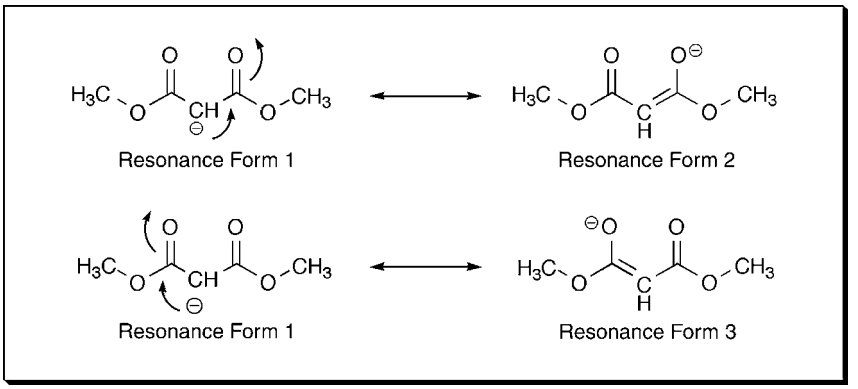
Scheme 2.4 *Rationalization of the carboxylate anion resonance forms using arrow pushing.*



Scheme 2.5 *Dimethyl malonate does not spontaneously liberate malonate anions.*



Scheme 2.6 *Potassium* tert*-butoxide partially deprotonates dimethyl malonate.*



Scheme 2.7 *Resonance forms of the malonate anion rationalized using arrow pushing.*

As illustrated in Schemes 2.2 and 2.5, different organic anions form under different conditions. Some, as illustrated in Scheme 2.2, form through spontaneous dissociation of an acid while others, as illustrated in Scheme 2.5, require bases to extract protons and liberate anions. Since, as illustrated in Scheme 2.1, acids are defined as substances that liberate protons, and since the anions illustrated in Schemes 2.2 and 2.5 form upon liberation of their respective protons, both carboxylic acids and substances such as dimethyl malonate must be defined as acids.

Although carboxylic acids and substances such as dimethyl malonate can be classified as acids, their relative acidities are clearly very different as illustrated by the different conditions required to liberate protons and anions. In order to understand this phenomenon, it is essential to first understand how acidities are measured.

2.3 HOW IS ACIDITY MEASURED?

Before discussing how acidity is measured, the definition of the **equilibrium constant** should be reviewed. Referring to Scheme 2.1, illustrating that an acid is in equilibrium with its dissociated ions, the degree of this dissociation as compared to the undissociated acid is measured according to its equilibrium constant (K_{eq}). From general chemistry coursework, we remember that K_{eq} is the product of the ion concentrations divided by the concentration of the undissociated acid (Fig. 2.3).

Since Figure 2.3 represents how equilibrium constants are calculated and since we are specifically studying dissociation of acids, K_{eq} can be redefined for acids as the **acid dissociation constant** (K_a) illustrated in Figure 2.4.

$$K_{eq} = \frac{[H^{\oplus}][A^{\ominus}]}{[HA]}$$

Figure 2.3 *Definition of the equilibrium constant (K_{eq}).*

Again referring to general chemistry coursework, the degree of acidity of a solution is measured according to the concentration of hydrogen ions present. The **pH** of a solution is defined as the negative logarithm of the hydrogen ion concentration (Fig. 2.5). Similarly, if K_a is converted to its negative logarithm, we calculate the **pK_a** (Fig. 2.6). It is, in fact, the pK_a that is used to represent the **acidity** associated with the various hydrogen atoms present in organic molecules.

When calculating the pK_a of a given hydrogen atom, it is important to remember that the pK_a is related to the pH of the solution. This relationship is represented in Figure 2.7. As illustrated, the pH value can be mathematically separated from the negative logarithm of the ratio of the anion concentration to the concentration of the undissociated acid. Taking this relationship to its final derivation, we find the **Henderson–Hesselbach equation** (Fig. 2.8), which provides us with the key to determining pK_a values and relative acidities. An important result derived from the Henderson–Hesselbach equation is that in a **perfect equilibrium** (a system where there is an equal amount of dissociated and undissociated acid), the pK_a is equal to the pH. This arises from the fact that in a perfect equilibrium, the concentration of HA is equal to the concentration of A^-, making the ratio of $[A^-]$ to [HA] equal to 1. Since the log of 1 is 0, this term drops out of the equation (Fig. 2.9).

$$K_{eq} = \frac{[H^{\oplus}][A^{\ominus}]}{[HA]} = K_a$$

Figure 2.4 *K_a is the K_{eq} specifically related to dissociation of acids.*

$$pH = -\log[H^{\oplus}]$$

Figure 2.5 *Definition of* pH.

$$pK_a = -\log K_a$$

Figure 2.6 *Definition of* pK_a.

$$pK_a = -\log K_a = -\log\left\{\frac{[H^{\oplus}][A^{\ominus}]}{[HA]}\right\} = -\log[H^{\oplus}] + \left\{-\log\frac{[A^{\ominus}]}{[HA]}\right\} = pH + \left\{-\log\frac{[A^{\ominus}]}{[HA]}\right\}$$

Figure 2.7 *pK_a values are related to* pH.

$$pK_a = pH - \log\left\{\frac{[A^{\ominus}]}{[HA]}\right\}$$

Figure 2.8 *Henderson–Hesselbach equation.*

When $[A^{\ominus}] = [HA]$,

$$pK_a = pH - \log\left\{\frac{[A^{\ominus}]}{[HA]}\right\} = pH - \log 1 = pH - 0 = pH$$

Figure 2.9 *In a perfect equilibrium,* $pK_a = pH$.

2.4 RELATIVE ACIDITIES

Having explored the relationships between solution pH and pK_a values, we can now explore the **relative acidities** of various hydrogen atoms and how these values are influenced by neighboring functional groups and heteroatoms. In this arena, it is important to remember that how a reaction proceeds is largely dependent upon the relative acidities of protons (hydrogen atoms) compared to one another and not on the **absolute acidity** of a given proton.

Considering a compound that produces a solution pH greater than 7, that compound is generally referred to as **basic**. However, a proton of interest (proton A) on this compound may be considered **acidic** compared to another proton (proton B) if the pK_a of proton A is lower than the pK_a of proton B. In other words, the lower the pK_a for a given proton, the more acidic that proton is. Consequently, in order to predict the mechanistic course of a given organic reaction, it is *extremely* important to be able to recognize the *most acidic proton* in a given molecule.

As previously stated, acidities of various protons are dependent upon their associated functional groups and nearby heteroatoms. Furthermore, these protons may be either components of relevant functional groups or adjacent to relevant functional groups. Figure 2.10 illustrates examples of compounds possessing acidic protons associated with representative functional groups, and Figure 2.11 illustrates examples of compounds possessing acidic protons adjacent to representative functional groups. In both figures, the acidic protons are highlighted in bold.

In studying the relationships between functional groups and proton acidities, we will first look at carboxylic acids. As illustrated in Scheme 2.2, carboxylic acids dissociate to form protons and carboxylate anions. Furthermore, as shown in Scheme 2.3, the carboxylate anion is stabilized through two resonance forms. It is this **resonance stabilization** that serves as the primary driving force behind the acidic nature of carboxylic acids. Further evidence of the relationship between resonance stabilization of anions and acidity can be seen when comparing the pK_a values of carboxylic acids to the pK_a values of **alcohols**.

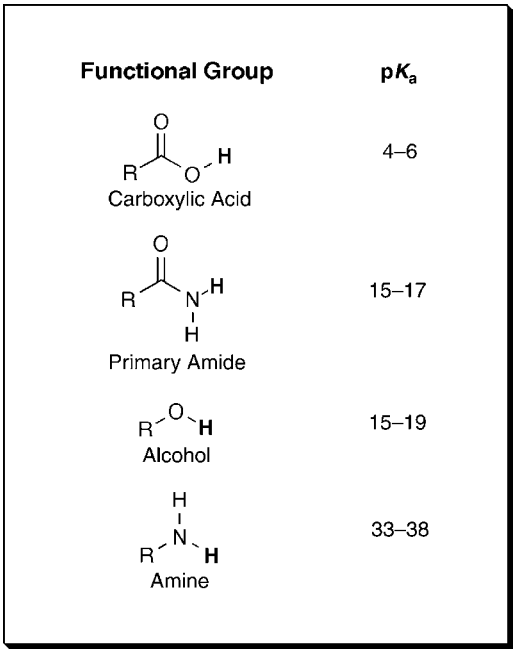


Figure 2.10 *Representative functional groups with associated acidic protons.*

As shown in Figure 2.10, carboxylic acids (compounds that dissociate into resonance-stabilized carboxylate anions) have pK_a values ranging from 4 to 6. However, alcohols (compounds that dissociate into alkoxide anions possessing no resonance stabilization) have pK_a values ranging from 15 to 19. A comparison of the resonance capabilities of carboxylic acids compared to alcohols is illustrated in Scheme 2.8. As shown, the resonance capabilities of the carboxylate anion are due to the presence of a **carbonyl** group adjacent to the OH. This carbonyl group imparts additional partial charges that attract the negative charge and distribute it over **multiple centers**. In the case of an alcohol, the deprotonated **alkoxide anion** has no place to distribute its charge and the charge remains entirely on the oxygen. Because alcohols have no resonance capabilities, their pK_a values are higher than those of carboxylic acids. Nevertheless, both carboxylic acids and alcohols are considered organic acids.

Having illustrated how resonance effects influence the relative acidities of different functional groups, it is important to understand why the same functional groups in different compounds can possess different acidities. In order to address this, we must move from the general representation of compounds presented above to a treatment of specific compounds. For example, the carboxylic acid represented in Scheme 2.2 possesses an "R" group. In organic chemistry, R groups are commonly used to represent regions of compounds that are variable. To illustrate this point, Figure 2.12 lists several common carboxylic acids and their respective pK_a values.

As illustrated in Figure 2.12, **formic acid** (R = H) has a pK_a of 3.75. However, if R is changed to an electron-withdrawing group such as CF_3, the anion resulting from dissociation becomes more stabilized resulting in a lower pK_a compared to formic acid. Alternately, if R is changed to an electron-donating group such as CH_3, the anion resulting

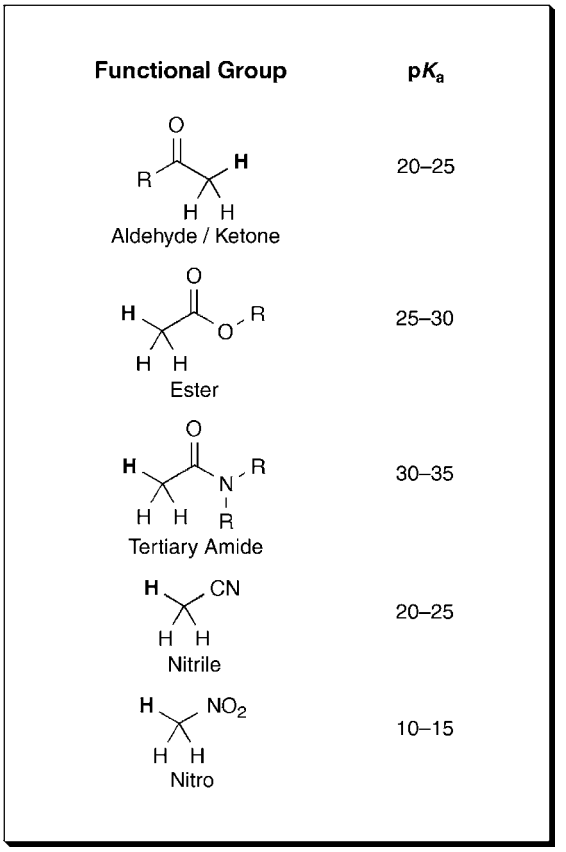
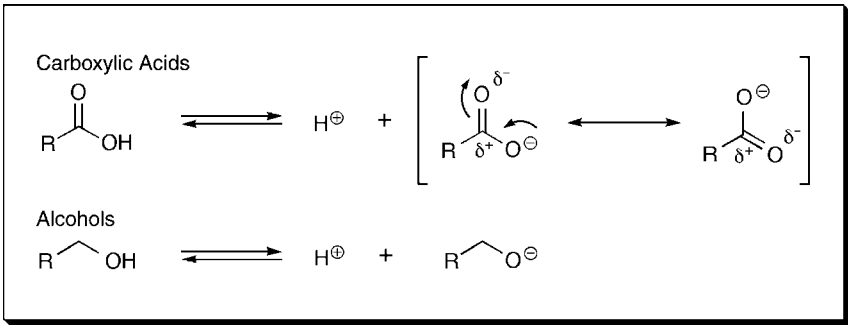


Figure 2.11 *Representative functional groups with adjacent acidic protons.*

from dissociation becomes less stable as illustrated by a higher pK_a compared to that of formic acid.

The changes in the pK_a values associated with different carboxylic acids are the result of inductive effects. Inductive effects occur when electronegative groups pull electron density away from acidic centers, rendering these centers more acidic. Conversely, inductive effects



Scheme 2.8 *Resonance capabilities of carboxylic acids compared to alcohols.*

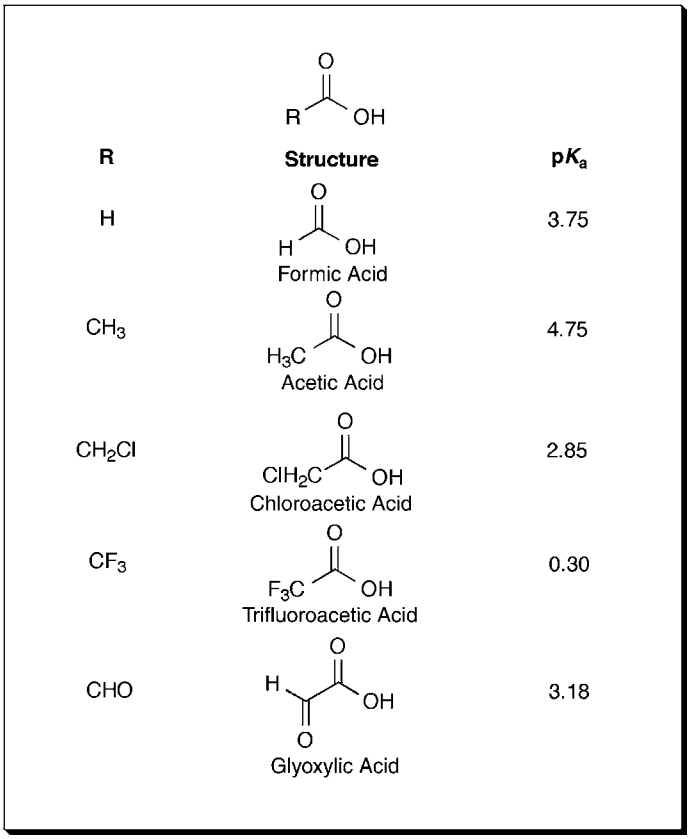
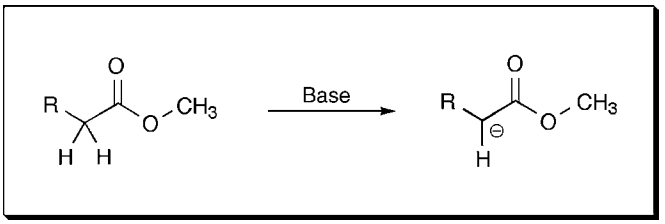


Figure 2.12 *Common carboxylic acids and their respective* pK_a *values.*

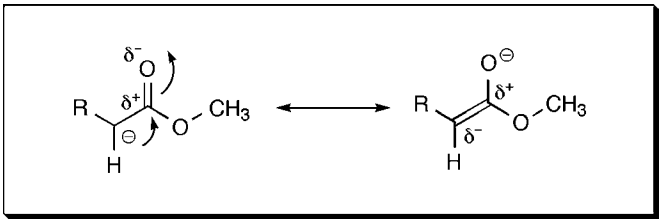
also occur when **electropositive** groups push electron density toward acidic centers, rendering these centers less acidic. The concept of electronegativity was introduced in Section 1.2 and referred to the periodic table of the elements as a resource for calibration. In comparing formic acid to **acetic acid**, the CH_3 group of acetic acid is electron-donating while the H of formic acid is not. This means that there is greater electron density present in the carboxylate anion of acetic acid than in the carboxylate anion of formic acid. An *increase* in electron density associated with a carboxylate anion *lowers* the **stability** of the anion and raises the pK_a. Thus, as mentioned at the end of Section 2.1, these observations demonstrate that inductive effects work in concert with resonance effects to alter pK_a values.

While carboxylic acids are among the most acidic of all organic compounds, we are more frequently interested in removing protons that are not directly associated with the carboxylic acid functional group. Additionally, reliance upon removal of protons from molecules containing functional groups other than carboxylic acids is common. In this context, **esters** represent the next functional group we will study.

Esters, as functional groups, are simply oxygen-alkylated carboxylic acids (see Fig. 1.3). As such, we cannot remove a proton from the oxygen as we are able to do with carboxylic acids. However, as shown in Scheme 2.9, the proton in the position α (adjacent) to the ester



Scheme 2.9 *Esters can be deprotonated α to ester carbonyls.*



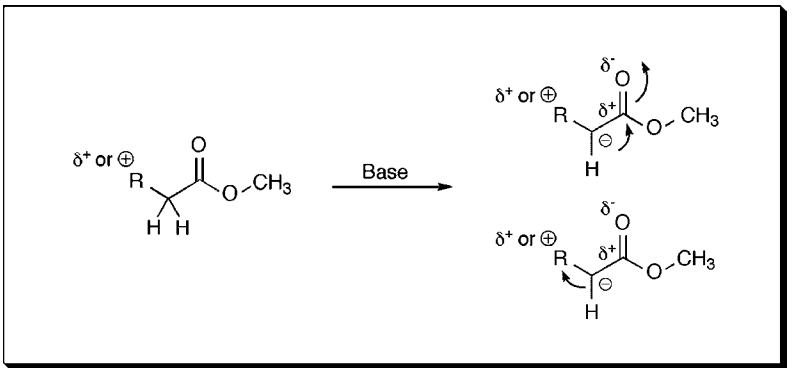
Scheme 2.10 *Rationalization of the acidity of protons α to ester carbonyls.*

carbonyl can be removed under basic conditions. Furthermore, the rationalization of the **acidity** of this proton is represented in Scheme 2.10 using arrow pushing and the placement of partial charges. The pK_a is approximately 25 for the illustrated ester when R is hydrogen.

As with carboxylic acids, pK_a values associated with esters will change accordingly when the molecule is changed. Specifically, the associated pK_a values are subject to the influence of inductive effects. An excellent example brings us back to dimethyl malonate illustrated in Schemes 2.6 and 2.7. If we consider the second ester group in dimethyl malonate as an electron-withdrawing group as illustrated by the additional resonance forms of the anion, we can understand that, compared to simple esters, the malonate diester will be more acidic. In fact, the pK_a associated with deprotonation of dimethyl malonate is approximately 12. Thus, considering inductive effects of neighboring groups, we can predict relative acidities for most organic compounds.

2.5 INDUCTIVE EFFECTS

Having introduced the concept of inductive effects using carboxylic acids and esters as examples, we will now explore these effects in greater detail. As alluded to through the pK_a values of the selected carboxylic acids shown in Figure 2.12, inductive effects can be either electron donating or electron withdrawing. Specifically, an electron-donating inductive effect will result from incorporation of an **electron-donating group**. Similarly, an electron-withdrawing inductive effect will result from incorporation of an **electron-withdrawing group**. When an electron-donating group is incorporated adjacent to an acidic proton, the acidity decreases and the pK_a increases. Similarly, when an electron-withdrawing group is incorporated adjacent to an acidic proton, the acidity increases and the pK_a decreases. Thus, it is imperative for those studying organic chemistry to fully understand what constitutes electron-donating groups and electron-withdrawing groups.

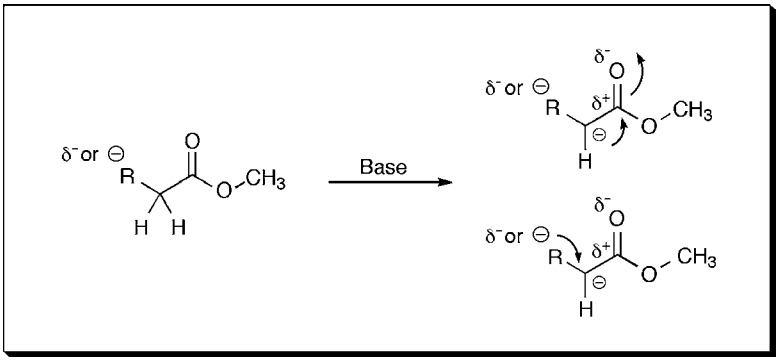


Scheme 2.11 *Electron-withdrawing groups increase acidity by increasing anionic stability.*

As illustrated in Scheme 2.11, electron-withdrawing groups are readily recognized when the group places either a partial or formal positive charge adjacent to an acidic center. This placement of a partial positive charge allows greater **delocalization** of the negative charge that develops when the acidic proton is removed. Through this increased delocalization of the developing negative charge, the stability of the developing anion increases, thus increasing the acidity of the target proton.

As illustrated in Scheme 2.12, electron-donating groups are readily recognized when the group places either a partial or formal negative charge adjacent to an acidic center. This placement of a negative charge forces destabilization of the negative charge that develops when the acidic proton is removed. To illustrate, imagine trying to force two magnets to meet at their negative poles. As the negative poles get closer, the repulsive forces between the magnets increase. As with magnets, two negative charges on adjacent atoms result in a destabilizing situation. By decreasing the stability of a developing negative charge, the stability of a developing anion decreases, thus decreasing the acidity of the target proton.

Functional groups were defined and discussed in Chapter 1 (Section 1.2). In that discussion, the concept was presented that functional groups can be either electron-withdrawing groups or electron-donating groups. In fact, all inductive effects result from the introduction of functional groups to organic molecules. Furthermore, through an understanding of the characteristics of the various functional groups, one can predict



Scheme 2.12 *Electron-donating groups decrease acidity by decreasing anionic stability.*

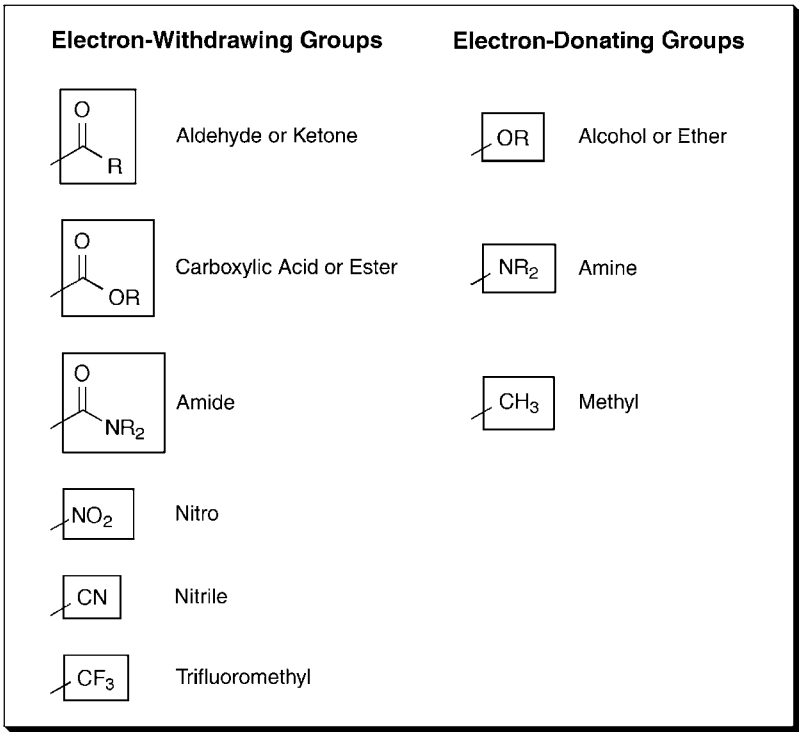


Figure 2.13 *Common electron-withdrawing groups and electron-donating groups.*

whether these functional groups are electron-donating groups or electron-withdrawing groups. In general, if a functional group is capable of absorbing electron density through delocalization, it will act as an electron-withdrawing group. Such groups include carbonyl-based groups, nitro groups, and nitriles. On the other hand, if a functional group possesses free lone pairs of electrons, this functional group will act as an electron-donating group regardless of the electronegativity of the specific atom involved. Such groups include alcohols, ethers, amines, and halogens. From the group of halogens, fluorine is the exception and serves as an electron-withdrawing group due to its high electronegativity. Finally, while inductive effects thus far have been tied to heteroatoms, it is important to note that alkyl groups are weak electron-donating groups and will impact pK_a values as we will soon discuss. Common electron-donating groups and electron-withdrawing groups are listed in Figure 2.13.

2.6 INDUCTIVE EFFECTS AND RELATIVE ACIDITIES

In Section 2.4, the concept of relative acidities was presented without fully defining the concept of inductive effects. In Section 2.5, the concept of inductive effects was defined and linked to functional groups. In this section, the concept of relative acidities is presented in conjunction with discussions of associated functional groups and their respective inductive effects. Since a treatment of this subject was already introduced in Section 2.4 as applied to carboxylic acids and esters, this section focuses on

oxygen- and nitrogen-containing functional groups lacking carbonyl components. Specifically, the relative acidities of alcohols and amines are discussed.

Beginning with alcohols, the simplest is methanol with a pK_a of 15. As illustrated in Figure 2.14, as **branching** of the alkyl group increases, so does the pK_a. This observation is a direct result of the inductive effect associated with **alkyl groups** such as methyl (CH_3). As mentioned in the previous section, the inductive effects of **methyl groups** result in donation of electron density. This increase in electron density in the vicinity of the oxygen atom destabilizes the anion resulting from deprotonation, thus increasing the pK_a. The more methyl groups adjacent to the OH, the greater the effect as illustrated in the case of *tert*-butanol with a pK_a of 18–19.

While our discussion of how inductive effects alter alcohol pK_a values has focused primarily on electron-donating groups, we cannot ignore the effect resulting from incorporation of electron-withdrawing groups. As one would expect, if electron-donating groups adjacent to alcohol functional groups increase pK_a values through destabilization of anions resulting from deprotonation, the opposite effect should be observed when electron-withdrawing groups are used. This is in fact the case as supported by the entry for 2,2,2-trifluoroethanol in Figure 2.14. The electron-withdrawing nature of the trifluoromethyl group adds stabilization to the anion resulting from deprotonation and reduces the pK_a compared to ethanol.

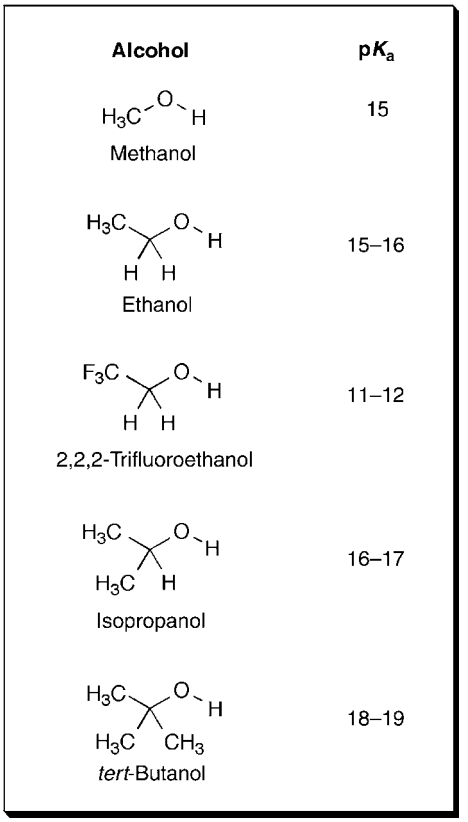
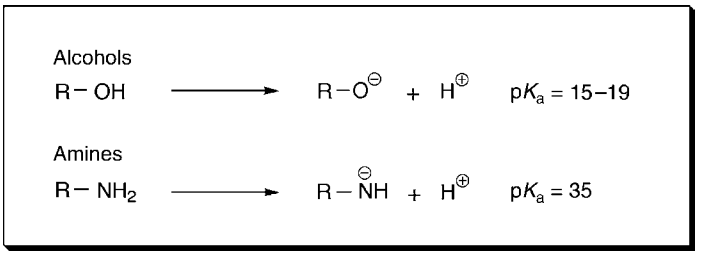


Figure 2.14 *pK_a values associated with alcohols increase as alkyl branching increases.*

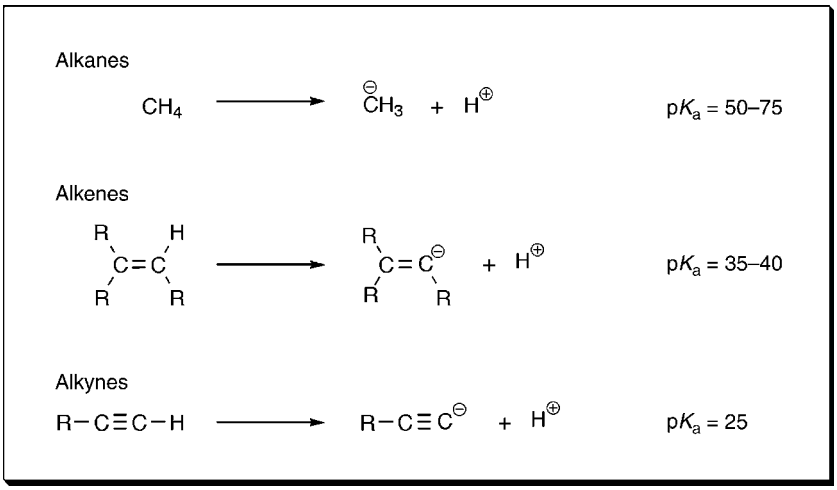


Scheme 2.13 *Amines and alcohols can both be deprotonated.*

Amines are similar to alcohols in that they can be deprotonated under basic conditions to generate anions (Scheme 2.13). However, because nitrogen is less electronegative than oxygen, considerably stronger bases are required to effect these deprotonations. This is further supported by the significantly higher pK_a values measured for amines as compared to alcohols (Scheme 2.13). These observations should not indicate in any way that the rules regarding inductive effects are different. In fact, they are exactly the same, and amines possessing electron-donating groups will exhibit higher pK_a values while amines possessing electron-withdrawing groups will exhibit lower pK_a values.

2.7 RELATIVE ACIDITIES OF HYDROCARBONS

Any discussion surrounding pK_a values would not be complete without addressing the deprotonation of hydrocarbons. Since hydrocarbons generally refer to organic molecules made up only of hydrogen and carbon, inductive effects resulting from introduction of functional groups is not relevant and we do not usually consider these compounds to be acidic. However, pK_a values of various protons associated with hydrocarbons have been measured. As illustrated in Scheme 2.14, saturated hydrocarbons are the least acidic while olefinic and



Scheme 2.14 *Hydrocarbons can be deprotonated and have measurable* pK_a *values.*

acetylenic protons have acidities on the same order of magnitude as those associated with esters and amines.

2.8 SUMMARY

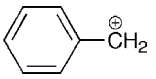
This chapter focused on the definition of acids as applied to **organic molecules**. Furthermore, the impacts of electronegativities and functional groups on the acidities of various types of protons were rationalized in the context of inductive effects. As discussions advance throughout this book and through organic chemistry coursework, a clear understanding of the various pK_a values associated with different environments and how they relate to one another will be beneficial. Consequently, a complete familiarization of the pK_a values presented in this chapter is essential. For convenience, all the pK_a values discussed in this chapter are listed in Appendix 1, and *their general magnitudes with respect to one another should be committed to memory*. This is the only recommended memorization task associated with this treatment of arrow pushing and will greatly facilitate the development of skills enabling the prediction of the mechanistic progression of organic reactions.

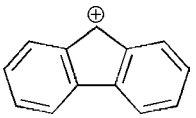
PROBLEMS

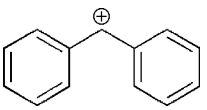
1. Explain how the Henderson–Hesselbach equation can be used, in conjunction with a titration curve, to determine a pK_a.

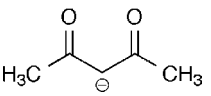
2. What is the pH of a solution of acetic acid ($pK_a = 4.75$) that has been titrated with $\frac{1}{4}$ an equivalent of NaOH?

3. Draw the resonance structures of the following charged molecules:

a. 

b. 

c. 

d. 

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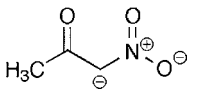

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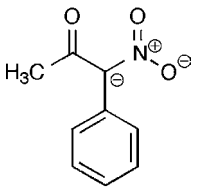

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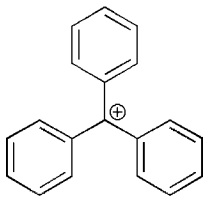
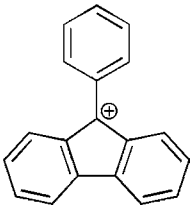


h.



4. Which cation from Problem 3 is more stable, 3(g) or 3(h)? Explain using partial charges.

5. How will the following substituents affect the pK_a of benzoic acid (raise, lower, or no change)? Explain using partial charges to illustrate inductive effects. Remember, *o* refers to *ortho* positions, *m* refers to *meta* positions, and *p* refers to the *para* position. In addressing these problems, assume that the acidity of the carboxylic acid is influenced solely by the partial charges induced by additional ring substituents.

a. *o*-NO_2

b. *p*-NO_2

c. *m*-NO_2

d. *p*-OH

e. *m*-OH

f. *p*-NH_2

g. *m*-CH_3

h. *p*-CH_3

i. *m*-CHO

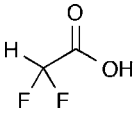
j. *p*-OCH_3

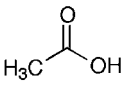
k. *o*-NO

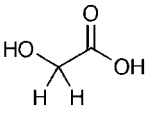
l. *p*-CI

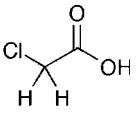
m. *m*-CI

6. Arrange the following groups of molecules in order of increasing acidity. Explain your results using partial charges and inductive effects.



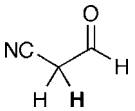




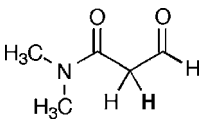


7. Predict pK_a values for the protons shown in boldface in the following molecules. Rationalize your answers.

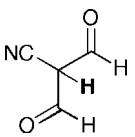
a.



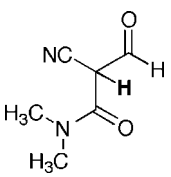
b.



c.

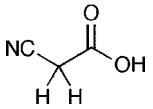


d.

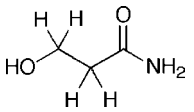


8. Predict the order of deprotonation of the various protons in the following molecules. Back up your answers with appropriate pK_a values.

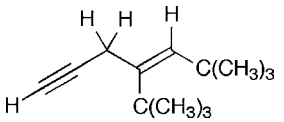
a.



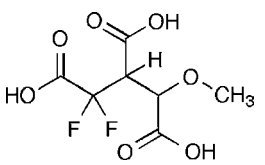
b.



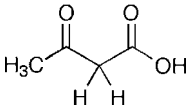
c.



d.

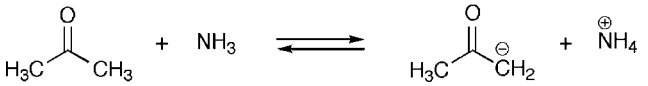


9. Which proton is the most acidic? Rationalize your answer.

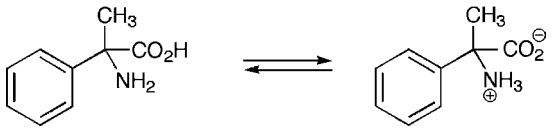


10. Using the pK_a values given in Appendix 1, calculate the equilibrium constants for the following reactions:

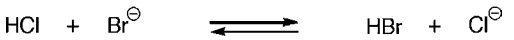
a.



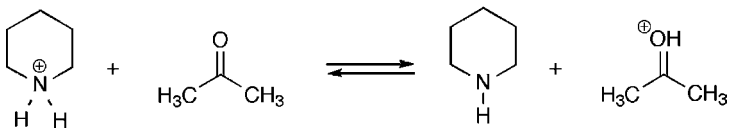
b.



c.



d.



Chapter 3

Bases and Nucleophiles

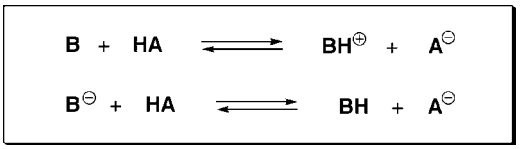
In the previous chapter, the concept of acidity was introduced and discussed as related to organic molecules. Additionally, various functional groups were presented along with the concepts of resonance effects and inductive effects. Moving forward, resonance effects and inductive effects were applied to rationalize variations in pK_a values that exist among compounds bearing similar functional groups. All of these factors were described using arrow pushing.

While relative acidities are extremely important to our abilities to accurately predict the mechanistic courses of organic reactions, we must recognize that in addition to acids, most heterolytic reactions involve bases as well. Furthermore, as will soon be discussed, in organic chemistry, bases generally are able to function as nucleophiles. Therefore, this chapter will serve as an introduction to the types of bases and nucleophiles that drive mechanistic organic chemistry.

3.1 WHAT ARE BASES?

The most general definition of a base is a molecule that has an affinity for protons. For example, if we consider a molecule, B, or an anion, B^-, these species are said to be bases if they react with an acid, HA, as shown in Scheme 3.1. As with the dissociation of acids, discussed in Chapter 2, the reaction of bases with acids is an equilibrium process that produces an anionic species, A^-, and, depending on the charged nature of the base, either a cationic or a neutral species. Furthermore, considering the species formed when a base reacts with an acid, the anionic component, A^-, is said to be the **conjugate base** of the starting acid, HA. Likewise, the cationic or neutral species formed, BH^+ or BH, is said to be the **conjugate acid** of the starting base, B^- or B.

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 3.1 *General representation of bases reacting with acids.*

Common base classes and examples of bases used in organic chemistry are shown in Figure 3.1 along with their conjugate acids and associated pK_a values.

In looking at the conjugate acid pK_a values listed in Figure 3.1, we realize that in order for the reactions represented in Scheme 3.1 to occur, the conjugate acid of a given base must have a pK_a value that is higher than the pK_a value associated with a proton of interest. For example, as shown in Scheme 3.2, we would not expect triethylamine to effectively deprotonate methyl acetate because the pK_a of methyl acetate is 15 pK_a units higher than the pK_a

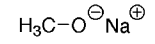
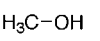
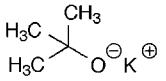
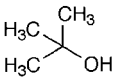
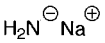
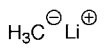
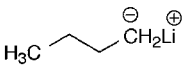
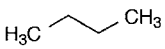
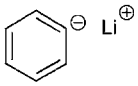
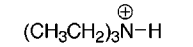
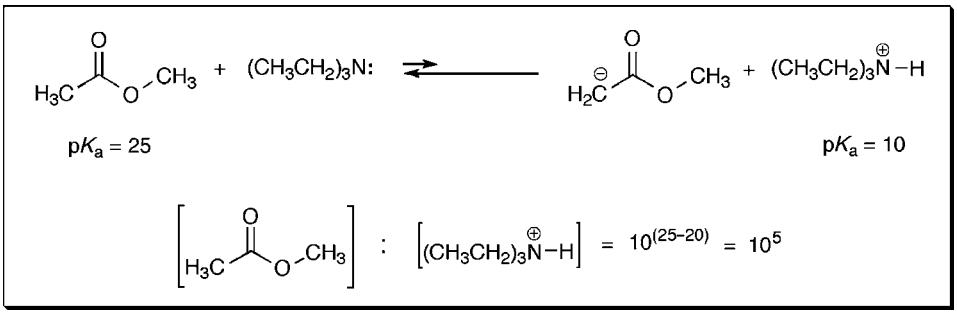
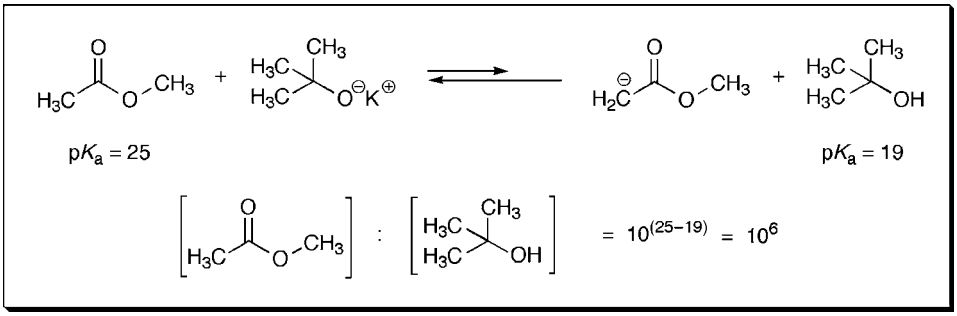
Base Class	Examples	Conjugate Acid	Conjugate Acid pK_a
 Alkoxide	 Sodium Methoxide	 Methanol	15
	 Potassium *tert*-Butoxide	 *tert*-Butanol	18–19
 Amide	 Sodamide	 Ammonia	35
 Alkyl	 Methyllithium	 Methane	50–75
	 Butyllithium	 Butane	50–75
 Phenyl	 Phenyllithium	 Benzene	40–45
R_3N: Amine	$(CH_3CH_2)_3N$: Triethylamine	 Triethylammonium Cation	10

Figure 3.1 *Common bases used in organic chemistry.*

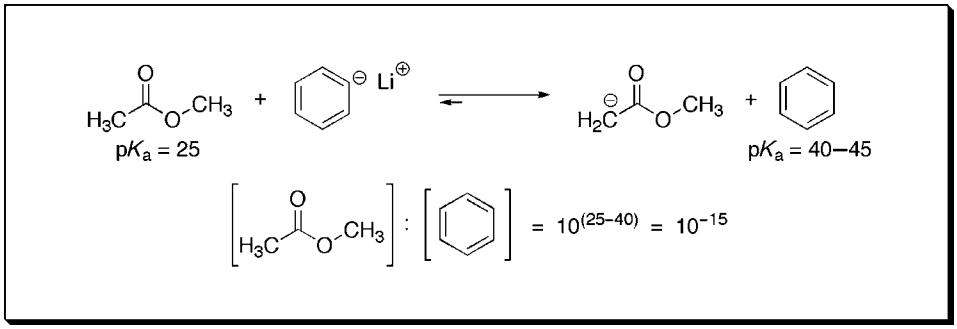


Scheme 3.2 *Equilibrium between methyl acetate and triethylamine.*

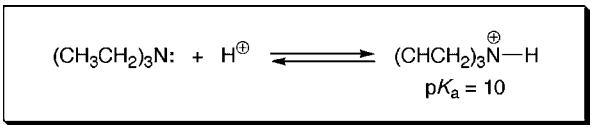


Scheme 3.3 *Equilibrium between methyl acetate and potassium* tert*-butoxide.*

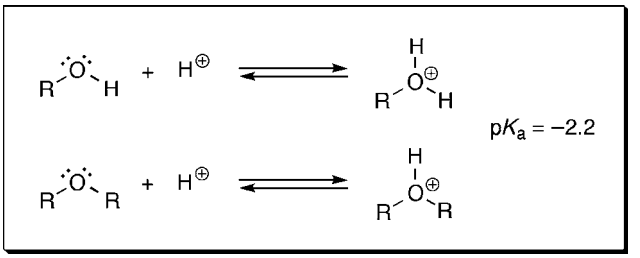
of the triethylammonium cation. Since each pK_a unit represents a factor of 10 (see the definition of pK_a described in Chapter 2), this differential indicates that for each 10^{15} molecules of methyl acetate, only one will be deprotonated. As shown in Scheme 3.3, the more basic potassium *tert*-butoxide will have a greater effect on this equilibrium because the pK_a differential between that of methyl acetate and that of *tert*-butanol is 6. By comparison, for every 10^6 molecules of methyl acetate, one will be deprotonated. Finally, in the absence of reactions other than deprotonation, Scheme 3.4 illustrates that very strong bases such as phenyllithium will effect essentially complete deprotonation. This is due to the pK_a differential between methyl acetate and benzene being at least -15, indicating



Scheme 3.4 *Equilibrium between methyl acetate and phenyllithium.*



Scheme 3.5 *Amine basicity is related to the nitrogen lone pair.*



Scheme 3.6 *Alcohol and ether oxygens can be protonated.*

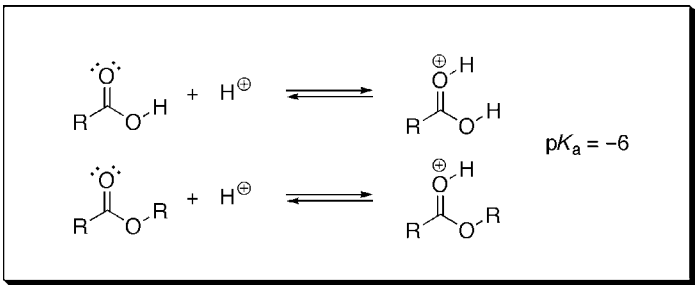
that for every molecule of methyl acetate, there will be 10^{15} molecules of benzene. Thus, it is important to understand the relative acidities of all components involved in organic reactions in order to predict the direction and outcome from a mechanistic perspective.

Again referring to the bases listed in Figure 3.1, triethylamine stands out because it is the only base listed that does not rely on a negative charge to impose basicity. In fact, the basicity of amines such as triethylamine is attributable to the lone pair associated with nitrogen (Scheme 3.5). Expanding upon the ability of lone pairs to act as bases and attract protons, we can expect that atoms and functional groups that possess lone pairs will also have measurable basicity and that their corresponding conjugate acids will have measurable pK_a values.

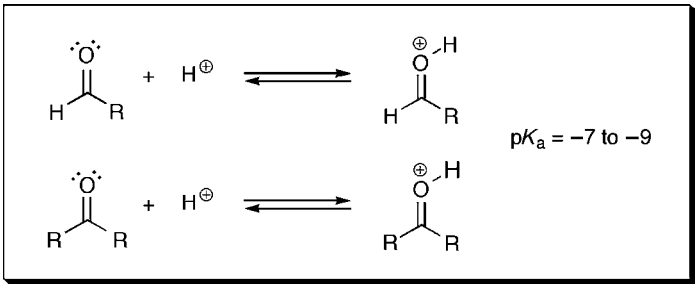
Moving beyond amines in our discussion of the acidity of conjugate acids of neutral bases, let us now consider alcohols and ethers. The protonation of these functional groups, illustrated in Scheme 3.6, results in positively charged trivalent oxygen atoms referred to as **oxonium ions**. While this protonation is possible due to oxygen possessing two **lone pairs** of electrons, it is not surprising that oxygen is far less basic than nitrogen due to its increased electronegativity. Consequently, oxonium ions are far more acidic than their corresponding **ammonium ions** and exhibit pK_a values around -2.2.

Extending beyond alcohols and ethers, conjugate acids of carbonyl-based functional groups are known. Specifically referring to carboxylic acids and esters, the corresponding conjugate acids, illustrated in Scheme 3.7, have pK_a values around -6. Furthermore, **protonated aldehydes and ketones**, illustrated in Scheme 3.8, have pK_a values ranging from -7 to -9.

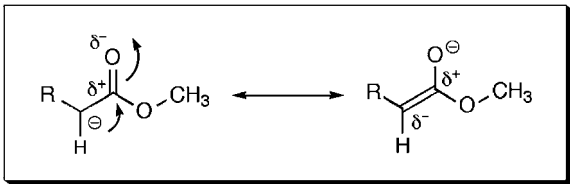
While not practical as bases, as demonstrated by pK_a values, the protonation of carbonyl-based functional groups is important. As previously discussed, carbonyl compounds possess partial positive charges and partial negative charges and, consequently, are capable of delocalizing adjacent charges through resonance. Scheme 3.9 illustrates this fact as applied to an ester. However, if we consider a protonated carbonyl compound, the resulting positive charge residing on the carbonyl oxygen is delocalized to the



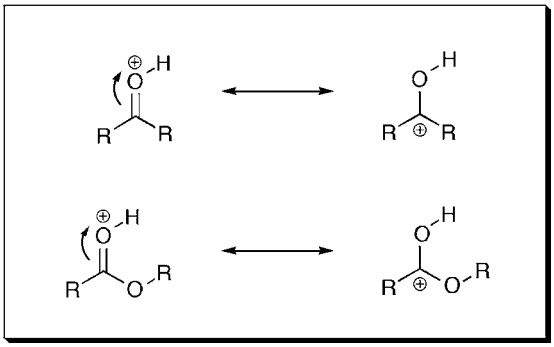
Scheme 3.7 *Carboxylic acids and esters can be protonated.*



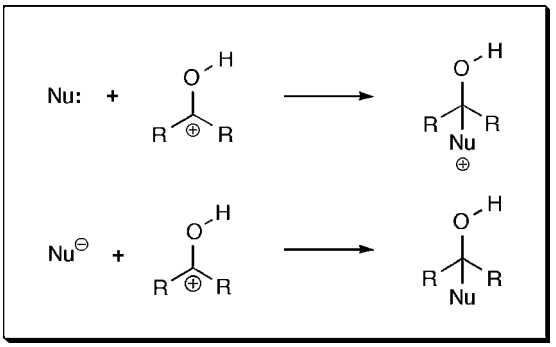
Scheme 3.8 *Aldehydes and ketones can be protonated.*



Scheme 3.9 *Carbonyl-based functional groups delocalize charges through resonance.*



Scheme 3.10 *Protonated carbonyl-based functional groups delocalize their positive charges.*



Scheme 3.11 *Protonated carbonyl-based functional groups are susceptible to reaction with nucleophiles.*

associated carbon atom (Scheme 3.10). The net result renders the carbon atom highly susceptible to reaction with nucleophiles (Scheme 3.11).

3.2 WHAT ARE NUCLEOPHILES?

As alluded to in Section 1.3 and in the previous section, heterolytic reactions generally involve species known as nucleophiles and complementary species known as electrophiles. By definition, a nucleophile is a compound that has an affinity for a positive charge. By analogy, an electrophile is a compound that has an affinity for a negative charge. Nucleophiles generally present themselves as either neutral species bearing available lone pairs of electrons or as anions (negatively charged ions). When a nucleophile is an anion, the anion is generally the conjugate base of an acid. Figure 3.2 lists common conjugate bases used as nucleophiles along with their parent acids and associated pK_a values.

In considering the information presented in Figure 3.2, it is important to become familiar with the general trends that influence the degree of **nucleophilicity** associated with the conjugate bases of various acids. From our discussions of acids, we know that as the pK_a increases, acidity decreases. Furthermore, as acidity decreases, the basicity associated with conjugate bases increases. Since, by definition, bases attract protons and since protons are, by definition, positively charged, we can translate this relationship to infer that bases exhibit affinities for positive charges. Since nucleophiles are defined as substances that have affinities for positive charges, we can understand the statement from the previous paragraph equating nucleophiles with conjugate bases of acids. Taking this discussion to the next level, the weaker the acid (higher pK_a), the stronger the conjugate base. Furthermore, the stronger the conjugate base, the stronger the nucleophile.

While the general trend relating **basicity** and nucleophilicity stands, we cannot simply rely on the pK_a values listed in Figure 3.2 as a guide for these trends. In fact, with respect to overall nucleophilicity, there are relevant factors other than basicity. Among these are **polarizability** of the nucleophilic atom, electronegativity of the nucleophilic atom, **steric factors**, and solvent effects. For our purposes, solvent effects will be discussed in the context of polarizability.

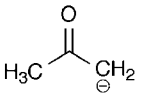
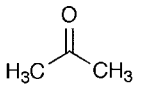
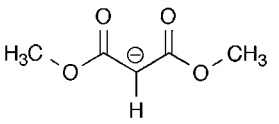
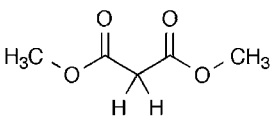
Nucleophile/ Conjugate base	Acid	pK_a
$F^{\ominus}$ Fluoride Anion	HF Hydrofluoric Acid	3.18
$Cl^{\ominus}$ Chloride Anion	HCl Hydrochloric Acid	−2.2
$Br^{\ominus}$ Bromide Anion	HBr Hydrobromic Acid	−4.7
$I^{\ominus}$ Iodide Anion	HI Hydroiodic Acid	−10
$N{\equiv}C^{\ominus}$ Cyanide Anion	H−CN Hydrocyanic Acid	9.3
$^{\ominus}N{=}\overset{\oplus}{N}{=}N^{\ominus}$ Azide Anion	$H-N_3$ Hydrazoic Acid	4.6
$H_3C-O^{\ominus}$ Methoxide Anion	H_3C-OH Methyl Alcohol	15
$H_3C-\overset{\ominus}{N}H$ Methylamide Anion	H_3C-NH_2 Methylamine	35
$N{\equiv}C-\overset{\ominus}{C}H_2$ Acetonitrile Anion	$N{\equiv}C-CH_3$ Acetonitrile	25
 Acetone Anion	 Acetone	20
 Dimethyl Malonate Anion	 Dimethyl Malonate	13
$H_3C^{\ominus}$ Methyl Anion	CH_4 Methane	50–75

Figure 3.2 *Representative nucleophiles and their corresponding acid forms.*

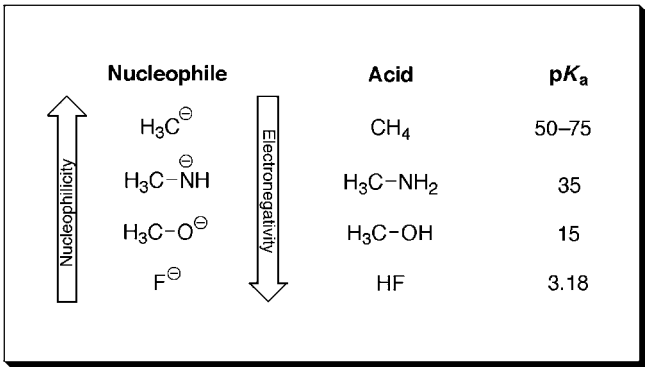


Figure 3.3 *Relationship between nucleophilicity, electronegativity, and basicity as illustrated using first-row elements.*

Electronegativity, discussed in Chapter 1, is a measure of an atom's affinity for electrons. Thus, as electronegativity increases, affinity for electrons increases. Furthermore, as affinity for electrons increases, so does acidity. This is reflected in the decreasing pK_a values moving from methane to methylamine to methanol to hydrofluoric acid (Fig. 3.3). In this sequence, the trend relating increasing basicity of conjugate bases to increasing nucleophilicity holds true. Furthermore, this relationship holds true for each row in the periodic table of the elements moving from left to right.

Polarizability refers to the ability of an atom to become polarized in the presence of external influences such as solvent effects. In general, polarizability increases as electronegativity decreases. Another way of looking at this relationship involves atomic size. Essentially, the larger an atom, the more diffuse its outer shell of electrons. As this electron shell becomes more diffuse, it also becomes more susceptible to polarizing influences. Furthermore, these polarizing influences can dramatically impact the order of nucleophilicity among atoms represented in any given column of the periodic table of the elements. In fact, polarizability can override the relationship between nucleophilicity and pK_a. This effect is illustrated using the relative nucleophilicities of Cl^-, Br^-, and I^-. If we refer to the pK_a values listed in Figure 3.2, we would expect the order of nucleophilicity among these halide ions to be $Cl^- > Br^- > I^-$. This is, in fact, the case in the presence of **polar aprotic solvents** (solvents not possessing a dissociable proton) such as dimethylformamide. However, in the presence of **polar protic solvents** (solvents possessing a dissociable proton) such as water or alcohols the order of nucleophilicity is $I^- > Br^- > Cl^-$. This effect, shown in Figure 3.4, illustrates that relative nucleophilicities are not absolute.

Another factor influencing nucleophilicity and related to polarizability is the **hardness** or **softness** of the nucleophilic base. Specifically, a **hard base** is high in electronegativity and low in polarizability. Alternatively, a **soft base** is low in electronegativity and high in polarizability. Using these definitions, F^- is considered a hard base because it is high in electronegativity, small in size and holds its electrons very tightly. On the other hand, I^- is considered a soft base because its large size causes it to hold its electrons loosely and renders it highly **polarizable**.

The relationship between hard bases and soft bases now relates back to solvent effects. if we consider a hard base in a polar solvent, we find that the concentrated electron density

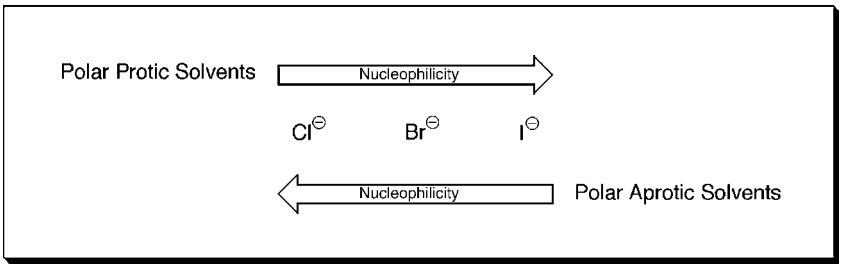


Figure 3.4 *Order of increasing nucleophilicity of halide ions is influenced by polarizing influences such as solvent effects.*

associated with a hard base attracts a tight shell of solvent surrounding it. This solvent shell blocks the hard base from reacting as a nucleophile. On the other hand, this solvent effect is minimized for a soft base due to its large size and diffuse electron concentration. The absence of a solvent shell around a soft base enhances its ability to react as a nucleophile. This effect is illustrated in Figure 3.5. Thus, while solvent effects can influence the order of nucleophilicity observed for halide ions, the general rule of thumb is that nucleophilicity increases as we move from the top to the bottom of any given column in the periodic table of the elements.

Of the factors influencing nucleophilicity, **steric effects** have perhaps the greatest influence. Steric effects occur when groups attached to a nucleophilic atom are too large

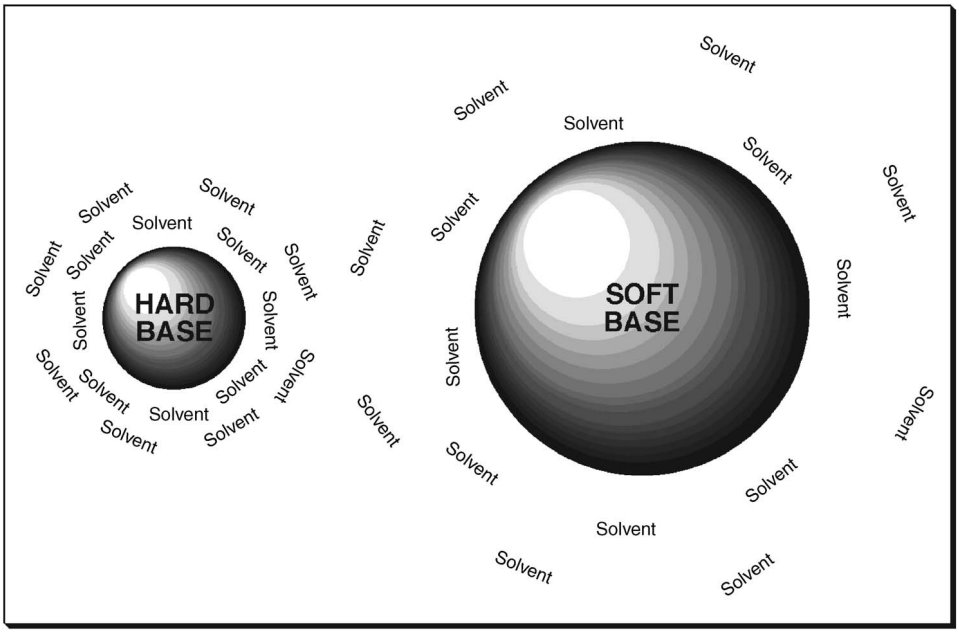


Figure 3.5 *Solvent shells surround hard bases rendering them less reactive nucleophiles than soft bases.*

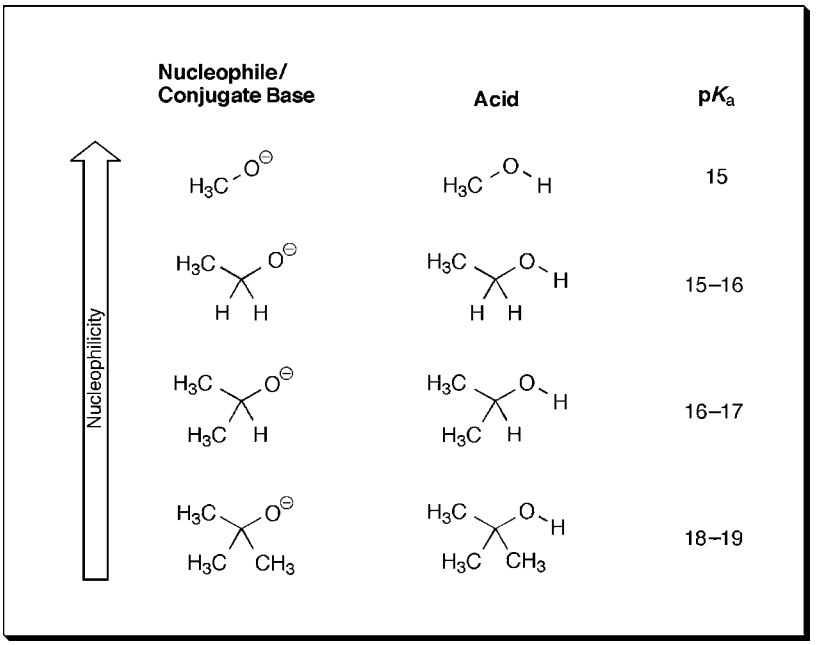
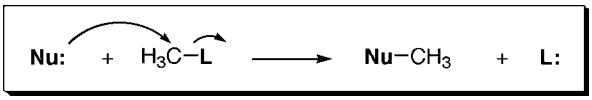


Figure 3.6 *Steric effects can override the influence of* pK_a *values on nucleophilicity.*

to allow the nucleophile to react. In fact, it is this effect that can differentiate between a reactive nucleophile and a true base. Consider the alkoxide ions illustrated in Figure 3.6. If we take into account only the pK_a values listed, we may expect that nucleophilicity would increase as we move from methoxide to ethoxide to isopropoxide to *tert*-butoxide. However, if we look at these conjugate bases not as a function of their corresponding pK_a values but as a function of their overall **structure**, we find a very different story. Specifically, a methyl group is small compared to an ethyl group. Furthermore, an ethyl group is small compared to an isopropyl group. Finally, an isopropyl group is small compared to a *tert*-butyl group. Therefore, if we consider that increasing **molecular volume** around a nucleophilic atom results in decreasing nucleophilicity, it is easy to reconcile the trend illustrated in Figure 3.6. Furthermore, when a nucleophilic atom becomes sterically blocked from acting as a nucleophile, the basic characteristics of this atom becomes manifested. In fact, *tert*-butoxide anions are commonly used as bases in organic chemistry due to the diminished nucleophilicity surrounding the oxygen. Finally, it is important to remember that this effect is generally applicable to all nucleophiles regardless of the atoms involved.

3.3 LEAVING GROUPS

No discussion of nucleophiles would be complete without addressing leaving groups. As mentioned in Chapter 1 and illustrated in Scheme 3.12, leaving groups are important components in nucleophilic reactions because they represent the molecular fragment that



Scheme 3.12 *Example of a nucleophilic reaction.*

detaches from the parent molecule during the course of the reaction. Specifically, a nucleophile, Nu, approaches an organic molecule and displaces the leaving group, L. This type of reaction raises the question of what relationship links nucleophiles to leaving groups. The answer to this question begins with pK_a values.

As previously discussed, relative acidities are important with respect to our ability to predict which proton will be removed first. Furthermore, relative acidity brings our attention to the relative stability of conjugate bases. Specifically, the more stable the conjugate base, the higher the acidity and, in general, the lower the nucleophilicity. This trend, as discussed in the previous section holds true when comparing nucleophiles from the same row in the periodic table of the elements. Keeping this trend in mind, we can argue that since a leaving group is essentially the opposite of a nucleophile, the trend regarding nucleophilicity should roughly reverse when considering trends regarding the efficiency of leaving groups. This is, in fact, the case and, as we will see as discussions progress through this book, the acid forms of leaving groups will generally exhibit higher pK_a values than the acid forms of competing nucleophiles.

3.4 SUMMARY

In this chapter, the concepts of organic bases and basicity were presented. These discussions were expanded to define nucleophiles and nucleophilicity. Trends associated with conjugate bases of acids and nucleophilicity were presented and translated to define the concept of leaving groups. As discussions continue, all of these concepts will play important roles in the various organic reaction mechanistic types presented in the following chapters.

PROBLEMS

1. In each case, circle the better nucleophile. Explain your answers.

a. 

b. 

c. 

d. 

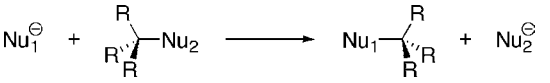
e. 

f. 

g. 

h. 

2. Nucleophiles often participate in nucleophilic substitution reactions. The general form of these reactions may be represented by the following equation where Nu_1^- and Nu_2^- are nucleophiles:



a. Explain what type of relationship between Nu_1^- and Nu_2^- is necessary in order for this reaction to be favored.

b. What does this say about the relative basicities of Nu_1^- and Nu_2^-?

c. Which nucleophile has the larger pK_a?

d. What generalization can be concluded about the relationship between bases and nucleophiles?

3. How can pK_a values be used to describe basicity?

4. As electron-donating and electron-withdrawing substituents will affect the acidity of organic molecules, so will they affect the basicity. How will the following substituents affect (raise, lower, or no change) the pK_a of aniline (aminobenzene)? Explain using partial charges to illustrate inductive effects. Remember, *o* refers to *ortho* positions, *m* refers to *meta* positions and *p* refers to the *para* position. *In addressing these problems, assume that the acidity of the amine is influenced solely by the partial charges induced by additional ring substituents.*

a. *o*-NO_2

b. *p*-NO_2

c. *m*-NO_2

d. *p*-NH_2

e. *m*-CH_3

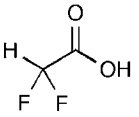
f. *p*-CH_3

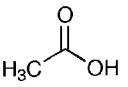
g. *p*-OCH_3

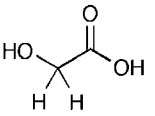
h. *p*-Cl

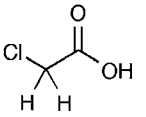
i. *m*-Cl

5. Arrange the following groups of molecules in order of increasing basicity. Explain your results using partial charges and inductive effects.



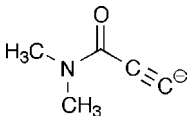




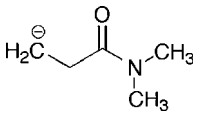


6. Predict the order of protonation of the basic sites on the following molecules. Support your answers with pK_a values.

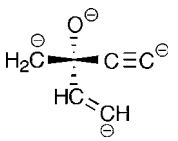
a.



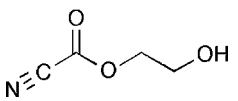
b.



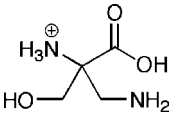
c.



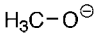
d.

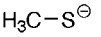


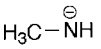
7. Which proton is the least acidic? Explain your answer.

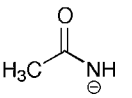


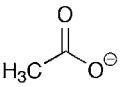
8. Separate the following group of bases into a group of hard bases and a group of soft bases. Rationalize your answers based on electronegativity and polarizability.

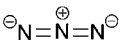






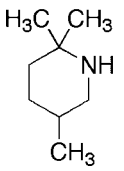


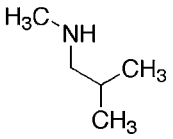


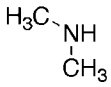


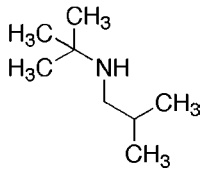
9. Arrange the following structures in order of increasing nucleophilicity:

a.

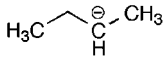


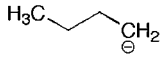


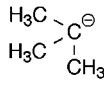




b.







10. For the following pairs of structures, circle the better leaving group.

a. $Cl^{\ominus}$ $I^{\ominus}$

b. $H_3C-O^{\ominus}$ $H_3C-\overset{\ominus}{N}H$

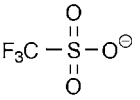
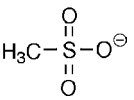
c. $CH_3CH_2-O^{\ominus}$ $CF_3CH_2-O^{\ominus}$

d. $H_3C-S^{\ominus}$ $H_3C-O^{\ominus}$

e. $F^{\ominus}$ $Br^{\ominus}$

f. $H_3C-\overset{\ominus}{N}H$ $H_3C-S^{\ominus}$

g. $Br^{\ominus}$ $H_3C-O^{\ominus}$

h.  

Chapter 4

S_N2 Substitution Reactions

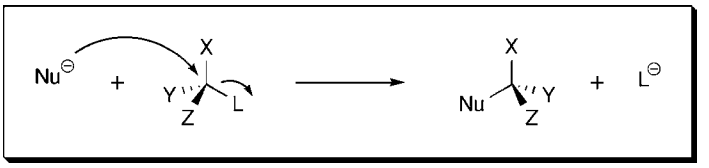
As alluded to in previous chapters, the study of organic chemistry requires an understanding of the mechanistic types that drive reactions. While the detailed mechanisms associated with some complex reactions may lie beyond the scope of an introductory organic chemistry course, the fundamental components are easily recognized and applied to the reactions contained within generally presented curricula. As stated in earlier discussions, this book presents the concept of arrow pushing with a focus on heterolytic reaction mechanisms. However, it is important to remember that the lessons presented herein are applicable to organic chemistry regardless of the mechanistic type.

While the fundamental mechanistic components of organic chemistry can be combined to describe complex mechanisms associated with complex reactions, the individual mechanistic components fall into a relatively small and well-defined group of four. These are **S_N1**, **S_N2**, **E1**, and **E2** reactions. In this chapter, the fundamentals associated with S_N2 reactions are presented.

4.1 WHAT IS AN S_N2 REACTION?

Among the mechanistic types relevant to organic chemistry, the S_N2 reaction mechanisms are the simplest. In progressing from starting materials to products, these reactions generally consist of a nucleophile displacing a leaving group. As illustrated in Scheme 4.1, consider a molecule where L^- is a leaving group. As shown, a nucleophile, Nu^-, can be introduced with displacement of the leaving group, thus generating a new molecule.

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 4.1 *Representation of an S_N2 reaction.*

While discussions of **stereochemistry** are left to the organic chemistry textbooks adopted for introductory classes, it is important to recognize the **stereochemical** implications of S_N2 reactions. In this respect, molecular bonds are drawn with either a straight line, a wedge, or a hashed wedge. Bonds drawn with straight lines are understood to lie in the same plane as the two-dimentional page on which they are drawn. Bonds drawn with wedges are understood to project above the plane of the page on which they are drawn. Finally, bonds drawn with hashed wedges are understood to project below the plane of the page on which they are drawn.

Recognizing that the substitutents residing on a tetra-substituted carbon atom are spherically spaced equidistant from one another, if all substituents are connected with lines, a **tetrahedron** is formed. Furthermore, as shown in Figure 4.1, if all four substituents are unique, they can be arranged in two configurations where the two molecules are mirror images and not superimposable. Because these two molecules are identical in composition but not configuration in three-dimensional space, they are referred to as

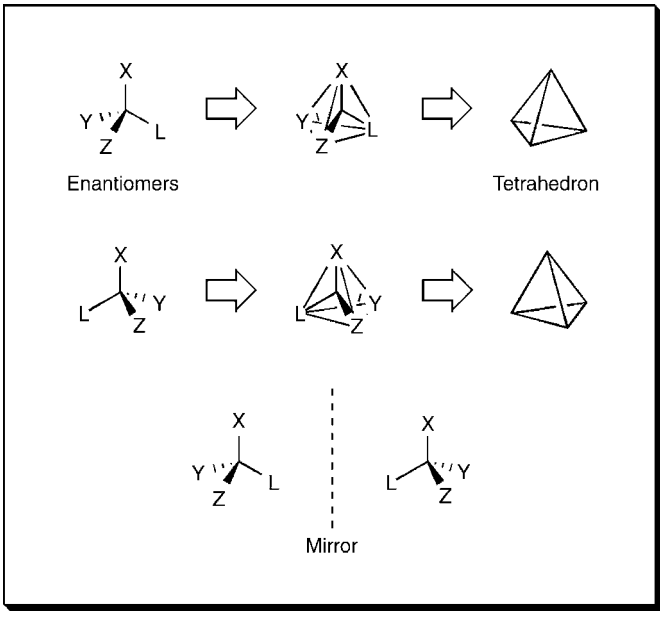
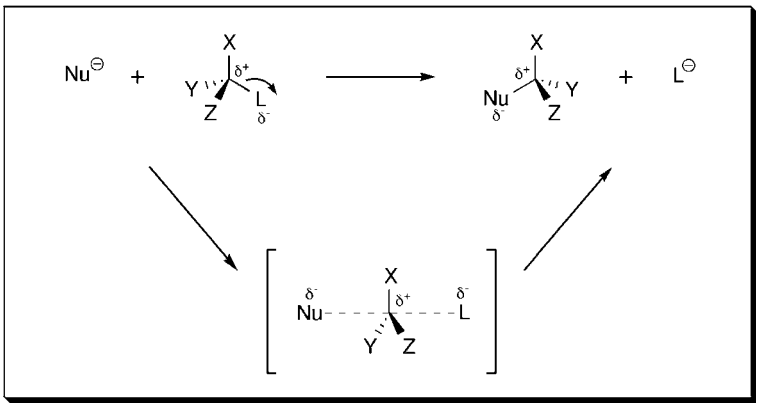


Figure 4.1 *Enantiomers are mirror images, not superimposable, and dependent upon the tetrahedral arrangement of carbon atom substituents.*



Scheme 4.2 *Mechanistic explanation of S_N2 reactions.*

stereoisomers. Furthermore, when two molecules differ only by the spatial arrangement of their substituents rendering them mirror images of each other, these molecules are called **enantiomers**.

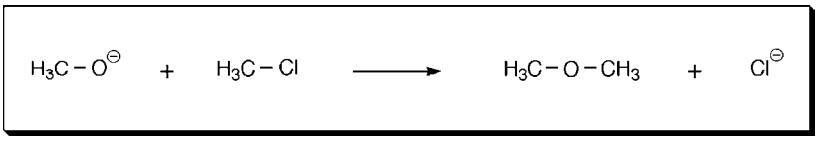
The above discussion of stereochemistry is important to the context of S_N2 reactions because, as illustrated in Scheme 4.1, when a nucleophile displaces a leaving group, the **configuration** of substituents X, Y, and Z with respect to L becomes inverted. Thus, the configuration of X, Y, and Z with respect to Nu is opposite to their configuration with respect to L. As shown in Scheme 4.2, this **inversion** of configuration is mechanistically explained through the simultaneous formation of the Nu–carbon bond and cleavage of the L–carbon bond. Elongated hashed lines are used to illustrate the partial formation or cleavage of molecular bonds. Electronically, this mechanism is explained with the placement of partial positive and partial negative charges.

Looking at Scheme 4.2, we recognize that an S_N2 reaction proceeds with the **S**ubstitution of a leaving group with a **N**ucleophile leading to the $\mathbf{S_N}$ designation. Because this mechanism proceeds with the initial approach of two species, it is referred to as a bimolecular reaction. The involvement of **2** species enhances the mechanistic designation to $\mathbf{S_N2}$.

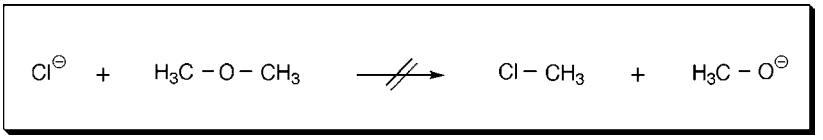
4.2 WHAT ARE LEAVING GROUPS?

The concept of leaving groups was introduced in Chapter 3 and presented in the context of nucleophiles and acid–base chemistry. However, with respect to S_N2 reactions, there are additional perspectives, relating nucleophiles to leaving groups, deserving attention. For example, in the context of **nucleophilic substitution** reactions, it is reasonable to conclude that leaving groups are nucleophiles. In fact, this is generally true, and one requirement for a nucleophilic substitution reaction to proceed is that the incoming nucleophile be a better nucleophile than the leaving group.

In consideration of the relationship between nucleophiles and leaving groups, recall that the pK_a values for methanol are 15–16 and the pK_a value for hydrochloric acid is −2.2. Because methanol is less acidic than hydrochloric acid, methoxide ions are expected to be better nucleophiles than chloride ions. This is, in fact, the case and the



Scheme 4.3 *S_N2 reactions proceed when incoming nuclophiles are more nucleophilic than outgoing leaving groups.*



Scheme 4.4 *S_N2 reactions do not proceed when incoming nuclophiles are less nucleophilic than outgoing leaving groups.*

S_N2 reaction illustrated in Scheme 4.3 will proceed to completion. Furthermore, as illustrated in Scheme 4.4, the reverse reaction will not proceed because relative to chloride ions, methoxide ions are poor leaving groups.

In summary, S_N2 reactions are defined by the principles surrounding organic acids and their conjugate bases as discussed in Chapters 2 and 3. Specifically, as discussed in Chapter 3, relative nucleophilicities can be estimated based on pK_a values. Finally, relative pK_a values can be used to predict whether a reaction will proceed and what component of the starting material will be the leaving group.

4.3 WHERE CAN S_N2 REACTIONS OCCUR?

With an understanding of what S_N2 reactions are, it is now important to understand where, on a given molecule, such reactions will take place. The answer to this question can be found by recognizing electronegativity trends. As previously discussed, an atom's electronegativity relates to how strongly it holds on to its electrons. This translates into greater partial negative charges residing on more electronegative atoms and smaller partial negative charges residing on less electronegative atoms. Regarding trends, as previously discussed, relative electronegativities of atoms are readily identified using the periodic table of the elements. For example, moving across each row of the periodic table, we find that electronegativity increases among the atoms, thus indicating that oxygen is more electronegative than nitrogen and that fluorine is more electronegative than oxygen.

As discussed in previous chapters, pK_a values are directly related to electronegativities. This is clearly reflected in the nitrogen–oxygen–fluorine trend discussed above, considering that amine pK_a values are approximately 35, alcohol pK_a values are approximately 15–19, and the pK_a value for hydrofluoric acid is approximately 3. The increase in acidity is related to increased electronegativity because more electronegative atoms are more stable in their anionic form. Thus, fluorine can stabilize a negative charge better than oxygen, which, in turn, can stabilize a negative charge better than nitrogen.

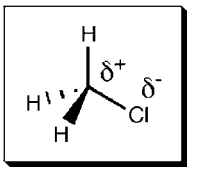


Figure 4.2 *Chloromethane bears a partial negative charge on the electronegative chlorine atom and a partial positive charge on the carbon atom.*

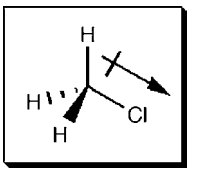


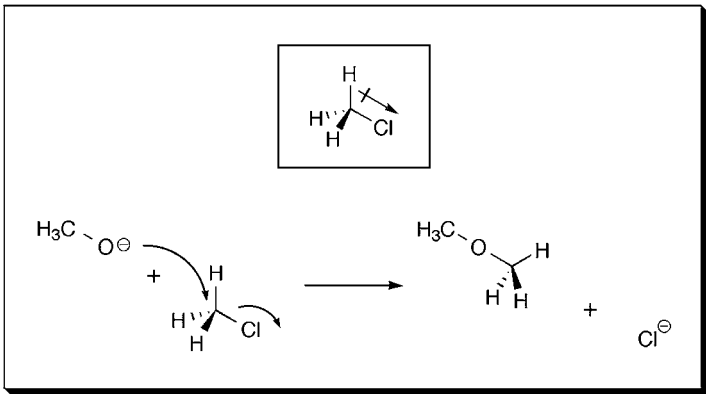
Figure 4.3 *The carbon–chlorine bond in chloromethane is polarized.*

Since nucleophiles, by definition, are attracted to positively charged centers, we must consider how such centers become attractive to nucleophiles. This effect relates to the electronegativity of the atoms attached to the center. Since an electronegative atom retains a partial negative charge, the electronegative atom pulls electron density from the atom on which it resides (usually carbon), leaving it with a partial positive charge. This effect is illustrated in Figure 4.2 where an electronegative chlorine atom is attached to carbon and inducing a partial positive charge.

When a bond joins an atom bearing a partial positive charge to an atom bearing a partial negative charge, the bond is said to be polarized. Much in the same way a magnet possesses a positive pole and a negative pole, the respective ends of a **polarized bond** are positively and negatively charged. When referring to polarity and polarized bonds, the direction of polarity is, by convention, from positive to negative. As shown in Figure 4.3, this is commonly illustrated using a special arrow with a + at the positive end and the tip pointing in the direction of the negative end.

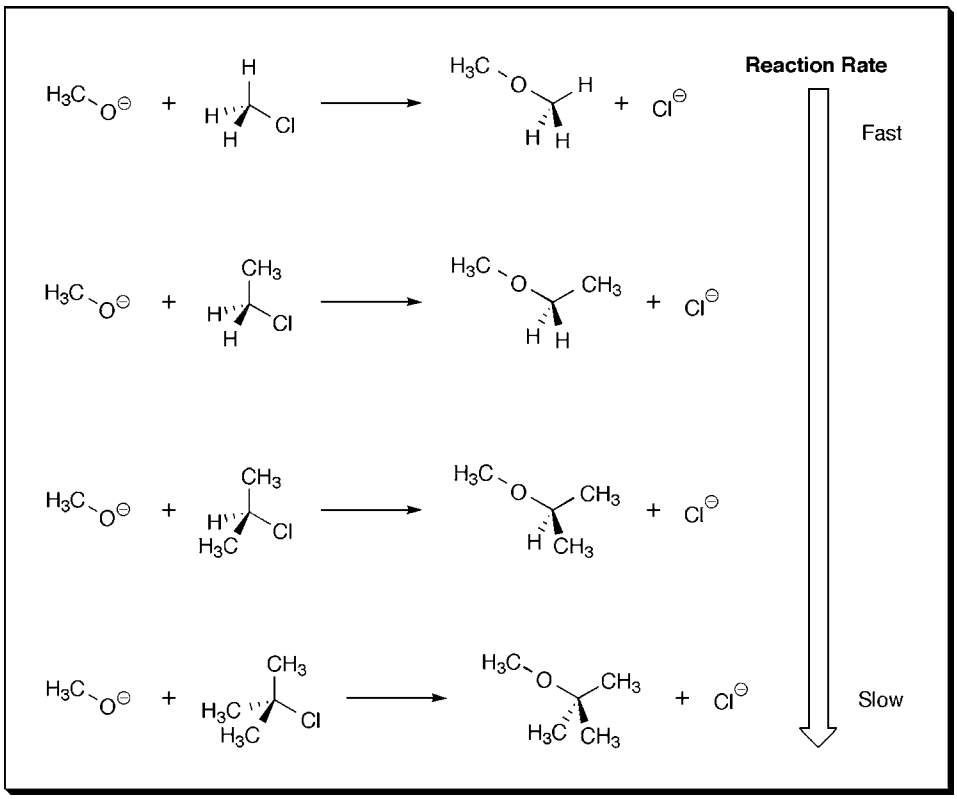
Because nucleophiles are attracted to sites of positive or partial positive charges, understanding the direction of polarity associated with a given bond serves three purposes. First, the site to which a given nucleophile is attracted is readily identified. Second, the spatial direction or trajectory of the reaction is readily identified. Lastly, the leaving group is readily identified. These are all graphically summarized in Scheme 4.5 using a different rendering of the S_N2 reaction illustrated in Scheme 4.3.

In Chapter 3, the relationship between nucleophiles and bases as influenced by **steric bulk** was addressed. What was not addressed is the complementary issue surrounding the accessibility of electrophilic (positively charged or partially positively charged) sites to nucleophiles. In fact, in the same way that nucleophilicity decreases with increasing steric bulk around the nucleophilic atom, the ability of a nucleophile to react with an electrophile also decreases with increasing steric bulk around the site of potential S_N2 reactions. This effect is illustrated in Scheme 4.6 using the reaction introduced in Scheme 4.3. As illustrated, successive introduction of methyl groups adjacent to the S_N2 reaction site results in *decreased reaction rates*.



Scheme 4.5 *Understanding the direction of bond polarity allows identification of reaction site, trajectory of nucleophile, and identification of the leaving group.*

Thus, when identifying sites where S_N2 reactions can occur, the following criteria must be met. First, S_N2 reactions occur at **tetrahedral** carbon atoms. Second, S_N2 reactions occur at molecular sites bearing the greatest degree of positive charge. Lastly, S_N2 reactions occur at sites that are **sterically accessible** to the incoming nucleophile.



Scheme 4.6 *Steric bulk slows down reaction rates for S_N2 reactions.*

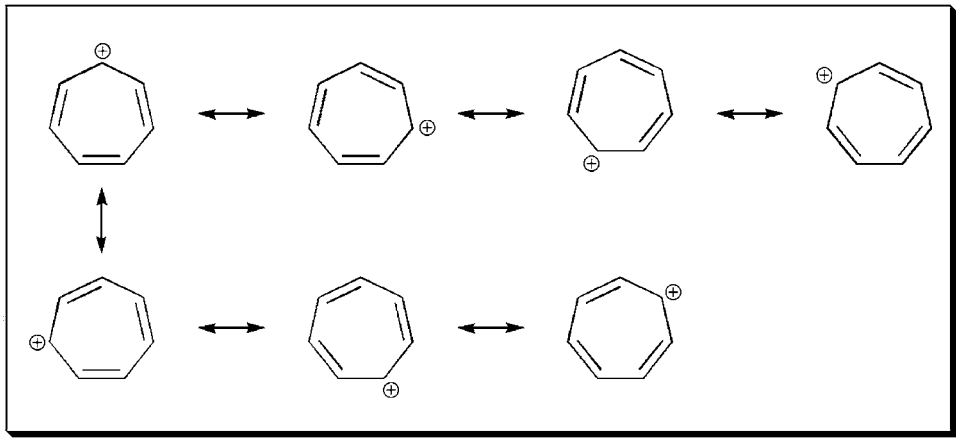
4.4 S_N2' REACTIONS

In the previous section, detailed discussions were presented illustrating conditions and criteria relevant to the initiation of S_N2 reactions. Furthermore, in previous chapters, the concept of resonance was introduced. When considering mechanistic organic chemistry, resonance is frequently recognized as contributing to the outcome of chemical reactions. In the following paragraphs, these contributions relative to S_N2 reactions are presented.

Resonance, as introduced in Chapter 2, explains stability of anions and rationalizes trends in pK_a values. However, resonance can also be used to rationalize the stability of **cations** (positively charged ions). As shown in Scheme 4.7, the stability of the cycloheptatriene cation is explained by its resonance forms. There is, of course, another reason for the stability of the cycloheptatriene cation, which relates to the principles of **aromaticity** and which will not be discussed in detail in this book.

As positively and negatively charged ions can be stabilized through resonance forms, so can species bearing partial positive charges and partial negative charges. As previously discussed, an electronegative atom attached to a carbon atom will induce a partial positive charge onto the carbon atom. As illustrated in Figure 4.4, when substituents possessing bond unsaturation are also attached to the partially positive carbon, the partial positive and partial negative charges are extended into the unsaturated system.

When partial positive charges are delocalized through **unsaturated** bonds, the result, as illustrated above, is the presence of multiple sites to which nucleophiles will be attracted. This principle is illustrated in Scheme 4.8 and explained through arrow pushing. As shown, when a nucleophile reacts with the terminal carbon atom, electrons from the double bond shift to displace the chloride ion. Since this is a **bimolecular nucleophilic substitution**, the mechanism type falls within the definition of S_N2 reactions. However, since this reaction occurs through a double bond, or an extended conjugated system, it is designated $\mathbf{S_N2'}$. In the case of the example shown in Scheme 4.8, the product is formed through a combination of S_N2 and S_N2' mechanisms.



Scheme 4.7 *Resonance forms can be used to rationalize the stability of cations adjacent to sites of bond unsaturation.*

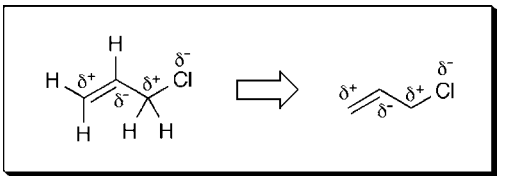
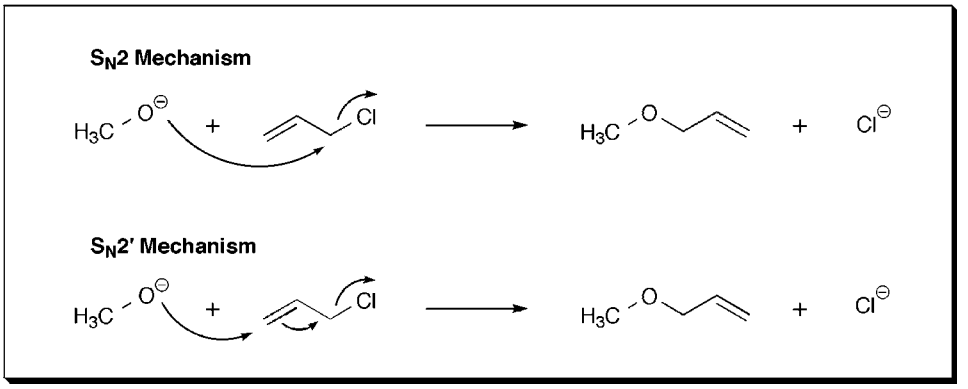
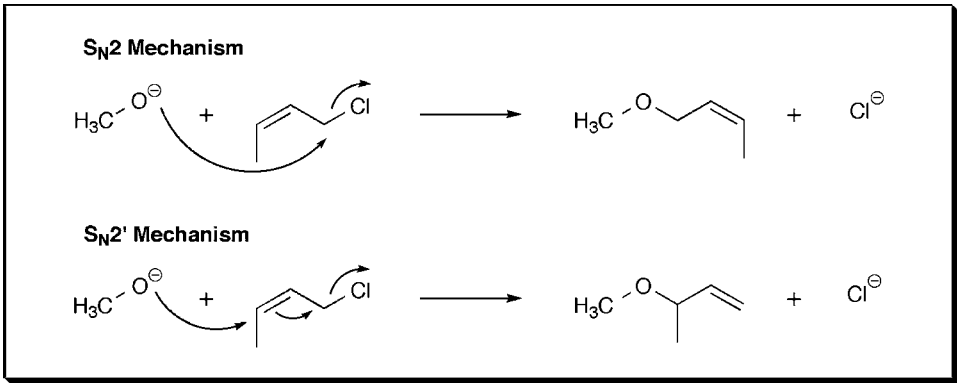


Figure 4.4 *Partial charges can be delocalized through unsaturated bonds.*



Scheme 4.8 *Comparison of S_N2 and S_N2' reactions as explained with arrow pushing.*

In the case of the reaction illustrated in Scheme 4.8, the product is not dependent upon which site the nucleophile is drawn to or which mechanism the reaction proceeds through. However, when the double bond possesses an additional substituent, product mixtures can form as illustrated in Scheme 4.9. In general, when predicting the outcome of reactions where both S_N2 and S_N2' reactions are possible, the major product will be dependent upon the steric constraints around the various reactive (or partially positively charged) sites. In cases where the nucleophile has comparable accessibility to electrophilic sites, product mixtures are usually the result.



Scheme 4.9 *Competing S_N2 and S_N2' reaction mechanisms can lead to product mixtures.*

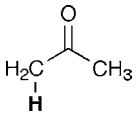
4.5 SUMMARY

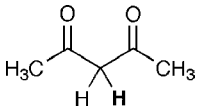
In this chapter, S_N2 reaction mechanisms were defined and presented in the context of nucleophiles displacing leaving groups at electrophilic centers. Furthermore, the conditions required for S_N2 reactions to proceed were discussed as well as factors that influence the progression of such reactions. In this context, discussions of S_N2 reactions were extended into the related S_N2' reaction mechanisms.

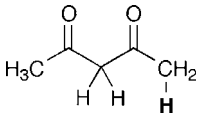
As the principles of this chapter, by nature, build upon those presented in previous chapters, the same will be for topics discussed in the remainder of this book. The study of organic chemistry is a progressive task with many overlapping principles. As should be apparent from topics discussed thus far, many of these principles reduce to the acid–base chemistry presented in the earliest chapters. This is also the case for the remaining topics presented herein.

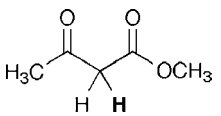
PROBLEMS

1. In many S_N2 reactions, the nucleophile is generated by deprotonation of an organic acid. For each molecule, choose the base best suited to completely remove the labeled proton. (Consider pK_a values and recognize that, in some cases, dianions should be considered.) Explain your answers.

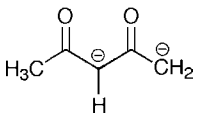
a.  $NaOCH_3 : (CH_3)_2NLi : CH_3Li$

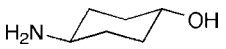
b.  $NaOCH_3 : (CH_3)_2NLi : CH_3Li$

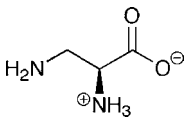
c.  $NaOCH_3 : (CH_3)_2NLi : CH_3Li$

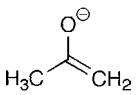
d.  $NaOH : NaOCH_3 : NaOCH_2CH_3$

2. In predicting the course of S_N2 reactions, it is important to recognize groups most likely to act as nucleophiles. For each molecule, label the most nucleophilic site.

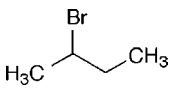
a. 

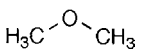
b. 

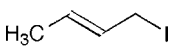
c. 

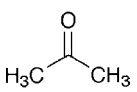
d.  (*Hint*: Consider resonance.)

3. For each molecule, show the partial charges, bond polarity, and where a nucleophile is most likely to react.

a. 

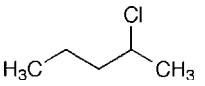
b. 

c. 

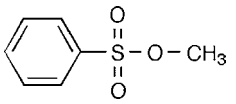
d. 

4. For each molecule, identify the leaving group assuming that H_3C^- is the nucleophile.

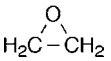
a.



b.

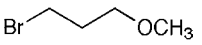


c.

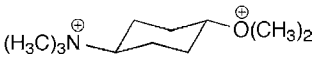


5. For each molecule, label the most likely leaving group. Explain your answers.

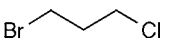
a.



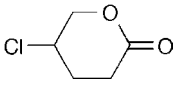
b.



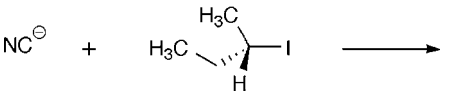
c.



d.

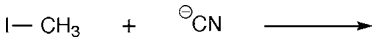


6. Detailed discussions focused on stereochemistry are not within the scope of this book. However, considering the products of typical S_N2 reactions, in addition to the transition state shown in Scheme 4.2, one may deduce the stereochemical course of this type of reaction. Predict the product of the following reaction and show the correct stereochemistry:

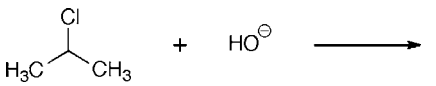


7. Predict the products of the following reactions by pushing arrows:

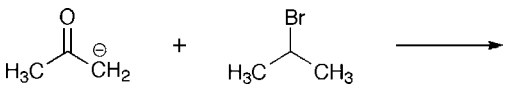
a.



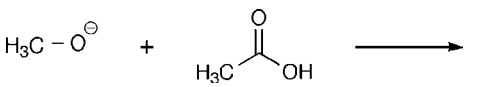
b.



c.



d.



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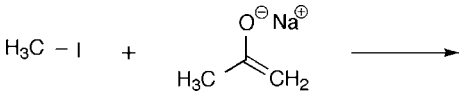
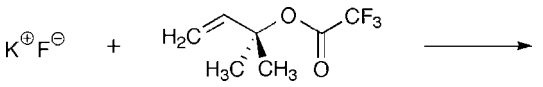
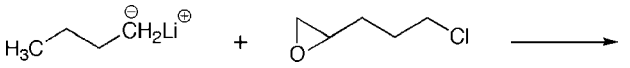


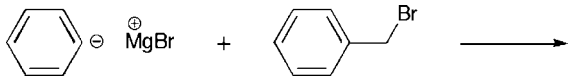
f.



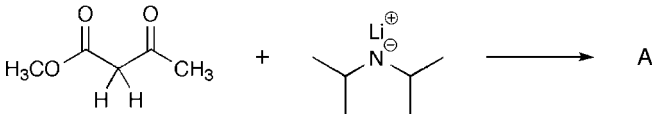
g.

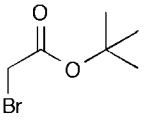


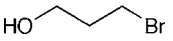
h.

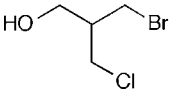


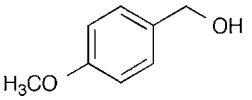
i.

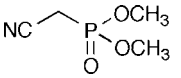


j. A +  ⟶

k.  ⟶ B ⟶ C

l.  ⟶ D ⟶ E

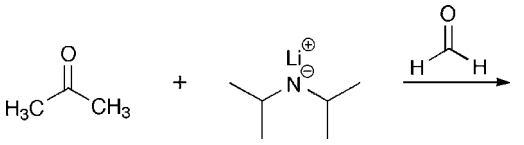
m. 

n.  ⟶ F

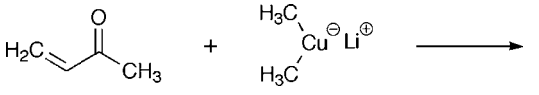
o. F +  ⟶

8. Addition reactions and conjugate addition reactions, to be discussed in Chapter 7, are related to S_N2 and S_N2' reactions, respectively. We can make these comparisons if we recognize that the carbonyl double bond contains a leaving group. Specifically, if a nucleophile adds to the carbon of a carbonyl, the carbonyl double bond becomes a carbon–oxygen single bond with a negative charge residing on the oxygen. Additionally, the trigonal-planar geometry of the carbonyl carbon is converted to tetrahedral geometry. With these points in mind, predict the products of the following reactions and explain your answers. For problem 8(**b**), the nucleophile is a methyl anion associated with the illustrated cuprate.

a.

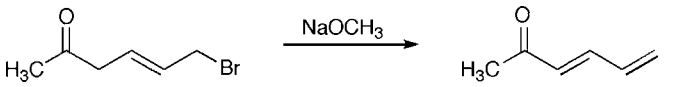


b.

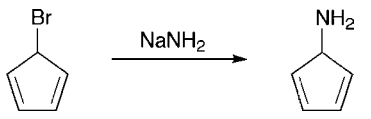


9. Propose a reasonable mechanism for each of the following reactions. Explain your answers by pushing arrows.

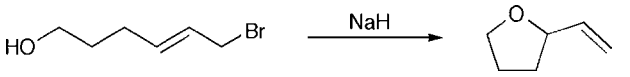
a.



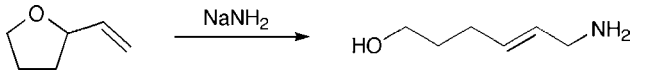
b.



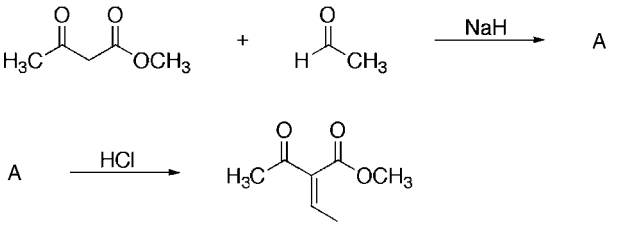
c.



d.



10. α,β-Unsaturated carbonyls are readily formed from the corresponding β-hydroxy ketones. Explain the product of the following reaction:



Chapter 5

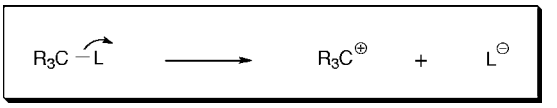
S_N1 Substitution Reactions

In Chapter 4, S_N2 reactions were defined and presented in the context of the various conditions necessary for such reactions to take place. However, as mentioned in the introductory comments of Chapter 4, there are additional fundamental mechanistic types relevant to organic chemistry that are essential to understand in order to advance in this subject. In this chapter, discussions of organic chemistry reaction mechanisms are advanced to the study of S_N1 reactions. While conditions required for S_N1 reactions to proceed are quite different from those essential for S_N2 reactions, the products of S_N1 reactions, in many cases, resemble those derived from S_N2 mechanisms. Additionally, unlike S_N2 reactions, S_N1 reaction mechanisms allow routes for unwanted or, in some planned cases, preferred side reactions.

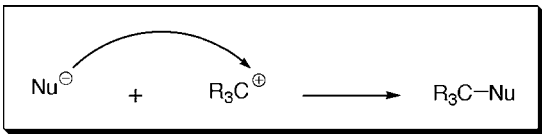
5.1 WHAT IS AN S_N1 REACTION?

As discussed in Chapter 4, an S_N2 reaction proceeds with the **S**ubstitution of a leaving group by a **N**ucleophile leading to the $\mathbf{S_N}$ designation. Because this mechanism proceeds with the initial approach of two species, it is referred to as a bimolecular reaction. The involvement of **2** species enhances the mechanistic designation to $\mathbf{S_N}2$. Extrapolating from this definition, an S_N1 reaction also proceeds with the **S**ubstitution of a leaving group by a **N**ucleophile leading to the $\mathbf{S_N}$ designation. However, unlike S_N2 reactions, $\mathbf{S_N}1$ reactions proceed through initial dissociation of the leaving group from the starting material as shown in Scheme 5.1. This occurs because of differences in reactants and reaction conditions as compared to those relevant to S_N2 processes. Once the leaving group has dissociated, the resulting **carbocation** (a carbon atom possessing a positive charge) is free to react

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 5.1 *Initial phase of an S_N1 reaction involves dissociation of a leaving group from the starting molecule, generating a carbocation.*



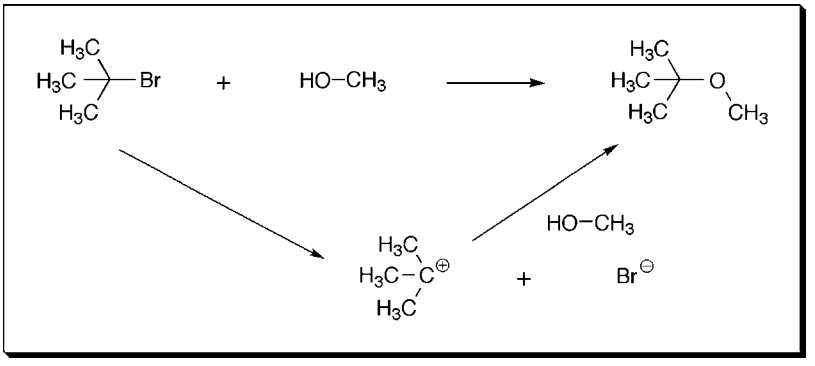
Scheme 5.2 *Second phase of an S_N1 reaction involves reaction of a carbocation with a nucleophile generating a new product.*

with a nucleophile as shown in Scheme 5.2. Because the initial step in this reaction involves a single molecule dissociating from its leaving group, the initial stage of this process is considered a unimolecular reaction. The involvement of only **1** species in the initial phase of the reaction enhances the mechanistic designation to $\mathbf{S_N1}$.

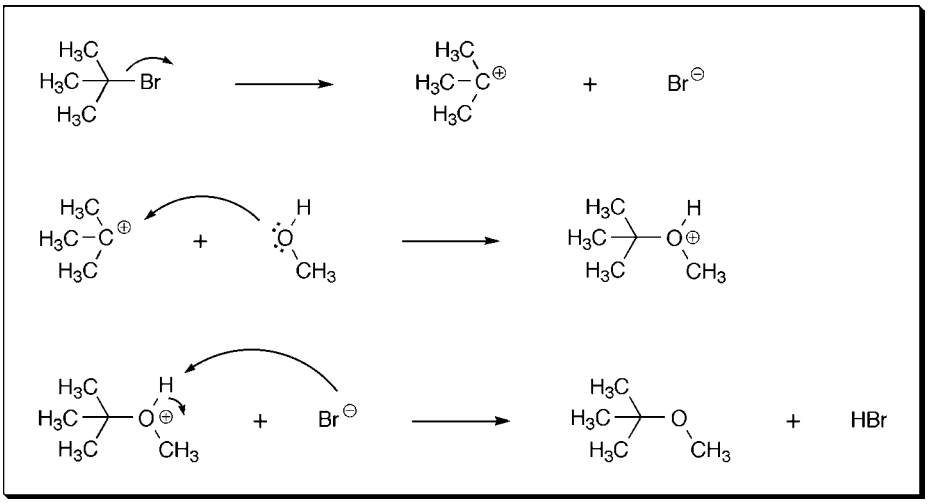
Because, with S_N1 reactions, a reactive carbocation is formed before incorporation of a nucleophile, other products may form in addition to the simple substituted materials anticipated. These additional products arise from the specific properties of carbocations. The properties of carbocations and their related mechanistic outcomes are presented in the following sections.

5.2 HOW ARE S_N1 REACTIONS INITIATED?

In order for an S_N1 reaction to proceed, initial formation of a carbocation is required. A primary method for the formation of carbocations occurs during solvolysis reactions.



Scheme 5.3 *Solvolysis of* tert*-butylbromide in methanol produces MTBE via an S_N1 mechanism.*

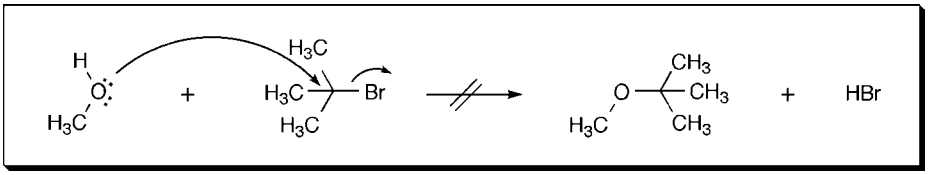


Scheme 5.4 *Explanation of the solvolysis of* tert*-butylbromide in methanol using arrow pushing.*

Solvolysis reactions, illustrated in Scheme 5.3, involve the reaction of an organic molecule with the surrounding solvent. Furthermore, these reactions generally proceed through initial separation of a carbocation from its leaving group followed by reaction of the carbocation with a surrounding solvent molecule forming a new compound. The example shown in Scheme 5.3 illustrates these steps for the reaction of *tert*-butylbromide with methanol, forming methyl *tert*-butylether (MTBE).

As shown in Scheme 5.4, the above-described solvolysis reaction can be explained using arrow pushing. Specifically, initial separation of the bromide leaving group from the *tert*-butyl cation proceeds with electrons residing on the bromide anion. Subsequent reaction of the *tert*-butyl cation with lone pairs of electrons donated by the solvent (methanol) molecules results in the formation of a new carbon–oxygen bond. Dissociation of hydrogen from the resulting oxonium (oxygen cation) ion liberates the product (MTBE) and hydrobromic acid. As a direct reference to the definition of S_N1 reactions, it is important to recognize that the first step (the rate-limiting step) involves only *tert*-butylbromide, thus rendering this step **unimolecular**.

In general, solvolysis reactions occur under circumstances where a molecule possessing an exceptionally good leaving group is dissolved in a polar solvent. Under these conditions, the polarity of the solvent renders formation of the carbocation more favorable by selectively solvating either the carbocation, its accompanying anion, or both. Once the carbocation is separated from its anion, it may undergo typical S_N1 reactions as discussed in the following paragraphs. Additionally, as shown in Scheme 5.5, the reaction illustrated



Scheme 5.5 *Methanol will not react with* tert*-butylbromide via an S_N2 mechanism.*

in Scheme 5.4 will not proceed by an S_N2 mechanism because of the steric bulk of the starting *tert*-butylbromide. Additional discussions surrounding the influence of steric factors are presented in Chapters 3 and 4.

5.3 THE CARBOCATION

As defined in the previous sections of this chapter, carbocations are positively charged carbon ions. However, simply defining this unique species of cations without exploring its associated properties does little to promote understanding of S_N1 reactions and the related side reactions observed for this mechanistic type. Therefore, this section focuses on the nature, stability, and reactivity of carbocations as explained using arrow pushing. While the alluded to side reactions include both **elimination** reactions and **rearrangements**, only rearrangements are presented in this chapter. Discussions focused on eliminations are found beginning in Chapter 6.

5.3.1 Molecular Structure and Orbitals

Before delving into more details regarding the reactive nature and stability of carbocations, it is important to understand the structure of these species. Recall that S_N2 reactions occur at carbon atoms bearing four substituents. Furthermore, recall that electrophilic carbon centers participating in S_N2 reactions are tetrahedral in geometry with all bond angles measuring approximately 109.5°–the tetrahedral bond angle. This equal spacing, illustrated in Figure 5.1, is only possible if the natures of all four bonds connecting the central carbon atom to its four substituents are identical.

Since an understanding of **orbital** theory is critical to understanding organic reaction mechanisms, *review of the material presented in primary organic chemistry textbooks is essential*. For the purposes of the discussions presented herein, recall that ground-state first-row elements (including C, N, and O) all possess one ***s* orbital** and three ***p* orbitals**. Figure 5.2 illustrates the shapes of *s* and *p* orbitals.

If we consider methane (CH_4), we find that not only does the central carbon atom possess four hydrogen substituents, these four hydrogens are equally spaced in a tetrahedral

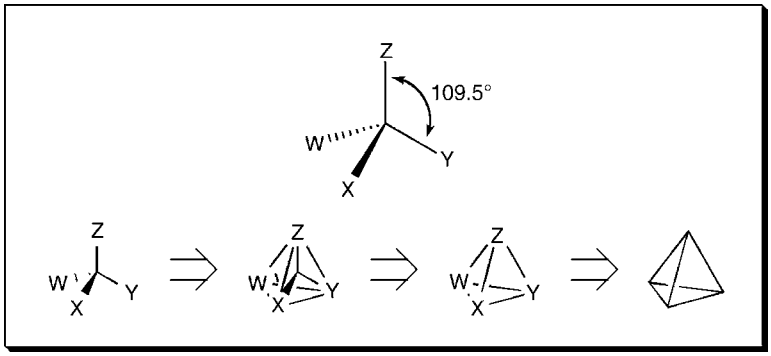


Figure 5.1 *Fully substituted carbon atoms present substituents in tetrahedral arrangements.*

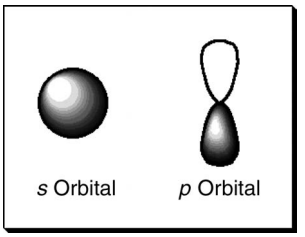


Figure 5.2 *s orbitals are spherical and p orbitals are shaped like hourglasses.*

arrangement with equal bond lengths. As ***s* orbitals** and ***p* orbitals** are spatially different, this level of structural equality cannot be explained through bonding with one *s* orbital and three *p* orbitals. Instead, this equality is explained by combining the single *s* orbital with the three *p* orbitals forming four equal sp^3 **hybrid orbitals**. Figure 5.3 illustrates the various hybrid orbitals involved in most chemical bonds found in organic chemistry.

Expanding upon Figure 5.3, an ***sp* hybrid orbital** is made up of one part *s* orbital and one part *p* orbital. Furthermore, an sp^2 **hybrid orbital** is made up of one part *s* orbital and two parts *p* orbital. Finally, an sp^3 **hybrid orbital** is made up of one part *s* orbital and three parts *p* orbital. In cases such as *sp* and sp^2 hybridization where only a subset of the three *p* orbitals are used in forming hybrid orbitals, the unhybridized *p* orbitals are utilized in the formation of double and triple bonds.

While the present discussions focus on **orbital hybridization** relative to bonds between atoms, it is important to recognize that nonbonding electron pairs (lone pairs) also participate in orbital hybridization. Thus, as illustrated in Figure 5.4 and relating to sp^3-hybridized centers, for the purposes of determining orbital hybridization, lone pairs can be treated as bonds between a central atom and nothing.

As alluded to in Figure 5.3, sp^3 hybridization occurs when a central atom possesses a total of four substituents comprised of any combination of atoms and lone pairs.

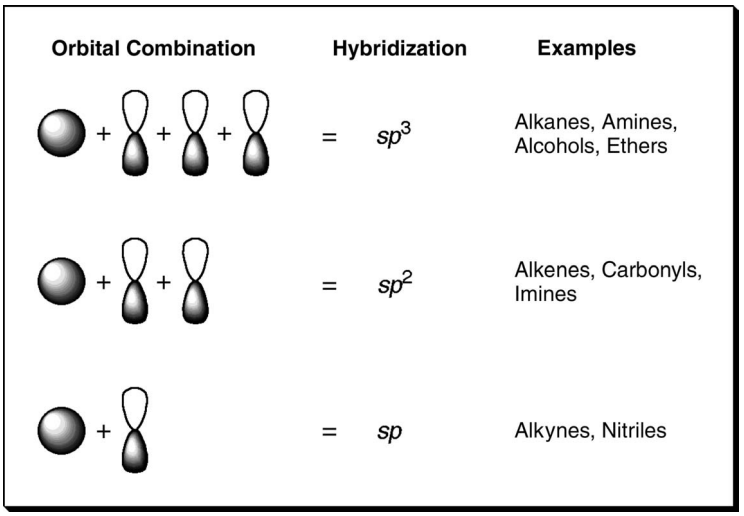


Figure 5.3 *Hybrid orbitals result from combinations of s and p orbitals.*

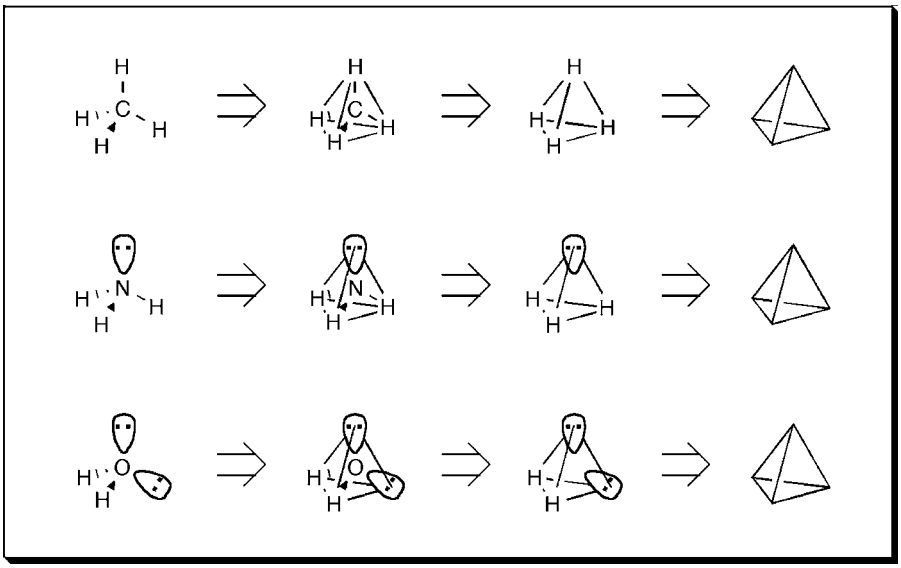


Figure 5.4 *Like substituents, lone pairs influence molecular geometry.*

Furthermore, sp^2 hybridization occurs when a central atom possesses a total of three substituents comprised of any combination of atoms and lone pairs. Finally, *sp* hybridization occurs when a central atom possesses a total of two substituents comprised of any combination of atoms and lone pairs. While thus far attention has been focused on the tetrahedral nature of sp^3-hybridized atoms, exploring the geometric consequences of sp^2 and *sp*-hybridized atoms reveals very different spatial relationships between substituents. Specifically, as shown in Figure 5.5, the three substituents of an sp^2-hybridized atom adopt a **trigonal planar** relationship with bond angles of 120° and all substituents residing in the same plane. Furthermore, the two substituents of an *sp*-hybridized atom adopt a **linear** relationship with bond angles of 180°.

Having addressed the geometric consequences of orbital hybridization, the above discussions can now be related to carbocations. Recalling the rules relating the number of substituents to specific orbital hybrids, we recognize that a carbocation possesses a maximum of three substituents and is thus rendered as no more than sp^2 hybridized. Furthermore, the carbocation positive charge resides in an unoccupied *p* orbital. The trigonal planar structure of an sp^2-hybridized carbocation is illustrated in Figure 5.6 and enhanced with the placement of a *p* orbital at the cationic center.

Having established the three-dimentional structure of carbocations as planar, we can now study the **stereochemical progression** of S_N1 reactions as compared to S_N2 reactions. As shown in Scheme 5.6, the stereochemical course of an S_N2 reaction is well defined because **nucleophilic displacement** of a leaving group proceeds with inversion of stereochemistry. Thus, the stereochemical outcome is defined by the stereochemistry of the starting material. As for S_N1 reactions, since the step required for initiation of these reactions involves formation of a planar species, incoming nucleophiles have equal access to both sides of the reactive carbocation. As shown in Scheme 5.7, this results in complete elimination of

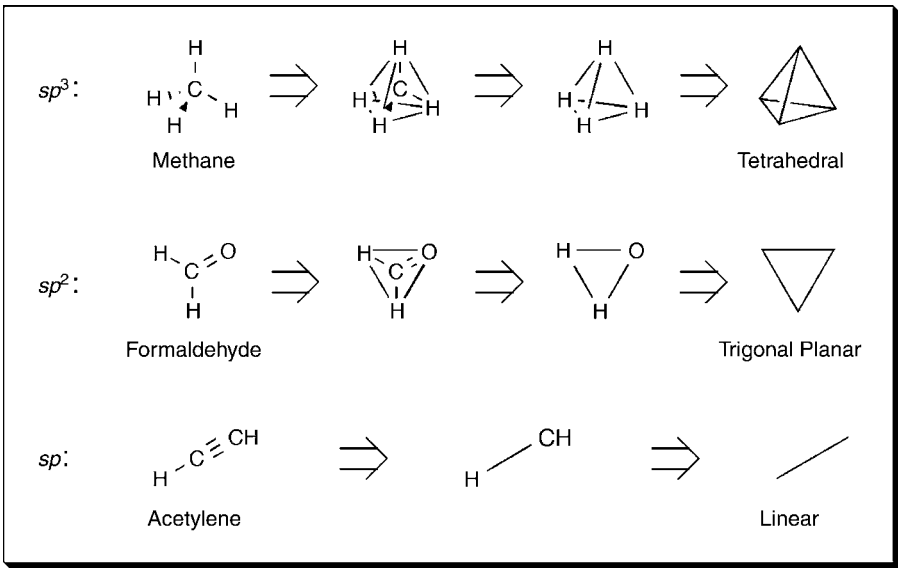


Figure 5.5 *Different orbital hybridizations result in different molecular geometries.*

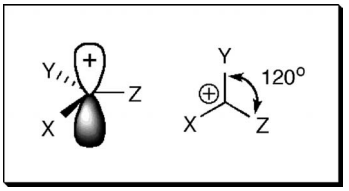
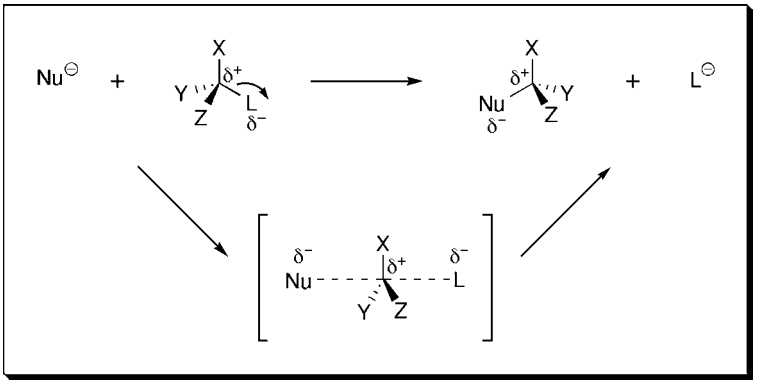
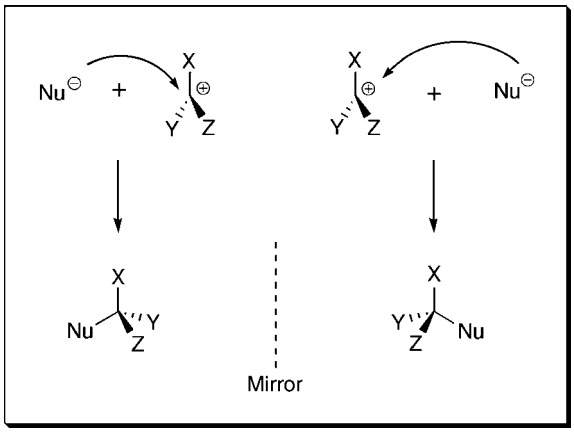


Figure 5.6 *sp^2-hybridized carbocations possess trigonal planar geometries.*



Scheme 5.6 *Stereochemical courses of S_N2 reactions are defined by the stereochemical configuration of the starting materials. One product is formed.*



Scheme 5.7 *Stereochemical identities of starting materials subjected to S_N1 reactions are lost due to the planarity of reactive carbocations. Two products are formed.*

stereochemical control over these reactions. Thus, where S_N2 reactions on **stereochemically pure** starting materials proceed with generation of a single stereoisomer, S_N1 reactions proceed with complete loss of **stereochemical identity** even when the starting material is stereochemically pure. Specifically, an S_N2 reaction on a chiral starting material yields **one chiral product**, and an S_N1 reaction on a chiral starting material yields a **racemic mixture** of two stereoisomers.

5.3.2 Stability of Carbocations

As alluded to at the beginning of this section, carbocations generated during S_N1 mechanisms are subject to **side reactions** that include eliminations and rearrangements. Considering the possibility of these side reactions, one must question the *stability* of carbocationic species. To clarify, if carbocations were inherently stable, they would not be readily subject to additional transformations. Having already addressed the structure of carbocations, attention can now be focused on the factors influencing stability.

In studying carbocations, it is important to recognize that **tertiary carbocations** are more stable than **secondary carbocations**. Furthermore, secondary carbocations are more stable than **primary carbocations**. This relationship, shown in Figure 5.7, results from an effect known as **hyperconjugation**. Specifically, hyperconjugation, illustrated in

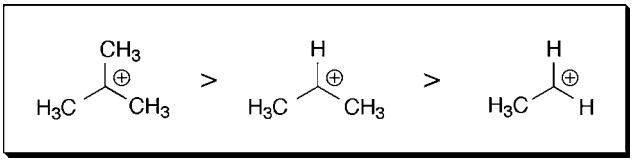


Figure 5.7 *Tertiary carbocations are more stable than secondary carbocations, and secondary carbocations are more stable than primary carbocations.*

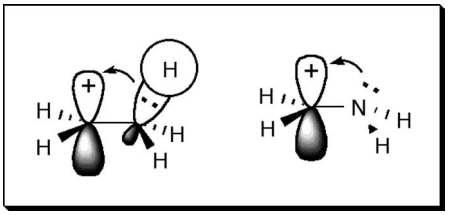


Figure 5.8 *Hydrogen atom* s *orbitals can donate electron density to adjacent cationic centers as can heteroatoms bearing lone electron pairs.*

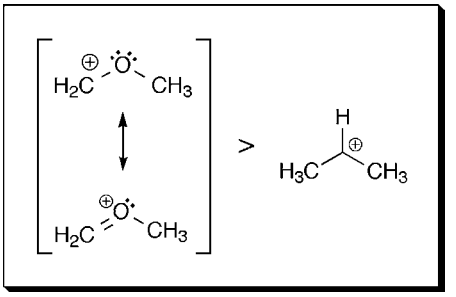


Figure 5.9 *Heteroatoms stabilize carbocations better than hyperconjugation effects.*

Figure 5.8, defines the ability of a hydrogen atom to donate electron density from its *s* orbital to sites of neighboring electron deficiency. This effect is similar to the stabilization of carbocations bearing heteroatoms with lone electron pairs. Thus, the greater number of carbon–hydrogen bonds located adjacent to a positive charge, the greater the stability of the cation.

As hyperconjugation can be related to **cationic stabilization** by neighboring lone pairs, relationships between these types of effects must be noted. As shown in Figure 5.9, heteroatom-induced stabilization is a stronger effect than hyperconjugation.

With the understanding that hyperconjugation and heteroatoms both stabilize cations through resonance effects, the influence of full conjugation to sites of unsaturation deserves mention. As shown in Figure 5.10, direct conjugation is generally a stronger effect than hyperconjugation. This effect is illustrated with an allylic carbocation compared to a secondary carbocation. However, if we consider a tertiary carbocation, as shown in Figure 5.11, this trend is reversed, thus emphasizing that while resonance stabilization is good, it is not as good as the stabilization obtained by having three alkyl groups associated with the cation.

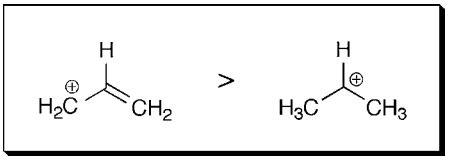


Figure 5.10 *Allylic carbocations are more stable than secondary carbocations.*

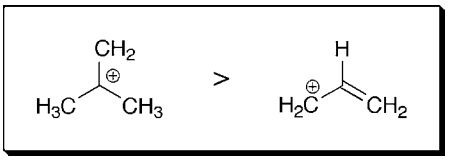


Figure 5.11 *Tertiary carbocations are more stable than allylic carbocations.*

5.4 CARBOCATION REARRANGEMENTS

Having addressed the structure and stability of carbocations, discussions will now be directed to the specific **side reactions** to which carbocations are subject. Specifically, this section focuses on rearrangements of carbocations known as **hydride shifts** and **alkyl shifts**.

5.4.1 1,2-Hydride Shifts

Recalling the role played by hyperconjugation in the stabilization of carbocations, a more detailed examination of this phenomenon is warranted. Looking at Figure 5.6, we note that carbocations are planar with an unoccupied *p* orbital extending both above and below the plane of the ion. Furthermore, looking at Figure 5.8, the electrons in a carbon–hydrogen bond adjacent to a carbocation can conjugate toward the positive charge residing in the vacant *p* orbital. This donation of electron density can only occur if the carbon–hydrogen bond is aligned with the vacant *p* orbital, as shown in Figure 5.12 using several perspective views. Specifically, the carbon–hydrogen bond must lie in the same plane as the vacant *p* orbital.

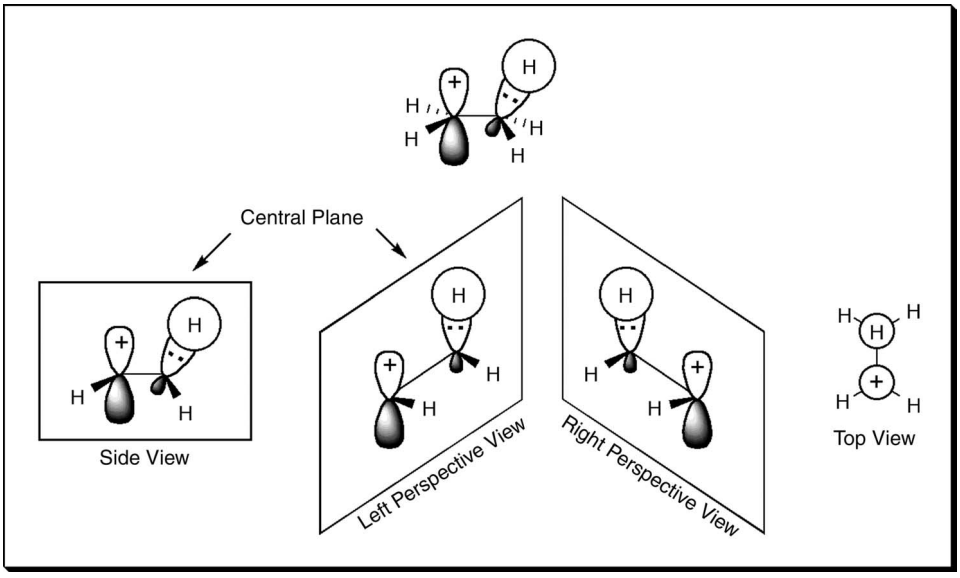


Figure 5.12 *Hyperconjugation occurs when a carbon–hydrogen bond lies in the same plane as a carbocation's vacant* p *orbital.*

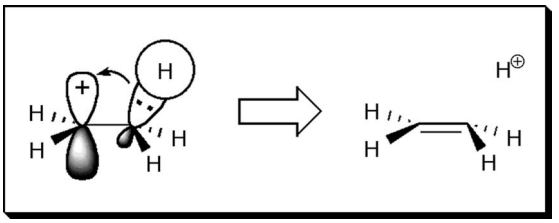
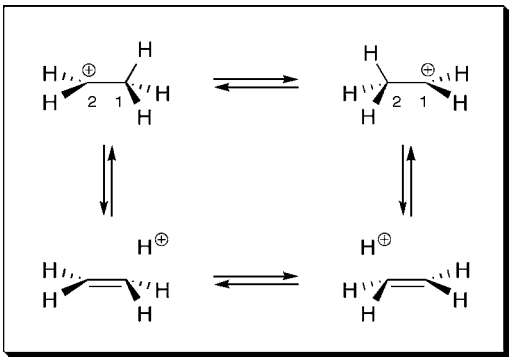


Figure 5.13 *Hyperconjugation can be viewed as formation of a pseudo-double-bond.*



Scheme 5.8 *Hyperconjugation leads to migration of hydrogen atoms through a 1,2-hydride shift.*

When the **alignment** of a carbon–hydrogen bond with a vacant *p* orbital takes place allowing for hyperconjugation, a "pseudo-double-bond" develops. As illustrated in Figure 5.13, this can be envisioned as a double bond with a closely associated hydrogen ion.

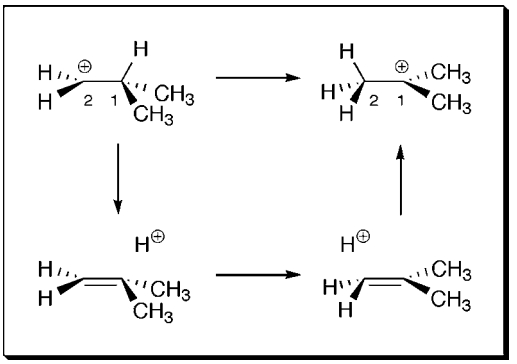
If, as shown in Figure 5.13, hyperconjugation results in the formation of species possessing both double-bond character and associated hydrogen ions, **equilibrium-controlled migration** of the associated hydrogen ion can be expected. This transformation, shown in Scheme 5.8, is known as a **1,2-hydride shift** and results in the migration of a proton from carbon 1 to carbon 2.

While the example illustrated in Scheme 5.8 shows equilibrium between two chemically identical carbocations, there are factors influencing the direction of these transformations when applied to more complex systems. If we consider Scheme 5.9, we notice that the positive charge migrates exclusively to the tertiary center, reflecting the increased stability of tertiary carbocations over primary carbocations. In general, where 1,2-hydride shifts are possible, rearrangement of less stable carbocations to more stable carbocations is expected.

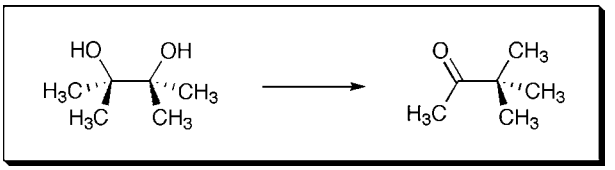
5.4.2 1,2-Alkyl Shifts

Moving from discussion of 1,2-hydride shifts to **1,2-alkyl shifts**, it is important to remember that hydride shifts occur much more readily than the corresponding alkyl shifts. In fact, as a general rule, alkyl shifts will not occur unless a hydride shift cannot take place.

Among the most famous examples of a reaction involving a 1,2-alkyl shift is the **pinacol rearrangement**. This reaction, shown in Scheme 5.10, results in the conversion of a **vicinal diol** to a ketone.



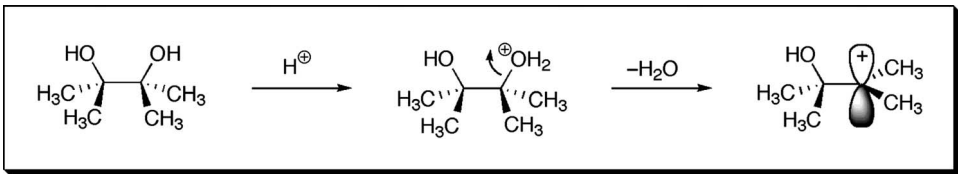
Scheme 5.9 *Rearrangements via 1,2-hydride shifts generate more stable carbocations from less stable carbocations.*



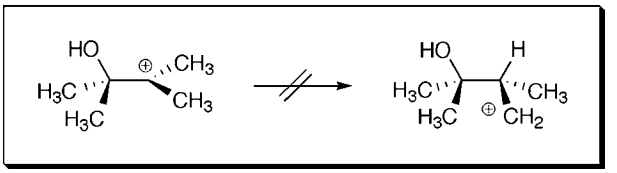
Scheme 5.10 *Pinacol rearrangement.*

Mechanistically, the pinacol rearrangement is explained by initial carbocation formation through solvolysis. This step, illustrated in Scheme 5.11, involves protonation of an alcohol followed by water leaving and generating a tertiary carbocation. In looking at this cation, one may imagine that a 1,2-hydride shift is possible. However, the only sources of hydrogens for such a shift are the methyl groups adjacent to the cationic center. If a hydride migrates from one of these methyl groups, as illustrated in Scheme 5.12, the result would be generation of a primary carbocation. Since primary carbocations are less stable than tertiary carbocations, this migration will not occur.

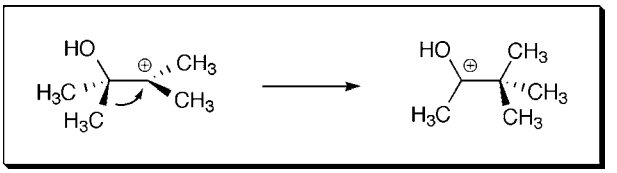
While the hydride shift illustrated in Scheme 5.12 cannot occur as a part of the pinacol rearrangement, the intermediate carbocation is subject to **alkyl migrations**. As shown in Scheme 5.13, a 1,2-alkyl shift results in transfer of the cation from a **tertiary center** to a center adjacent to a heteroatom. As the oxygen heteroatom possesses lone electron pairs, these lone pairs serve to stabilize the cation. Thus, the illustrated 1,2-alkyl shift transforms a carbocation into a more stable carbocation.



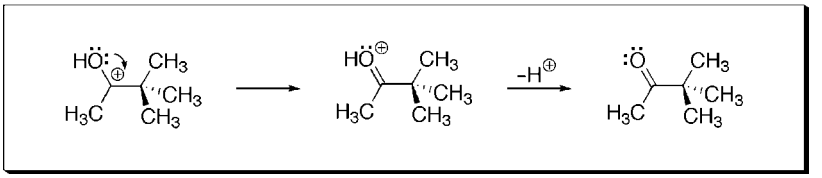
Scheme 5.11 *Pinacol rearrangement proceeds through solvolysis-mediated cation formation.*



Scheme 5.12 *1,2-Hydride shifts will not occur when the product cation is less stable than the starting cation.*



Scheme 5.13 *Alkyl migrations occur when the resulting carbocation is more stable than the starting carbocation.*



Scheme 5.14 *Conclusion of the pinacol rearrangement involves migration of the positive charge to the adjacent oxygen atom followed by deprotonation.*

Mechanistic conclusion of the pinacol rearrangement is illustrated in Scheme 5.14 and involves initial donation of an oxygen lone pair to the cation, thus migrating the charge to the oxygen atom. The resulting oxygen cation then releases a proton, liberating the illustrated neutral ketone.

As the mechanistic steps discussed for the pinacol rearrangement have been illustrated using arrow pushing, it is important to recognize that in all cases, the arrows have been drawn pushing electrons toward positive charges. This point has been previously discussed and will continue to be emphasized.

5.4.3 Preventing Side Reactions

Because of 1,2-hydride and alkyl shifts, it is possible to obtain **multiple products** from S_N1 reactions. Thus, to induce one product to predominate, we must find a way to stabilize the carbocation. This is done by using highly **polar solvents** such as **acetic acid**, **dimethyl formamide**, and **dimethyl sulfoxide**. In using this strategy, the lifetime of a carbocation can be extended, allowing the most stable product more time to form. As a result,

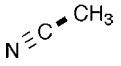
control over formation of desired products in reasonable yields from S_N1 reactions can be achieved.

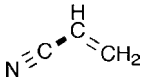
5.5 SUMMARY

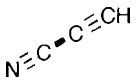
In this chapter, S_N1 reactions were introduced, compared to S_N2 reactions and discussed mechanistically. Through these discussions, the involvement of electron orbitals, and their various **hybrids**, was addressed. Furthermore, complicating side reactions such as **hydride** and **alkyl migrations** were presented. As discussions move into more advanced mechanistic types, it is important to maintain awareness of the involvement and orientation of orbitals, the steric environment at reactive centers, and the overall reactivity of nucleophiles and electrophilic centers.

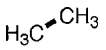
PROBLEMS

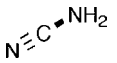
1. For the following molecules, state the hybridization (*sp*, sp^2, sp^3) of the orbitals associated with the highlighted bond. Also, state the geometry of the bound atomic centers (linear, bent, trigonal planar, tetrahedral).

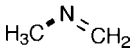
a. 

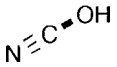
b. 

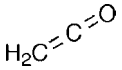
c. 

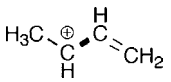
d. 

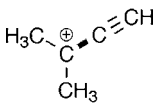
e. 

f. 

g. 

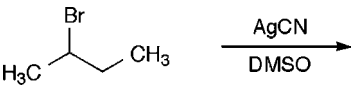
h.  (Answer for both double bonds.)

i. 

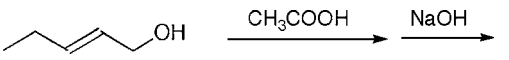
j. 

2. Predict all of the products of the following reactions:

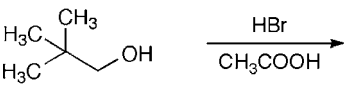
a.



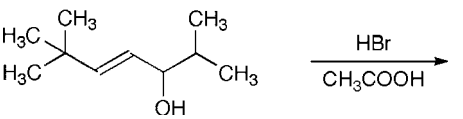
b.



c.

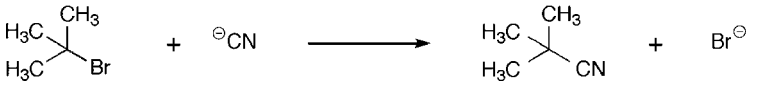


d.

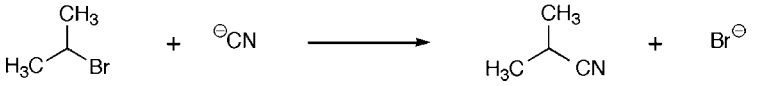


3. For each of the following reactions, determine which will proceed via an S_N1 or an S_N2 mechanism. In cases where both may be applicable, list appropriate reaction conditions (e.g., solvents, reagents) that would favor S_N1 over S_N2 and vice versa. Explain your answers.

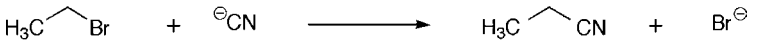
a.



b.

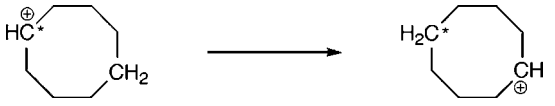


c.



4. In studying 1,2-alkyl and hydride shifts, we explored the observation that shifts will not occur unless the newly formed carbocation is more stable than the starting carbocation. Additionally, as illustrated in Figure 5.12, these shifts were explained using hyperconjugation, thus requiring that the orbital containing the positive charge and the bond containing the shifting group lie within the same plane. This is necessary in order to allow sufficient orbital overlap for the shift to take place.

In addition to 1,2-shifts, which occur between adjacent bonds, other shifts are possible where the migrating group apparently moves across space. As with 1,2-shifts, these additional shifts can only occur when the positively charged empty *p* orbital lies within the same plane as the bond containing the migrating group, thus allowing sufficient orbital overlap. With this in mind, explain the following 1,5-hydride shift. (*Hint*: Consider different structural conformations. You may want to use models.) Asterisk (*) marks enrichment with ^{13}C.



Chapter 6

Elimination Reactions

Until now, discussions have focused only on how **carbanions** and **carbocations** behave under conditions favorable for nucleophilic substitutions. However, these species may undergo other types of reactions in which unsaturation is introduced into the molecule. Such reactions are called **elimination reactions** and should be considered whenever charged species are of importance to the mechanistic progression of a molecular transformation. In previous chapters, S_N1 and S_N2 reactions were discussed. In this chapter, the corresponding **E1** and **E2** elimination mechanisms are presented.

6.1 E1 ELIMINATIONS

Having addressed the chemistry of carbocations and associated S_N1 reaction mechanisms, it is appropriate to begin discussions of elimination reactions with the related E1 mechanism. As addressed in Chapter 5, carbocations generated from solvolysis reactions can undergo various types of rearrangements that include hydride and alkyl shifts. Furthermore, these shifts were rationalized when the empty *p* orbital associated with the positive charge is aligned in the same plane with the migrating group. Figure 6.1 reiterates the process of hyperconjugation necessary for these shifts to occur. Furthermore, Figure 6.2 reiterates that hyperconjugation can be viewed as introducing **double-bond character** to a carbocation. Carrying this rationale one step further, if the double-bond character in a given carbocation becomes stabilized through full **dissociation** of a proton, the result, illustrated in Scheme 6.1, is formation of a full double bond through an E1 elimination mechanism.

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

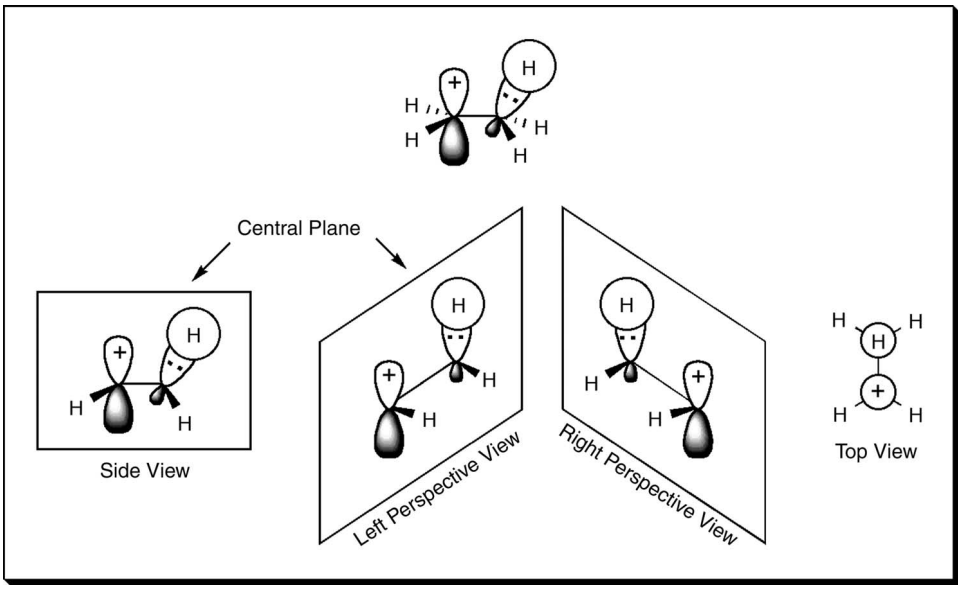


Figure 6.1 *Hyperconjugation occurs when a carbon–hydrogen bond lies in the same plane as a carbocation's vacant* p *orbital.*

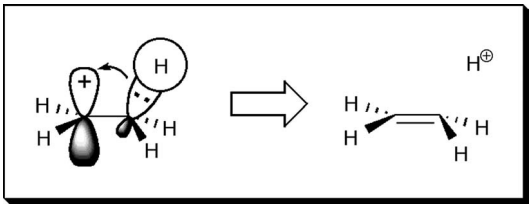
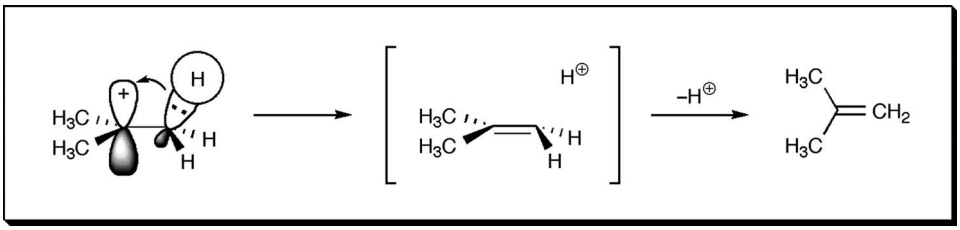
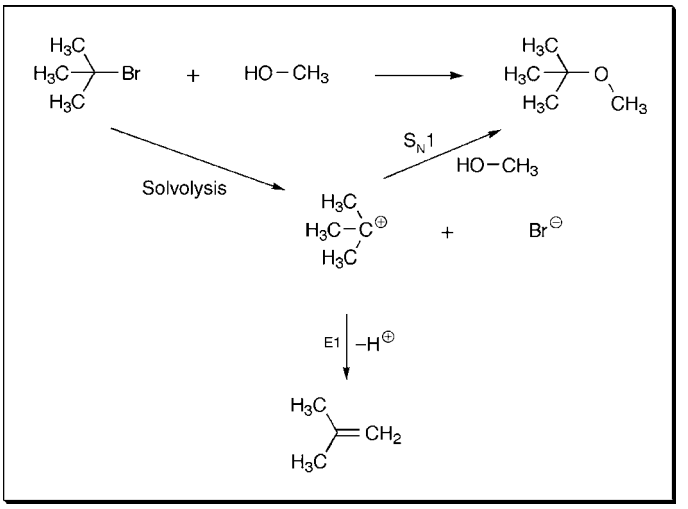


Figure 6.2 *Hyperconjugation can be viewed as formation of a "pseudo-double-bond."*

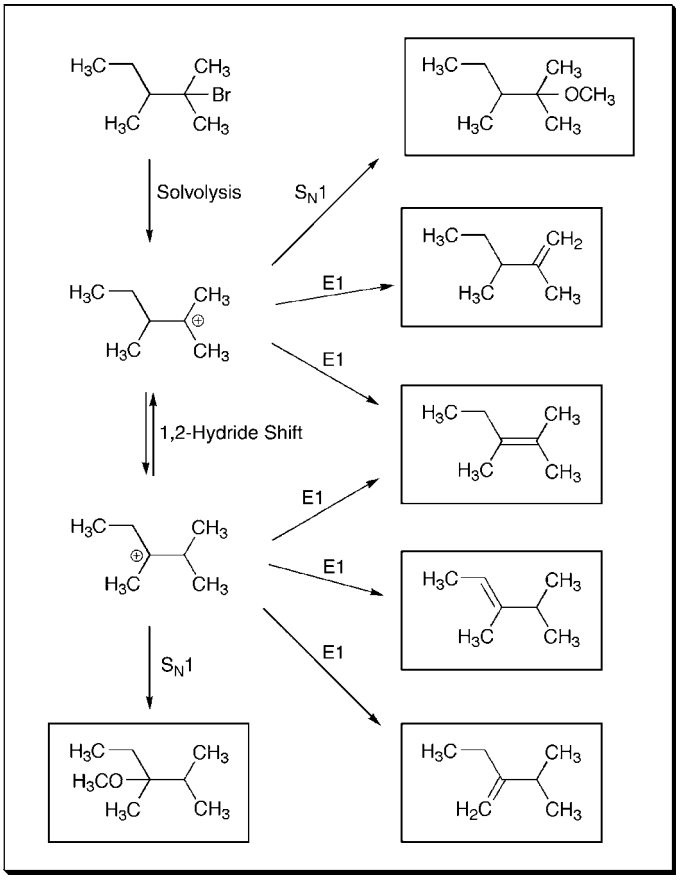
As alluded to above, E1 reactions are integrally related to S_N1 reactions by virtue of the carbocations common to both mechanisms. Thus, revisiting the solvolysis reaction leading to the conversion of *tert*-butyl bromide to MTBE illustrated in Scheme 6.2, we understand how formation of isobutylene occurs. Formation of isobutylene only occurs through the E1 process and comprises approximately 20 percent of the reaction mixture.



Scheme 6.1 *Dissociation of a proton through hyperconjugation completes the final stage of an E1 elimination mechanism.*



Scheme 6.2 *E1 mechanisms explain additional products observed during S_N1 reactions.*



Scheme 6.3 *Solvolysis of 2-bromo-2,3-dimethylpentane in methanol leads to formation of up to six different products via multiple mechanistic pathways.*

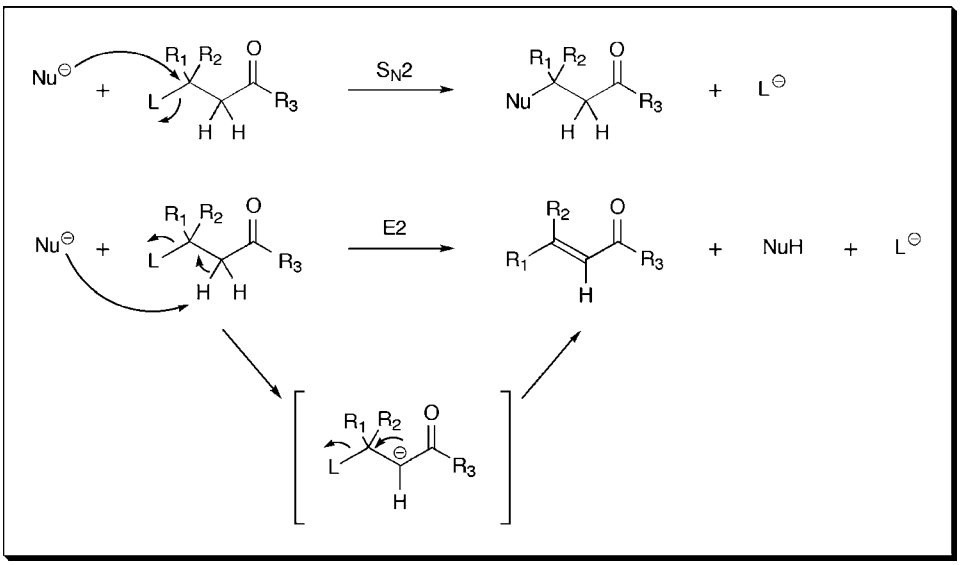
As can be deduced from discussions presented above and in Chapter 5, it is very important to recognize that when designing reactions involving carbocations, both **migration reactions** and **elimination reactions** can complicate the outcome of intended S_N1 transformations. An example illustrating the potential formation of multiple side products is shown in Scheme 6.3 with the solvolysis of 2-bromo-2,3-dimethylpentane in methanol.

Returning to Scheme 6.1, we recognize that an E1 reaction proceeds with the **E**limination of a leaving group, leading to the **E** designation. Because this mechanism proceeds with the initial dissociation of a single starting material forming a carbocation, this process is considered a unimolecular reaction. The involvement of only **1** species in the initial phase of the reaction enhances the mechanistic designation to **E1**.

6.2 E2 ELIMINATIONS

To this point, considerable time has been spent discussing acids, bases, nucleophiles, and leaving groups. These were ultimately all presented in the context of S_N2 reactions. Like the complicating side reactions associated with carbocations formed during S_N1 reactions, depending upon the nature of substituents adjacent to acidic protons, S_N2 reaction conditions can induce similar complications. For example, consider a molecule with an acidic proton and a leaving group, L, on the carbon adjacent to the acidic proton. Consider also that nucleophiles are bases. As shown in Scheme 6.4, an alternative to **nucleophilic displacement** of the leaving group is found in initial **deprotonation**. Subsequent displacement of the leaving group by the resulting anion results in formation of an **olefin**.

In studying Scheme 6.4, we recognize that an E2 reaction proceeds through initial extraction of a proton by a base or nucleophile leading to **E**limination of a leaving group, justifying the **E** designation. Because this mechanism proceeds through the interaction of two species (substrate and base/nucleophile), E2 reactions are recognized



Scheme 6.4 *S_N2 Substitution reactions can occur in competition with E2 elimination reactions.*

as bimolecular. Thus, the involvement of **2** species in the initial phase of the reaction enhances the mechanistic designation to **E2**. Finally, it is important to note that while E1 reactions proceed through cationic intermediates, E2 reactions proceed through anionic intermediates.

6.3 HOW DO ELIMINATION REACTIONS WORK?

In addressing the mechanistic basis behind elimination reactions, we must refer to discussions surrounding carbocations in the context of S_N1 reactions. Furthermore, consideration of carbocation-associated hydride/alkyl shifts and E1 related products is essential. Recall that carbocations are stabilized by phenomena such as hyperconjugation. Furthermore, recall that hydride shifts, alkyl shifts, and E1 eliminations are dependent upon the planar alignment of an empty *p* orbital and an adjacent bond bearing either a migrating group or a dissociable hydrogen atom as illustrated in Figure 6.1.

The mechanistic basis behind the stability and reactivity of carbocations, regardless of the reaction outcome, depends on the alignment of an empty *p* orbital and the orbitals comprising an adjacent bond. Specifically, if there are no **planar alignments**, then hyperconjugation, hydride/alkyl shifts, or eliminations cannot occur. Perhaps there is no better illustration of this fact than a comparison of the stability of primary, secondary, and tertiary carbocations. As reiterated from Chapter 5, Figure 6.3 illustrates the order of stability from most stable to least stable. This trend in stability is directly related to the number of adjacent carbon–hydrogen bonds available for hyperconjugation.

Looking at the structures shown in Figure 6.3, we notice that the *tert*-butyl carbocation possesses nine carbon–hydrogen bonds adjacent to the cation, while the secondary carbocation possesses six, and the primary carbocation possesses only three. This tabulation of bonds is relevant in that the more adjacent carbon–hydrogen bonds, the more opportunities there are for hyperconjugation to occur. In this discussion, the term *opportunities* is important because single bonds employing sp^3 orbitals are not rigid and can rotate around the bond axis as shown in Figure 6.4 in much the same way a wheel rotates on an axle. Thus, when empty *p* orbitals and adjacent bonds are not in alignment, there can be no associated **orbital overlap** and the observed reactions are only possible due to the intermittent alignment of a system that is continually in motion.

As already discussed, E1 and E2 eliminations differ, in part, by the electronic nature of the mechanism. Specifically, E1 eliminations depend on **cationic** intermediates, whereas E2 eliminations depend on **anionic** intermediates. This difference, however, does not eliminate the mechanistic similarities of these reactions as related to the necessary alignment of adjacent chemical bonds. While, as shown in Figure 6.4, E1 eliminations require alignment of a carbon–hydrogen bond with an adjacent empty *p* orbital, E2 eliminations, as shown in

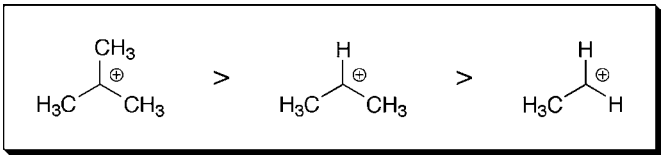


Figure 6.3 *Tertiary carbocations are more stable than secondary carbocations, and secondary carbocations are more stable than primary carbocations.*

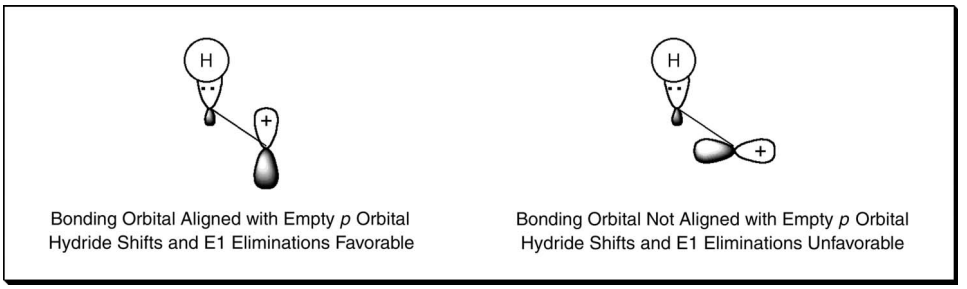


Figure 6.4 *When a carbon–hydrogen (or carbon–alkyl) bond is aligned with an empty* p *orbital, 1,2-hydride/alkyl shifts and E1 eliminations are favorable.*

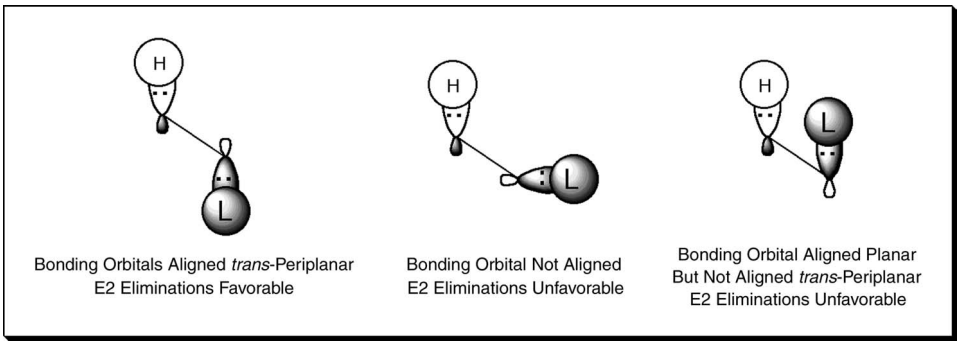
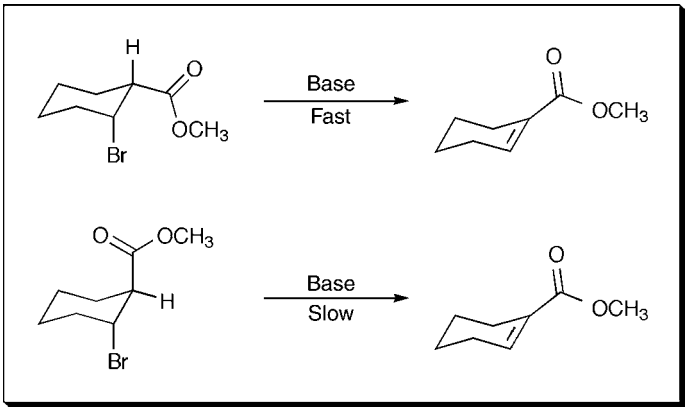
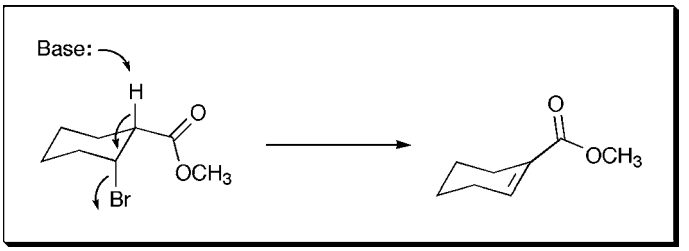


Figure 6.5 *When a carbon–hydrogen bond is aligned* trans*-periplanar with a carbon-leaving group bond, E2 eliminations are favorable.*

Figure 6.5, require alignment of a carbon–hydrogen bond with an adjacent carbon-leaving group bond. Furthermore, as shown in Figure 6.5, the relationship between these bonds is critical for elimination to occur. Specifically, the relevant bonds must adopt a *trans* relationship within the same plane. This relationship is referred to as ***trans*-periplanar**.

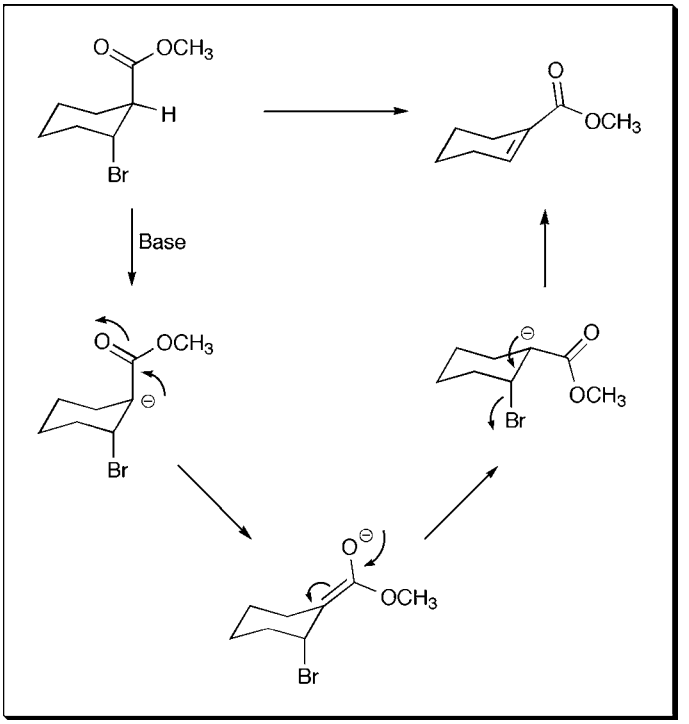


Scheme 6.5 *Rates and reactivity of substrates for potential E2 eliminations are influenced by the presence of* trans*-periplanar relationships.*



Scheme 6.6 trans-*Periplanar relationships lead to direct E2 eliminations.*

A practical example demonstrating the importance of the *trans*-periplanar relationship between protons and leaving groups is illustrated in Scheme 6.5. As shown, when treated with base, the 1,2-*cis*-substituted cyclohexane analog rapidly converts to the illustrated cyclohexene. However, the same reaction conditions applied to the 1,2-*trans* analog results in conversion to the cyclohexene analog at a much slower rate. These observations are mechanistically explained in Schemes 6.6 and 6.7. As shown in Scheme 6.6, the 1,2-*cis* analog, possessing a *trans*-periplanar relationship, reacts through a direct E2 elimination mechanism. However, as shown in Scheme 6.7, the 1,2-*trans* analog must first proceed through deprotonation followed by delocalization of the resulting anion into the ester



Scheme 6.7 *E2 eliminations can proceed in the absence of a* trans-*periplanar relationship in the reaction substrate if reaction intermediates can obtain conformations that are favorable for elimination reactions to occur.*

functionality. Once the negative charge is delocalized into the ester, the anion can displace the bromide through the intermediate double bond as illustrated with arrow pushing.

6.4 SUMMARY

In this chapter, elimination reactions were presented both independently and in association with their related **nucleophilic substitution** mechanisms. Furthermore, the processes by which molecules undergo both E1 and E2 eliminations were presented and explained using **bonding** and **nonbonding orbitals** and their required relationships to one another. While much emphasis was placed on the planar relationships of orbitals required for both elimination reaction mechanisms, the special case of *trans*-periplanar geometries were described as necessary for efficient E2 eliminations to occur.

While *trans*-periplanar relationships are important to E2 elimination reactions, it is important to remember that, as illustrated in Schemes 6.6 and 6.7, E2 elimination reaction mechanisms do not have to occur in a **concerted** manner. After deprotonation, if the relevant orbitals do not line up, elimination will not occur until they do. Furthermore, recall that **rotation** around an acyclic **single bond**, as illustrated in Figures 6.4 and 6.5, occurs readily. Therefore, elimination reactions should not be removed from consideration if a molecule is drawn in a conformation that makes these reactions appear unfavorable. When looking at any type of nucleophilic reaction, initial identification of relevant *trans*-periplanar relationships will aid in the identification of potential side products and their respective mechanisms of formation.

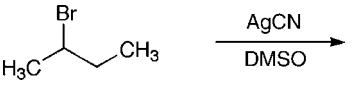
PROBLEMS

1. E2 eliminations do not necessarily require acidic protons in order to proceed. Explain how this can occur.

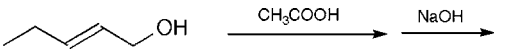
2. When $CH_3OCH_2CH_2CH_2Br$ is treated with magnesium, we get the Grignard reagent $CH_3OCH_2CH_2CH_2MgBr$. However, when $CH_3OCH_2CH_2Br$ is treated with magnesium, the product isolated is $H_2C{=}CH_2$. Explain this result.

3. With an understanding of E1 mechanisms, one may realize that under S_N1 reaction conditions multiple products may form. In addition to the products predicted in Chapter 5 for the following molecules, predict plausible elimination products.

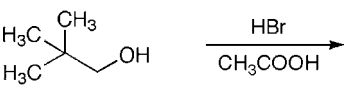
a.



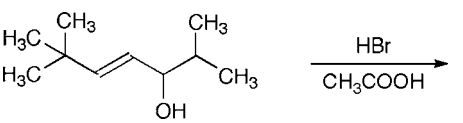
b.



c.

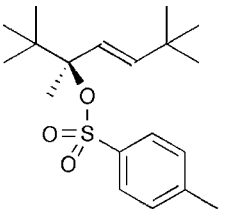


d.



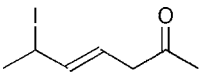
4. Presently, several different organic reaction mechanisms have been presented. Keeping all of these in mind, predict all of the possible products of the following reactions and list the mechanistic type or types from which these products result.

a.



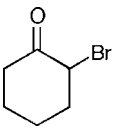
CH_3COOH →

b.



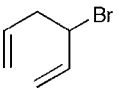
$NaNH_2$ →

c.



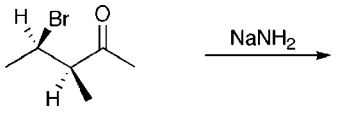
NaOH →

d.



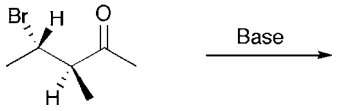
$AgNO_3$ →

5. As mentioned earlier, stereochemistry is not of great concern in this book. However, certain mechanistic types will show specific stereochemical consequences when acting on chiral molecules. With this in mind, predict the product resulting from the E2 elimination of HBr when the shown isomer of 4-bromo-3-methyl-2-pentanone is treated with sodamide. Show all stereochemistry and explain your answer.

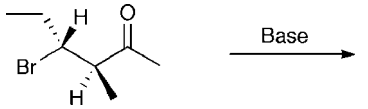


6. Based on the answer to Problem 5, predict the product of the following reactions and show all stereochemistry:

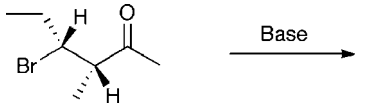
a.



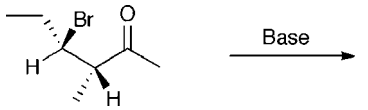
b.



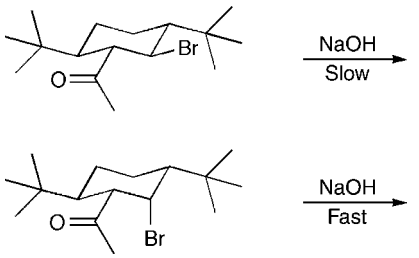
c.



d.



7. Explain the results of the following experiment:



Chapter 7

Addition Reactions

In Chapter 6, elimination reactions were presented. In the context of elimination reactions, the formation of double bonds was noted regardless of the elimination mechanism discussed. Continuing from the concept of using elimination reactions to form sites of unsaturation, one may reason that **addition reactions** can be used to remove sites of unsaturation. Thus, elaborating upon addition reactions, this chapter provides an introduction to relevant **mechanisms** applied to both carbon–carbon double bonds (olefins) and carbon–oxygen double bonds (**carbonyls**).

7.1 ADDITION OF HALOGENS TO DOUBLE BONDS

Throughout this book, the various mechanistic types driving reactions were shown to rely upon interactions between **charged species** such as nucleophiles and electrophiles. However, when looking at **ethylene**, the simplest of olefins, there are no partial charges (or steric factors) that distinguish one side of the double bond from the other. Due to its **symmetry**, there can be no pure nucleophilic or electrophilic sites. Furthermore, when looking at **bromine** in its natural form of Br_2, there are no interactions between the two atoms other than a single and **unpolarized** bond joining them. Nevertheless, when ethylene and bromine are brought together, the reaction illustrated in Scheme 7.1 occurs.

To explain this reaction, consider the fact that, due to the overlapping *p* orbitals, double bonds are **electron rich**. This property allows olefins, under certain conditions, to act as nucleophiles. In the case of a double bond reacting with molecular bromine, the result is formation of a **three-membered ring** containing a positively charged bromine atom. This three-membered ring is known as a bridged **bromonium ion**. Concurrent to formation

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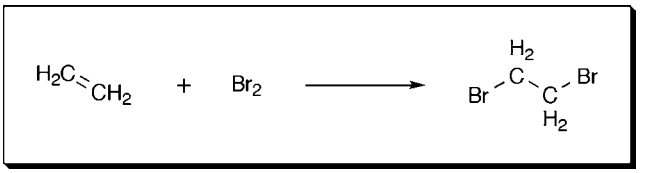
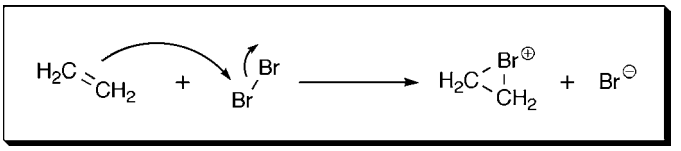
By Daniel E. Levy



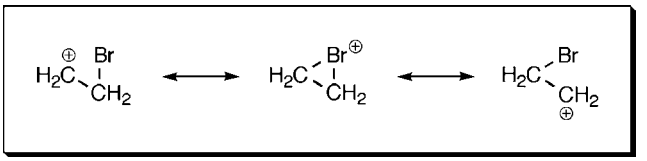
Scheme 7.1 *Addition of bromine to ethylene.*



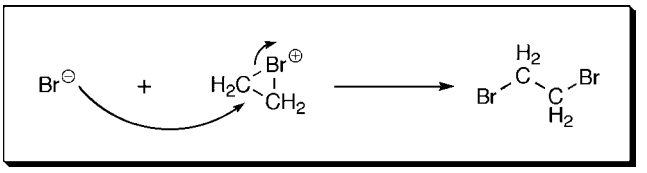
Scheme 7.2 *Molecular bromine reacts with double bonds, generating a bromonium ion and a bromide anion.*

of this species, a **bromide anion** is *displaced*. The initial reaction between bromine and ethylene is illustrated in Scheme 7.2 using arrow pushing.

Once the bromide anion becomes liberated from its parent molecular bromine, it is free to act as a nucleophile. Due to the positive charge residing on the bridged bromonium ion, the adjacent carbon atoms now possess partial positive charges. This is due to the positively charged bromine pulling **electron density** from the carbon atoms. The electrophilic nature of the adjacent carbon atoms is illustrated in Scheme 7.3 using resonance structures. Because the **carbon atoms** are now electrophilic, they are susceptible to reaction with the bromide anion that has dissociated as shown in Scheme 7.2. As illustrated in Scheme 7.4, using arrow pushing, this sequence of events leads to the formation of **1,2-dibromoethane**.



Scheme 7.3 *Bromonium ions possess electrophilic carbon atoms.*



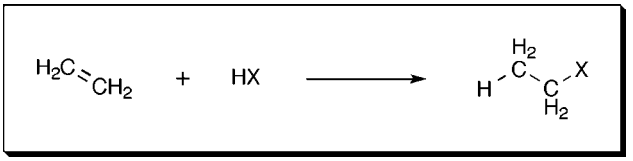
Scheme 7.4 *Nucleophilic reaction between a bromide anion and a bromonium ion generates 1,2-dibromoalkanes.*

7.2 MARKOVNIKOV'S RULE

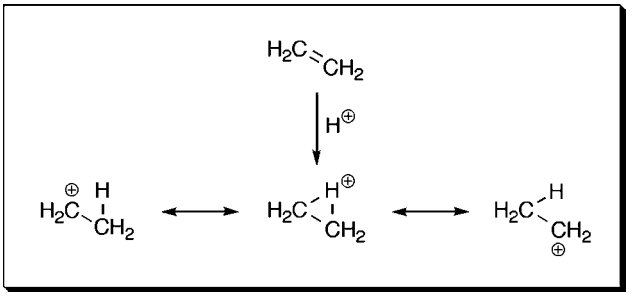
Diatomic halogen molecules such as bromine are not the only chemicals that can add across double bonds. In fact, any **protic acid**, under the proper conditions, can undergo such reactions. Specifically, as shown in Scheme 7.5, reaction of ethylene with an acid, HX, where X is OH, CN, or any halide produces a substituted ethane.

Mechanistically, the addition of acids across double bonds is very similar to the reaction of olefins with **halogens**. To understand this, it is important to recognize the electron-rich character of double bonds described in Section 7.1. With this property of olefins in mind, one recognizes that double bonds can become protonated under acidic conditions. As illustrated in Scheme 7.6, **protonated olefins** are electronically very similar to the bromonium ion shown in Scheme 7.3 and, as such, can be described with **charge-delocalized resonance structures**. Furthermore, these resonance structures are identical to those conceptually presented in Chapters 5 and 6 during discussions of hyperconjugation. Recall that hyperconjugation is the effect leading to stabilization of carbocations (Chapter 5) as well as being the driving force behind 1,2-hydride shifts (Chapter 6). Bringing these concepts into the addition of protic acids to olefins, the step following protonation (illustrated in Scheme 7.7) is no different than the second step of an S_N1 substition reaction.

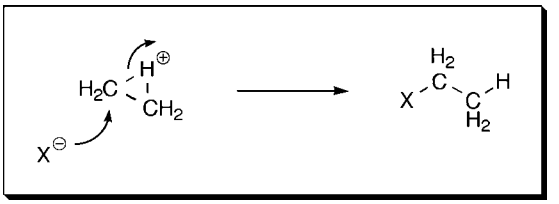
Unlike the addition of halogens across double bonds, addition of acids results in formation of **asymmetrical products**. Specifically, a different group is added to each side of the double bond. Thus, if this reaction is applied to **asymmetrical olefins** such as **propene**, multiple products might be expected to form as illustrated in Scheme 7.8. In fact, while a mixture of products is formed, there is an overwhelming presence of the **secondary substituted product** compared to that with substitution at the **primary position**. This preference of reaction products resulting from addition of protic acids across double bonds is governed by **Markovnikov's rule**.



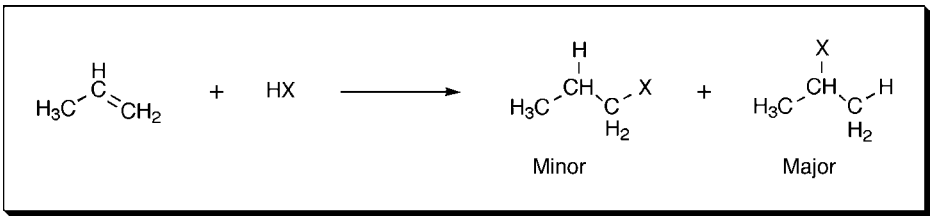
Scheme 7.5 *Protic acids can add across double bonds.*



Scheme 7.6 *Double bonds can become protonated under acidic conditions.*



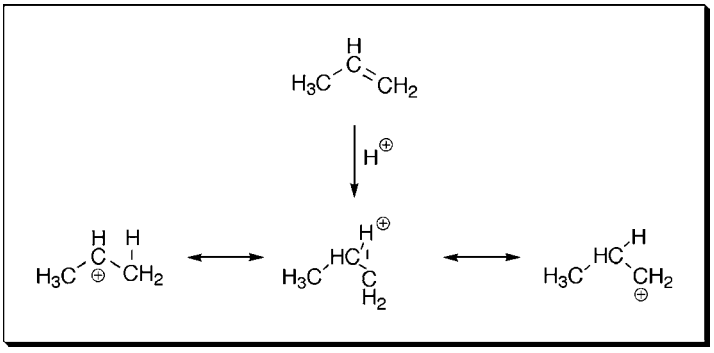
Scheme 7.7 *Nucleophiles add to protonated olefins.*



Scheme 7.8 *Multiple potential products are possible from addition of protic acids across double bonds.*

To understand the mechanistic basis behind Markovnikov's rule, it is useful to refer to the mechanisms through which acids add across double bonds. Of particular relevance are the resonance forms of the protonated olefins illustrated in Scheme 7.6. Since, for ethylene, the two carbon atoms are both primary, there is no distinction between them. However, as illustrated in Scheme 7.9, in the case of propene, protonation of the olefin results in introduction of **cationic character** to both a **primary carbon atom** and a **secondary carbon atom**.

Referring to the discussions presented in Chapter 5 regarding the relative stabilities of carbocations (and hyperconjugation), we are reminded that tertiary carbocations are more stable than secondary carbocations, which, in turn, are more stable than primary carbocations. Since, as shown in Scheme 7.9, protonation of propene results in cationic character at both a secondary carbon and a primary carbon, a greater presence of cationic character on the secondary site is expected compared to the primary. This allows



Scheme 7.9 *Protonation of propene introduces cationic character to both primary and secondary centers.*

a nucleophile to add, preferentially, to the secondary site generating the reaction outcome presented in Scheme 7.8. Thus, in general, Markovnikov's rule states that *when an acid is added across a double bond, the conjugate base adds to the more substituted carbon atom.*

7.3 ADDITIONS TO CARBONYLS

Olefins, in the absence of attached **polarizing groups**, generally react as described above with reactivity mediated through the nucleophilicity of the double bond. However, replacing one of the olefinic carbon atoms with oxygen results in formation of a polar carbonyl. As shown in Figure 7.1, the polarity is described through placement of a partial negative charge on the oxygen and a partial positive charge on the carbon. Discussions describing the polarity of carbonyls (and other functional groups), based on the electronegativities of the various atoms involved, were presented in Chapter 1. Addition reactions involving carbonyls are discussed in the following paragraphs.

7.3.1 1,2-Additions

Because of the inherent polarity associated with carbonyl groups, nucleophiles are drawn to the carbonyl carbon atoms in much the same way that nucleophiles participate in S_N2 reactions. This mechanism, alluded to in several problems presented in previous chapters, is illustrated in Scheme 7.10 using arrow pushing. As shown, a bonding pair of electrons joining the carbonyl oxygen atom to its associated carbon atom acts as the leaving group, placing a full negative charge on the oxygen atom. Generally, this type of reaction

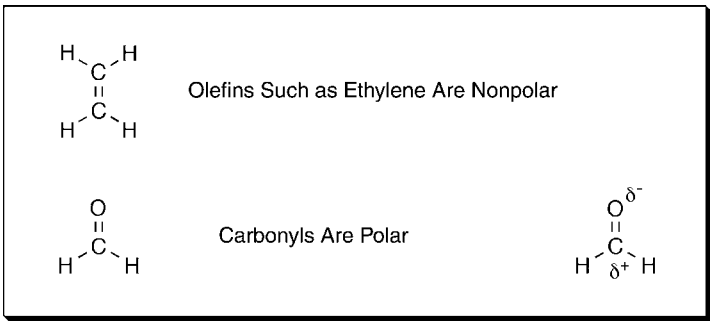
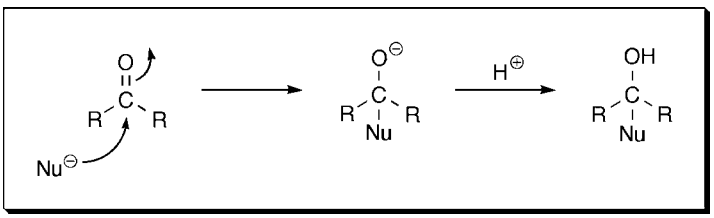
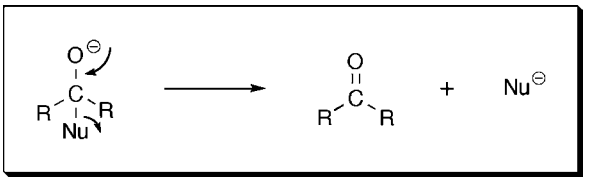


Figure 7.1 *While unsubstituted olefins are not polar, carbonyls are polar.*



Scheme 7.10 *Nucleophiles can add to carbonyls to form alcohols.*

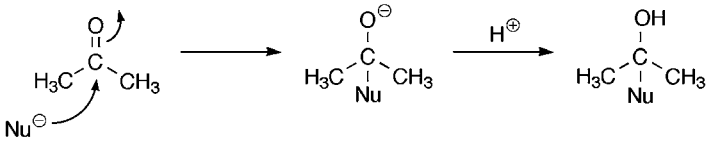


Scheme 7.11 *Addition of nucleophiles to carbonyls is reversible.*

produces alcohols from carbonyls. Because of the trigonal planar geometry of a carbonyl group, there is no stereochemical preference associated with these addition reactions.

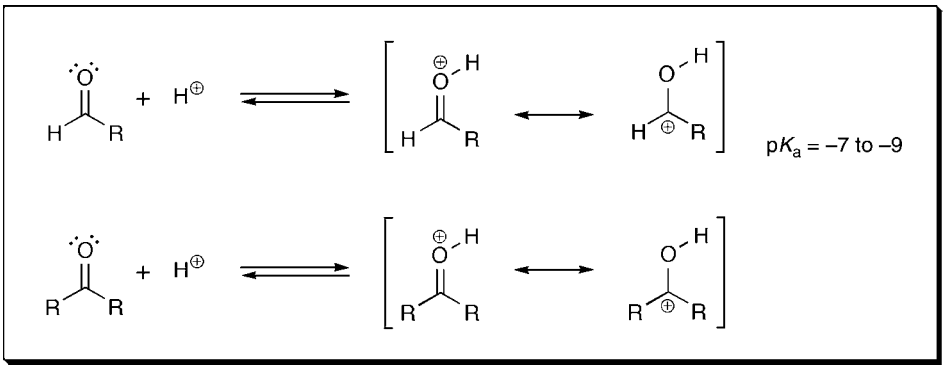
When considering reactions involving the addition of nucleophiles to carbonyls, it is important to understand that many nucleophiles can also serve as leaving groups. Therefore, to prevent the reverse reaction (elimination of the added nucleophile) illustrated in Scheme 7.11, **carbon-based nucleophiles** are generally utilized. Such nucleophiles include, but are not limited to, **Grignard reagents**, **alkyllithium reagents**, and **potassium cyanide**. In the case of Grignard and alkyllithium reagents, the result is formation of alcohols. Using potassium cyanide, **cyanohydrins** are formed. These reagents and the products of their reactions with acetone are illustrated in Scheme 7.12.

Thus far, all examples related to the addition of nucleophiles to carbonyls involve basic (anionic) conditions. However, such conditions are not required. Recalling that a carbonyl oxygen atom possesses a partial negative charge, we recognize that under acidic conditions it can be protonated. The protonation of carbonyl groups, illustrated in Scheme 7.13, was discussed in Chapter 3. Thus, as shown in Scheme 7.14 using acetone, treatment of

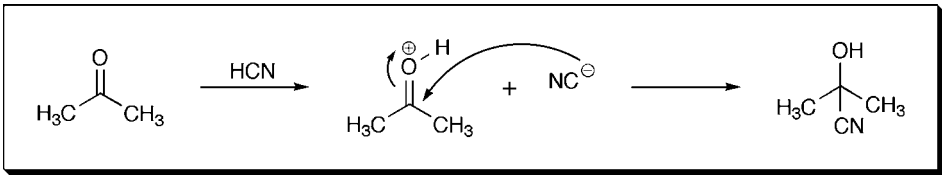


Reagent	Nucleophile	Product
H_3CMgBr Methylmagnesium Bromide (methyl Grignard)	$H_3C^{\ominus}$	*tert*-Butyl Alcohol
H_3CCH_2Li Ethyllithium	$H_3C\overset{\ominus}{C}H_2$	2-Methyl-2-butanol
KCN Potassium Cyanide	$NC^{\ominus}$	Acetone Cyanohydrin

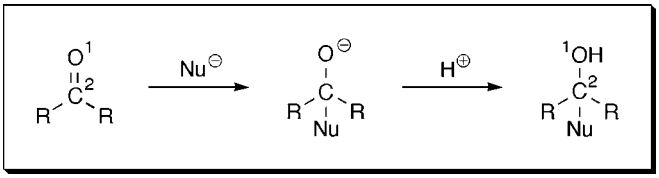
Scheme 7.12 *Products resulting from addition of nucleophiles to acetone.*



Scheme 7.13 *Carbonyls can become protonated.*



Scheme 7.14 *Addition of nucleophiles to carbonyls can occur under acidic conditions.*



Scheme 7.15 *Addition of nucleophiles to simple carbonyls results in 1,2-additions.*

carbonyls with acids such as HCN (**hydrocyanic acid**) provides another route for the formation of functional groups such as cyanohydrins.

If, as shown in Scheme 7.15, the atoms of a carbonyl are numbered with 1 representing the oxygen and 2 representing the electrophilic carbonyl carbon atom, we notice that addition of a nucleophile to the carbonyl results in the introduction of a new substituent at atom 2. Therefore, this type of addition is known as a **1,2-addition**.

7.3.2 1,4-Additions

The concept of S_N2 reactions was presented in Chapter 4. In the context of this discussion, the S_N2 mechanism was extended to allylic systems. These **allylic displacements**, because of their mechanistic similarities to S_N2 reactions, were designated S_N2' reactions. A representation of an S_N2' mechanism, compared to an S_N2 mechanism, is illustrated in Figure 7.2 using arrow pushing.

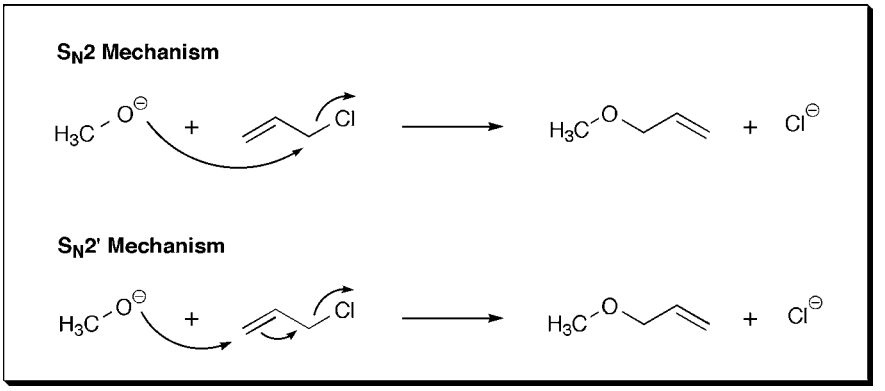
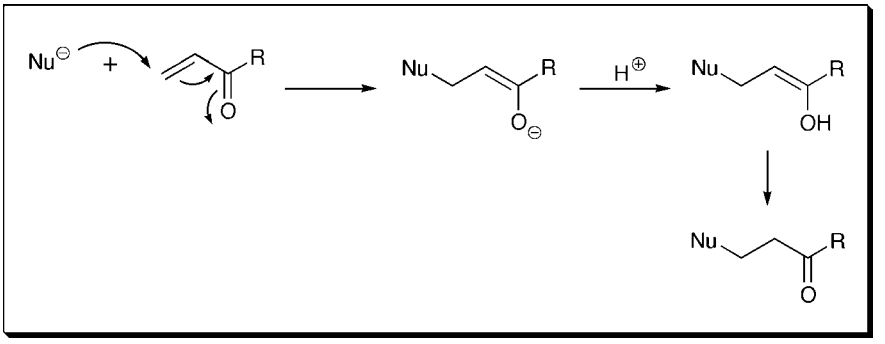


Figure 7.2 *Comparison of S_N2 and S_N2' reactions as explained using arrow pushing.*

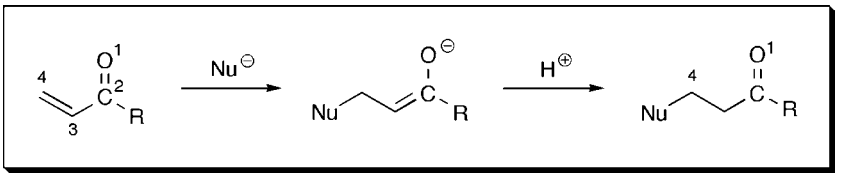


Scheme 7.16 *Addition of nucleophiles to α,β-unsaturated carbonyl groups as explained using arrow pushing.*

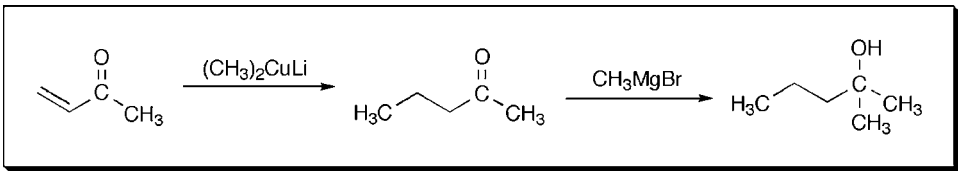
In Section 7.3.1, the addition of nucleophiles to carbonyls was directly compared to S_N2 reactions. In recognition of these mechanistic similarities, one may anticipate that nucleophiles can similarly add to **α,β-unsaturated carbonyl** systems. Such additions are, in fact, common and, as such, are illustrated in Scheme 7.16 using arrow pushing. As shown, the nucleophile initially *adds* to the double bond with delocalization of the negative charge into the carbonyl group generating an **enolate anion**. Once treated with acid, the enolate anion becomes protonated and forms an enol. **Enols**, being high-energy species, readily isomerize and regenerate the carbonyl functionality.

If, as shown in Scheme 7.17, the atoms of an α,β-unsaturated carbonyl are numbered with 1 representing the oxygen, 2 representing the carbonyl carbon atom, and 3 and 4 sequentially representing the adjacent two olefinic carbon atoms, we notice that addition of a nucleophile in the manner illustrated in Scheme 7.16 results in the introduction of a new substituent at atom 4. Therefore, this type of addition is known as a **1,4-addition**.

While 1,4-additions to carbonyls are common, it is important to recognize that the same α,β-unsaturated carbonyl systems are also subject to 1,2-additions. Fortunately, these two types of additions are highly dependent upon the form of the nucleophiles used.



Scheme 7.17 *Addition of nucleophiles to α,β-unsaturated carbonyls can result in 1,4-additions.*



Scheme 7.18 *α,β-Unsaturated carbonyl systems can be sequentially subjected to 1,4-additions and 1,2-additions.*

For example, simple organometallic reagents such as alkyllithium reagents and Grignard reagents tend to participate in 1,2-additions while **organocuprates** generally participate in 1,4-additions. These trends, however, are not absolute, and the reader is referred to general organic chemistry textbooks for broader and more detailed treatments of these addition mechanisms.

In a final consideration regarding 1,2- and 1,4-addition reactions, α,β-unsaturated carbonyl systems can be sequentially subjected to both mechanisms. As illustrated in Scheme 7.18, if **methyl vinyl ketone** is treated first with **dimethyllithiocuprate** and then with **methylmagnesium bromide**, the resulting product is **2-methyl-2-pentanol**.

7.3.3 Addition–Elimination Reactions

In our present discussions, 1,2- and 1,4-additions to carbonyl systems were introduced. However, these reactions were not presented in the context of specific carbonyl-based functional groups. Expanding upon this concept, the three types of functional groups generally used in **addition reactions** to carbonyls are aldehydes, ketones, and esters.

With respect to all of the above-mentioned functional groups, 1,4-additions are generally applicable. However, of these three groups, only aldehydes and ketones are generally useful as substrates for 1,2-additions. Figure 7.3 illustrates the products resulting from both 1,2- and 1,4-additions of nucleophiles to aldehydes, ketones, and esters. As shown, while the products of 1,4-additions all result in retention of the carbonyl functionality, 1,2-additions result in conversion of the respective carbonyl groups into alcohols. However, when an ester is involved, the illustrated product is a ketone and retains the carbonyl of the starting ester.

In examining the mechanism leading to the nucleophile-mediated conversion of an ester to a ketone, initial addition of a nucleophile to the carbonyl results in formation of a **hemiacetal** intermediate. Subsequent **collapse** of the hemiacetal intermediate liberates a ketone and an **alkoxide leaving group**. This mechanistic sequence, illustrated in Scheme 7.19

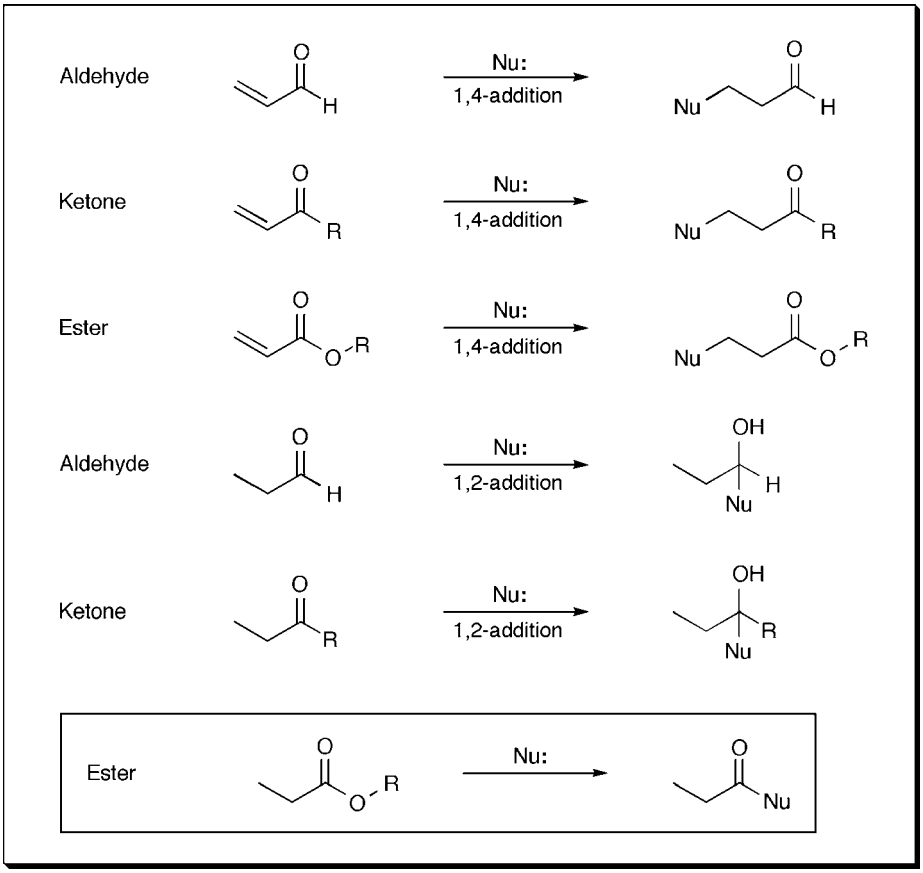
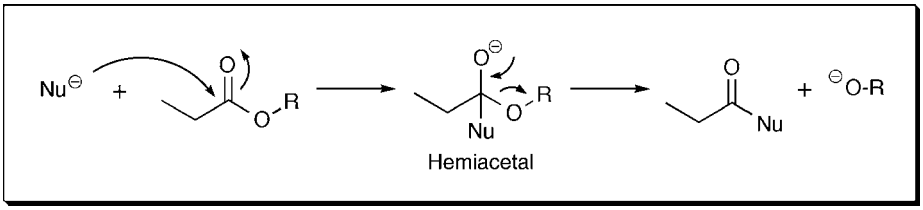


Figure 7.3 *Unlike most carbonyl-based functional groups, nonconjugated esters can react with nucleophiles and retain the carbonyl unit.*

using arrow pushing, is known as an addition–elimination and involves initial addition of a nucleophile to a carbonyl followed by elimination of an alkoxide leaving group. As a cautionary note, the conversion of esters to ketones can be difficult to control due to sequential reaction of the newly formed ketones with nucleophiles present in the reaction mixture.

Addition–elimination reactions are not exclusive to esters. In fact, these reactions can occur with any carbonyl-based system where the leaving group is a weaker nucleophile



Scheme 7.19 *The addition–elimination mechanism illustrated with arrow pushing.*

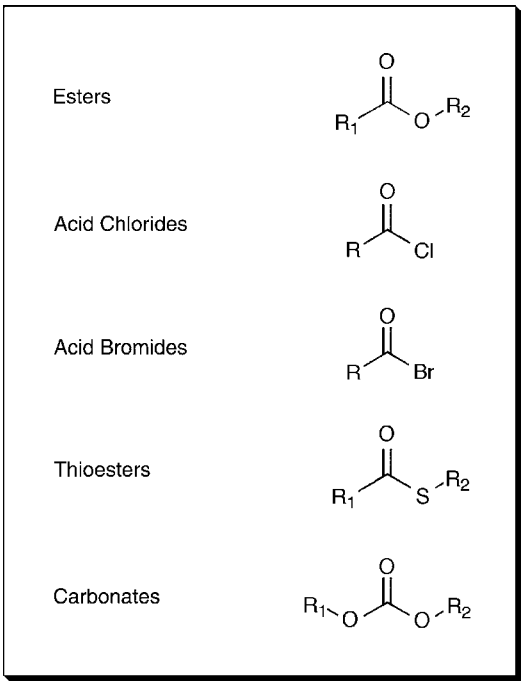


Figure 7.4 *Functional groups capable of participating in addition–elimination reactions.*

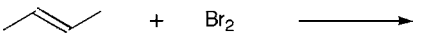
than that initially reacting. Such systems, illustrated in Figure 7.4, include, but are not limited to, esters, **acid halides**, **thioesters**, and **carbonates**. Finally, when predicting the products of potential addition–elimination reactions, guidance is readily obtained through consideration of the relative pK_a values of the respective nucleophiles and leaving groups.

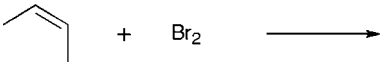
7.4 SUMMARY

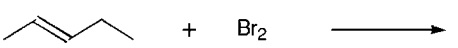
In this chapter, the principles presented in Chapter 4 (S_N2 reactions) were extended into olefinic and carbonyl-based systems. In exploring these areas, the electronic properties and nucleophilic/electrophilic nature of these groups were discussed. Finally, discussions of nucleophilic additions into these functionalities were extended into conjugated unsaturated systems leading to strategies for the incorporation of diverse modifications to relatively simple substrates. Specifically, this diversity of modifications becomes much more apparent when combining the principles presented in this chapter with those of Chapters 4 and 6. All of these principles will be useful when working through the problems of this chapter as well as advancing through introductory organic chemistry coursework.

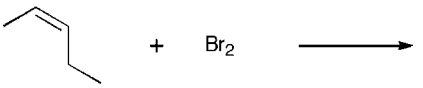
PROBLEMS

1. Predict the products of the following reactions and then answer the following questions. Consider stereochemistry.

I. 

II. 

III. 

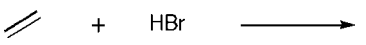
IV. 

a. Are the products of reactions I and II the same or are they different? Explain your answer.

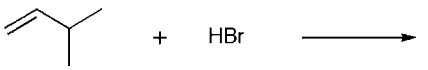
b. How do you account for the products of reactions I and II?

c. Are the products of reactions III and IV the same or are they different? Explain your answer.

2. Predict all of the products of the following reactions:

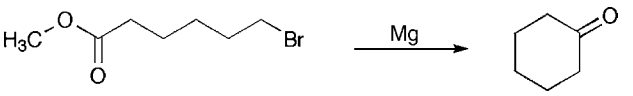
a. 

b. 

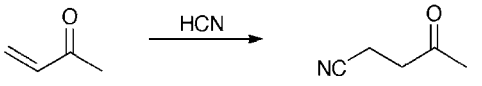
c. 

3. Explain the results of the following reactions. Use arrow pushing and specify mechanistic types.

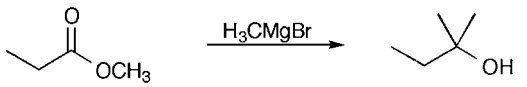
a.



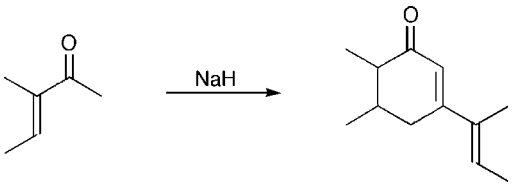
b.



c.

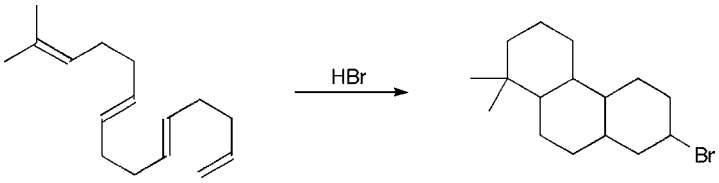


d.

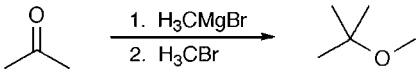


4. Explain the following reactions in mechanistic terms. Show arrow pushing.

a.



b.



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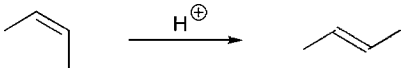
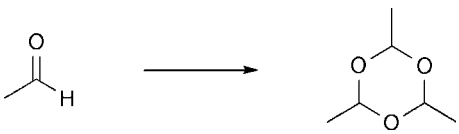
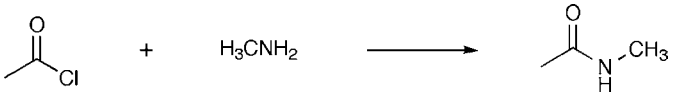
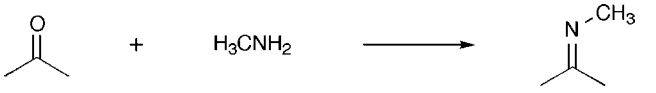


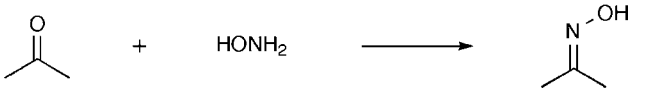
d.

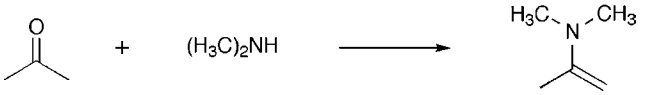


5. Explain the following products resulting from the reaction of amines with carbonyls. Use arrow pushing and specify mechanistic types.

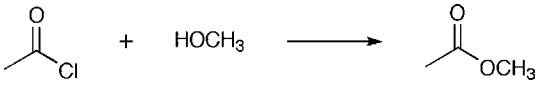
a. 

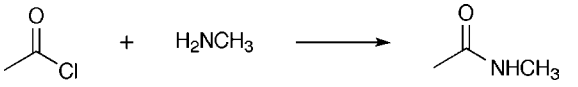
b. 

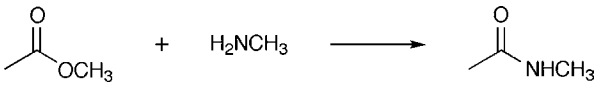
c. 

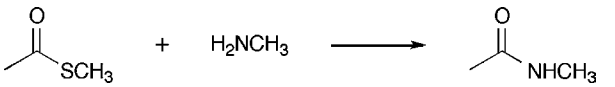
d. 

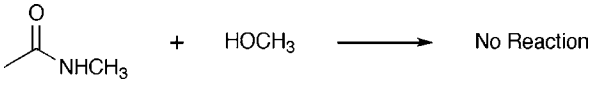
6. Provide mechanisms for the following reactions. Show arrow pushing.

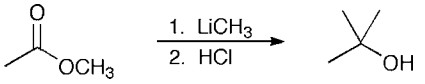
a. 

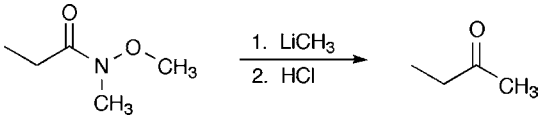
b. 

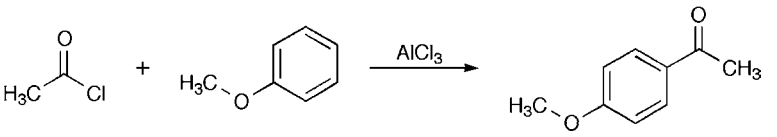
c. 

d. 

e. 
O
NHCH3
+
HOCH3
No Reaction

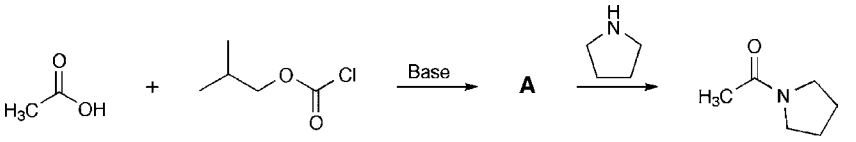
f. 
O
OCH3
1. LiCH3
2. HCl
OH

g. 
O
N
O
CH3
CH3
1. LiCH3
2. HCl
O
CH3

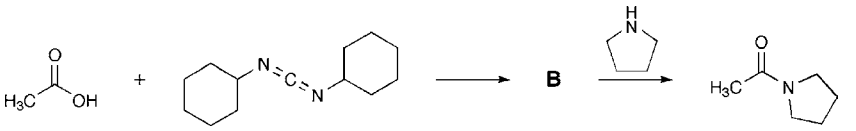
h. 
O
H3C
Cl
+
H3C
O
AlCl3
O
CH3
H3C
O

7. Explain the following amide-forming reactions using arrow pushing. Specify the structures of **A**, **B**, and **C** and show all relevant mechanistic steps.

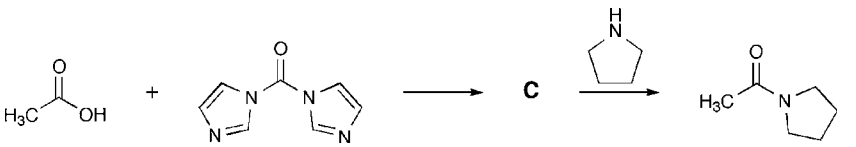
a.



b.



c.



Chapter 8

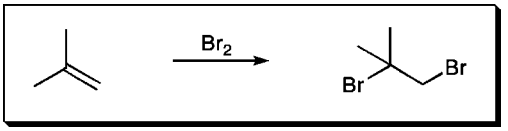
Moving Forward

Organic chemistry is a very mature science upon which numerous disciplines depend. These disciplines range from pharmaceuticals and food science to agrochemicals and material science. In approaching organic chemistry, the chapters thus far focused on utilizing the acid/base properties of organic molecules, in conjunction with the electronic properties of associated functional groups, to rationalize chemical reactions through the movement of electrons. This technique of arrow pushing was presented as an alternative to the memorization of the numerous **name reactions** available to organic chemists today. However, along with the treatments of various **mechanistic components** of organic reactions, this book includes introductions to many of the fundamental reactions studied in introductory organic chemistry courses. In this chapter, these reactions are revisited in order to emphasize that, through the application of arrow pushing, a broader and deeper understanding of organic chemistry can be derived.

8.1 FUNCTIONAL GROUP MANIPULATIONS

Functional group manipulations involve the transformation of one functional group to another with no additional changes to the core molecular structure. Throughout this book, many different functional groups were presented beginning with those illustrated in Figure 1.3 and continuing through each chapter and their associated problem sets. Considering olefins, among the simplest of functional groups, transformations into alkyl halides were presented in Chapter 7. Specific examples, illustrated in Schemes 8.1 and 8.2, included both the addition of halogens across double bonds as well as the application of Markovnikov's rule when adding acids across double bonds.

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy



Scheme 8.1 *Addition of bromine across a double bond.*

Scheme 8.2 *Markovnikov addition of hydrobromic acid across a double bond.*

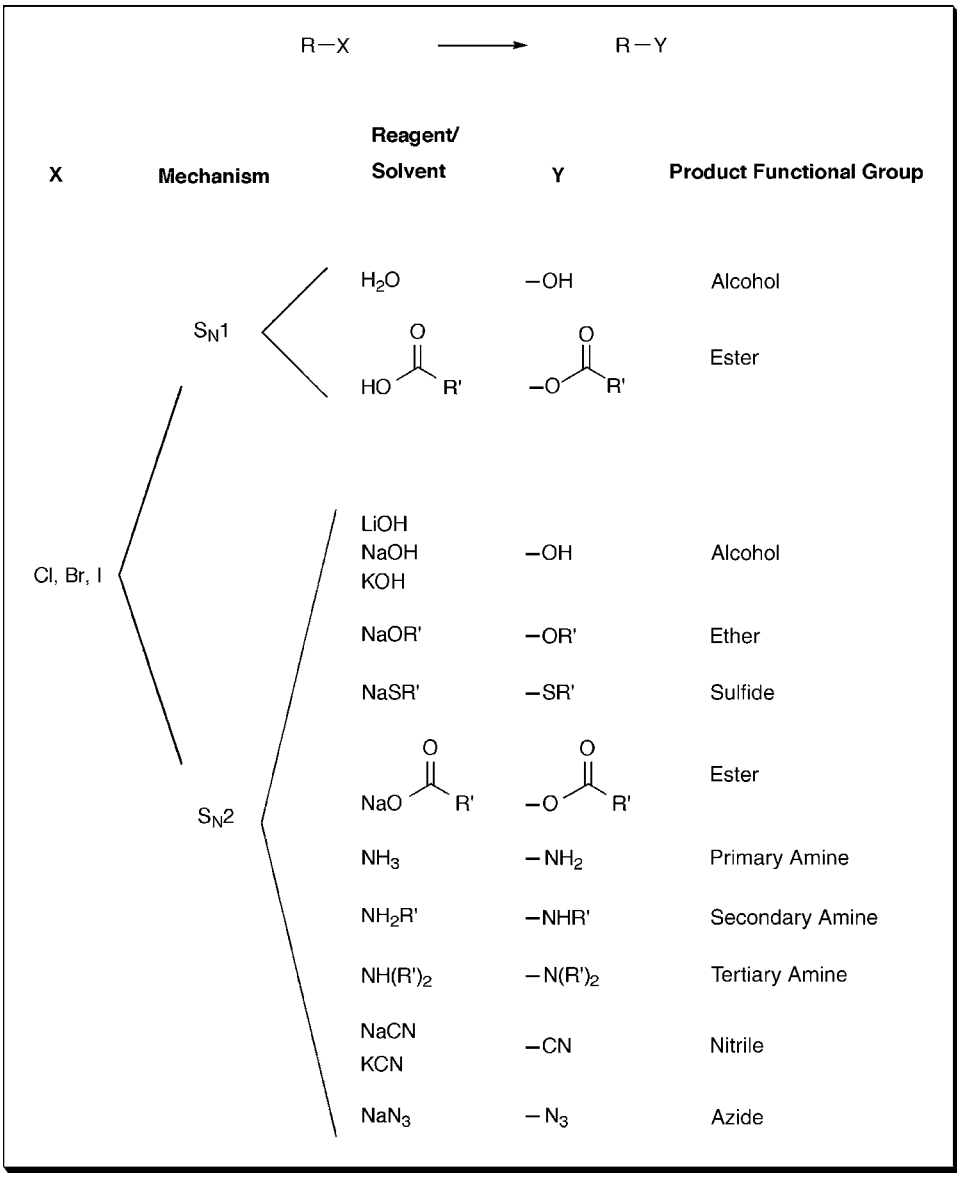
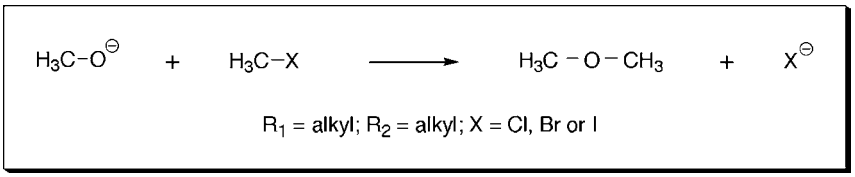


Figure 8.1 *Functional groups available from alkyl halides via S_N1 and S_N2 mechanisms.*



Scheme 8.3 *Conversion of alcohols to ethers—the Williamson ether synthesis.*

While the examples presented in Schemes 8.1 and 8.2 illustrate only the formation of **alkyl bromides**, it is important to recognize that halogens can be replaced through **nucleophilic displacements**. These displacements can occur via either S_N1 or S_N2 mechanisms. Regarding S_N1 reactions, ionization generally occurs under **solvolytic conditions**, limiting the nucleophile to the solvent used. In the case of S_N2 reactions, the only limiting factors relate to the relative nucleophilicities of the incoming nucleophiles compared to those of the leaving groups. Thus, as illustrated in Figure 8.1, alkyl halides can be converted into a wide variety of useful functional groups.

Upon further examination of the **functional group transformations** summarized in Figure 8.1, there are a number of additional conversions applicable to the product functional groups. Among these are the conversions of alcohols to ethers illustrated in Scheme 8.3.

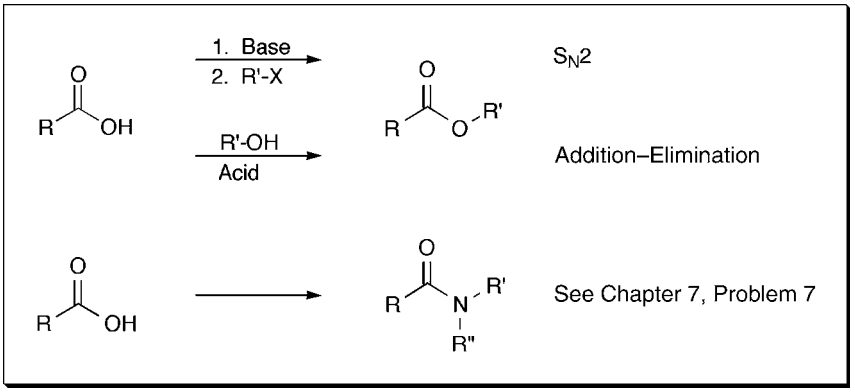


Figure 8.2 *Transformations of carboxylic acids to esters and amides.*

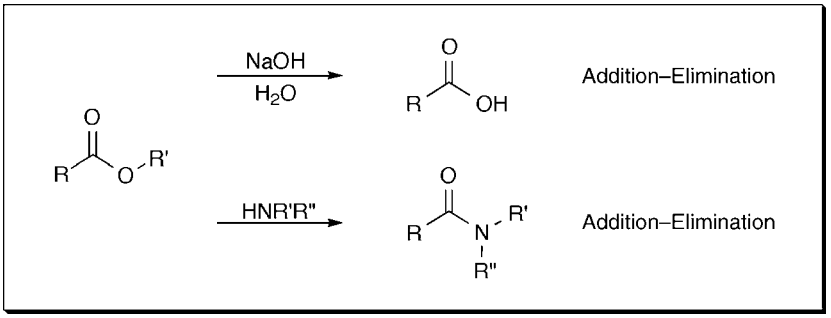


Figure 8.3 *Transformations of esters to carboxylic acids and amides.*

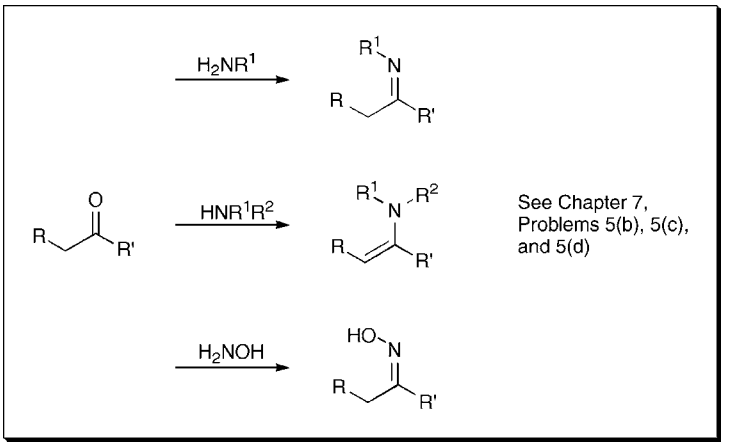


Figure 8.4 *Transformations of aldehydes and ketones to imines, oximes, and enamines.*

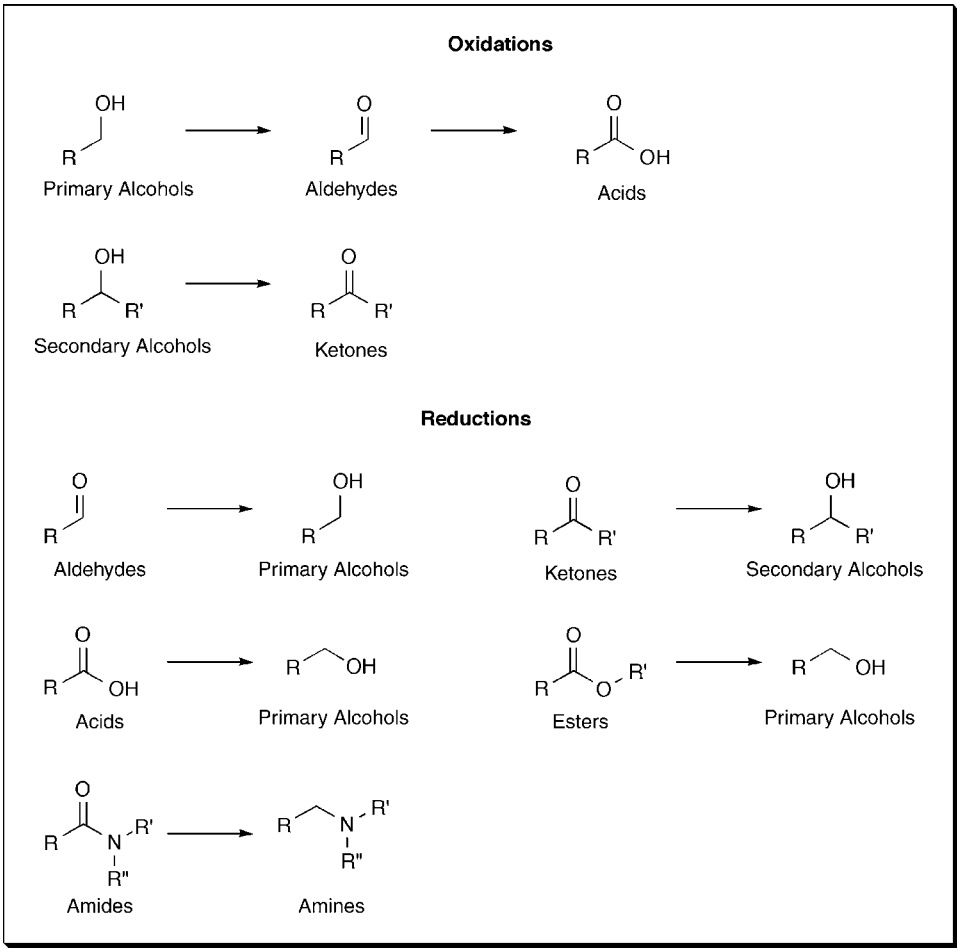


Figure 8.5 *Oxidative and reductive conversions of functional groups.*

Additionally, transformation of carboxylic acids to esters and amides are illustrated in Figure 8.2. The related conversions of esters to acids and amides are shown in Figure 8.3. Finally, transformations of aldehydes and ketones to **imines**, **oximes**, and **enamines** are summarized in Figure 8.4.

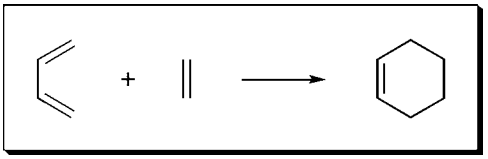
In addition to the functional group transformations discussed in this book, there are many more that depend on **oxidative** and **reductive mechanisms**. These mechanisms are covered in depth in introductory organic chemistry courses and will not be presented here in detail. As an introduction, Figure 8.5 summarizes such transformations, which include the **oxidation** of alcohols to aldehydes, ketones, and carboxylic acids. Likewise, Figure 8.5 introduces the reductive transformations of aldehydes, ketones, and carboxylic acids to alcohols as well as amides to amines. As will be revealed through further coursework, additional functional group manipulations are available and rationalized utilizing the principles of arrow pushing discussed throughout this book.

8.2 NAME REACTIONS

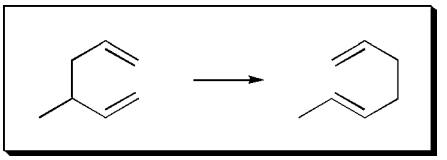
While the focus of the chapters to this point was to introduce the technique of arrow pushing as a strategy for understanding the general principles of organic chemistry, some name reactions were mentioned. These name reactions were presented for two reasons. First, their underlying mechanisms highlight the principles of focus in the chapters in which they were presented. Second, they represent important and fundamental tools for general organic chemistry transformations. While the focus of this book advocates development of a full understanding of organic reaction mechanisms as a means of learning the subject, once this understanding is achieved, recognition of these reactions by name presents a significant shortcut to the description of synthetic processes. The name reactions presented in this book are reviewed in the following paragraphs.

In the introductory chapters of this book, **electrocyclic reactions** were presented as early examples utilizing arrow pushing techniques. These were selected because of their simplicity relating to the nonionic character of the reactions. Specifically, the acid–base properties of the starting molecules are of lesser importance as the reactions illustrated proceed through the movement of electrons through the existing systems. The reactions illustrated include the **Diels–Alder reaction** (Scheme 8.4), the **Cope rearrangement** (Scheme 8.5), and the **Claisen rearrangement** (Scheme 8.6). These and related electrocyclic reactions, depending upon the same mechanistic principles, are covered in depth in introductory organic chemistry coursework.

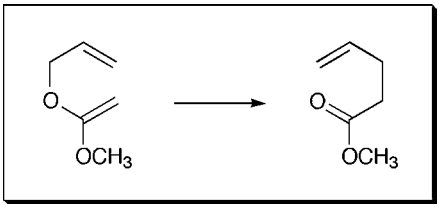
The above-described rearrangement reactions are not the only ones presented within this book. In addition to electrocyclic rearrangements, some rearrangements dependent upon ionic mechanisms were presented. These include the pinacol rearrangement



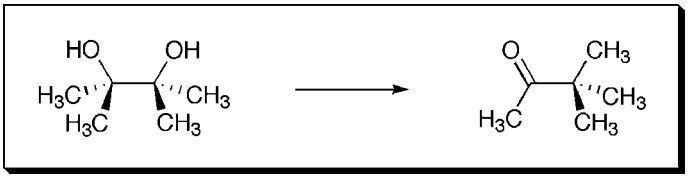
Scheme 8.4 *Diels–Alder reaction.*



Scheme 8.5 *Cope rearrangement.*



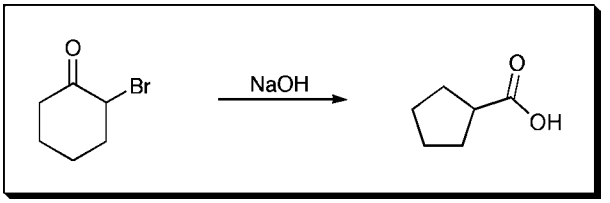
Scheme 8.6 *Claisen rearrangement.*



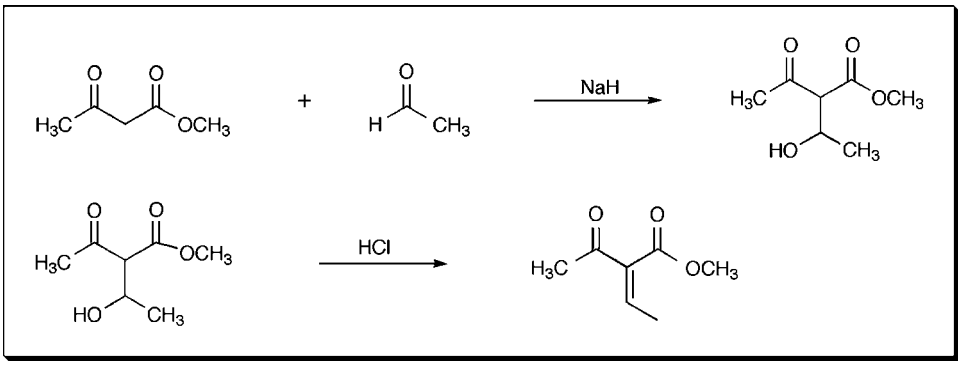
Scheme 8.7 *Pinacol rearrangement.*

(Scheme 8.7) and the **Favorskii rearrangement** (Scheme 8.8). These examples were presented within the context of alkyl shifts and the related hydride shifts. Through these examples, the concepts of **ionic stability** and **spontaneous ionic transformations** to more stable ionic species were explored. These concepts are especially prevalent when examining solvolysis-mediated processes where S_N1 and E1 mechanisms are involved.

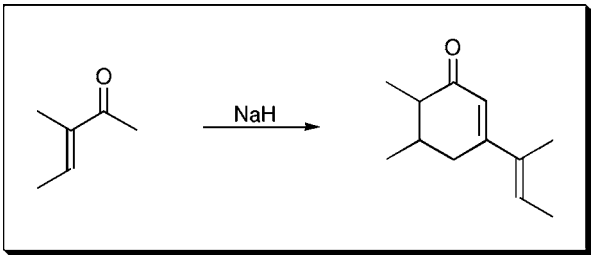
Moving from rearrangements, condensation reactions were also presented. Condensation reactions occur when two reactive species condense with one another forming a new compound. The first was the **aldol condensation** (Scheme 8.9). Later, a more complex application of the aldol condensation was presented in the form of the **Robinson annulation** (Scheme 8.10). For both of these reactions, the underlying lessons relate to the ability to induce reactions and incorporate substitutions at carbon atoms adjacent to carbonyl groups. Similar reactivities of such carbon atoms can be utilized for **alkylation** (S_N2) and **acylation** (addition–elimination) reactions as illustrated in Scheme 8.11.



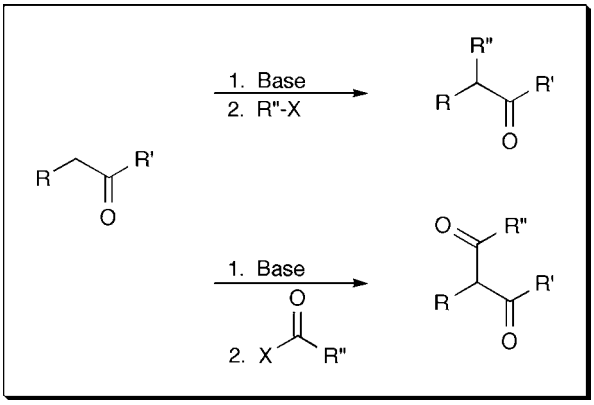
Scheme 8.8 *Favorskii rearrangement.*



Scheme 8.9 *Aldol condensation.*

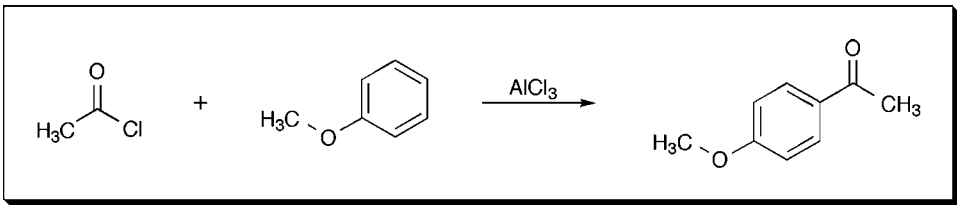


Scheme 8.10 *Robinson annulation.*



Scheme 8.11 *Alkylation and acylation reactions adjacent to carbonyls.*

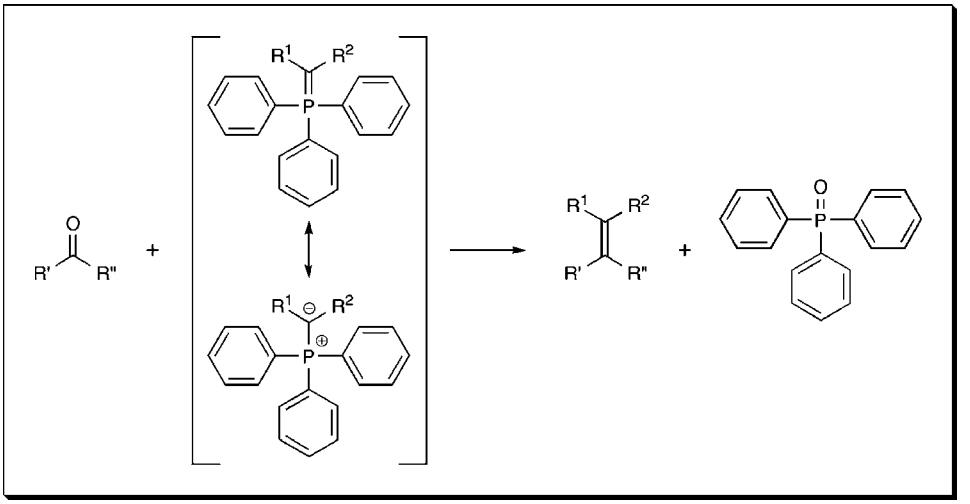
Regarding acylation reactions, acylation of alcohols produces esters and acylation of amines produces amides Both of these transformations are illustrated in Figure 8.2. These, in addition to the introduction of **acyl groups** adjacent to carbonyls (Scheme 8.11), only hint at the breadth of related acylation reactions available and useful in organic synthesis. One additional reaction is the **Friedel–Crafts acylation** illustrated in Scheme 8.12. Through this transformation, extended functionalization of **aryl groups** becomes accessible.



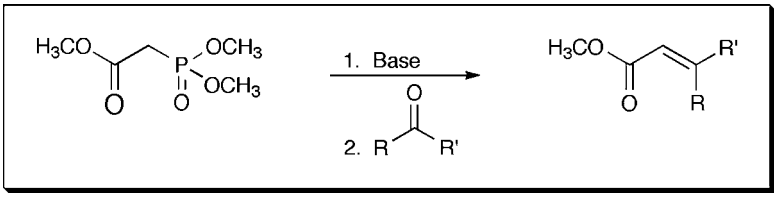
Scheme 8.12 *Friedel–Crafts acylation*

While mechanistically distinct, the aldol condensation and the Friedel–Crafts acylation result in the incorporation of additional carbon atoms to the starting structure. This type of extension is extremely important when planning the synthesis of more complex organic molecules. To this end, the greater the number of available reactions, the greater the versatility in synthetic planning.

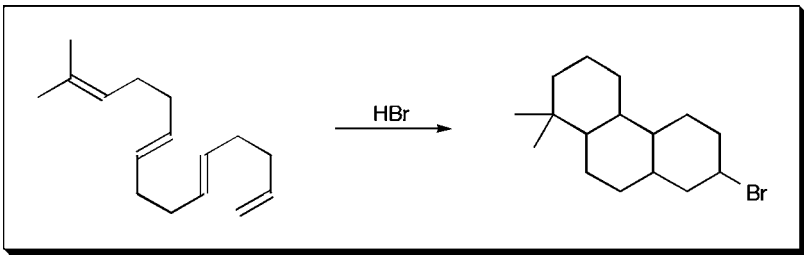
Thus far, the aldol condensation was presented as a method for adding carbon atoms adjacent to carbonyl groups, and the Friedel–Crafts acylation was presented as useful for the addition of carbon atoms to **aromatic rings**. In addition to these reactions, the **Wittig reaction** (Scheme 8.13) and the **Horner–Emmons reaction** (Scheme 8.14) were



Scheme 8.13 *Wittig reaction.*



Scheme 8.14 *Horner–Emmons reaction.*



Scheme 8.15 *Cation–π cyclization.*

presented as capable of replacing the carbon–oxygen double bond of aldehydes and ketones with carbon–carbon double bonds. The new extensions can be simple or functionalized. Additionally, the newly formed double bonds can be modified through addition of halogens or acids.

One final example of a name reaction presented within the text of this book is the **cation–π cyclization**. This reaction, illustrated in Scheme 8.15, returns to the previously described reaction classes that include electrocyclic reactions and rearrangements. Inclusion of this reaction complements the various nucleophiles used throughout the examples of this book by highlighting the nucleophilic nature of double bonds.

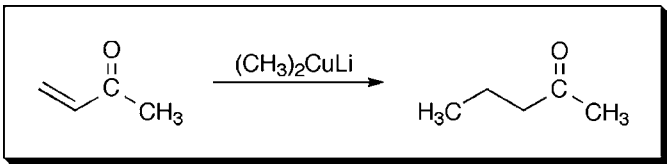
As will be revealed through further coursework, many more name reactions are available. Furthermore, new reactions, yet to be named, are continually being discovered. In approaching all of these reactions, it is imperative to develop mechanistic understandings in order to correctly apply the reactions within the scope of their utilities and limitations. In this respect, arrow pushing presents a valuable approach to the derivation of mechanistic understanding prior to committing the reaction names to memory.

8.3 REAGENTS

Throughout this book, and in association with the various reactions presented, various **reagents** were presented that, due to their specific properties, react in very specific ways. These reagents differ in their basicity, nucleophilicity, and preferred sites of reaction. Table 8.1 summarizes the various properties of the reagent classes presented.

Of the reagents listed in Table 8.1, dialkyllithiocuprates stand out because of their unique ability to participate in 1,4-addition reactions. Such reactions, also known as **conjugate additions**, are generally referred to as **Michael additions**. This name reaction is illustrated in Scheme 8.16 with the reaction of dimethyllithiocuprate with methyl vinyl ketone.

When considering the reagents listed in Table 8.1, it is important to remember that this table is not inclusive. There are many permutations of the reagents listed in the table as well as innumerable additional reagents that have been made useful to various aspects of organic chemistry. In fact, many research groups focus exclusively on the design and preparation of novel reagents capable of solving difficult synthetic problems. It is through this aspect of organic chemistry that some of the most significant advances have been realized.



Scheme 8.16 *Michael addition.*

TABLE 8.1 Reagent Classes and Associated Properties

Reagent Class (Class Name)	Examples	Properties	Uses
R-Li (alkyllithium)	Methyllithium Butyllithium *sec*-Butyllithium *tert*-Butyllithium	Strong base Strong nucleophile when R is not bulky.	Deprotonation of weak organic acids, E2 eliminations S_N2/S_N2' displacements, addition reactions, addition–elimination reactions
R-MgBr (alkylmagnesium bromide, alkyl Grignard)	Methylmagnesium bromide (methyl Grignard)	Strong nucleophile when R is not bulky.	S_N2/S_N2' displacements, addition reactions, addition–elimination reactions
R_2CuLi (dialkyl lithiocuprate)	Dimethyl lithiocuprate	General reactive nucleophile	1,4-Addition reactions
R_2N-Li (lithium dialkylamide)	Lithium diisopropylamide	Strong base, not nucleophilic when R is bulky.	Deprotonation of weak organic acids with acidities as high as $pK_a = 35$
M-H (metal hydride)	Sodium hydride Potassium hydride	Strong, not nucleophilic base	Deprotonation of weak organic acids with acidities as high as $pK_a = 25$
RO-K (potassium alkoxide)	Potassium *tert*-butoxide	Not nucleophilic base	Deprotonation of organic acids with acidities as high as $pK_a = 18$
M-OH (metal hydroxide)	Sodium hydroxide Potassium hydroxide	Nucleophilic bases	Deprotonation of organic acids with acidities as high as $pK_a = 16$, hydrolysis of esters, amides, and nitriles
R_3N (trialkylamine)	Triethylamine Diisopropylethylamine	Not nucleophilic base	Deprotonation of organic acids, acid scavenger

8.4 FINAL COMMENTS

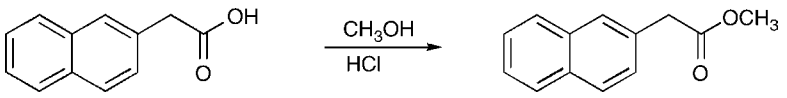
By now, having worked through the material in this book, readers should be well acquainted with the fundamental principles of arrow pushing. Furthermore, through the examples

presented herein, the reader should have acquired an understanding of how to apply arrow pushing to explain reaction processes and to predict reaction products. While this book was intended to serve solely as a supplement to introductory organic chemistry texts, the content was designed to move from the basic foundation of organic chemistry to the direct application of arrow-pushing techniques, thus enabling the reader to begin to advance through the study of organic chemistry. Finally, in closing, readers should endeavor to understand the underlying principles of organic chemistry in order to embrace the full substance of this mature and continually relevant discipline.

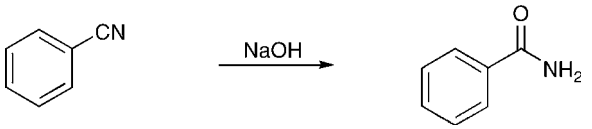
PROBLEMS

1. Describe the following functional group transformation in mechanistic terms. Show arrow pushing.

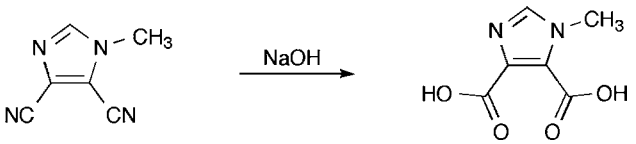
a.



b.

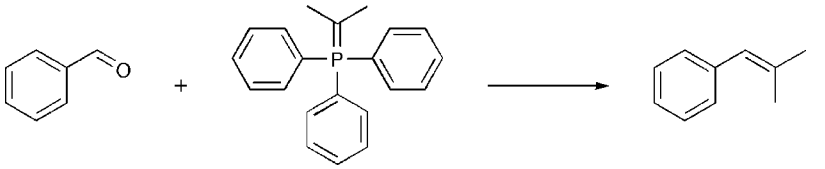


c.

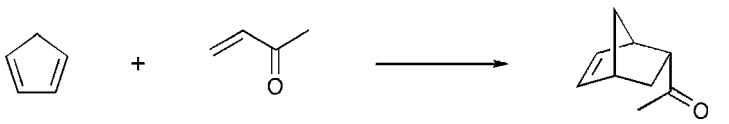


2. Explain the following reactions in mechanistic terms. Show arrow pushing and describe the reaction as a name reaction.

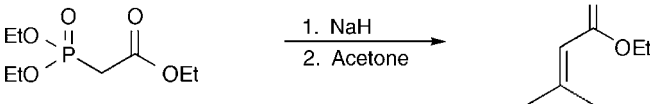
a.



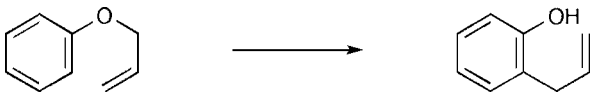
b.



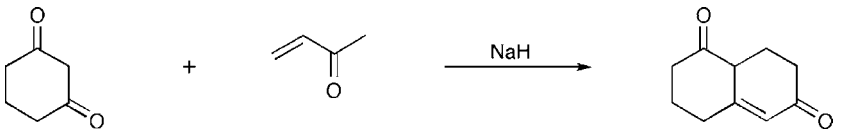
c.



d.

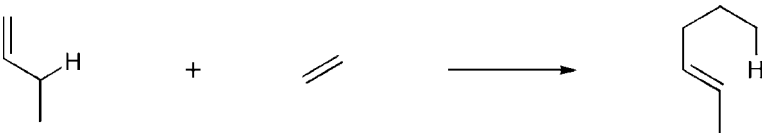


e.



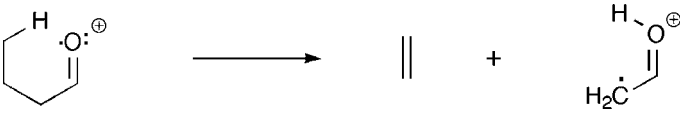
3. Explain the following name reactions in mechanistic terms. Show arrow pushing.

a. The ene reaction



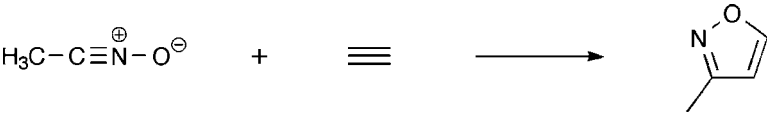
Note: Only the hydrogen involved in the reaction is shown.

b. The McLafferty rearrangement

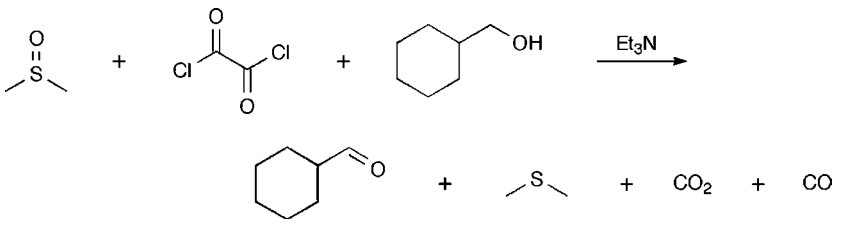


Note: The radical cation present in the starting material is the result of the carbonyl oxygen losing a single electron. This reaction is generally observed during electron impact mass spectrometry.

c. 1,3-Dipolar cycloaddition



d. The Swern oxidation

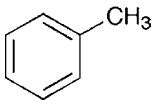


Hint: The oxygen atom in dimethyl sulfoxide is nucleophilic.

4. The Friedel–Crafts acylation, illustrated in Scheme 8.12, shows the formation of one product. However, the reaction, as illustrated, actually forms a mixture of two products. Using the arguments presented in the solution set for Chapter 7, identify the second product. Show partial charges and arrow pushing.

5. Predict all products formed from a Friedel–Crafts acylation on the following compounds with acetyl chloride. Rationalize your answers using partial charges.

a.



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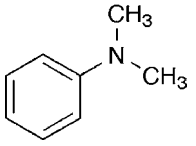

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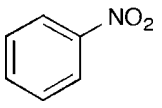

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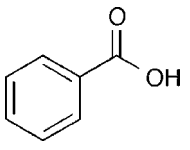

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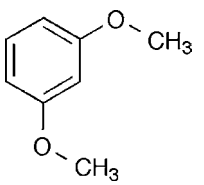

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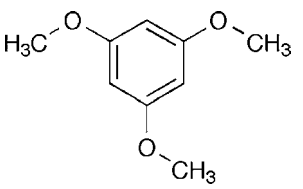
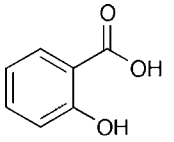
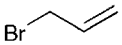
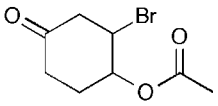
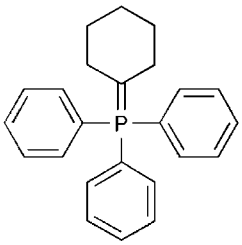
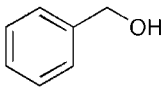
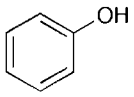
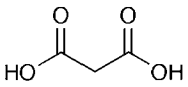
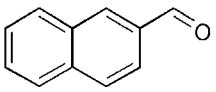
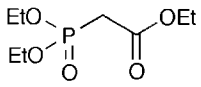


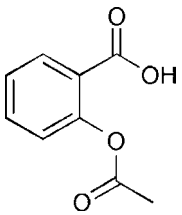
6. From the following list of compounds propose a synthetic strategy for the specified compounds. Up to four synthetic steps may be required. Any chemical reagents may be used. Show all arrow pushing.



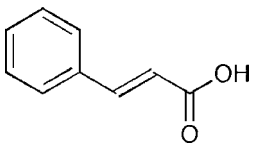







a.

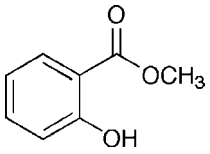


(acetylsalicylic acid, aspirin)

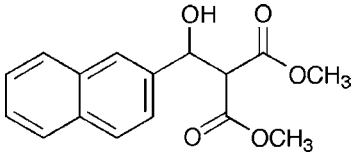
b.

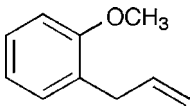


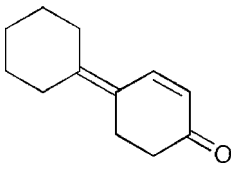
(cinnamic acid)

c. 

(methyl salicylate, oil of wintergreen)

d. 

e. 

f. 

Appendix 1

*p*K$_a$ *Values of Protons Associated with Common Functional Groups*

While this book teaches that organic chemistry can be learned without relying upon memorization of a multitude of chemical reactions, familiarity with pK_a values associated with various functional groups is essential. The pK_a values listed below provide a general calibration of the acidities of protons associated with common functional groups. In advancing through organic chemistry, accurate recollection of these values is indispensable.

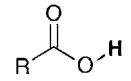
Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

Common Protic Acids

H-F Hydrofluoric Acid	**3.18**	H-I Hydroiodic Acid	**−10**
H-Cl Hydrochloric Acid	**−2.2**	H-CN Hydrocyanic Acid	**9.3**
H-Br Hydrobromic Acid	**−4.7**	H-N_3 Hydrazoic Acid	**4.6**

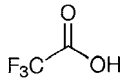
Neutral Functional Groups

Carboxylic Acids and Amides



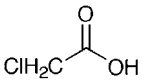
Carboxylic Acids

4–6



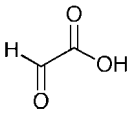
Trifluoroacetic Acid

0.30



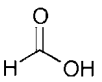
Chloroacetic Acid

2.85



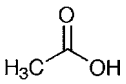
Glyoxylic Acid

3.18



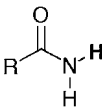
Formic Acid

3.75



Acetic Acid

4.75



Amides

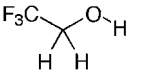
15–17

Neutral Functional Groups—Continued

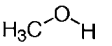
Alcohols, Amines, and Thiols


Alcohols

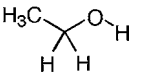
15–19


2,2,2-Trifluoroethanol

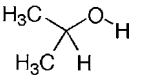
11–12


Methanol

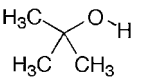
15


Ethanol

15–16


2-Propanol

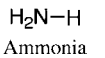
16–17


2-Methyl-2-propanol

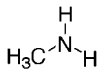
18–19


Amines

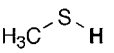
33–38


Ammonia

35

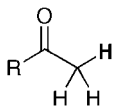

Methylamine

35

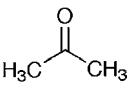

Methanethiol

10.4

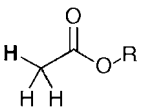
Aldehydes, Ketones, Esters, and Amides


Aldehydes and Ketones

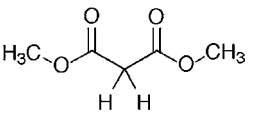
20–25


Acetone

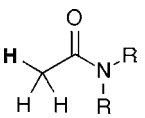
20


Esters

25–30


Dimethyl Malonate

13


Second Amides

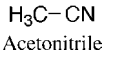
30–35

Neutral Functional Groups—Continued

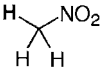
Nitriles and Nitro Compounds


Nitriles

20–25


Acetonitrile

25

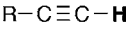

Nitromethane

10–15

Alkanes, Alkenes, and Alkynes


Alkanes

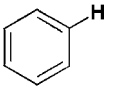
50–75


Alkynes

25


Alkenes

35–40


Benzene

40–45

Protonated Functional Groups

Alcohols and Ethers

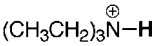

Alcohols

−2.2


Ethers

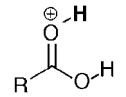
−2.2

Amines

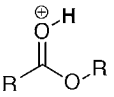

Amines

10

Carboxylic Acids and Esters

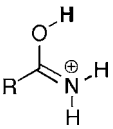

Carboxylic Acids

−6

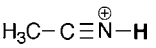

Esters

−6

Amides and Nitriles

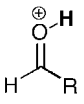

Amides

0

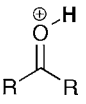

Nitriles

−10

Aldehydes and Ketones


Aldehydes

−7 to −9


Ketones

−7 to −9

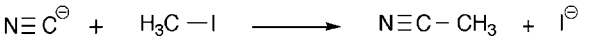
Appendix 2

Answers and Explanations to Problems

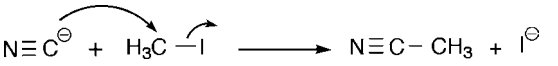
CHAPTER 1 SOLUTIONS

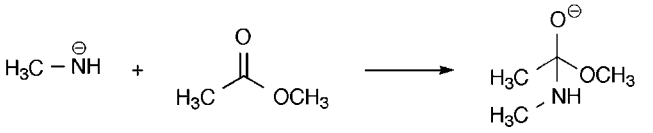
1. *Use arrow pushing to explain the following reactions.*

When drawing arrows to illustrate movement of electrons, it is important to remember that electrons form the bonds that join atoms. The following represent heterolytic-type reaction mechanisms:

a. 

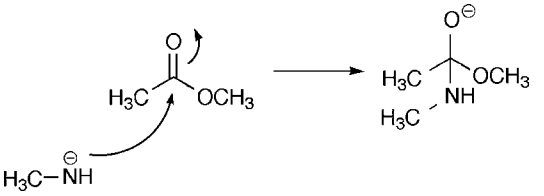
This is an example of an S_N2 reaction mechanism converting an alkyl iodide (iodomethane) to an alkyl nitrile (acetonitrile). Arrow pushing is illustrated below:



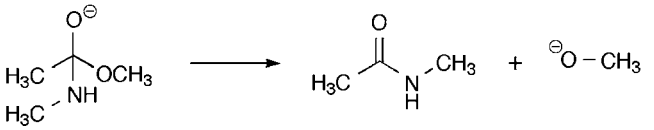
b. 

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

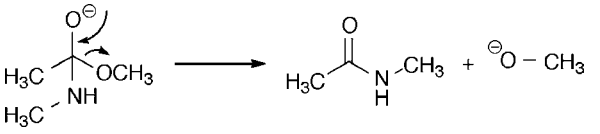
This is an example of the first step of an addition–elimination reaction mechanism converting an ester (methyl acetate) to an amide (*N*-methylacetamide). For clarity, the anion was repositioned in the scheme. Arrow pushing is illustrated below:



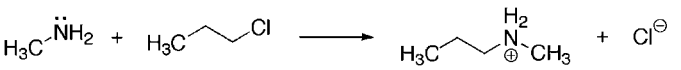
c.



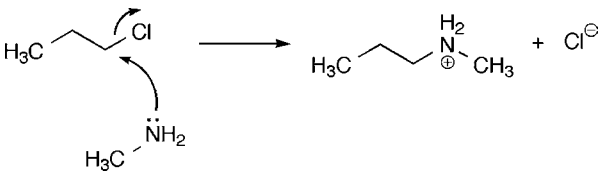
This is an example of the second step of an addition–elimination reaction mechanism converting an ester (methyl acetate) to an amide (*N*-methylacetamide). Arrow pushing is illustrated below:



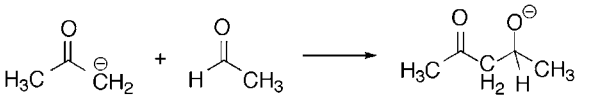
d.



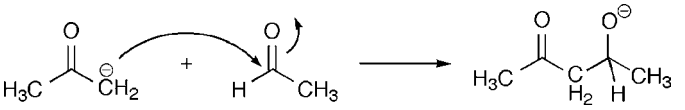
This is an example of an S_N2 reaction mechanism converting an alkyl chloride (chloropropane) to an ammonium salt (*N*-methyl, *N*-propylammonium chloride). For clarity, the amine was repositioned in the scheme. Arrow pushing is illustrated below:



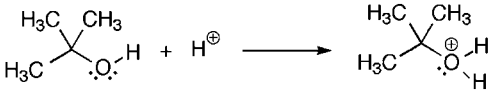
e.



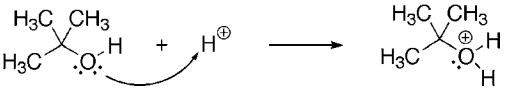
This is an example of an aldol condensation between an acetone anion and acetaldehyde. Note the mechanism proceeds through addition of an anion to an aldehyde carbonyl. Arrow pushing is illustrated below:



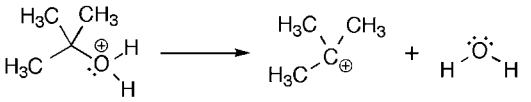
f.



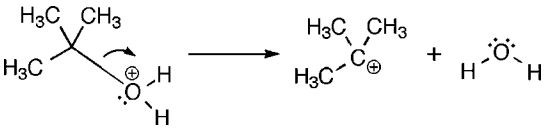
This is an example of the first step in the acid-mediated solvolysis of a tertiary alcohol. Note that protonation of the alcohol occurs under strongly acidic conditions with electrons moving toward the positive charge residing on the proton. Arrow pushing is illustrated below:



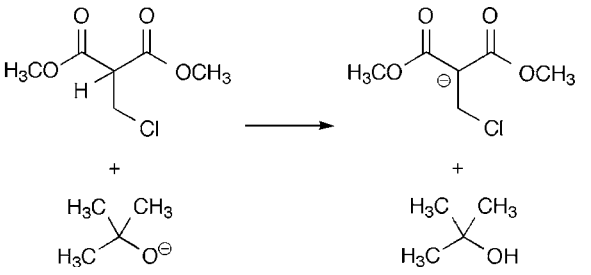
g.



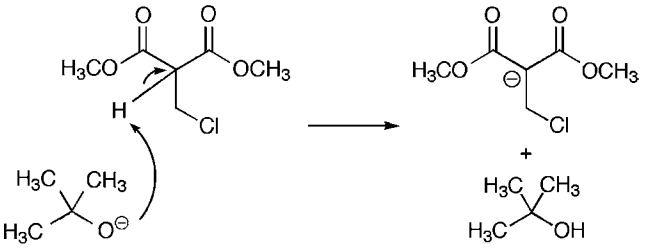
This is an example of the second step in the acid-mediated solvolysis of a tertiary alcohol. Note that the protonated alcohol separates as water and leaves the positive charge on the carbon atom. For clarity, the bond was lengthened to allow space for the arrow. Note that the electrons in the bond move toward the positive charge residing on the oxygen. Arrow pushing is illustrated below:



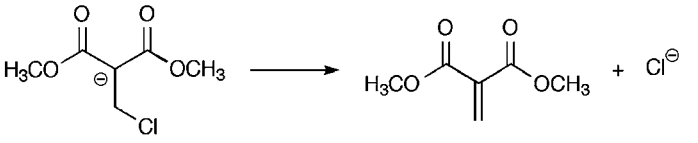
h.



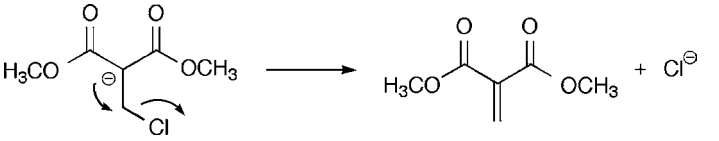
This is an example of the first step of an E2 (bimolecular elimination) reaction mechanism. Note the base-mediated deprotonation of the diester converting the *tert*-butoxide anion to *tert*-butanol. For clarity, the anion was repositioned and the bond was lengthened. Arrow pushing is illustrated below:



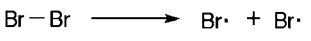
i.



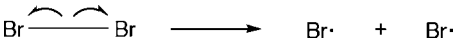
This is an example of the second step of an E2 (bimolecular elimination) reaction mechanism. Note the displacement of the chloride anion is the result of an anion present on an adjacent carbon atom. Arrow pushing is illustrated below:

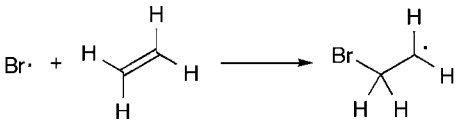


The following represent reaction mechanisms involving free radicals:

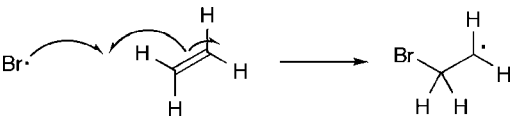
j. 

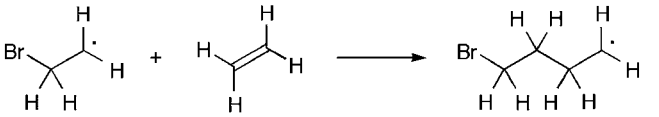
This is an example of the homolytic cleavage of a bromine molecule to form two bromide radicals. Note the use of single-barbed arrows to describe radical-based mechanisms resulting in the movement of single electrons. For clarity, the bond is elongated. Arrow pushing is illustrated below:



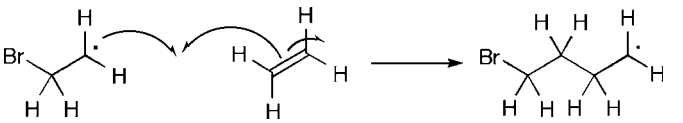
k. 

This is an example of the addition of a bromide radical to an olefin. Note that a single-barbed arrow is used for each electron that is moving. Arrow pushing is illustrated below:

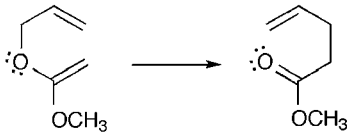


l. 

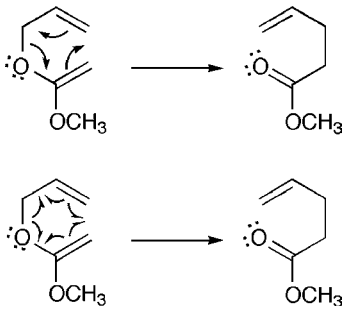
This is an example of a step in the free-radical-mediated polymerization of ethylene, forming polyethylene. As in the previous example, note that a single-barbed arrow is used for each electron that is moving. Arrow pushing is illustrated below:



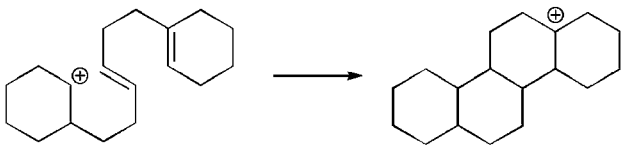
The following represents a concerted reaction mechanism:

m. 

This is an example of a Claisen rearrangement and occurs through a concerted reaction mechanism. As illustrated, concerted mechanisms can be described either by movement of electron pairs or by movement of single electrons. However, these mechanisms are generally represented by movement of electron pairs using double-barbed arrows as is done for heterolytic reaction mechanisms. Although, mechanistically, the movement of electron pairs is preferred over the movement of single electrons, both processes are illustrated below using arrow pushing:

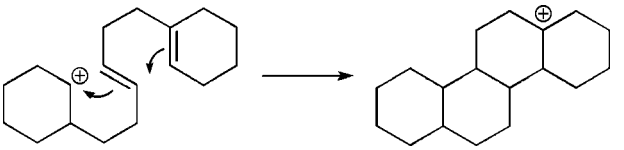


The following represents a heterolytic-type reaction mechanism:

n. 

This is an example of a cation–π cyclization. Note that unlike the previously described heterolytic reaction mechanisms, this reaction is influenced by a positive charge. Also, please note that this reaction shares some characteristics with

concerted mechanisms in that formation of the new bonds occurs almost simultaneously. Arrow pushing is illustrated below:

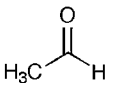


2. *Place the partial charges on the following molecules.*

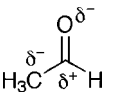
a.

Carbonyls are polarized such that a partial negative charge resides on the oxygen and a partial positive charge resides on the carbon.

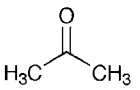
b.



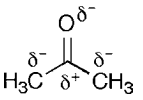
Because of the polarity of the carbonyl, adjacent groups are also polarized. In general, where a partial positive charge rests, an adjacent atom will bear a partial negative charge.

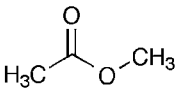


c.

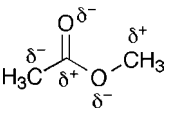


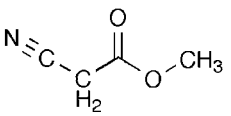
Because of the polarity of the carbonyl, adjacent groups are also polarized. In general, where a partial positive charge rests, an adjacent atom will bear a partial negative charge. This can occur on more than one adjacent atom.



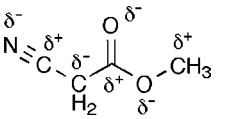
d. 

Because of the polarity of the carbonyl, adjacent groups are also polarized. In general, where a partial positive charge rests, an adjacent atom will bear a partial negative charge. This can occur on more than one adjacent atom or heteroatom.



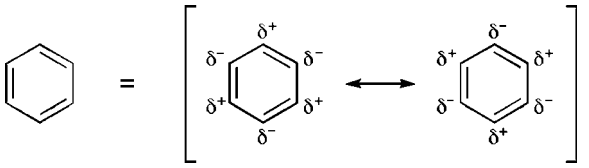
e. 

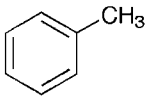
Nitriles, like carbonyls, are polarized with the nitrogen bearing a partial negative charge and the carbon possessing a partial positive charge.



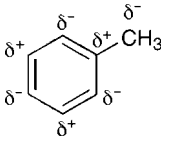
f. 

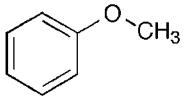
Benzene has no localized positive or negative charges because of its symmetry. The two illustrated resonance forms are equivalent, rendering benzene a nonpolar molecule.



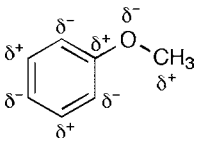
g. 

As will be discussed in Chapter 2, methyl groups are electron donating. This is not due to any defined positive charges on the carbon atom and is more the result of hyperconjugation. Hyperconjugation, in this case, relates to the ability of the carbon–hydrogen σ bonds of the methyl group to donate electrons into the conjugated system of benzene. While this effect will be discussed in more detail later, let us, for now, define methyl groups as possessing a formal partial negative charge. This resulting negative charge thus polarizes each double bond in the ring.

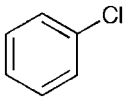


h. 

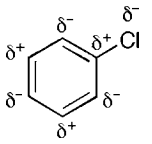
As with the previous example, groups possessing partial negative charge characteristics donate electrons into conjugated systems and polarize the double bonds. This effect is generally noted with heteroatoms such as oxygen. Also, while in the previous example a methyl group was argued to possess a partial negative charge, the partial positive charge illustrated here is due to the overriding partial negative characteristics of the oxygen atom.



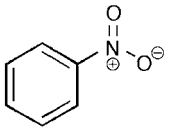
i.



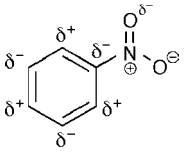
As with the previous example, heteroatoms such as chlorine possess partial negative charge characteristics and donate electrons into conjugated systems polarizing the double bonds.



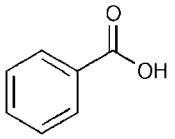
j.



As with groups possessing negative charge characteristics, when a positive charge is present on an atom connected to a conjugated system, the double bonds are polarized. This polarization is opposite of that observed for negatively charged groups.

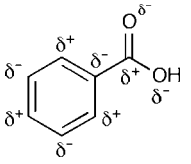


k.



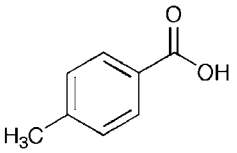
As with groups possessing negative charge characteristics, when a partial positive charge is present on an atom connected to a conjugated system, the

double bonds are polarized. This polarization is opposite that observed for negatively charged groups.

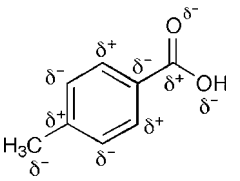


Please note for Problems 2l through 2r: When multiple groups are present on conjugated systems, their charged characteristics can work together or oppose each other depending on where they are placed relative to each other. The following problems address this point:

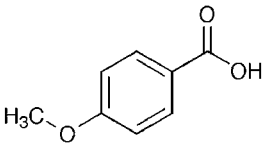
l.



In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *para* position. This is the same position where an electron-donating methyl group is placed. *Consider what impact the methyl group has on the acidity of the carboxylic acid.*

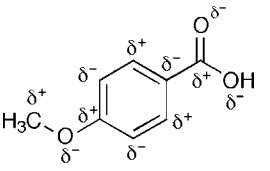


m.

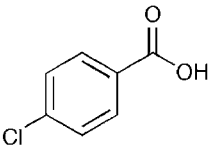


In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *para* position. This is the same position where an electron-donating methoxy group is placed. Also, while in a previous example a methyl group was argued to possess a partial negative charge, the partial positive charge illustrated here is due to the overriding partial negative characteristics of the

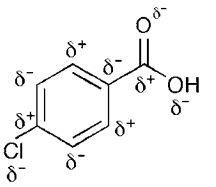
oxygen atom. *Consider what impact the methoxy group has on the acidity of the carboxylic acid.*



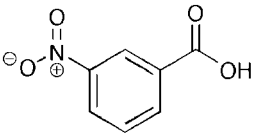
n.



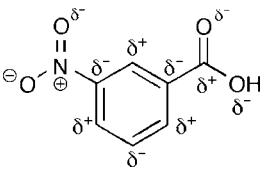
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *para* position. This is the same position where an electron-donating chloride is placed. *Consider what impact the chloro group has on the acidity of the carboxylic acid.*



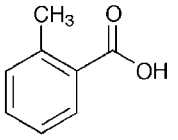
o.



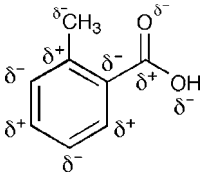
In this case, the carboxylic acid being electron withdrawing induces a partial negative charge at the *meta* position. This is the same position where an electron-withdrawing nitro group is placed. *Consider what impact the nitro group has on the acidity of the carboxylic acid.*



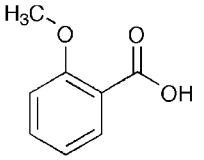
p.



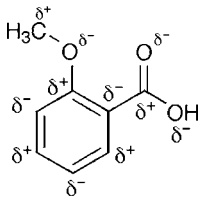
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *ortho* position. This is the same position where an electron-donating methyl group is placed. *Consider what impact the methyl group has on the acidity of the carboxylic acid.*

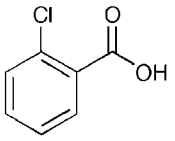


q.

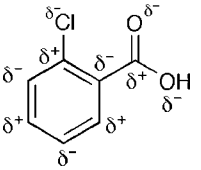


In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *ortho* position. This is the same position where an electron-donating methoxy group is placed. Also, while in a previous example a methyl group was argued to possess a partial negative charge, the partial positive charge illustrated here is due to the overriding partial negative characteristics of the oxygen atom. *Consider what impact the methoxy group has on the acidity of the carboxylic acid.*



r. 

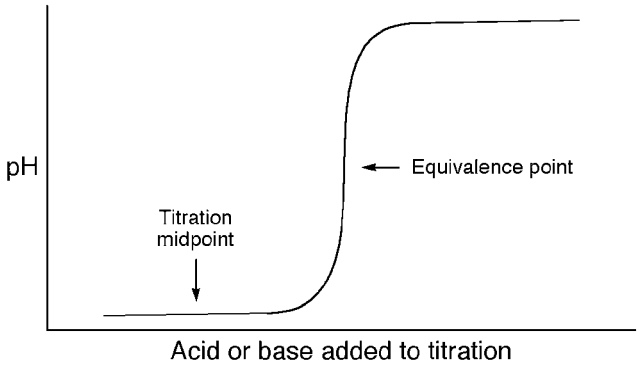
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *ortho* position. This is the same position where an electron-donating chloride is placed. *Consider what impact the chloro group has on the acidity of the carboxylic acid.*



CHAPTER 2 SOLUTIONS

1. *Explain how the Henderson–Hesselbach equation can be used, in conjunction with a titration curve, to determine a* pK_a.

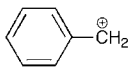
When the progression of an acid–base titration is graphed as a function of pH vs the volume of acid or base added, the curve will appear as shown below. If we recall, from general chemistry coursework, that the steepest point on the curve represents the equivalence point of the titration (the point where the amount of acid and base are equal), we can locate the point on the curve that represents the midpoint of the titration. This point is found at half the concentration of base added to acid (or acid added to base) to reach the equivalence point. Once we have done this, we recall the Henderson–Hesselbach equation (Fig. 2.8)—specifically, the term dealing with the concentrations of the ionic and the neutral species. Realizing that at the midpoint of the titration, these concentrations are equal, the logarithmic term in the Henderson–Hesselbach equation reduces to log(1), which is equal to zero. Therefore, the equation reduces to $pK_a = pH$ at the midpoint of the titration.



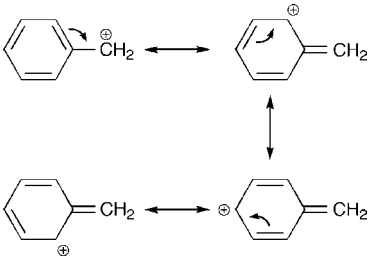
2. *What is the pH of a solution of acetic acid* ($pK_a = 4.75$) *that has been titrated with* $\frac{1}{4}$ *an equivalent of NaOH?*

When acetic acid is titrated with $\frac{1}{4}$ an equivalent of base, we realize that the term $\log\{[A^-]/[HA]\}$ becomes $\log\left(\frac{1}{3}\right)$ because one part out of four parts of acetic acid has been deprotonated. This leaves three parts acid to one part conjugate base. Filling in this value and that of the pK_a of acetic acid into the Henderson–Hesselbach equation (Fig. 2.8), solving for pH gives us a value of 4.27 as our answer.

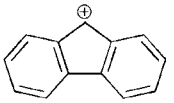
3. *Draw the resonance structures of the following charged molecules:*

a. 

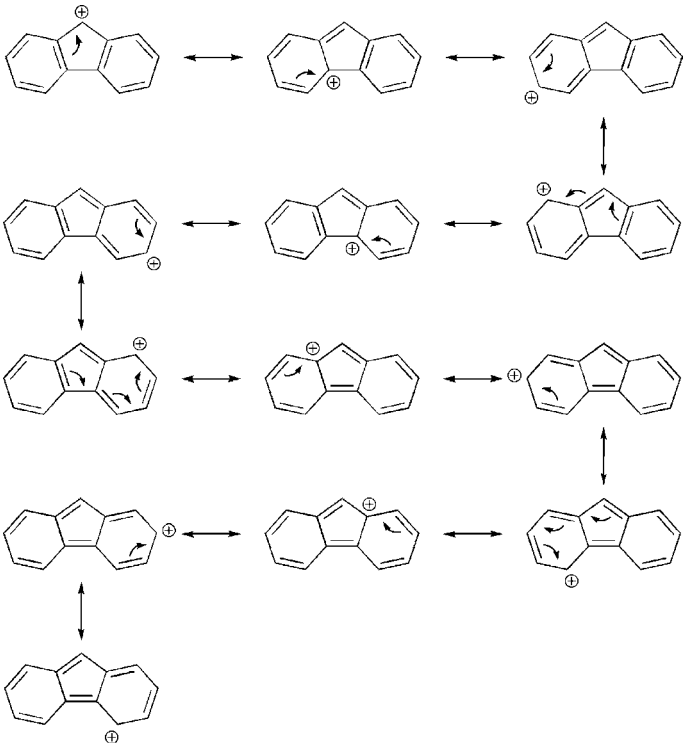
The following represent the resonance forms of the benzyl cation:



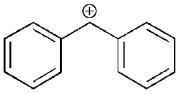
b.



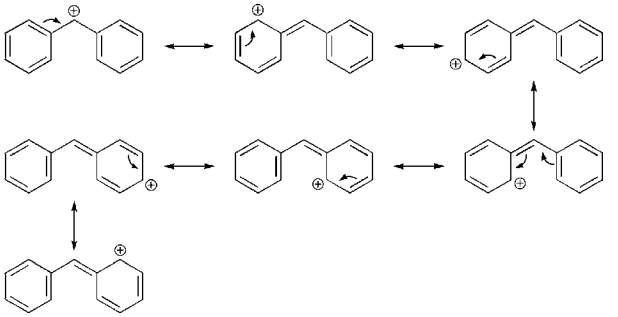
The following represent the resonance forms of the fluorenyl cation:



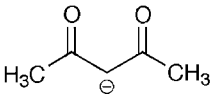
c.



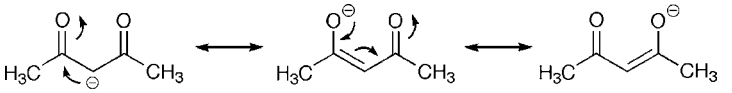
The following represent the resonance forms of the diphenylmethyl cation:



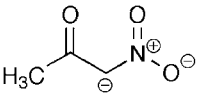
d.



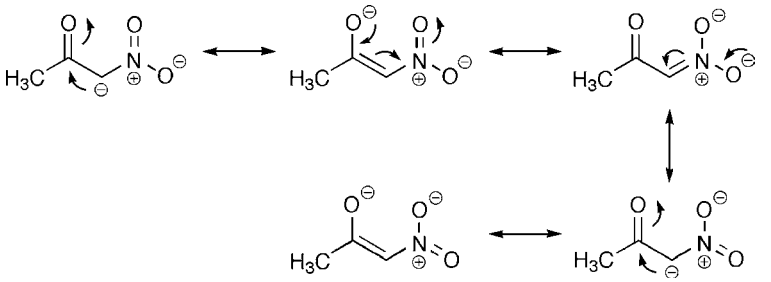
The following represent the resonance forms of the acetylacetone anion:



e.

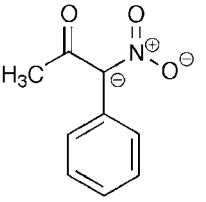


The following represent the resonance forms of the nitroacetone anion:

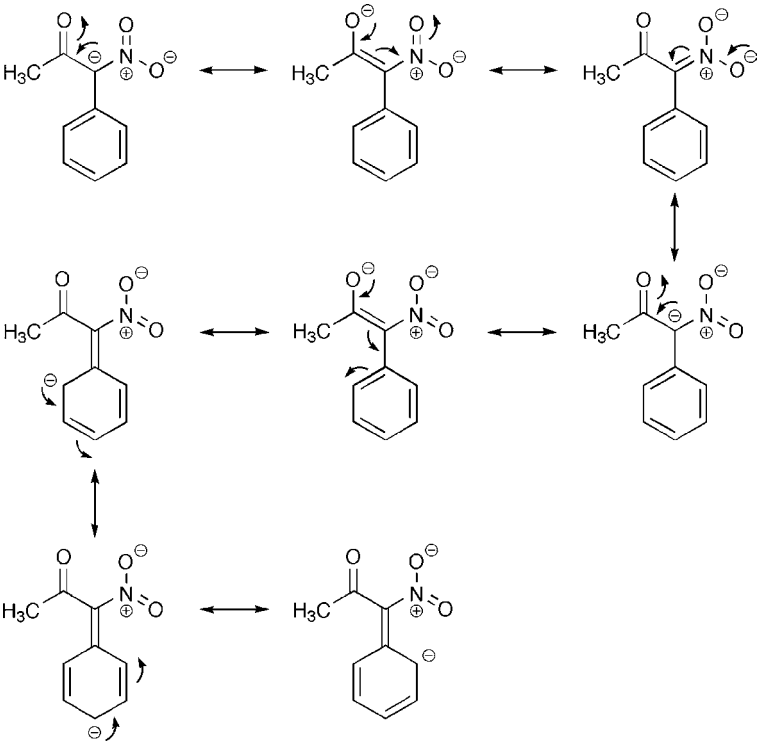


Please note that while nitro groups are so electron withdrawing that delocalization of their associated positive charge plays a minimal role in any family of resonance structures, this delocalization is technically possible. Try to identify additional resonance structures where the positive charge is delocalized.

f.



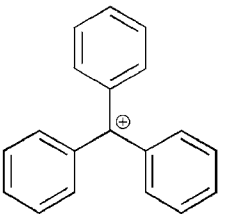
The following represent the resonance forms of the 3-nitroacetophenone anion:



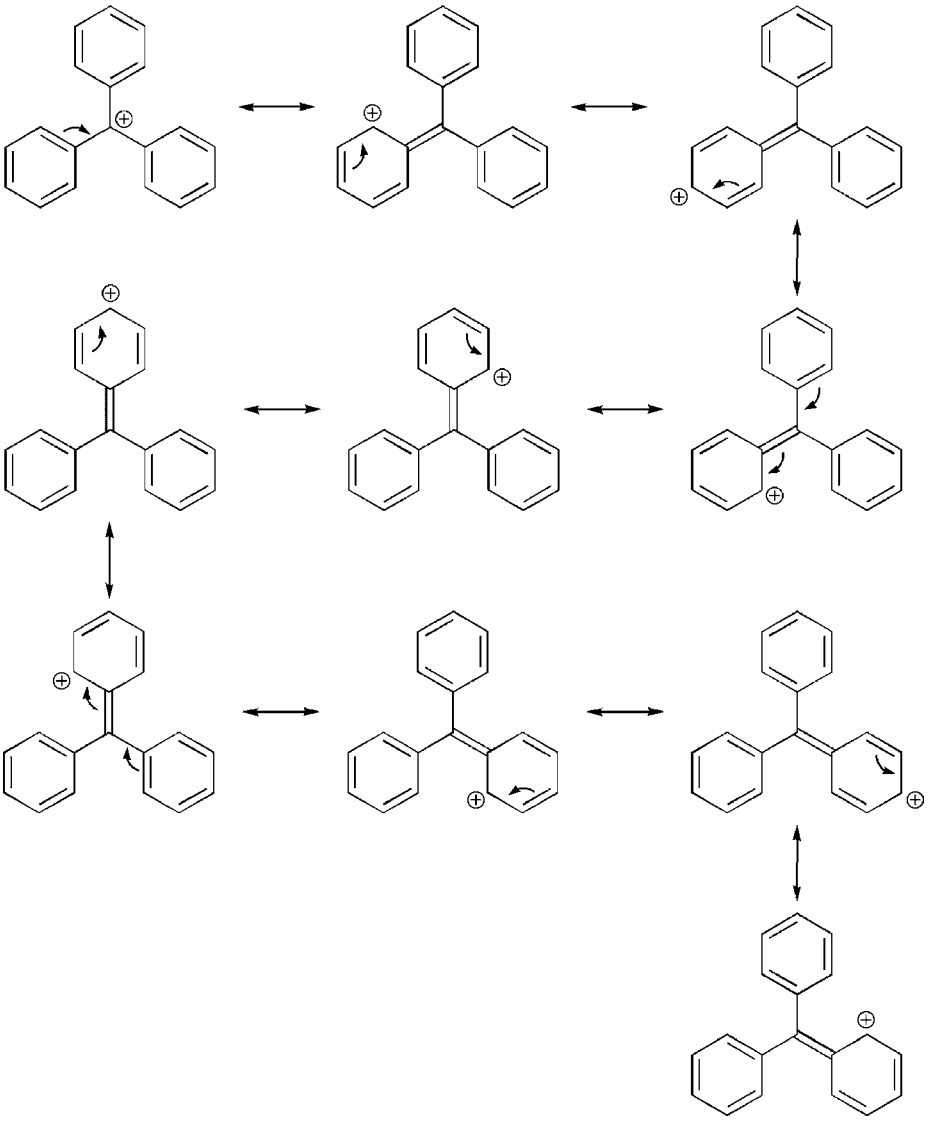
Please note that while nitro groups are so electron withdrawing that delocalization of their associated positive charge plays a minimal role in any family of resonance

structures, this delocalization is technically possible. Try to identify additional resonance structures where the positive charge is delocalized.

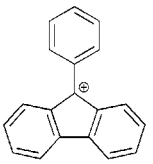
g.



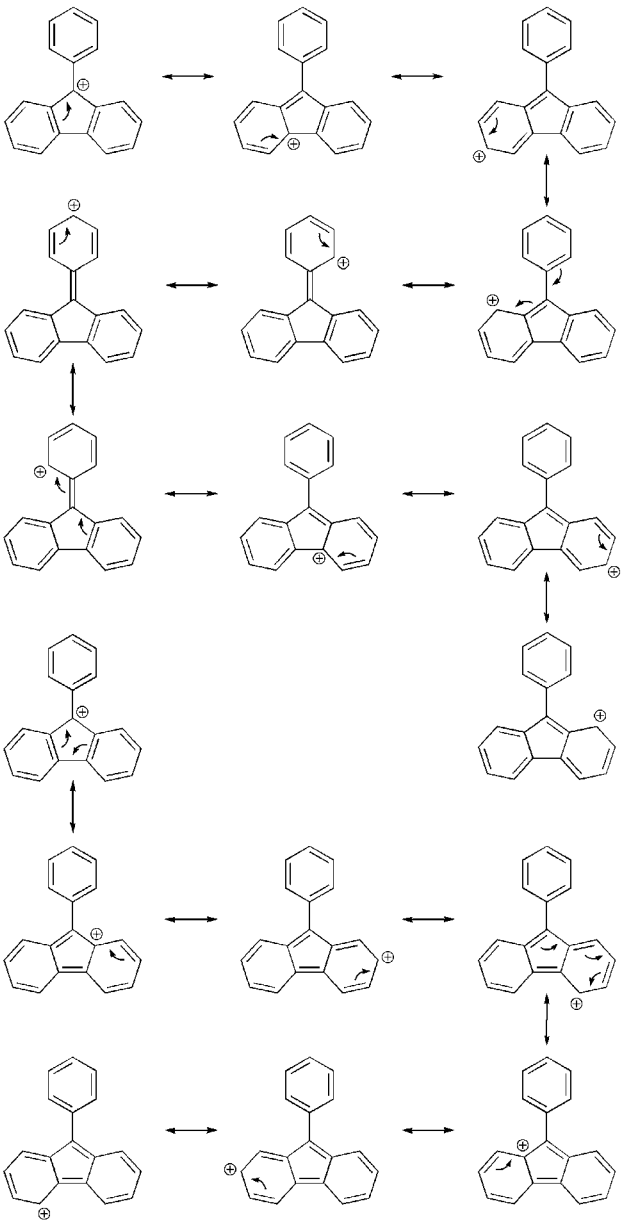
The following represent the resonance forms of the triphenylmethyl cation:



h.

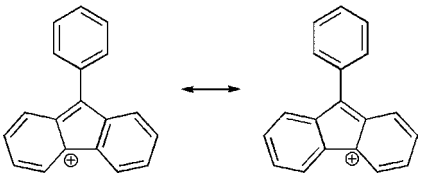


The following represent the resonance forms of the phenylfluorenyl cation:



4. *Which cation from Problem 3 is more stable,* (***g***) *or* (***h***)? *Explain using partial charges.*

Of the 16 resonance forms of the triphenylmethyl cation shown in the solution for Problem 3(**g**), no two resonance forms place the positive charge on adjacent atoms. However, when looking at the 16 resonance forms of the phenylfluorenyl cation shown in the solution for Problem 3(**h**), there are multiple pairs of resonance forms (one of which is shown below) where the positive charge may be placed on adjacent atoms. This is a disfavored electronic relationship and is destabilizing to the cation itself. Thus, through charge distribution and delocalization, because the phenylfluorenyl cation possesses partial positive charges on two adjacent atoms, the triphenylmethyl cation [Problem 3(**g**)] is more stable.

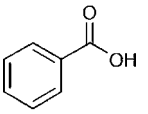


Note: There is another explanation relating to the definitions of aromatic and antiaromatic ring systems. See if you can explain the answer to this problem using these definitions.

5. *How will the following substituents affect the* pK_a *of benzoic acid* (*raise, lower, or no change*)? *Explain using partial charges to illustrate inductive effects. Remember,* o *refers to ortho positions,* m *refers to meta positions, and* p *refers to the para position.* ***In addressing these problems, assume that the acidity of the carboxylic acid is influenced solely by the partial charges induced by additional ring substituents.***

Note: It is important to realize that in addition to inductive effects, there are other factors that influence acidity and pK_a values. Therefore, while this problem asks for expectations regarding how ***inductive effects*** influence pK_a values, in actuality, the measured values may be different than anticipated.

The pK_a of benzoic acid is 4.19

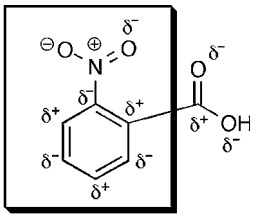


Benzoic Acid

a. o-NO_2

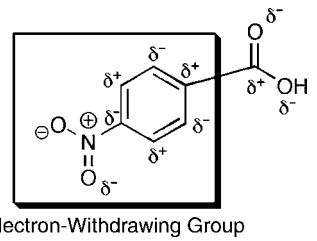
The structure of *o*-nitrobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *ortho* to the

carboxylic acid, electron density is reduced adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *ortho* to the nitro group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *o*-nitrobenzoic acid is 2.16, thus supporting the conclusion of this problem.



b. p-NO_2

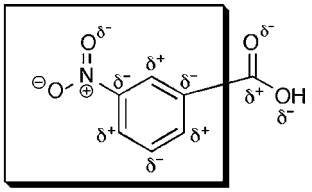
The structure of *p*-nitrobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *para* to the carboxylic acid, electron density is reduced adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *para* to the nitro group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *p*-nitrobenzoic acid is 3.41, thus supporting the conclusion of this problem.



c. m-NO_2

The structure of *m*-nitrobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *meta* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *meta* to the nitro group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *m*-nitrobenzoic acid is 3.47, reflecting the electron-withdrawing nature of the nitrophenyl group. While this value does not strictly support the conclusion of this problem, the trend, compared to Problems 5(a) and 5(b), indicates

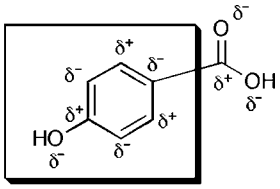
that the *m*-NO_2 has less of an effect on acidity than *o*-NO_2 and *p*-NO_2. In fact, NO_2 groups are so electron-withdrawing that they render the phenyl ring electron-withdrawing in its entirely.



Electron-Withdrawing Group
(Regardless of Partial Charges)

d. p-*OH*

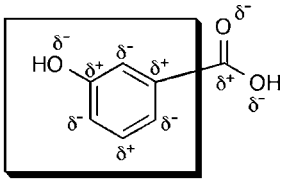
The structure of *p*-hydroxybenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating hydroxy group is located *ortho* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the hydroxyl group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-hydroxybenzoic acid is 4.48, thus supporting the conclusion of this problem.



Electron-Donating Group

e. m-*OH*

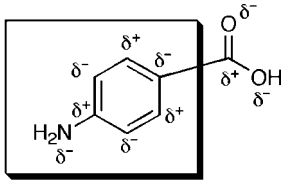
The structure of *m*-hydroxybenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating hydroxy group is located *meta* to the carboxylic acid, electron density is decreased adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the hydroxyl group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-hydroxybenzoic acid is 4.06, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

f. p-NH_2

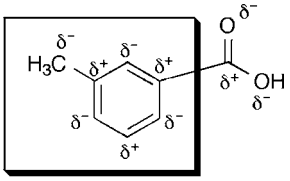
The structure of *p*-aminobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating amino group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the amino group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-aminobenzoic acid is 4.65, thus supporting the conclusion of this problem.



Electron-Donating Group

g. m-CH_3

The structure of *m*-methylbenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *meta* to the carboxylic acid, electron density is decreased adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the methyl group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-methylbenzoic acid is 4.27. In fact, because methyl groups are electron-donating, they render the phennyl ring weakly electron-donating in its entirety.

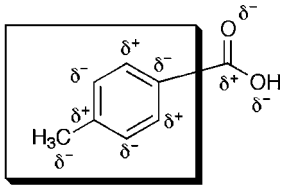


Electron-Donating Group
(Regardless of Partial Charges)

h. p-CH_3

The structure of *p*-methylbenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the methyl group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In

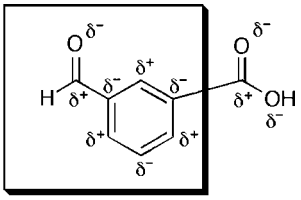
actuality, the pK_a of *p*-methylbenzoic acid is 4.36, thus supporting the conclusion of this problem.



Electron-Donating Group

i. m-*CHO*

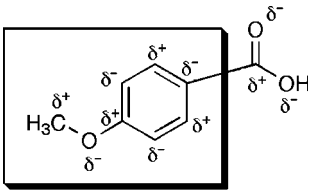
The structure of *m*-carboxybenzaldehyde is shown below with partial charges assigned to the ring system. Because the electron-withdrawing aldehyde group is located *meta* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *meta* to the carboxy (aldehyde) group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *m*-formylbenzoic acid is 3.85, reflecting the electron-withdrawing nature of the carboxyphenyl group. In fact, formyl groups (aldehydes) are so electron-withdrawing that they render the phenyl ring electron-withdrawing in its entirety.



Electron-Withdrawing Group
(Regardless of Partial Charges)

j. p-OCH_3

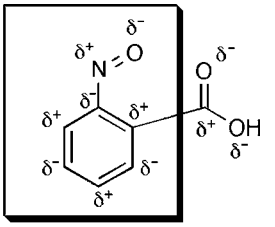
The structure of *p*-methoxybenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating methoxy group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the methoxy group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methoxybenzoic acid is 4.47, thus supporting the conclusion of this problem.



Electron-Donating Group

k. o-*NO*

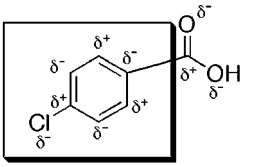
The structure of *o*-nitrosobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitroso group is located *ortho* to the carboxylic acid, electron density is reduced adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *ortho* to the nitroso group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *o*-nitrosobenzoic acid is <4, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

l. p-*Cl*

The structure of *p*-chlorobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the chloro group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-chlorobenzoic acid is 3.98, reflecting the electron-withdrawing nature of the chlorophenyl group.

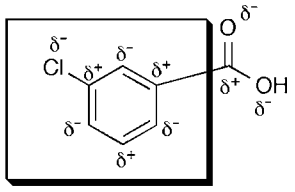


Electron-Withdrawing Group
(Regardless of Partial Charges)

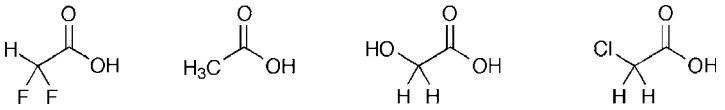
m. m-*Cl*

The structure of *m*-chlorobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *meta* to the carboxylic acid, electron density is decreased adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the chloro group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its

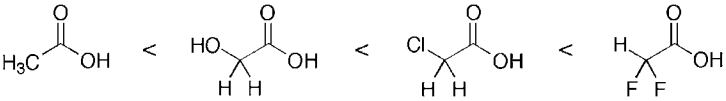
pK_a. In actuality, the pK_a of *m*-chlorobenzoic acid is 3.82, thus supporting the conclusion of this problem.



6. *Arrange the following groups of molecules in order of increasing acidity. Explain your results using partial charges and inductive effects.*



Initially, when considering inductive effects, we realize that F, O, and Cl all possess partial negative charges. Therefore, we realize that all of these atoms will pull electron density from the carboxylic acid, thus stabilizing the anion resulting from deprotonation and lowering the pK_a values compared to the baseline acetic acid. The question now focuses on how strong this effect is for each atom. The answer is found in the periodic table of the elements and relates to electronegativities. Of the three atoms in question, F is the most electronegative. Moving to the second row, Cl is more electronegative than O. Since the most acidic compound will have the most electronegative atoms associated with it, the order of increasing acidity is as follows:

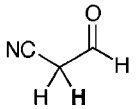


7. *Predict* pK_a *values for the protons shown in boldface in the following molecules. Rationalize your answers.*

When estimating the pK_a values for protons adjacent to multiple functional groups, the pK_a values can be calculated according to the following formula where n is defined as the number of relevant functional groups:

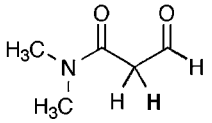
$$pK_a = \frac{\frac{pK_a^1}{n} + \frac{pK_a^2}{n} + \cdots + \frac{pK_a^n}{n}}{n}$$

a.



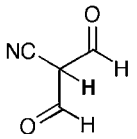
According to Appendix 1, the pK_a value for a proton adjacent to a nitrile is approximately 20–25, as is the pK_a value for a proton adjacent to an aldehyde. Recognizing that there are two relevant functional groups (an aldehyde and a nitrile), the above formula gives us a pK_a value of approximately 10–12.5.

b.



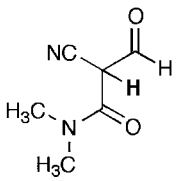
According to Appendix 1, the pK_a value for a proton adjacent to an amide is approximately 30–35, and the pK_a value for a proton adjacent to an aldehyde is approximately 20–25. Recognizing that there are two relevant functional groups (an aldehyde and an amide), the above formula gives us a pK_a value of approximately 12.5–15.

c.



According to Appendix 1, the pK_a value for a proton adjacent to a nitrile is approximately 20–25, as is the pK_a value for a proton adjacent to an aldehyde. Recognizing that there are three relevant functional groups (two aldehydes and a nitrile), the above formula gives us a pK_a value of approximately 6.7–8.3.

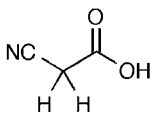
d.



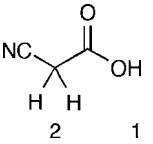
According to Appendix 1, the pK_a value for a proton adjacent to an amide is approximately 30–35, the pK_a value for a proton adjacent to an aldehyde is approximately 20–25 and the pK_a value for a proton adjacent to a nitrile is approximately 20–25. Recognizing that there are three relevant functional groups (a nitrile, an aldehyde, and an amide), the above formula gives us a pK_a value of approximately 7.8–9.4.

8. *Predict the order of deprotonation of the various protons in the following molecules. Back up your answers with appropriate* pK_a *values.*

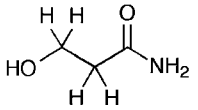
a.



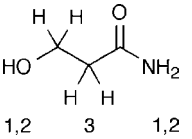
According to Appendix 1, the pK_a value for a carboxylic acid is approximately 4.75. Furthermore, if we imagine converting the carboxylic acid to an ester, we recognize that protons adjacent to esters have p*K*a values of approximately 25–30. Finally, the pK_a value for a proton adjacent to a nitrile is approximately 20–25. Using the formula described in Problem 7, we calculate a pK_a value of approximately 11.25–13.75 for the protons between the two functional groups. Therefore, the order of deprotonation is as follows:



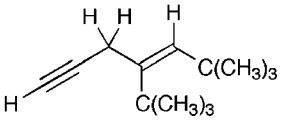
b.



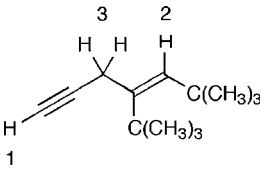
According to Appendix 1, the pK_a value for an amide is approximately 15–17, the pK_a of a primary alcohol is approximately 15–16, and the pK_a of a proton adjacent to an amide is approximately 30–35. Therefore, the order of deprotonation is as follows:



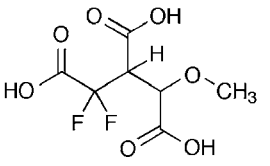
c.



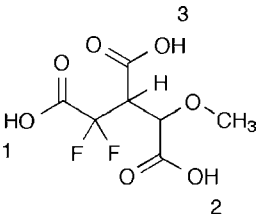
According to Appendix 1, the pK_a value for an acetylene is approximately 25, and the pK_a of a vinyl proton is approximately 35–40. While the acetylene and olefin lend delocalization effects to adjacent anions, the absence of heteroatoms incorporated in these functional groups minimizes this effect, and the pK_a at this position will resemble something between a vinyl pK_a and a hydrocarbon pK_a. Therefore, the order of deprotonation is as follows:



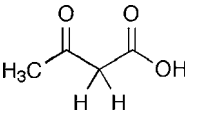
d.



This problem relies entirely on inductive effects. Realizing that fluorine is more electronegative than oxygen, the order of deprotonation is as follows:



9. *Which proton is the most acidic? Rationalize your answer.*



The pK_a value of a proton adjacent to a ketone carbonyl is approximately 20–25. The pK_a value of a carboxylic acid is approximately 4.75. Using the same calculations presented in the solution for Problem 8(a), the pK_a value of the protons between the ketone and the carboxylic acid is approximately 11.25–13.75. Since the acidity of a proton increases as its pK_a value decreases, the most acidic proton belongs to the carboxylic acid.

10. *Using the pK_a values given in Appendix 1, calculate the equilibrium constants for the following reactions:*

Recall from general chemistry that the equilibrium constant, K_{eq}, for a given reaction is defined as

$$A + B \rightleftharpoons C + D$$

$$K_{eq} = \frac{[C][D]}{[A][B]}$$

Also, recall that the definition of the acid dissociation constant, K_a, is

$$AH \rightleftharpoons A^- + H^+$$

$$K_a = \frac{[A^-][H^+]}{[AH]}$$

Finally, we recognize, as shown, that an acid–base equilibrium consists of two related reactions for which K_a values can be calculated and that at equilibrium, the $[H^+]$ is equivalent for each equation.

$$AH + B^- \rightleftharpoons A^- + BH$$

$$AH \rightleftharpoons A^- + H^+$$

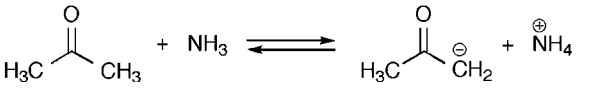
$$H^+ + B^- \rightleftharpoons BH$$

Therefore, with K_a^1 and K_a^2 defined, K_{eq} is derived as shown:

$$K_{eq} = \frac{K_a^1}{K_a^2} = \frac{\dfrac{[A^-][H^+]}{[AH]}}{\dfrac{[B^-][H^+]}{[BH]}} = \frac{[A^-][H^+][BH]}{[B^-][H^+][AH]} = \frac{[A^-][BH]}{[B^-][AH]}$$

and K_{eq} is simply the ratio of the two relevant K_a values.

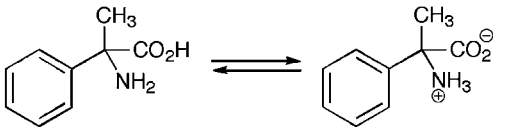
a.



From Appendix 1, we know that pK_a^1, the dissociation constant associated with protons adjacent to ketone carbonyls, is approximately 20–25. Furthermore, from Appendix 1, we know that pK_a^2, the dissociation constant associated with protonated amines, is approximately 10. Finally, remembering that $pK_a = -\log K_a$, the K_{eq} for this reaction ranges from

$$\frac{10^{-20}}{10^{-10}} \text{ to } \frac{10^{-25}}{10^{-10}} \quad \text{or} \quad 10^{-10} \text{ to } 10^{-15}$$

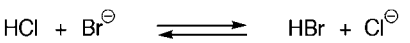
b.



From Appendix 1, we know that pK_a^1, the dissociation constant associated with carboxylic acid protons, is approximately 4.75. Furthermore, from Appendix 1, we know that pK_a^2, the dissociation constant associated with protonated amines, is approximately 10. Finally, remembering that $pK_a = -\log K_a$, the K_{eq} for this reaction is approximately

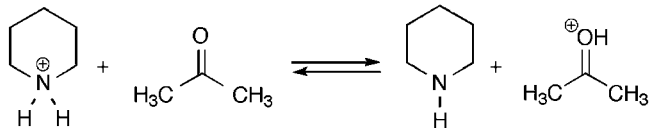
$$\frac{10^{-4.75}}{10^{-10}} \quad \text{or} \quad 10^{5.25}$$

c.



From Appendix 1, we know that pK_a^1, the dissociation constant associated with hydrochloric acid, is approximately -2.2. Furthermore, from Appendix 1, we know that pK_a^2 the dissociation constant associated with hydrobromic acid, is approximately -4.7. Finally, remembering that $pK_a = -\log K_a$, the K_{eq} for this reaction is approximately

$$\frac{10^{-2.2}}{10^{-4.7}} \quad \text{or} \quad 10^{-2.5}$$

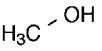
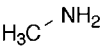
d. 

From Appendix 1, we know that pK_a^1, the dissociation constant associated with protonated amines, is approximately 10. Furthermore, from Appendix 1, we know that pK_a^2, the dissociation constant associated with protonated ketones, is approximately -7 to -9. Finally, remembering that $pK_a = -\log K_a$, the K_{eq} for this reaction ranges from

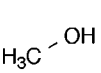
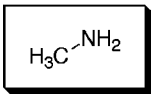
$$\frac{10^{-10}}{10^{7}} \text{ to } \frac{10^{-10}}{10^{9}} \quad \text{or} \quad 10^{-17} \text{ to } 10^{-19}$$

CHAPTER 3 SOLUTIONS

1. *In each case, circle the better nucleophile. Explain your answers.*

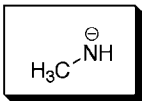
a.  

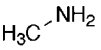
Oxygen is more electronegative than nitrogen. Therefore, the lone pair on nitrogen is not held as tightly as the lone pairs of oxygen. This greater availability of the nitrogen lone pair compared to the oxygen lone pairs makes the amine the better nucleophile.

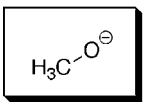
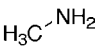
b.  

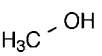
Oxygen is more electronegative than nitrogen. This difference in electronegativity is reflected in the greater acidity of alcohols compared to amines. As oxygen lone pairs are held more tightly than the nitrogen lone pair, negative charges on oxygen are more stable than negative charges in nitrogen. Thus, the nitrogen anion is more available to react, making it the better nucleophile.

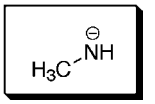
c.  

While in equivalent states, nitrogen functionalities are better nucleophiles than oxygen nucleophiles [see Problem 1(a) and 1(b)], when comparing different electronic states, the more reactive species will be the better nucleophile. Thus, the oxygen anion is the better nucleophile compared to an amine.

d.  

For all the reasons discussed under Problem 1(a), 1(b), and 1(c), the nitrogen anion is the better nucleophile.

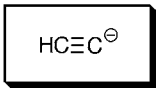


e. $Cl^{\ominus}$ $I^{\ominus}$

The answer to this question depends on the solvent used for reaction as illustrated in Figure 3.4. Also relevant is recognition that chloride anions are hard bases and iodide anion are soft bases. Iodide is the better nucleophile in polar protic solvents while chloride is the better nucleophile in polar aprotic solvents.

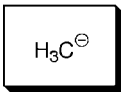
f. $N{\equiv}C^{\ominus}$ $HC{\equiv}C^{\ominus}$

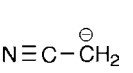
As shown in Appendix 1, the pK_a value for hydrocyanic acid is approximately 9.3, and the pK_a value for acetylene is approximately 25. Thus, the acetylene anion is more reactive than the cyanide anion and is therefore the better nucleophile.



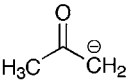
g. $H_3C^{\ominus}$ $N{\equiv}C-\overset{\ominus}{C}H_2$

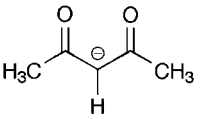
As shown in Appendix 1, the pK_a value for methane is approximately 50–75, and the pK_a value for acetonitrile is approximately 25. Thus, the methyl anion is more reactive than the acetonitrile anion and is therefore the better nucleophile.





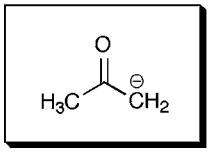
h.

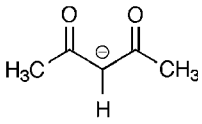




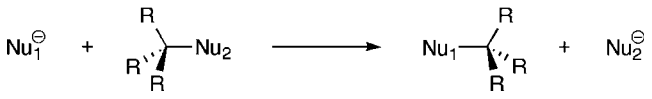
As shown in Appendix 1, the pK_a value for acetone is approximately 20. Furthermore, the pK_a value for acetylacetone is approximately 10 as estimated using the formula

presented in Chapter 2, Problem 7. Thus, the acetone anion is more reactive than the acetylacetone anion and is therefore the better nucleophile.





2. *Nucleophiles often participate in nucleophilic substitution reactions. The general form of these reactions may be represented by the following equation where Nu_1^- and Nu_2^- are nucleophiles*:



a. *Explain what type of relationship between, Nu_1^- and Nu_2^- is necessary in order for this reaction to be favored.*

In order for this reaction to proceed, Nu_1^- must be a better nucleophile than Nu_2^-.

b. *What does this say about the relative bacisities of Nu_1^- and Nu_2^-?*

In general the stronger nucleophile is also the stronger base. Therefore, Nu_1^- is more basic than Nu_2^-.

c. *Which nucleophile has the larger pK_a?*

Remembering that a strong base is derived from a weak conjugate acid, if we consider the conjugate acids of Nu_1^- and Nu_2^-, we expect that since Nu_1^- is more basic, its conjugate acid has the larger pK_a than the conjugate acid of Nu_2^-.

d. *What generalization can be concluded about the relationship between bases and nucleophiles?*

Since nucleophiles, by definition, are species attracted to positive charges and since, by definition, protons are positively charged, nucleophiles are bases. The extent of nucleophilicity associated with a given nucleophile largely depends on the degree of its basicity. Thus, in general terms, the more nucleophilic a given nucleophile, the more basic it is.

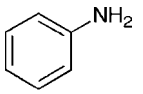
3. *How can pK_a values be used to describe basicity?*

By definition, pK_a values relate to the degree of acidity associated with a given acid. Referring to the Henderson–Hesselbach equation, as acidity increases, pK_a values decrease. Conversely, as acidity decreases, pK_a values increase. Referring to the definition of a base, we realize that as acidity increases, basicity decreases. Conversely, as acidity decreases, basicity increases. Recognizing that as acidity decreases, pK_a values increase, we recognize that as pK_a values increase, basicity increases. Therefore, the higher the pK_a value, the greater the basicity and the lower the pK_a value, the lower the basicity.

4. *As electron-donating and electron-withdrawing substituents will affect the acidity of organic molecules, so will they affect the basicity. How will the following substituents affect (raise, lower, or no change) the pK_a of aniline (aminobenzene)? Explain using partial charges to illustrate inductive effects. Remember,* o *refers to ortho positions,* m *refers to meta positions, and* p *refers to the para position.* ***In addressing these problems, assume that the acidity of the amine is influenced solely by the partial charges induced by additional ring substituents.***

Note: It is important to realize that, in addition to inductive effects, there are other factors that influence acidity and pK_a values. Therefore, while this problem asks for expectations regarding how **inductive effects** influence pK_a values, in actuality, the measured values may be different than anticipated.

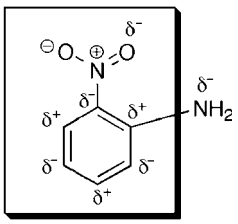
The pK_a of aniline is 4.63



aniline

a. o-NO_2

The structure of *o*-nitroaniline is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *ortho* to the amine, electron density is reduced adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *ortho* to the nitro group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *o*-nitroaniline is -0.26, thus supporting the conclusion of this problem.

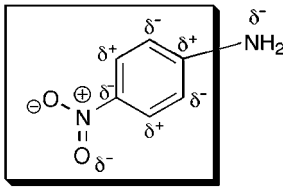


Electron-Withdrawing Group

b. p-NO_2

The structure of *p*-nitroaniline is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *para* to the amine, electron density is reduced adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *para* to the nitro group. An electron-withdrawing group attached to an amine stabilizes the anion resulting

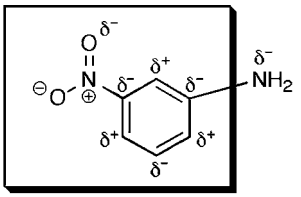
from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *p*-nitroaniline is 1.0, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

c. m-NO_2

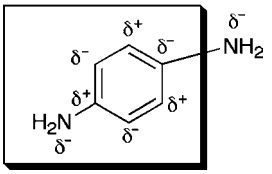
The structure of *m*-nitroaniline is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *meta* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *meta* to the nitro group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *m*-nitroaniline is 2.47, thus supporting the conclusion of this problem reflecting the electron-withdrawing nature of the nitrophenyl group. While this value does not strictly support the conclusion of this problem, the trend, compared to Problems 4(a) and 4(b), indicates that the *m*-NO_2 has less of an effect on acidity than *o*-NO_2 and *p*-NO_2. In fact, NO_2 groups are so electron-withdrawing that they render the phenyl ring electron-withdrawing in its entirety.



Electron-Withdrawing Group
(Regardless of Partial Charges)

d. p-NH_2

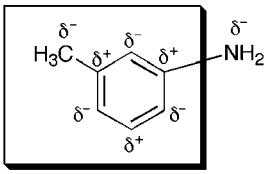
The structure of *p*-aminoaniline is shown below with partial charges assigned to the ring system. Because the electron-donating amino group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the amino group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-phenylenediamine is 6.2, thus supporting the conclusion of this problem.



Electron-Donating Group

e. m-CH_3

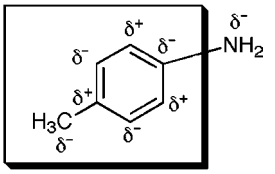
The structure of *m*-methylaniline is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *meta* to the amine, electron density is decreased adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the methyl group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-methylaniline is 4.73. In fact, because methyl groups are electron-donating, they render the phenyl ring weakly electron-donating in its entirety.



Electron-Donating Group
(Regardless of Partial Charges)

f. p-CH_3

The structure of *p*-methylaniline is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the methyl group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methylaniline is 5.08, thus supporting the conclusion of this problem.

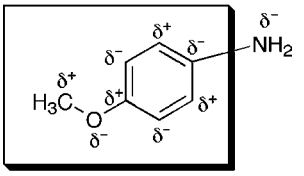


Electron-Donating Group

g. p-OCH_3

The structure of *p*-methoxyaniline is shown below with partial charges assigned to the ring system. Because the electron-donating methoxy group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the methoxy group. An electron-donating group attached to an amine destabilizes the anion resulting

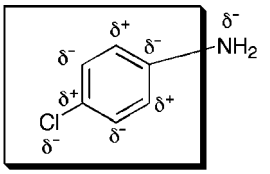
from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methoxyaniline is 5.34, thus supporting the conclusion of this problem.



Electron-Donating Group

h. p-*Cl*

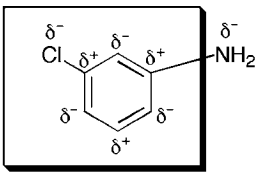
The structure of *p*-chloroaniline is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the chloro group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-chloroaniline is 4.15, reflecting the electron-withdrawing nature of the chlorophenyl group.



Electron-Withdrawing Group
(Regardless of Partial Charges)

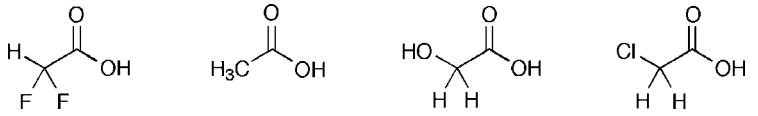
i. m-*Cl*

The structure of *m*-chloroaniline is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *meta* to the amine, electron density is decreased adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the chloro group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-chloroaniline is 3.46, thus supporting the conclusion of this problem.

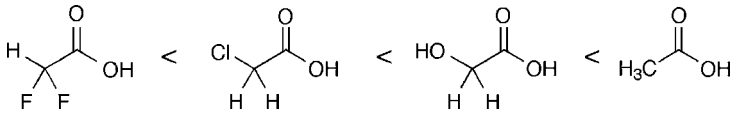


Electron-Withdrawing Group

5. *Arrange the following groups of molecules in order of increasing basicity. Explain your results using partial charges and inductive effects.*



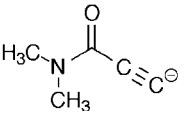
Initially, when considering inductive effects, we realize that F, O, and Cl all possess partial negative charges. Therefore, we realize that all of these atoms will pull electron density from the carboxylic acid, thus stabilizing the anion resulting from deprotonation and lowering the pK_a values compared to the baseline acetic acid. The question now focuses on how strong this effect is for each atom. The answer is found in the periodic table of the elements and relates to electronegativities. Of the three atoms in question, F is the most electronegative. Moving to the second row, Cl is more electronegative than O. Since the most basic compound will have the least electronegative atoms associated with it, the order of increasing basicity is as follows:



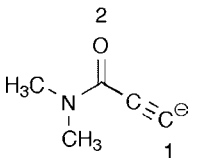
Note that this is the opposite sequence as that presented in Chapter 2, Problem 6.

6. *Predict the order of protonation of the basic sites on the following molecules. Support your answers with pK_a values.*

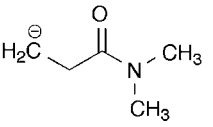
In addressing this problem, it is important to recognize that the order of protonation depends upon the basicity associated with the respective functional groups. As discussed above, basicity can be relayed back to the pK_a values associated with the conjugate acids of the respective sites of protonation. Thus conjugate acids with the higher pK_a values will be protonated first while conjugate acids with lower pK_a values will be protonated last.

a. 

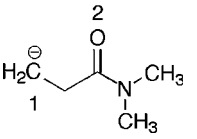
According to Appendix 1, the pK_a value for an acetylene proton is approximately 25, and the pK_a value for a carbonyl-protonated amide is approximately 0. Therefore, the order of protonation is as follows:



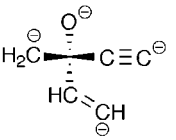
b.



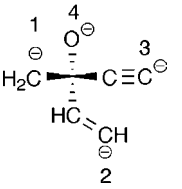
According to Appendix 1, the pK_a value for an alkane proton is approximately 50–75, and the pK_a value for a carbonyl-protonated amide is approximately 0. Therefore, the order of protonation is as follows:



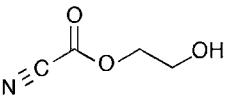
c.



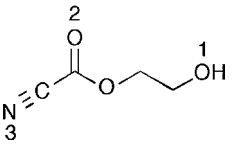
According to Appendix 1, the pK_a value for an alkane proton is approximately 50–75, the pK_a value for a vinyl proton is approximately 35–40, the pK_a value for an acetylene proton is approximately 25, and the pK_a value for an alcohol is approximately 15–19. Therefore, the order of protonation is as follows:



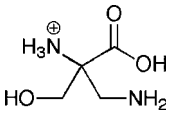
d.



According to Appendix 1, the pK_a value for a protonated nitrile is approximately -10, the pK_a value for a carbonyl-protonated ester is approximately -6, and the pK_a value for a protonated alcohol is approximately -2. Therefore, the order of protonation is as follows:

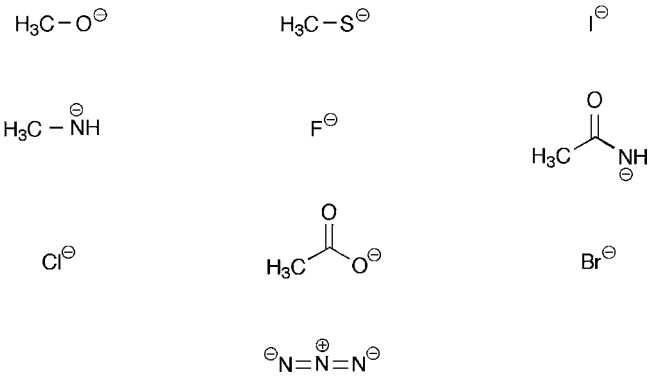


7. *Which proton is the least acidic? Explain your answer.*

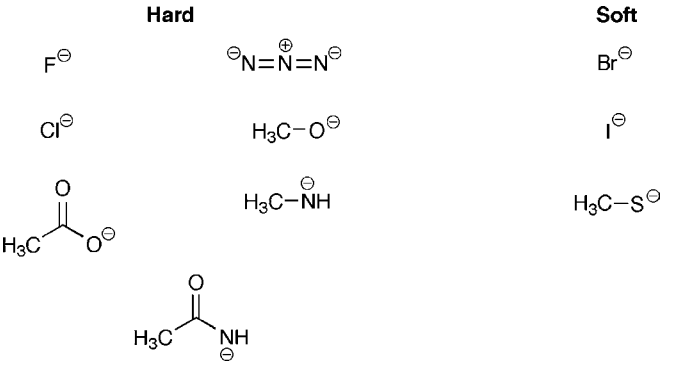


The pK_a value associated with carboxylic acid is approximately 4.75. The pK_a value of a primary alcohol is approximately 16. The pK_a value of an amine is approximately 35. The pK_a value of a protonated amine is approximately 10. Since the highest pK_a value belongs to the amine, protons associated with the amine functionality are the least acidic.

8. *Separate the following group of bases into a group of hard bases and a group of soft bases. Rationalize your answers based on electronegativity and polarizability.*



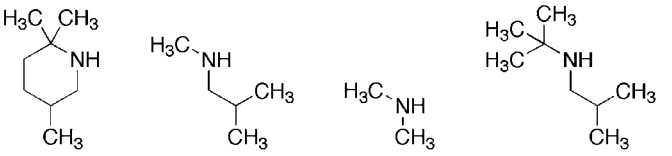
As a general rule, the basic atoms associated with soft bases have lower electronegativities and are more polarizable. Likewise, the basic atoms associated with hard bases have higher electronegativities and are less polarizable. Therefore, using the periodic table of the elements, the group of bases listed above can be separated as illustrated.



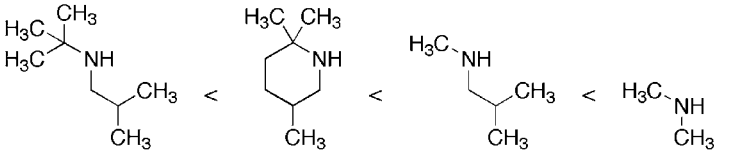
9. *Arrange the following structures in order of increasing nucleophilicity:*

When a nucleophilic atom is surrounded by additional substituents, the degree of nucleophilicity is altered. This observation is explained because nucleophilicity depends, in part, on the ability of a given nucleophile to react with electrophiles. If the nucleophilic atom cannot approach the electrophile because of steric congestion surrounding the nucleophilic atom, then the nucleophile is rendered less effective as a nucleophile and more effective as a base.

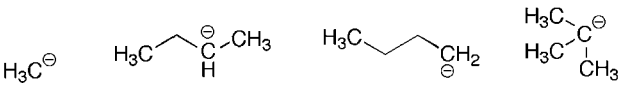
a.



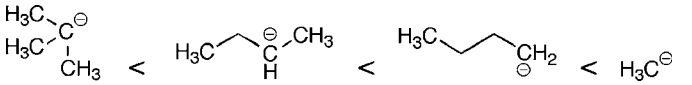
Based on the above argument, the order of increasing nucleophilicity for this group of amines is shown below. Regarding the first two amines, the piperidine is more nucleophilic because, unlike *tert*-butyl isobutylamine, the alkyl groups are tied back into a ring and not able to move. This allows the nitrogen to more readily present its lone pair.



b.



Based on the above argument, the order of increasing nucleophilicity for this group of alkyl anions is shown below.



10. *For the following pairs of structures, circle the better leaving group.*

a. $Cl^{\ominus}$ $I^{\ominus}$

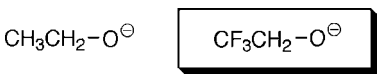
Compared to the chloride ion, the iodide ion is less electronegative and more polarizable. This polarizability stabilizes the anion as is reflected in the pK_a value for hydroiodic acid (-10) compared to the pK_a value for hydrochloric acid (-2.2). Therefore, iodide is the better leaving group.

b. 

Compared to nitrogen, oxygen is more electronegative and thus holds onto its electrons more tightly. This stabilization of the oxygen anion compared to the amine anion is reflected in the pK_a values for alcohols (15–19) compared to the pK_a value for amines (35). Therefore, the alkoxide is the better leaving group.

c. 

When comparing leaving groups where the departing atoms are the same, inductive effects must be considered. Since fluorine is more electronegative than hydrogen, the presence of three fluorides pulls electron density from the alkoxide ion, thus stabilizing the anion. This is reflected in the pK_a values for trifluoroethanol (11–12) compared to the pK_a values for ethanol (15–16). Therefore, trifluoroethoxide is the better leaving group.



d. 

Compared to oxygen, sulfur is less electronegative and more polarizable. This increase in polarizability stabilizes the anion, as is reflected in the pK_a value for methanethiol (10.4) compared to the pK_a values for methanol (15–16). Therefore, the methylsulfide anion is the better leaving group.

e. $F^{\ominus}$ $Br^{\ominus}$

Compared to the fluoride ion, the bromide ion is less electronegative and more polarizable. This polarizability stabilizes the anion, as is reflected in the pK_a value for hydrobromic acid (-4.7) compared to the pK_a value for hydrofluoric acid (3.18). Therefore, bromide is the better leaving group.

$F^{\ominus}$ **$Br^{\ominus}$**

f. $H_3C-\overset{\ominus}{N}H$ $H_3C-S^{\ominus}$

Like oxygen, sulfur is more electronegative than nitrogen. Additionally, sulfur is more polarizable. These differences stabilize the sulfur anion as reflected in the pK_a value for methyl sulfide (10.4) compare to the pK_a value for amines (35). Therefore, the methylsulfide anion is the better leaving group.

$H_3C-\overset{\ominus}{N}H$ **$H_3C-S^{\ominus}$**

g. $Br^{\ominus}$ $H_3C-O^{\ominus}$

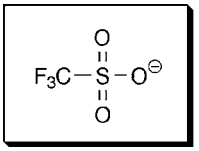
Bromine is more electronegative and more polarizable than oxygen. This translates to increased stability of the bromide anion compared to the oxygen anion. This stabilization is reflected in the pK_a value for hydrobromic acid (-4.7) compared to the pK_a values for methanol (15–16). Therefore, bromide is the better leaving group.

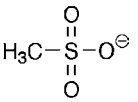
$Br^{\ominus}$ $H_3C-O^{\ominus}$

h. $F_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O^{\ominus}$ $H_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O^{\ominus}$

When comparing leaving groups where the departing atoms are the same, inductive effects must be considered. Since fluorine is more electronegative than hydrogen, the

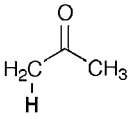
presence of three fluorides pulls electron density from the sulfonate ion, thus stabilizing the anion. This is the same effect noted under Problem 10(c). Therefore, trifluoromethane sulfonate is the better leaving group.





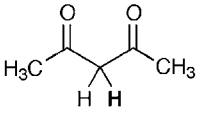
CHAPTER 4 SOLUTIONS

1. *In many S_N2 reactions, the nucleophile is generated by deprotonation of an organic acid. For each molecule, chose the base best suited to completely remove the labeled proton. (Consider pK_a values and recognize that, in some cases, dianions should be considered.) Explain your answers.*

a. 

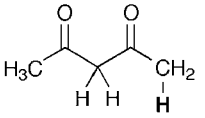
$NaOCH_3$: $(CH_3)_2NLi$: CH_3Li

The pK_a of the highlighted proton is approximately 20. Therefore, $NaOCH_3$ (pK_a of conjugate acid methanol = 16) is not a strong enough base. CH_3Li (pK_a of conjugate acid methane = 50) will deprotonate this molecule; however, it is too nucleophilic a base and will predominantly add to the carbonyl to produce a tertiary alcohol (see Chapter 7). $(CH_3)_2NLi$ (pK_a of conjugate acid dimethylamine = 35) is a bulkier base than CH_3Li and is, therefore, less nucleophilic and the best base for this case.

b. 

$NaOCH_3$: $(CH_3)_2NLi$: CH_3Li

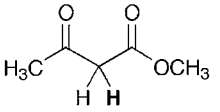
The pK_a of the highlighted proton is approximately 12. As described in the answer for Problem 1(a), CH_3Li (pK_a of conjugate acid methane = 50) will deprotonate this molecule; however, it is too nucleophilic a base and will predominantly add to the carbonyls to produce tertiary alcohols (see Chapter 7). While $(CH_3)_2NLi$ (pK_a of conjugate acid dimethylamine = 35) is a bulkier base than CH_3Li and is, therefore, less nucleophilic, it is also more basic than required for removal of the specified proton. $NaOCH_3$ (pK_a of conjugate acid methanol = 16), on the other hand, is a milder base and, based on pK_a values, is adequate to fully deprotonate the illustrated compound.

c. 

$NaOCH_3$: $(CH_3)_2NLi$: CH_3Li

In this case, the most acidic proton is not the proton of interest. Therefore, it is important to remember that once the most acidic proton is removed, the resulting enolate

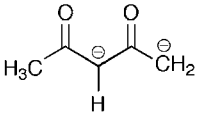
anion renders the proton of interest even less acidic because the enolate anion is less able to stabilize the second anion. Thus, removal of the desired proton will require a comparatively stronger base. Additionally, it is important to understand (as will be explained in Chapter 7), that a negative charge next to a carbonyl makes the carbonyl much less susceptible to nucleophilic attack. Therefore, once the most acidic proton is removed with $NaOCH_3$, removal of the desired proton can subsequently be achieved using CH_3Li.

d. 

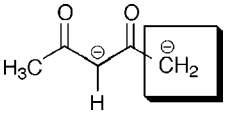
$NaOH : NaOCH_3 : NaOCH_2CH_3$

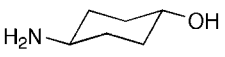
In this problem, three bases are presented that all possess comparable pK_a values and are all basic enough to remove the desired proton. In this case, however, the problem is not to recognize which base will remove the desired proton, but to understand the reactivity of the target molecule in the presence of the various bases. The specific functionality of concern is the methyl ester. While the chemistry of ester groups is discussed in the next chapter, using the principles of arrow pushing, the answer to this problem can be derived from information already presented. Specifically, if any one of these bases is used, addition to the ester, followed by subsequent elimination of the CH_3O^- group follows. This addition–elimination sequence produces a carboxylic acid, an ethyl ester, or a methyl ester. Since the starting molecule possesses a methyl ester, and since there is no instruction to change the nature of the ester, $NaOCH_3$ is the best base for this job.

2. *In predicting the course of S_N2 reactions, it is important to recognize groups most likely to act as nucleophiles. For each molecule, label the most nucleophilic site.*

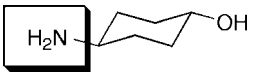
a. 

Considering the pK_a values of the respective conjugate acids, protons between two carbonyl groups have pK_a values around 12 while protons adjacent to only one carbonyl have pK_a values around 20. Therefore, the most nucleophilic site is

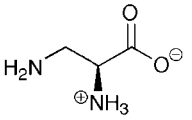


b. 

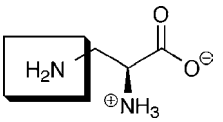
Oxygen is more electronegative than nitrogen. As such, oxygen holds its lone pairs of electrons more tightly than does nitrogen. Therefore, the most nucleophilic site is



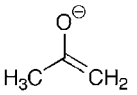
c.



Ammonium ions, having no available electron pairs, are not nucleophilic. Carboxylate anions are nucleophilic, but the anions are stabilized through delocalization of the negative charge, thus decreasing their nucleophilicity. As mentioned in Problem 2(b), nitrogen is less electronegative than oxygen. As the only oxygen atoms in this compound are associated with a stable carboxylate anion, the most nucleophilic site is

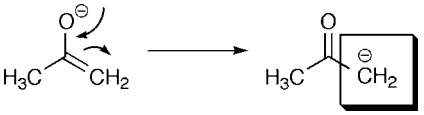


d.



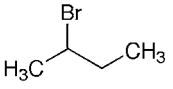
(Hint: Consider resonance.)

This structure represents an acyl anion with the negative charge delocalized to the oxygen. Since the carbon and the oxygen both possess partial negative charge characteristics, the degree of nucleophilicity depends upon the relative electronegativities of carbon versus oxygen. Since oxygen is more electronegative than carbon, the most nucleophilic site is

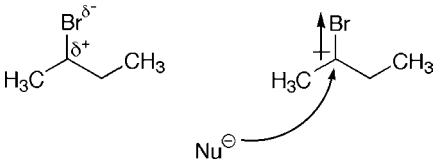


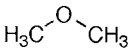
3. *For each molecule, show the partial charges, bond polarity, and where a nucleophile is most likely to react.*

a.

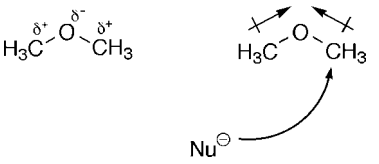


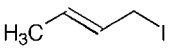
The polarity and partial charges of 2-bromobutane are dictated by the electronegativity of bromine versus the electronegativity of carbon. Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at the carbon bearing the bromine atom.



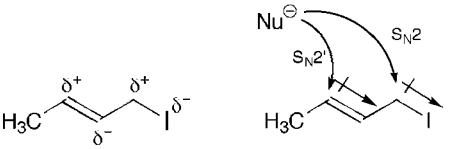
b. 

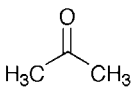
The polarity and partial charges of dimethyl ether are dictated by the electronegativity of oxygen versus the electronegativity of carbon. Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at either of the carbon atoms.



c. 

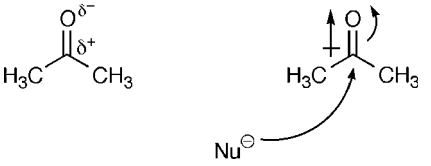
The polarity and partial charges of 1-iodo-2-butene are dictated by the electronegativity of oxygen versus the electronegativity of carbon. Additionally, delocalization through the double bond extends the chain of partial charges. Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at either of the specified carbon atoms via an S_N2 or an S_N2' mechanism.



d. 

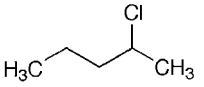
The polarity and partial charges of acetone are dictated by the electronegativity of oxygen versus the electronegativity of carbon as associated with a carbonyl.

Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at the carbonyl carbon as will be discussed in Chapter 7.

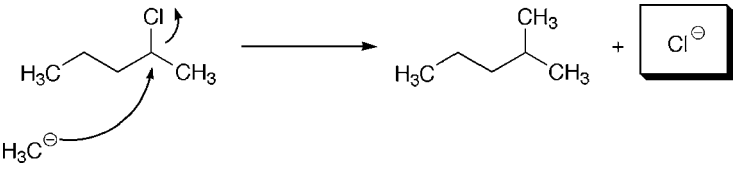


4. *For each molecule, identify the leaving group assuming that H_3C^- is the nucleophile.*

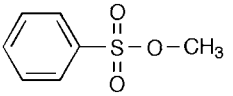
a.



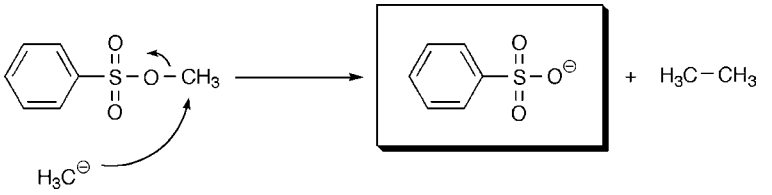
Applying partial charges based on the discussions presented in this chapter, the chlorine atom is recognized as the most electronegative. Therefore, as shown below, the chloride anion is the leaving group.



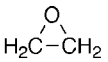
b.



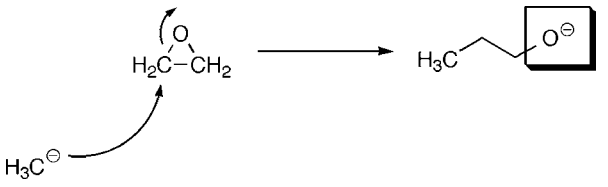
Applying partial charges based on the discussions presented in this chapter, the oxygen is recognized as more electronegative than carbon. Furthermore, an oxygen anion, derived from cleavage of a carbon–oxygen bond, is delocalized into the sulfur–oxygen double bonds and increasing its stability. Therefore, as shown below, the phenylsulfonate anion is the leaving group.



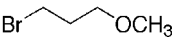
c.



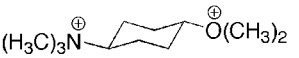
Applying partial charges based on the discussions presented in this chapter, the oxygen is recognized as more electronegative than carbon. Therefore, as shown below, the oxygen anion is the leaving group. Please note that in the case of an epoxide, the leaving group is attached to the reaction product.



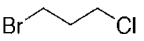
5. *For each molecule, label the most likely leaving group. Explain your answers.*

a. 

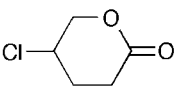
Bromine is more electronegative than oxygen. Furthermore, a bromide ion is a softer base than a methoxide ion. Because bromine can stabilize a negative charge better than oxygen, Br^- is the better leaving group.

b. 

Oxygen is more electrophilic than nitrogen. Therefore, $(CH_3)_2O$ is the better leaving group.

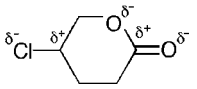
c. 

Bromide ions are softer bases than chloride ions. Therefore, bromine is more polarizable than chlorine, making Br^- the better leaving group.

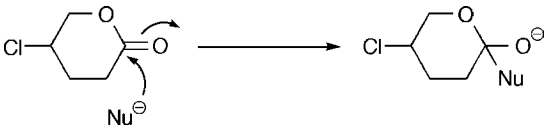
d. 

The answer to this question depends on information presented in Chapter 7. However, through an understanding of the nature of various nucleophiles coupled with application of arrow-pushing techniques, the answer can be derived from information presented thus far.

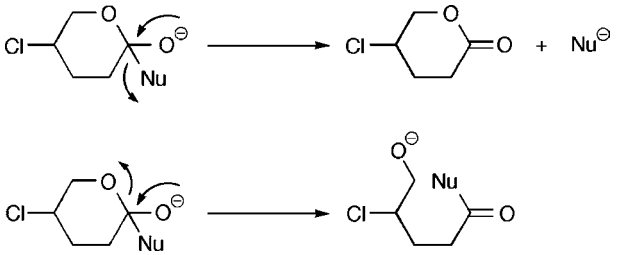
First, analyzing this structure for partial charges, we recognize the charge distribution as represented below.



Recognizing that nucleophiles can react at two different sites, an initial thought might be direct displacement of the chloride anion in an S_N2 manner. However, as alluded to in Problem 3(d), nucleophiles can add to carbonyl groups as shown below.



Once a nucleophile reacts with an ester carbonyl as shown above, the next phase of reaction depends on whether the better leaving group is an oxygen anion or the nucleophile itself. This is illustrated below through the ability of the newly formed oxygen anion to displace either the nucleophile or a second oxygen anion.

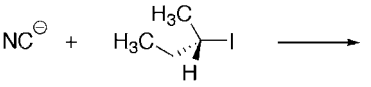


As shown above, if the better leaving group is the nucleophile, the result is regeneration of the starting material and the realization that displacement of Cl^- through an S_N2 mechanism is the most likely course of this reaction. However, if the better leaving group is the oxygen anion, then displacement of Cl^- generally will be a secondary reaction depending upon how much nucleophile is added to this system.

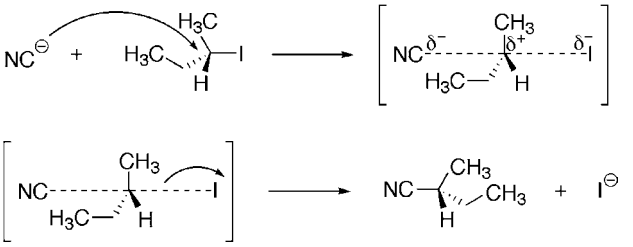
In summary, the purpose of this problem is not to solicit identification of a leaving group, but rather to induce consideration of the different reaction processes that can occur. Through such an understanding, starting materials and reaction conditions can be chosen that maximize the chances of generating a desired product with minimal side reactions.

6. *Detailed discussions focused on stereochemistry are not within the scope of this book. However, considering the products of typical S_N2 reactions, in addition to the transition state shown in Scheme 4.2, one may deduce the stereochemical course of*

this type of reaction. Predict the product of the following reaction and show the correct stereochemistry:



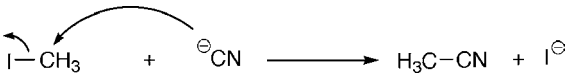
As shown below, initial reaction of a cyanide anion results in formation of the transition state shown in brackets. Release of the iodide anion results in complete inversion of the stereochemistry generating the illustrated final product.

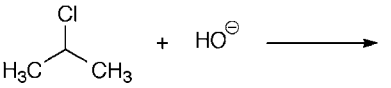


7. *Predict the products of the following reactions by pushing arrows*:

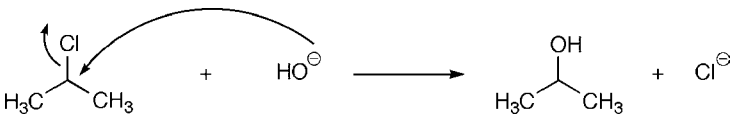
a. 

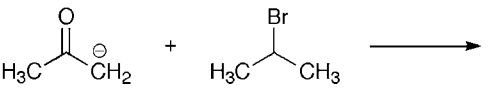
This is a direct S_N2 displacement of an iodide anion by a cyanide anion.



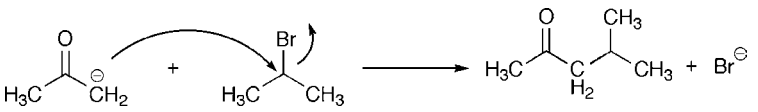
b. 

This is a direct S_N2 displacement of a chloride anion by a hydroxide anion.

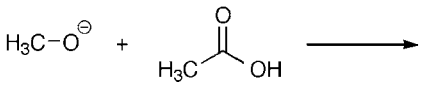


c. 

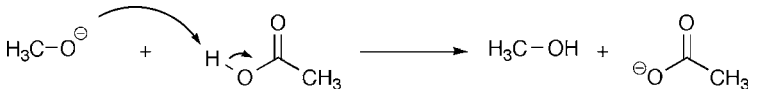
This is a direct S_N2 displacement of a bromide anion by an acyl anion.



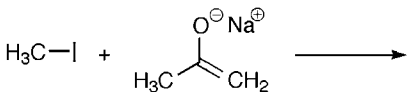
d.



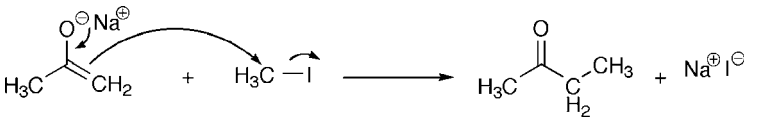
This is an acid–base proton exchange between a methoxide anion (pK_a of methanol is approximately 15) and acetic acid ($pK_a = 4.75$).



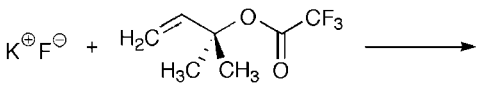
e.



This is a direct S_N2 displacement of an iodide anion by an acyl anion. Please note that the negative charge of the acyl anion is delocalized into the carbonyl and that the negative charge is paired with a cation.

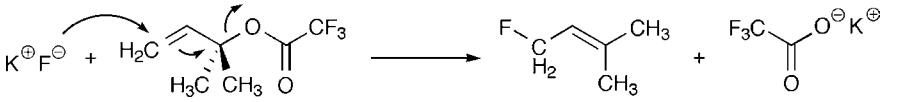


f.

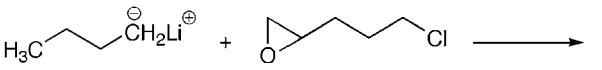


This is an S_N2' displacement of a trifluoroacetoxy anion by a fluoride anion. The related S_N2 mechanism is not favored because of steric factors. Specifically, the trifluoroacetate resides at a tertiary center. Please note that the fluoride anion is

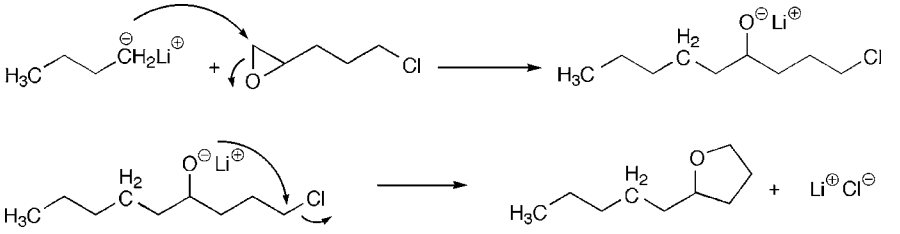
accompanied by a potassium cation and that the final trifluoroacetoxy group is presented as its potassium salt.



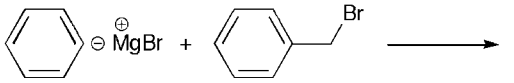
g.



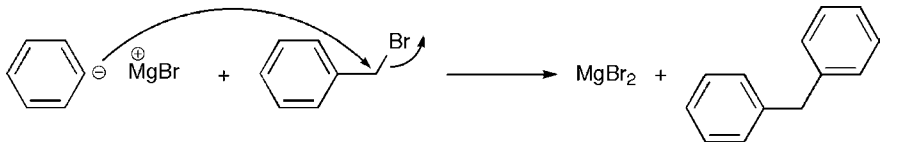
This is a two-step reaction with initial S_N2 opening of an epoxide. The opening of the epoxide is favored because of the strain associated with a three-membered ring. Subsequent S_N2 displacement of the chloride by the alkoxide resulting from epoxide opening leads to the illustrated tetrahydrofuran derivative. The purpose of this example is to illustrate that in many cases, organic reactions do not stop after an initial stage and frequently advance to generate products over several mechanistic steps.



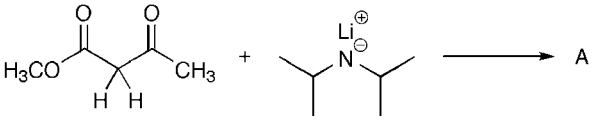
h.



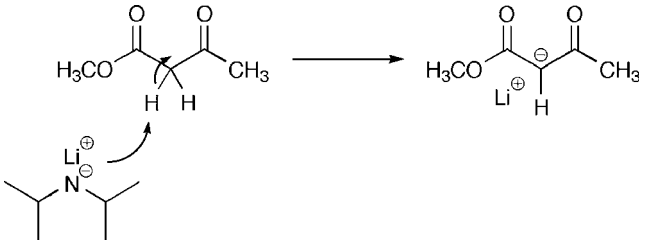
This is a direct S_N2 displacement of a bromide anion by a phenyl anion. Please note that the negative charge of the phenyl anion is accompanied by a magnesium bromide complex. This class of organic salt is known as a Grignard reagent and is characterized by the presence of magnesium and a halide such as chloride, bromide, or iodide.



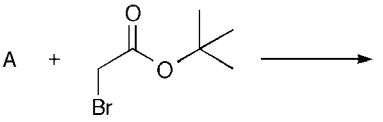
i.



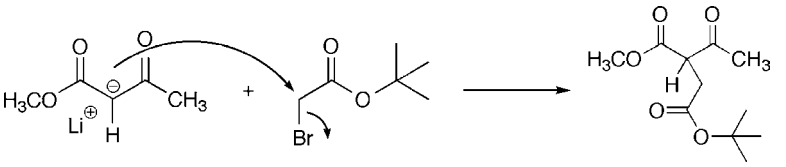
This is an acid–base proton exchange between lithium diisopropylamide (LDA, pK_a of diisopropylamine is approximately 35) and methyl acetoacetate (pK_a is approximately 12). Please note the transfer of the lithium counter ion from LDA to the deprotonated methyl acetoacetate.



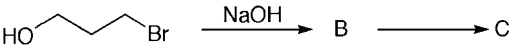
j.



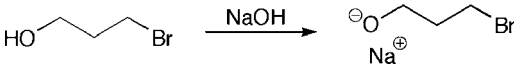
This is a direct S_N2 displacement of the bromide anion of *tert*-butyl bromoacetate by a methyl acetoacetate anion. Lithium bromide (LiBr), the salt by-product, is not shown in the reaction below.



k.

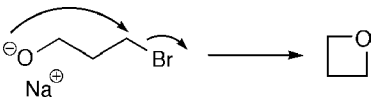


The first step of this reaction is an acid–base proton exchange between a hydroxide anion (pK_a of water is approximately 16) and a primary alcohol (pK_a is approximately 16) forming the illustrated alkoxide, **B**. Formation of water, the by-product, is not shown in this step.

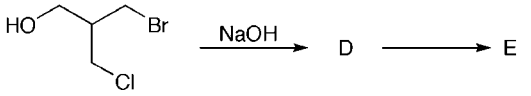


The second step of this reaction is a direct S_N2 displacement of a bromide anion by the alkoxide anion present in the same molecule. This step leads to formation of

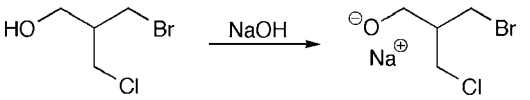
oxetane, **C**. Formation of sodium bromide (NaBr), the salt by-product of this step, is not shown.



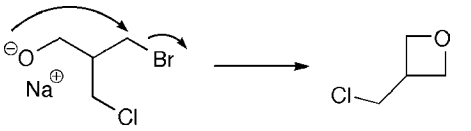
l.



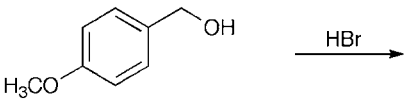
The first step of this reaction is an acid–base proton exchange between a hydroxide anion (pK_a of water is approximately 16) and a primary alcohol (pK_a is approximately 16) forming the illustrated alkoxide, **D**. Formation of water, the by-product, is not shown in this step.



The second step of this reaction is a direct S_N2 displacement of a bromide anion by the alkoxide anion present in the same molecule. This step leads to formation of the oxetane, **E**. Please note that displacement of the bromide is preferred over displacement of the chloride because bromide is a better leaving group than chloride. Formation of sodium bromide (NaBr), the salt by-product of this step, is not shown.

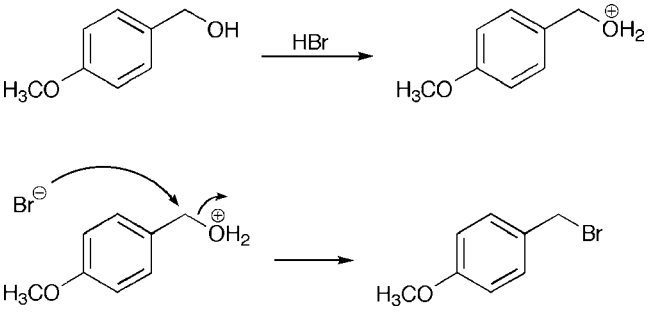


m.

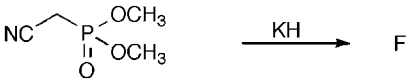


This is a solvolysis reaction that proceeds in two steps. The first step involved protonation of the hydroxy group of *p*-methoxybenzyl alcohol. Once protonated, a bromide ion displaces water, generating the illustrated product. The reaction shown below demonstrates this reaction through an S_N2 mechanism; however, this reaction can also be represented through an S_N1 reaction involving initial

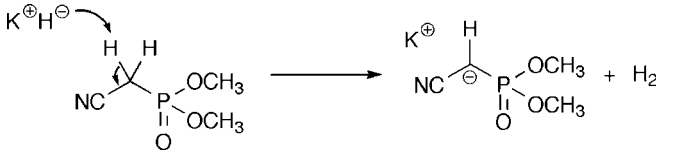
dissociation of water followed by reaction of the resulting cation with a bromide anion.



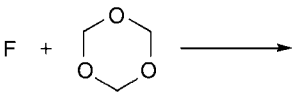
n.



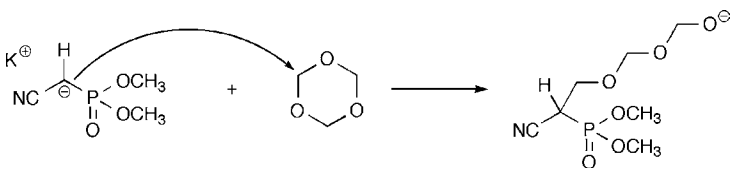
Potassium hydride (KH) is a reactive base possessing a potassium cation and a hydrogen anion (hydride ion). The hydride ion reacts as any other base mentioned thus far and extracts acidic protons generating hydrogen gas and leaving behind anions with associated potassium cations. In this case, the dimethyl cyanomethylphosphonate anion, **F**, is formed.



o.

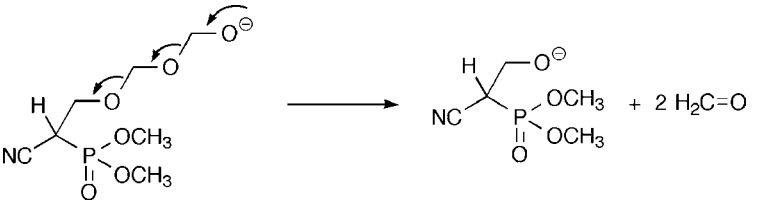


At first glance, this reaction appears simple with the phosphonate anion illustrated in Problem 7(n) displacing an alkoxide anion from trioxane as illustrated below.

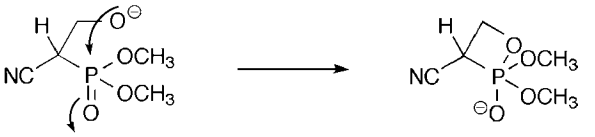


However, as continually alluded to, anions, once formed, can participate in further reactions. Trioxane is essentially a trimer of formaldehyde ($H_2C{=}O$) and is more

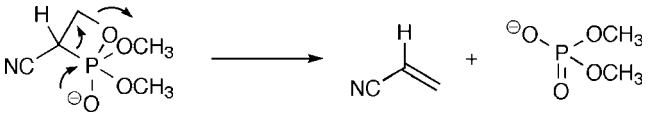
stable and easier to handle than its monomeric form. When an anion opens the trioxane ring, the resulting anion degrades, as shown below, with release of two equivalents of formaldehyde. The resulting species is essentially that resulting from reaction of the initial phosphonate anion with formaldehyde itself. Please note the net incorporation of only one carbon atom and only one oxygen atom. Additionally, the potassium cation is omitted from the remainder of the illustrations for clarity.



Again, referring to the ability of anions to undergo further transformations, we must recognize that phosphorus is a unique element with a strong affinity for oxygen. Furthermore, the phosphorus–oxygen double bond bears much of the same reactivity of a carbon–oxygen double bond and will accept addition of a nucleophile into the system as shown below. The illustrated four-membered species is known as a phosphetane.



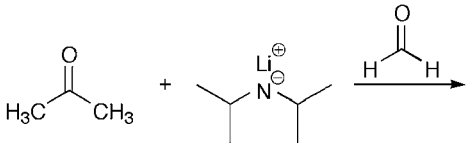
As phosphorus exhibits a strong affinity for oxygen, phosphetane rings are known to undergo further reactions. As illustrated below, the negative charge on the oxygen is capable of breaking the adjacent carbon–phosphorus bond and transferring the negative charge to the carbon atom. Carrying this cycle forward, the negatively charged carbon atom participates in an E2 elimination (Chapter 6) with formation of a new double bond and cleavage of the adjacent carbon–oxygen bond. The resulting two species are an olefin and a phosphate anion.



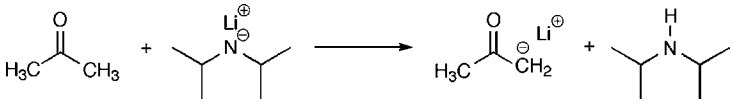
This reaction, known as a Horner–Emmons olefination, was presented to illustrate that through consideration of the electronic nature of a given starting material and the transient species involved in reactions with this material, products of more complex reactions may be identified. However, it is important to note that while this sequence appears complex, each step involved utilizes principles of arrow pushing easily applied from material presented in this book.

8. *Addition reactions and conjugate addition reactions, to be discussed in Chapter 7, are related to S_N2 and S_N2' reactions, respectively. We can make these comparisons if we recognize that the carbonyl double bond contains a leaving group. Specifically, if a nucleophile adds to the carbon of a carbonyl, the carbonyl double bond becomes a carbon–oxygen single bond with a negative charge residing on the oxygen. Additionally, the trigonal-planar geometry of the carbonyl carbon is converted to tetrahedral geometry. With these points in mind, predict the products of the following reactions and explain your answers. For Problem 8(b), the nucleophile is a methyl anion associated with the illustrated cuprate.*

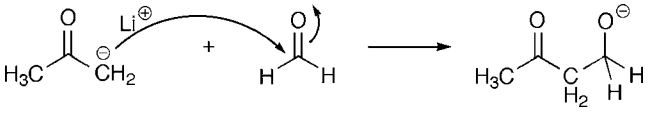
a.



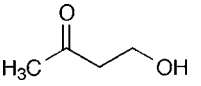
The first stage of this reaction is deprotonation of acetone by LDA in a manner analogous to that demonstrated in Problem 7(i).



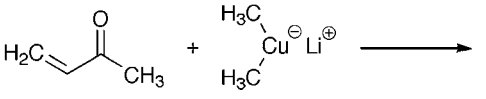
The second stage of the reaction is addition of the acetone anion to formaldehyde as shown below.



Protonation of the resulting alkoxide anion leads to the alcohol illustrated below. This reaction is known as an aldol condensation.

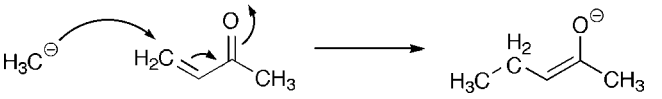


b.

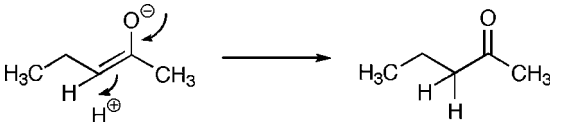


The copper-based reagent shown in the above reaction is known as a cuprate. This specific compound is dimethyl lithiocuprate and is an excellent carrier of methyl

anions. Cuprates are unique in their ability to preferentially deliver nucleophiles to carbonyl groups through adjacent double bonds and in manners analogous to S_N2' mechanisms. Thus, as illustrated below, arrow pushing demonstrates how cuprates add nucleophiles to unsaturated carbonyl systems.

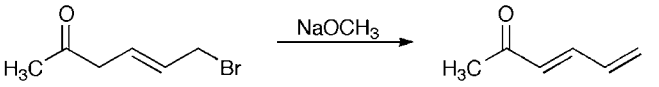


When the illustrated anion is treated with acid, proton transfer generates the final product as shown below.

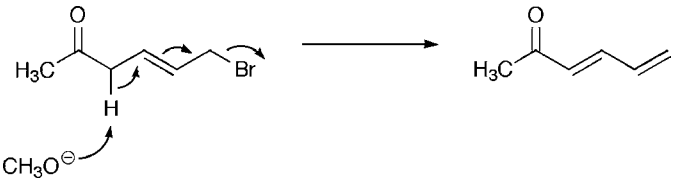


9. *Propose a reasonable mechanism for each of the following reactions. Explain your answers by pushing arrows.*

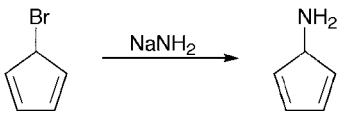
a.



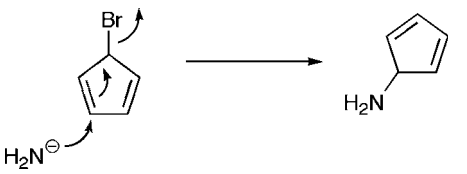
This reaction proceeds through initial deprotonation adjacent to the ketone followed by an S_N2'-type movement of electrons through the double bond and elimination of a bromide ion.



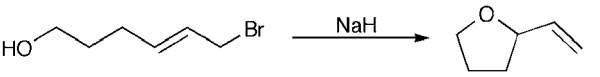
b.



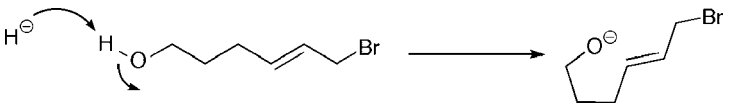
This reaction is an S_N2' displacement of a bromide anion.



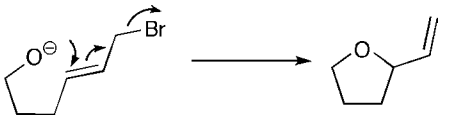
c.



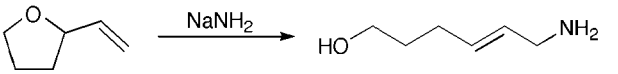
The first step of this reaction is deprotonation of the alcohol with sodium hydride.



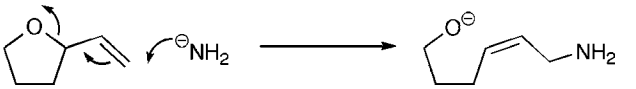
The second step of this reaction is an intramolecular S_N2' reaction with the alkoxide anion displacing the bromide anion through the double bond.



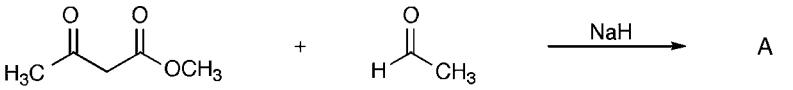
d.

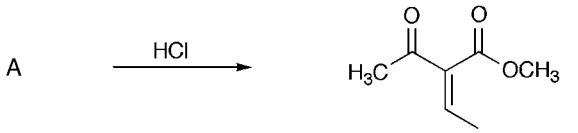


This reaction is an S_N2' displacement of an alkoxide anion through the double bond.



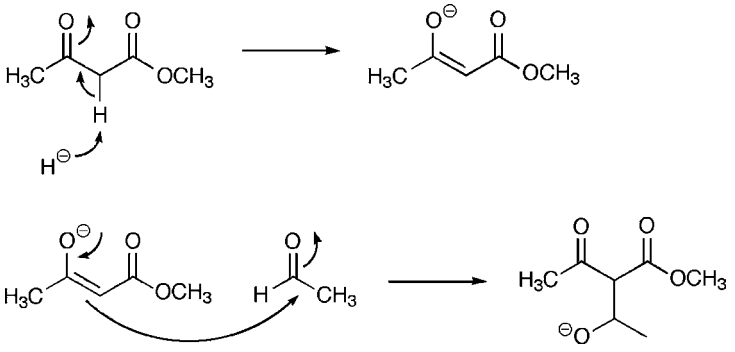
10. α,β-*unsaturated carbonyls are readily formed from the corresponding* β-*hydroxy ketones. Explain the product of the following reaction*:



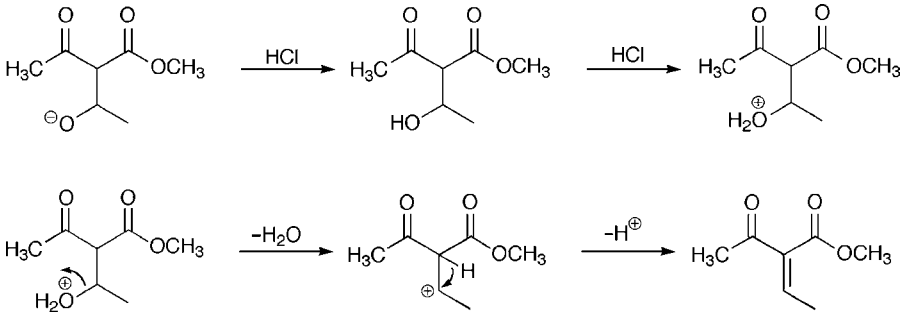


Upon examining the reaction, the initial phase of this sequence can be defined as an aldol condensation [see Problem 8(a)]. Under the specified conditions, hydride is

used to deprotonate methyl acetoacetate and the resulting anion adds to the acetaldehyde carbonyl giving the aldol product, **A**.



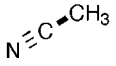
Treating the aldol adduct, **A**, with hydrochloric acid protonates the alkoxide anion and then protonates the resulting alcohol as part of a solvolysis reaction. Water then leaves, generating a carbocation. The carbocation then undergoes an E1 elimination (see Chapter 6) giving the illustrated product.



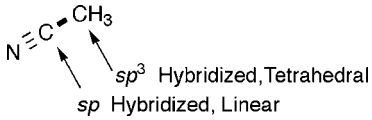
CHAPTER 5 SOLUTIONS

1. *For the following molecules, state the hybridization (*sp, sp^2, sp^3*) of the orbitals associated with the highlighted bond. Also, state the geometry of the bound atomic centers (linear, bent, trigonal planar, tetrahedral).*

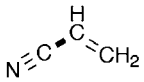
a.



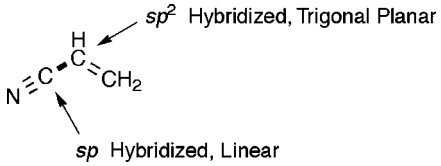
The highlighted bond joins a nitrile carbon atom to a methyl carbon atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the methyl carbon is joined to the nitrile carbon and three hydrogen atoms. Therefore, because the methyl carbon is bound to four separate atoms, this carbon is sp^3 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the methyl carbon is connected to its bound atoms in a tetrahedral geometry.

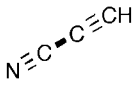


b.

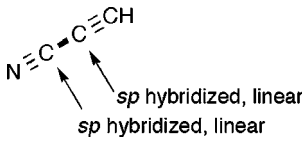


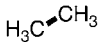
The highlighted bond joins a nitrile carbon atom to a vinyl carbon atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the vinyl carbon is joined to the nitrile carbon, a hydrogen atom, and a second vinyl carbon atom. Because the two vinyl carbon atoms are joined by a double bond, there can be no more than three atoms bound to the highlighted vinyl carbon. Therefore, because the vinyl carbon is bound to three separate atoms, this carbon is sp^2 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the vinyl carbon is connected to its bound atoms in a trigonal planar geometry.



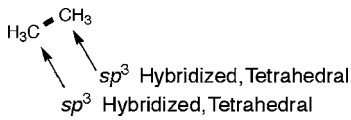
c. 

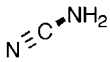
The highlighted bond joins a nitrile carbon atom to an alkyne carbon atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. Additionally, the alkyne carbon is joined to the nitrile carbon and a second alkyne carbon atom. Because the two alkyne carbon atoms are joined by a triple bond, there can be no more than two atoms bound to the highlighted alkyne carbon. Therefore, because the alkyne carbon is bound to two separate atoms, this carbon is *sp* hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the alkyne carbon is connected to its bound atoms in a linear geometry.



d. 

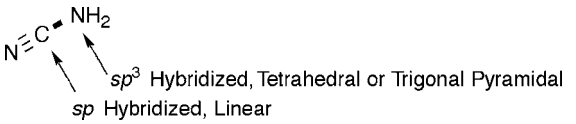
The highlighted bond joins two methyl carbon atoms. Each methyl carbon is joined to a methyl carbon and three hydrogen atoms. Therefore, because each methyl carbon is bound to four separate atoms, they are sp^3 hybridized. Based on the atomic hybridizations, each methyl carbon is connected to its bound atoms in tetrahedral geometries.

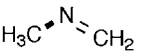


e. 

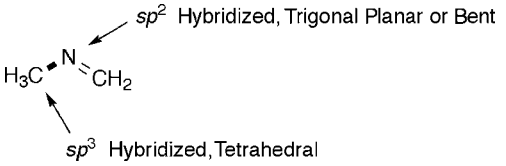
The highlighted bond joins a nitrile carbon atom to an amine nitrogen atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the amine nitrogen is joined to the nitrile carbon and two hydrogen atoms. Additionally, the amine nitrogen possesses one lone electron pair. Therefore, because the amine nitrogen is bound to three separate atoms and possesses one lone electron pair, this nitrogen is sp^3 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the amine

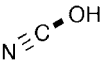
nitrogen is connected to its bound atoms and lone electron pair in a tetrahedral geometry. Please note that because the nitrogen is only bound to three atoms, the tetrahedral relationship between the bound atoms and lone electron pair can also be referred to as trigonal pyramidal (not considering the contributions of the lone electron pair to the geometry) because the geometry represents a three-sided pyramid.



f. 

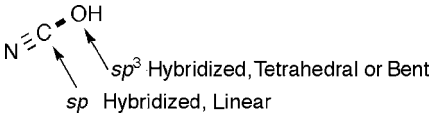
The highlighted bond joins a methyl carbon atom to an imine nitrogen atom. The methyl carbon atom, being joined to three hydrogen atoms and an imine nitrogen atom, is bound to four separate atoms and is, therefore, sp^3 hybridized. The imine nitrogen atom is bound to a methyl carbon atom through a single bond and to a second carbon atom through a double bond. Additionally, the imine nitrogen possesses one lone electron pair. Therefore, because the imine nitrogen is bound to two separate atoms and possesses one lone electron pair, this nitrogen is sp^2 hybridized. Based on the atomic hybridizations, the methyl carbon is connected to its bound atoms in a tetrahedral geometry, and the imine nitrogen is connected to its bound atoms and lone electron pair in a trigonal planar geometry. Please note that the molecular structure is referred to as bent.

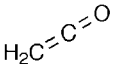


g. 

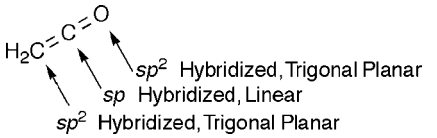
The highlighted bond joins a nitrile carbon atom to a hydroxy oxygen atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the hydroxy oxygen is joined to the nitrile carbon and one hydrogen atom. Additionally, the hydroxy oxygen possesses two lone electron pairs. Therefore, because the hydroxy oxygen is bound to two separate atoms and possesses two lone electron pairs, this oxygen is sp^3 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the hydroxy oxygen is connected to its bound atoms and lone electron pairs

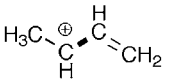
in a tetrahedral geometry. Please note that the molecular structure is referred to as bent at the oxygen atom.



h.  *(Answer for both double bonds.)*

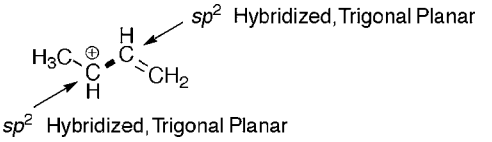
For this compound, the CH_2 carbon is bound to the central carbon through a double bond. Furthermore, this carbon atom is bound to two hydrogen atoms. Because this carbon atom is bound to only three atoms, it is sp^2 hybridized. However, the central carbon atom, being bound to the CH_2 carbon atom through a double bond, is bound to an oxygen atom through a double bond. Thus, the central carbon atom is bound to only two atoms and is *sp* hybridized. Finally, the oxygen atom is bound to the central atom through a double bond. Additionally, the oxygen atom possesses two lone electron pairs. Because the oxygen atom is bound to only one atom and possesses two lone electron pairs, it is sp^2 hybridized. Regarding geometry, the CH_2 carbon, being bound to three atoms, is trigonal planar. Furthermore, the central carbon, being bound to two atoms, is linear. Lastly, the oxygen atom, being bound to only one atom and possessing two lone electron pairs, is trigonal planar.



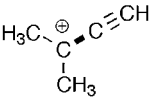
i. 

For this compound, the positively charged CH carbon is bound to a vinyl carbon, a methyl carbon, and a hydrogen through single bonds. Because this carbon atom is bound to only three atoms, it is sp^2 hybridized. Additionally, the vinyl carbon atom is bound to the positively charged carbon atom, a hydrogen and a second vinyl carbon. Because the two vinyl carbon atoms are joined by a double bond, there can be no more than three atoms bound to the highlighted vinyl carbon. Therefore, because the vinyl carbon is bound to three separate atoms, this carbon is sp^2 hybridized. Based on the atomic hybridizations, the positively charged carbon is connected

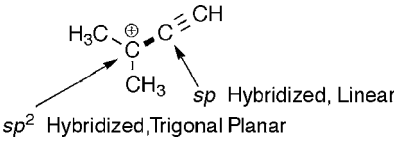
to its bound atoms in a trigonal planar geometry. Likewise, the vinyl carbon is connected to its bound atoms in a trigonal planar geometry.



j.

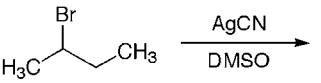


For this compound, the positively charged carbon is bound to an alkyne carbon and two methyl carbons through single bonds. Because this carbon atom is bound to only three atoms, it is sp^2 hybridized. Additionally, the alkyne carbon atom is bound to the positively charged carbon atom and a second alkyne carbon atom. Because the two alkyne carbon atoms are joined by a triple bond, there can be no more than two atoms bound to the highlighted alkyne carbon. Therefore, because the alkyne carbon is bound to two separate atoms, this carbon is *sp* hybridized. Based on the atomic hybridizations, the positively charged carbon is connected to its bound atoms in a trigonal planar geometry, and the alkyne carbon is connected to its bound atoms in a linear geometry.

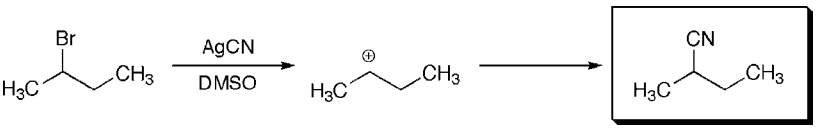


2. *Predict all of the products of the following reactions:*

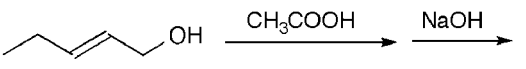
a.



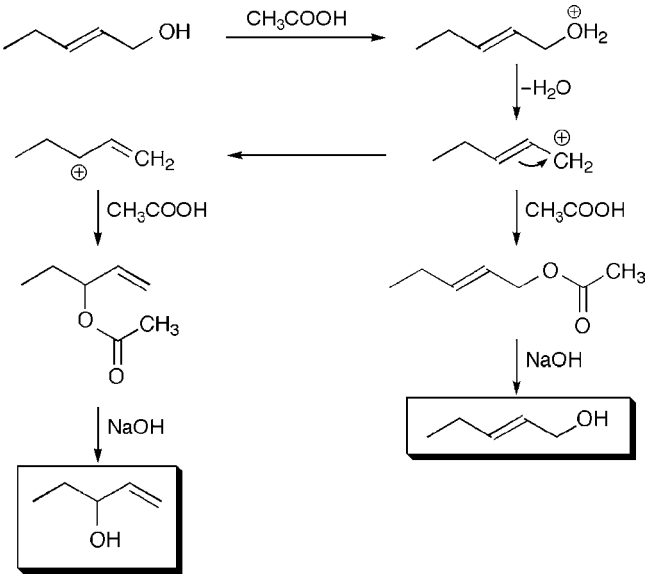
Silver is very efficient at removing halides, resulting in generation of carbocations. Because, once a carbocation is formed, a 1,2-hydride shift applied to the illustrated secondary carbocation can only generate a less stable primary carbocation or an identical secondary carbocation, therefore, there is only one product formed in this reaction.



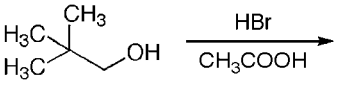
b.



This is a solvolysis reaction where the alcohol is protonated and water leaves, generating a carbocation. The resulting carbocation then joins with acetic acid or migrates through the double bond (note the arrow pushing). The migrated carbocation then joins with acetic acid. In both cases, the resulting acetates are cleaved with sodium hydroxide generating a mixture of two alcohols—regenerated starting material and 3-hydroxy-1-pentene.

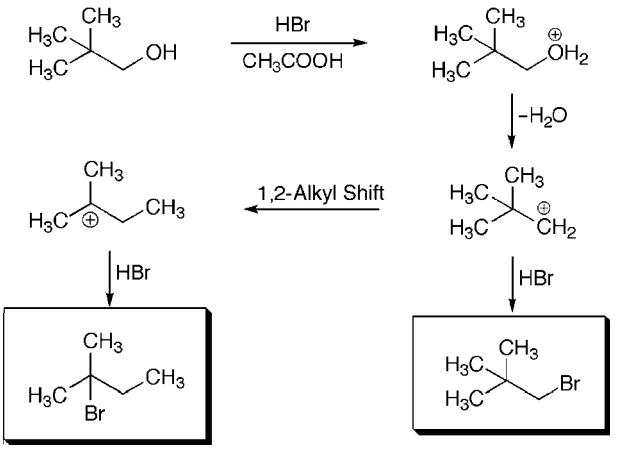


c.

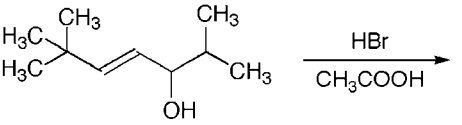


Like the previous example, this is a solvolysis reaction. Initial protonation of the alcohol followed by water leaving generates a primary carbocation. The bromide can then add to this carbocation generating neopentyl bromide. Since, for this carbocation, 1,2-hydride shifts cannot occur, a 1,2-alkyl shift generates a more stable tertiary carbocation. This new carbocation is not subject to possible 1,2-hydride shifts because any such transformation would generate either a less stable

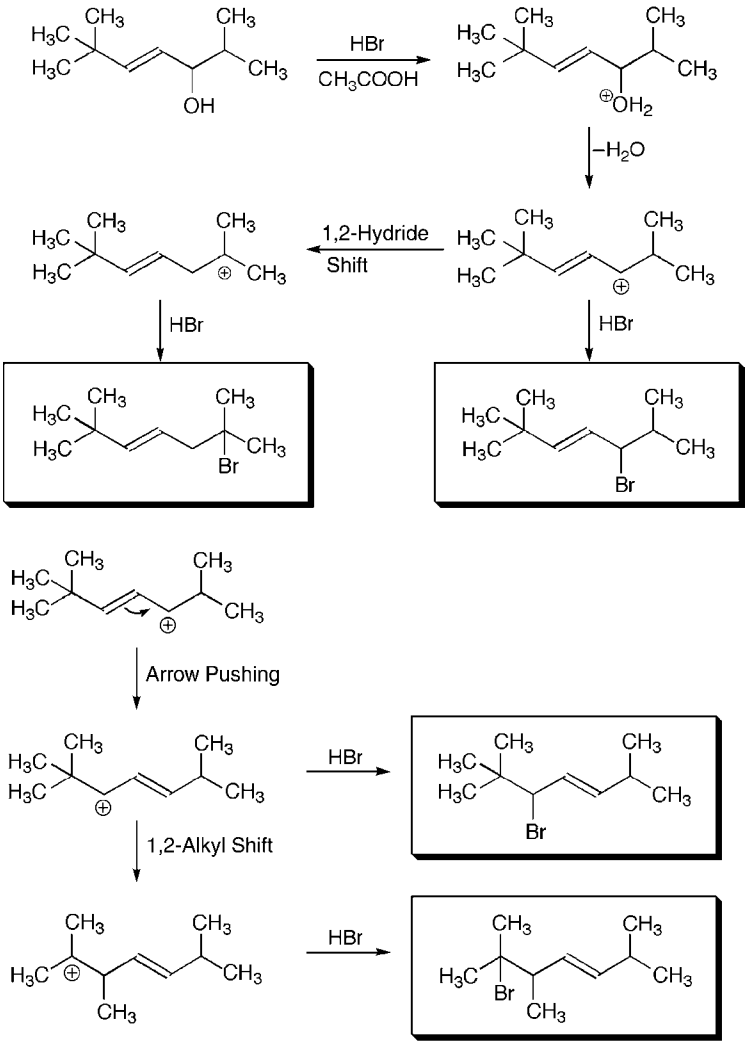
secondary carbocation or a less stable primary carbocation. When bromide adds to the tertiary carbocation, a second alkyl bromide is formed.



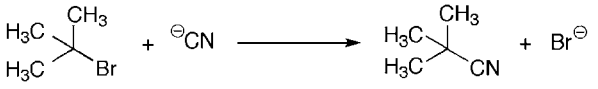
d.



Like Problems 2(b) and 2(c), this is also a solvolysis reaction. However, due to the increased complexity of the starting compound, the potential product mixture is more complex. Specifically, if we consider the initial solvolysis step and elimination of water, we notice that an allyl carbocation is formed that is adjacent to a migratable hydrogen atom. While reaction of this carbocation with bromide generates a secondary allyl bromide, a 1,2-hydride shift followed by reaction with bromide generates a tertiary bromide. Alternatively, if the positive charge migrates through the double bond (see arrow pushing), an allylic carbocation adjacent to a *tert*-butyl group results. Reaction of this carbocation with bromide generates a new allyl bromide. However, if a 1,2-alkyl shift occurs, the resulting tertiary carbocation can react with bromide to form a new tertiary bromide.

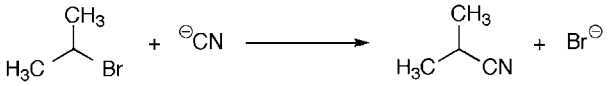


3. *For each of the following reactions, determine which will proceed via an S_N1 or an S_N2 mechanism. In cases where both may be applicable, list appropriate reaction conditions (e.g., solvents, reagents) that would favor S_N1 over S_N2 and vice versa. Explain your answers.*

a. 

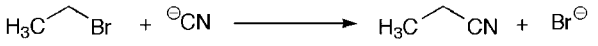
Because tertiary centers are not susceptible to S_N2 reactions, this reaction will proceed via an S_N1 mechanism.

b.



This reaction will show competition between S_N1 and S_N2 mechanisms due to the fact that this center is less hindered than a tertiary center but more hindered than a primary center. An S_N1 mechanism will be favored using highly polar, aprotic solvents to stabilize the forming carbocation. An S_N2 mechanism will be favored when nonpolar solvents are used.

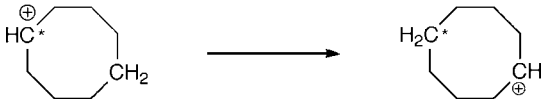
c.



This reaction will proceed through an S_N2 mechanism. In general, primary centers are not sterically encumbered enough to inhibit S_N2 reactions. Additionally, recall that primary carbocations are much less stable than tertiary carbocations, making an S_N1 mechanism highly unlikely for this transformation.

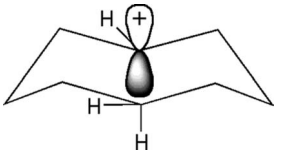
4. *In studying 1,2-alkyl and hydride shifts, we explored the observation that shifts will not occur unless the newly formed carbocation is more stable than the starting carbocation. Additionally, as illustrated in Figure 5.12, these shifts were explained using hyperconjugation, thus requiring that the orbital containing the positive charge and the bond containing the shifting group lie within the same plane. This is necessary in order to allow sufficient orbital overlap for the shift to take place.*

In addition to 1,2-shifts, which occur between adjacent bonds, other shifts are possible where the migrating group apparently moves across space. As with 1,2-shifts, these additional shifts can only occur when the positively charged empty p *orbital lies within the same plane as the bond containing the migrating group, thus allowing sufficient orbital overlap. With this in mind, explain the following 1,5-hydride shift. (Hint: Consider different structural conformations. You may want to use models.) Asterisk (*) marks enrichment with* ^{13}C.



If the eight-membered ring is drawn as illustrated below, a planar relationship can be found between the empty *p* orbital and a carbon–hydrogen bond on the opposite side of the ring. If the hydrogen atom is located on a carbon atom designated 1, by numbering the carbon atoms around the ring, the positive charge is localized on carbon atom 5. Thus, the established relationship between a hydrogen atom on carbon 1 and a positive

charge on carbon 5 allows recognition that a 1,5-hydride shift can occur and is required to explain the described transformation.



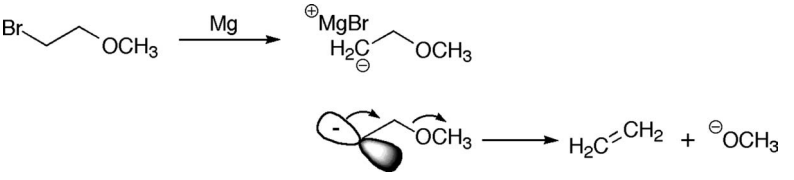
CHAPTER 6 SOLUTIONS

1. *E2 eliminations do not necessarily require acidic protons in order to proceed. Explain how this can occur.*

The orientation of any proton in a *trans*-periplanar relationship to a given leaving group is usually enough to allow elimination to occur under basic conditions even when, in the absence of an electron-withdrawing group, the proton is not acidic enough to be removed.

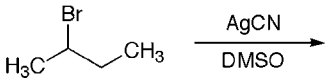
2. *When* $CH_3OCH_2CH_2CH_2Br$ *is treated with magnesium, we get the Grignard reagent* $CH_3OCH_2CH_2CH_2MgBr$. *However, when* $CH_3OCH_2CH_2Br$ *is treated with magnesium, the product isolated is* $H_2C{=}CH_2$. *Explain this result.*

Grignard reagents are carbanions stabilized by a MgBr cation. As with all anionic species, if a leaving group is situated on an adjacent center, the structure is subject to an E2 elimination process. Furthermore, CH_3O^- is a sufficient leaving group when it is located adjacent to an anionic center. Therefore, in the case of bromomethoxyethane, E2 elimination leads to formation of ethylene when the negative charge adopts a *trans*-periplanar relationship to the methoxy group.



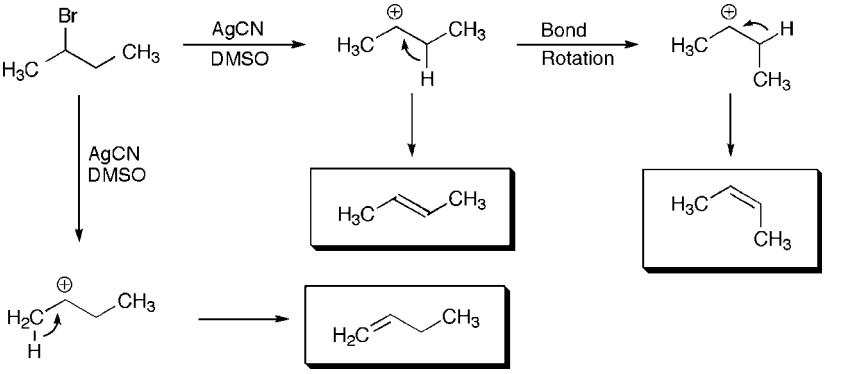
3. *With an understanding of E1 mechanisms, one may realize that under* S_N1 *reaction conditions multiple products may form. In addition to the products predicted in Chapter 5 for the following molecules, predict plausible elimination products.*

a.

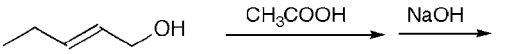


Silver is very efficient at removing halides, resulting in generation of carbocations. Because protons adjacent to carbocations are acidic and, therefore, participate in

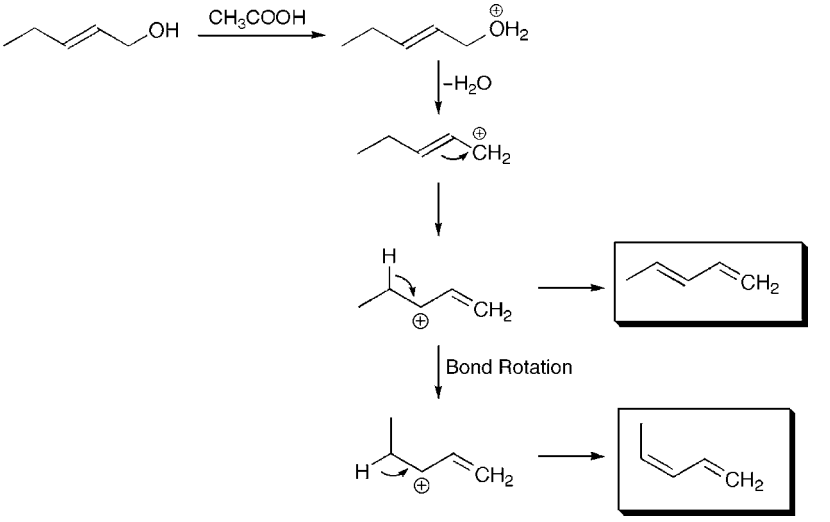
E1 elimination reactions, several potential products can be identified. These are illustrated below using arrow pushing.



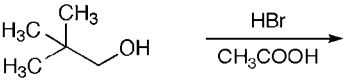
b.



This is a solvolysis reaction where the alcohol is protonated and water leaves, generating a carbocation. Because protons adjacent to carbocations are acidic and, therefore, participate in E1 elimination reactions, several potential products can be identified. These are illustrated below using arrow pushing.

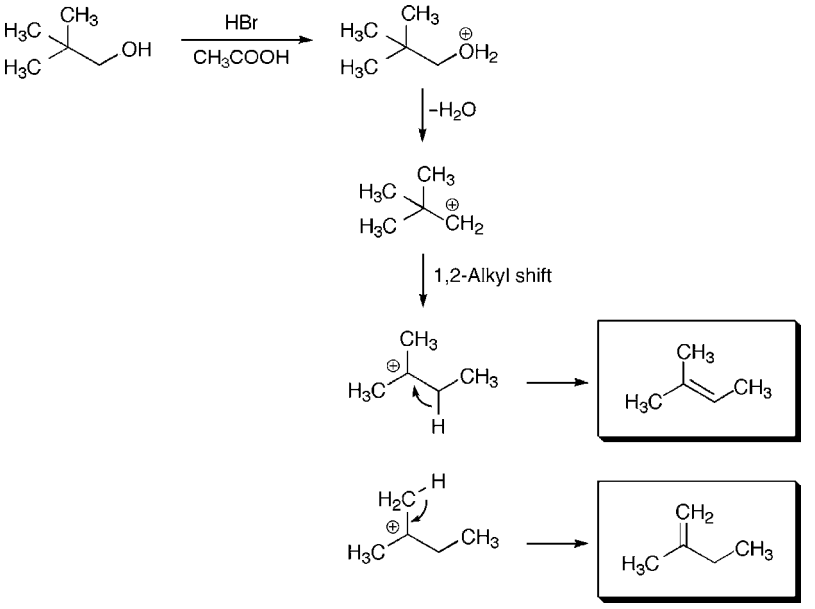


c.

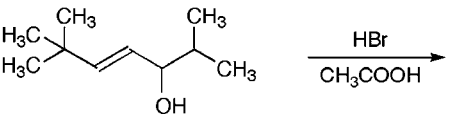


Like the previous example, this is a solvolysis reaction. Initial protonation of the alcohol followed by water leaving generates a primary carbocation. Since, for this

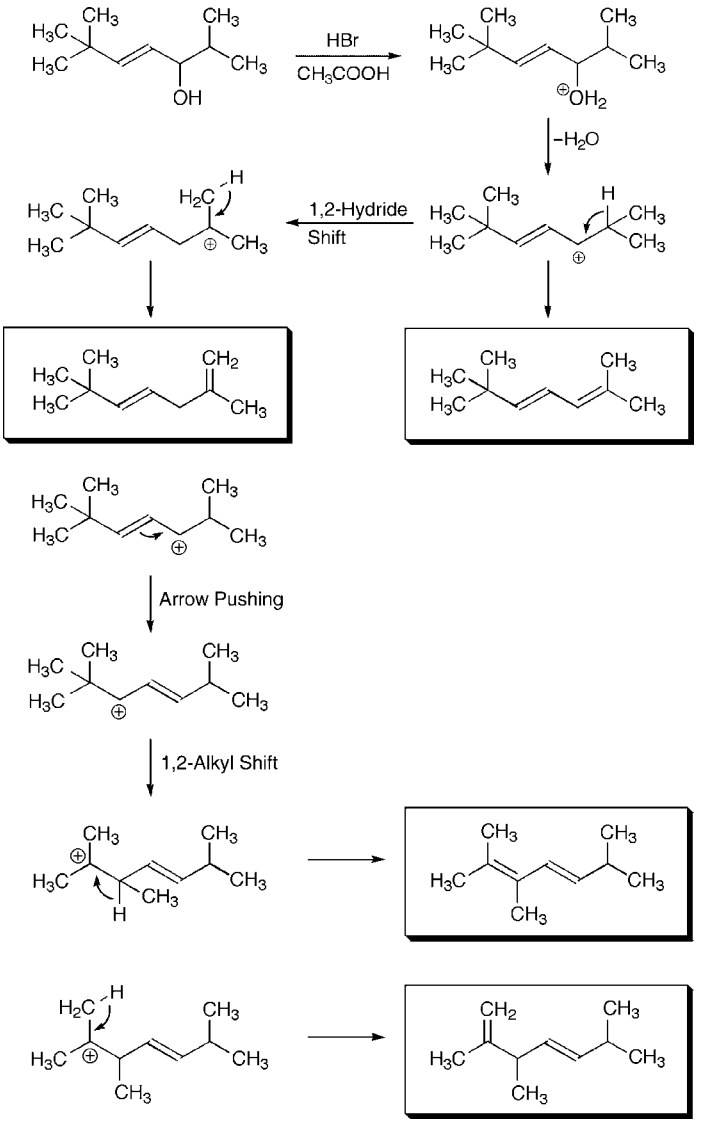
carbocation, there are no protons adjacent to the carbocation, no direct E1 elimination products can form. However, if a 1,2-alkyl shift occurs, the resulting tertiary carbocation can participate in such reactions. Potential E1 elimination products are illustrated below using arrow pushing.



d.



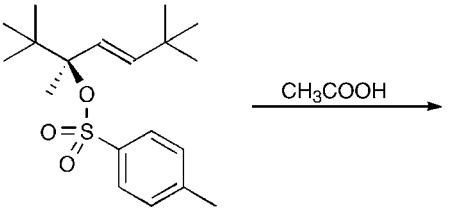
Like Problems 3(b) and 3(c), this is a solvolysis reaction. However, due to the increased complexity of the starting compound, the potential product mixture is more complex. Specifically, if we consider the initial solvolysis step and elimination of water, we notice that an allyl carbocation is formed that is adjacent to a migratable hydrogen atom. While this carbocation can undergo an E1 elimination reaction, a 1,2-hydride shift generates a new carbocation that is also capable of E1 forming E1 elimination products. Furthermore, if the positive charge migrates through the double bond (see arrow pushing), an allylic carbocation adjacent to a *tert*-butyl group results. While this new carbocation bears no adjacent hydrogen atoms, a 1,2-alkyl shift generates a new carbocation that does possess adjacent protons. This new carbocation can liberate E1 elimination products. All potential E1 elimination products are illustrated below using arrow pushing.



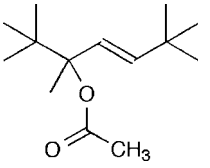
Please note: The most stable products possess conjugated double bonds.

4. *Presently, several different organic reaction mechanisms have been presented. Keeping all of these in mind, predict all of the possible products of the following reactions and list the mechanistic type or types from which these products result.*

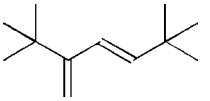
a.



Following initial solvolysis of the tosylate, addition of acetic acid to the carbocation generates an S_N1 product. Please note that there is no preservation of the stereochemical configuration in this reaction.

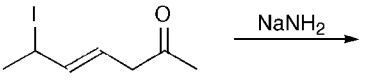


E1 elimination applied to the carbocation formed during solvolysis liberates an olefin.

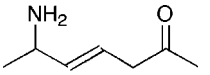


Please note: Since the carbocation formed during solvolysis is both tertiary and allylic, it is very stable and migration reactions are not likely to occur.

b.

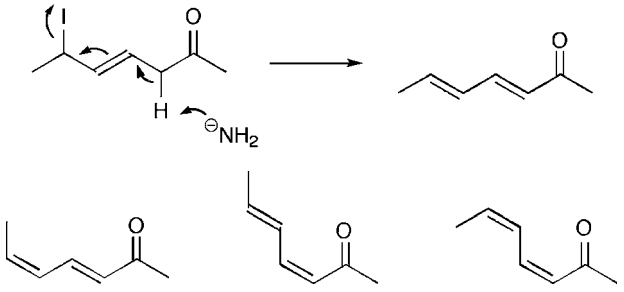


S_N2 displacement of the iodide generates an allylic amine.

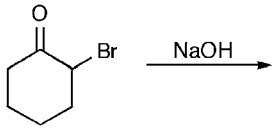


S_N2' displacement of the iodide generates a mixture of two allylic amines with the amine placed on the opposite side of the double bond.

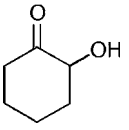
E2 elimination resulting from removal of a proton adjacent to the carbonyl liberates a diene. Please note that, depending upon the spatial relationship between the carbonyl and the double bond, additional illustrated dienes can form.



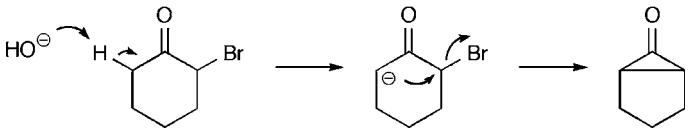
c.



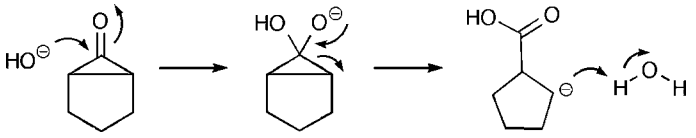
Direct S_N2 displacement of the bromide would be expected to liberate the illustrated hydroxyketone.



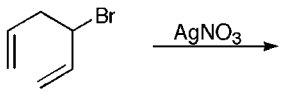
However, this is a special case reaction known as the Favorskii rearrangement. As illustrated below using arrow pushing, sodium hydroxide extracts a proton adjacent to the ketone, and the resulting anion displaces the bromide ion, generating a new three-membered ring.



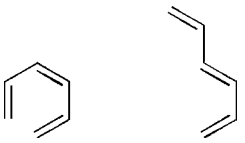
As alluded to in previous discussions, carbonyl groups are polarized with a partial positive charge residing on the carbon atom and a partial negative charge residing on the oxygen atom. This polarization has been used in discussions of charge delocalization. As will be addressed in the next chapter, the polarized nature of carbonyls render them good electrophiles and, as such, capable of accepting nucleophiles at the partial positive center. As illustrated below, a hydroxide anion can now add to the carbonyl, placing a negative charge on the original carbonyl oxygen. That negative charge can then return to the original carbonyl carbon atom and open the three-membered ring, relieving strain and forming a cyclopentane carboxylic acid.



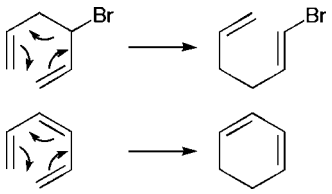
d.



As previously mentioned (see Problem 3(a)), silver cations are very efficient at removing halide anions. Therefore, under these conditions, liberation of an allylic cation is favorable. This cation can then generate the E1 elimination products shown. Please note that these products are dependent upon the relationship between the two terminal double bonds.

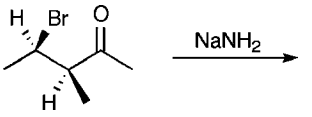


Additionally, as mentioned in Chapter 1, concerted reaction mechanisms can be described using arrow pushing. As illustrated below, both the starting bromide and one of the trienes can undergo Cope rearrangements to form new products. While these reactions are not within the scope of this book, it is important to recognize these reactions. For more detailed information, readers are referred to their introductory organic chemistry textbooks.

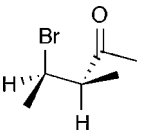


5. *As mentioned earlier, stereochemistry is not of great concern in this book. However, certain mechanistic types will show specific stereochemical consequences when*

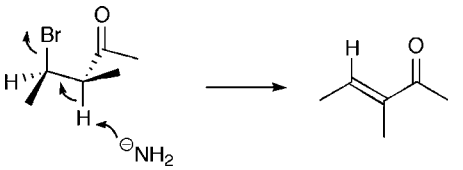
acting on chiral molecules. With this in mind, predict the product resulting from the E2 elimination of HBr when the illustrated isomer of 4-bromo-3-methyl-2-pentanone is treated with sodamide. Show all stereochemistry and explain your answer.



In order to approach this problem, we must first identify the structure of the starting compound when the acidic proton is oriented *trans*-periplanar to the bromide. The relevant configuration is illustrated below and can be visualized using molecular models.

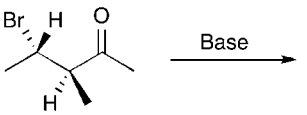


Realizing that the two methyl groups are oriented as projecting out of the same side of the molecule, E2 elimination of HBr can only form a product with the methyl groups *cis* to one another. The formation of this product is illustrated below using arrow pushing.

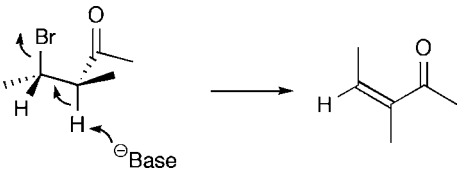


6. *Based on the answer to Problem 5, predict the product of the following reactions and show all stereochemistry*:

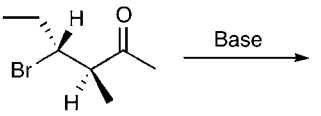
a.



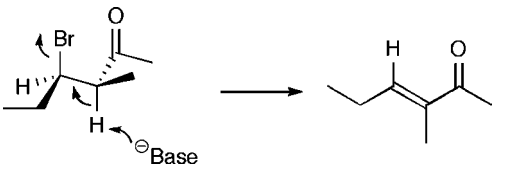
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



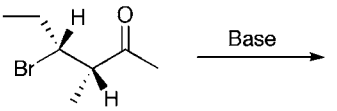
b.



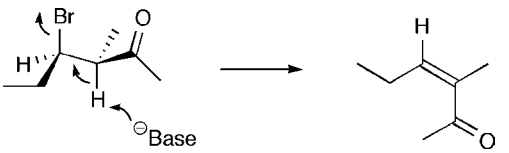
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



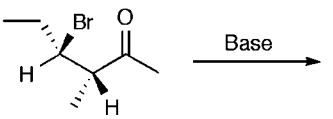
c.



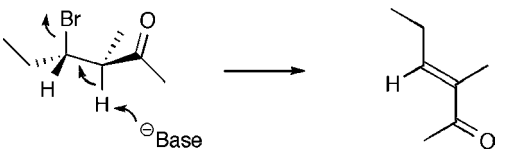
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



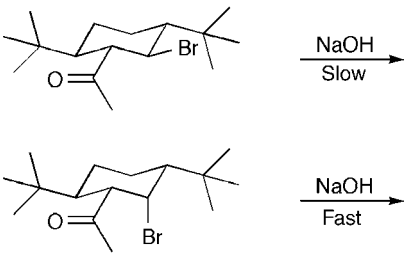
d.



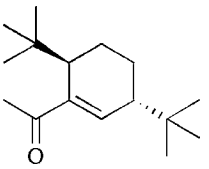
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



7. *Explain the results of the following experiment*:

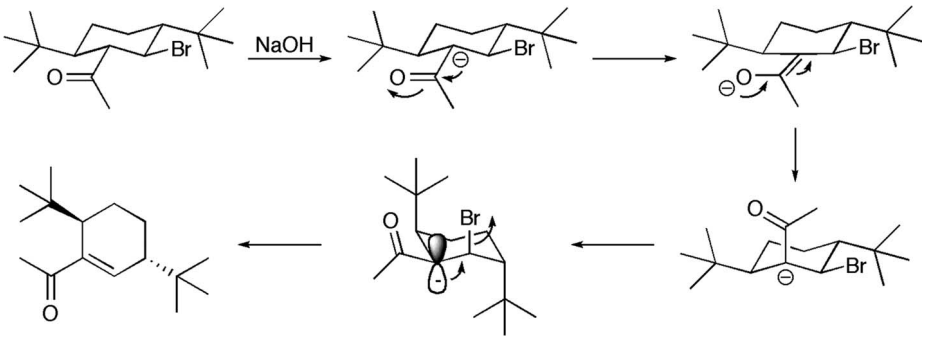


The product for both of these reactions is the cyclohexene shown below.



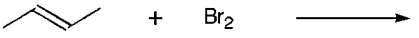
This product forms via an E2 elimination mechanism. Consequently, the elimination reaction is only favored if a *trans*-periplanar relationship exists between the acidic proton and the bromide. In the case of the starting material used in the "fast" reaction, this is the case. However, looking at the starting material used in the "slow" reaction, no *trans*-periplanar relationship exists between the acidic proton and the bromide.

Because the slow reaction does, in fact, form the same product as that formed in the fast reaction, transformations allowing a *trans*-periplanar arrangement to form must take place. As illustrated below, these transformations begin with initial deprotonation adjacent to the carbonyl group. The resulting anion then inverts through reversible delocalization of the negative charge into the carbonyl. Next, the chair form of the ring inverts, allowing placement of the bromide and anion into axial positions. At this point, elimination to the cyclohexene occurs.

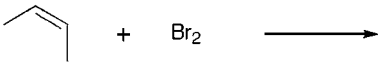


CHAPTER 7 SOLUTIONS

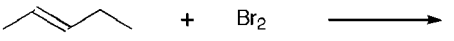
1. *Predict the products of the following reactions and then answer the following questions. Consider stereochemistry.*

I. 

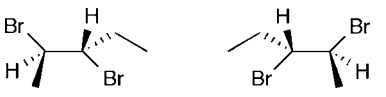
The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.

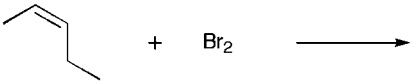
II. 

The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.

III. 

The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.



IV. 

The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.

a. *Are the products of reactions I and II the same or are they different? Explain your answer.*

The products of the first two reactions I and II are different. While the mechanistic delivery of a bromine to opposite faces of an olefin is the same for both reactions, the products of reaction I are diastereomers relative to the products of reaction II. The difference in stereochemistry is the result of the olefin of reaction I being *trans* while the olefin of reaction II is *cis*.

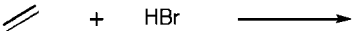
b. *How do you account for the products of reactions I and II?*

When the initial addition of bromine to the double bond occurs, the addition takes place on only one side of the molecule. Therefore, the resulting three-membered intermediate retains the geometry of the starting olefin. Nucleophilic attack then occurs from the opposite side of the molecule, thus inverting the stereochemistry at one of the two centers. Since the substrates are symmetrical, only enantiomers are formed in reactions I and II.

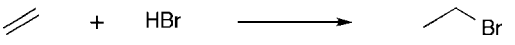
c. *Are the products of reactions III and IV the same or are they different? Explain your answer.*

The products of the first two reactions III and IV are different. While the mechanistic delivery of a bromine to opposite faces of an olefin is the same for both reactions, the products of reaction III are diastereomers relative to the products of reaction IV. The difference in stereochemistry is the result of the olefin of reaction III being *trans* while the olefin of reaction IV is *cis*.

2. *Predict all of the products of the following reactions:*

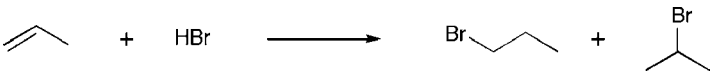
a. 

Since the starting olefin is symmetrical, there can be only one product as illustrated below.

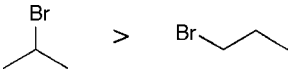


b. 

Since the starting olefin is asymmetrical, there are two possible products as illustrated below.

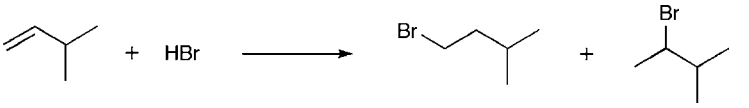


Considering Markovnikov's rule, 2-bromopropane is expected to form in greater quantity compared to 1-bromopropane.

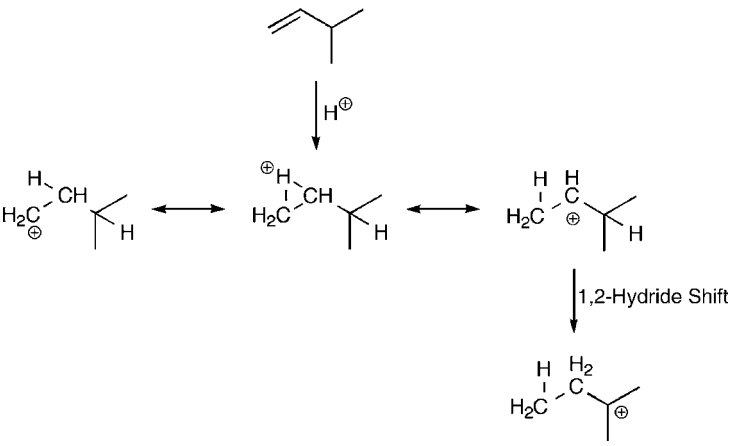


c.

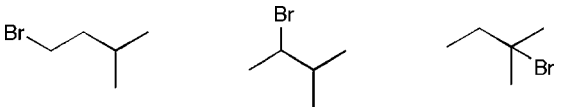
Since the starting olefin is asymmetrical, there are initially only two products to consider as illustrated below.



However, recognizing that the initial protonation of the olefin generates positive charges on two adjacent carbon atoms (Scheme 7.6) and that the positive charge at the secondary center is capable of receiving a 1,2-hydride shift (Chapter 5), generation of a tertiary carbocation is possible as illustrated below.

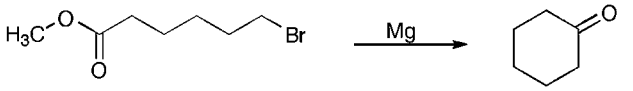


Thus, there are three potential products from this reaction.

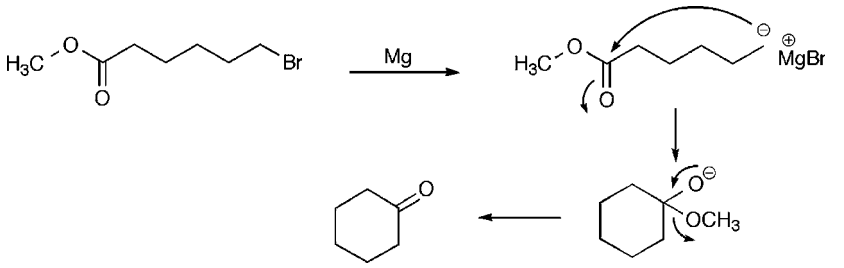


3. *Explain the results of the following reactions. Use arrow pushing and specify mechanistic types.*

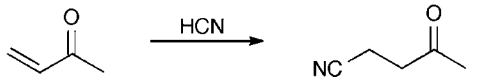
a.



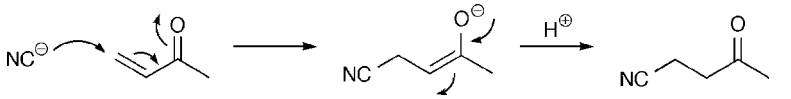
Magnesium reacts with alkyl halides to form alkyl magnesium bromide salts known as Grignard reagents. As mentioned throughout this book, these species bear nucleophilic carbon atoms. As illustrated using arrow pushing, the alkyl anion adds to the carbonyl and subsequently eliminates methoxide. This addition–elimination process leads to the formation of cyclohexanone.



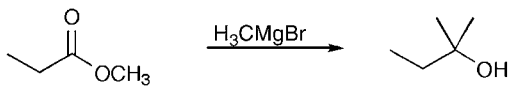
b.



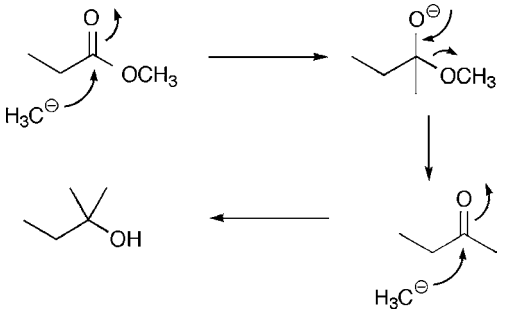
As illustrated using arrow pushing, the cyanide anion adds to the unsaturated ketone via a 1,4-addition.



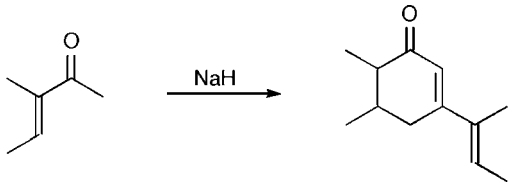
c.



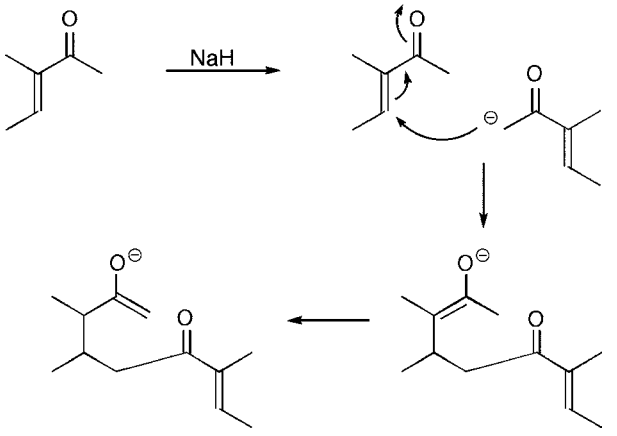
As illustrated using arrow pushing, the first methyl anion drives an addition–elimination reaction forming a ketone. The second methyl anion then adds to the carbonyl in a 1,2-addition, generating the final alcohol.



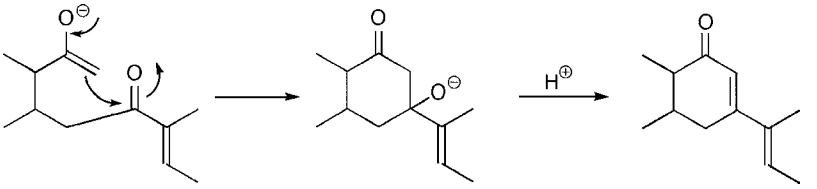
d.



The illustrated product results from a dimerization of the starting material through a multistep process. As illustrated below, initial deprotonation of the starting material with sodium hydride generates an acyl anion that adds, through a 1,4-addition, to the carbonyl of a second starting material molecule. Subsequent proton transfer sets up the intermediate species for an aldol condensation.



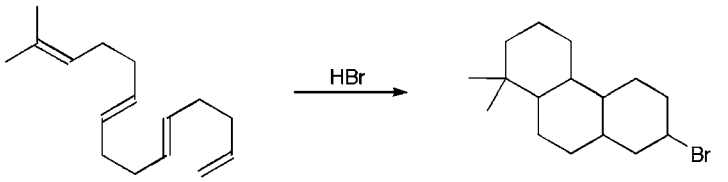
In the second phase of this transformation, illustrated below, a six-membered ring is formed through an intramolecular 1,2-addition. Subsequent protonation of the alkoxide anion and elimination of water generates the final product.



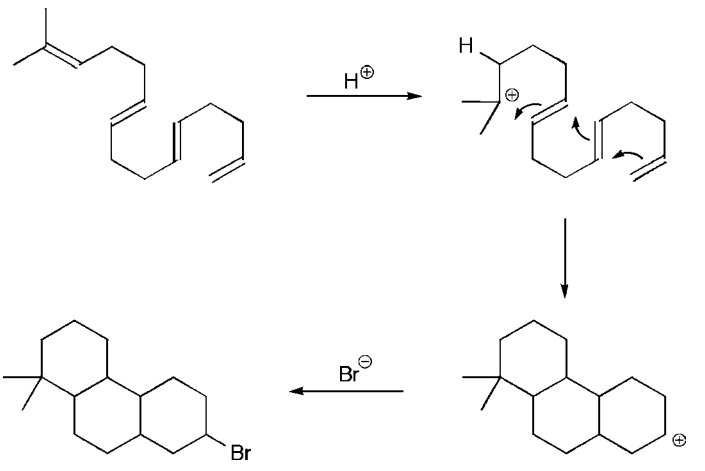
This sequence of steps is known as the Robinson annulation.

4. *Explain the following reactions in mechanistic terms. Show arrow pushing.*

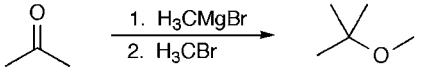
a.



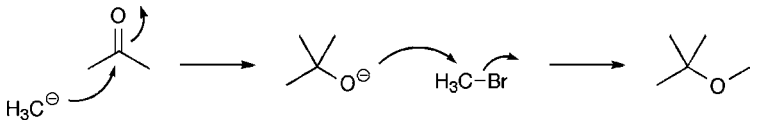
As presented in this chapter, olefins can become protonated under acidic conditions, leading to the formation of electrophilic and cationic carbon atoms. Furthermore, because olefins have nucleophilic character, they can add to sites of positive charge. The cascading of this mechanism, illustrated below, generates polycyclic systems through the cation–π cyclization.



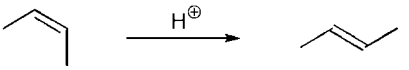
b.



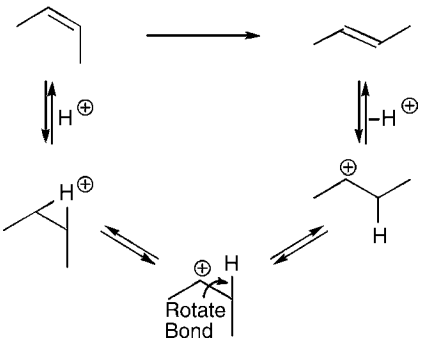
The first step in this sequence is a 1,2-addition of methyl magnesium bromide to acetone. The second step is an S_N2 displacement of bromide with the alkoxide formed in the first step. This two-step process is illustrated below using arrow pushing.



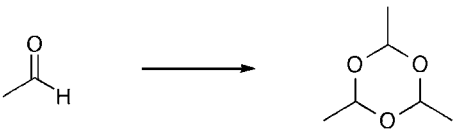
c.



The product of this reaction is the result of a sequence of equilibrium processes. As illustrated below, initial protonation of the *cis*-olefin allows transient formation of single-bond character. This single-bond character then allows for rotation around the central carbon–carbon bond. Final deprotonation liberates the *trans*-olefin. The overall process is driven by the reduced steric interactions present in the *trans*-olefin compared to the *cis*. Specifically, the *cis*-olefin possesses methyl–methyl interactions that are not present in the *trans*.

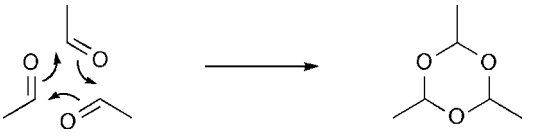


d.



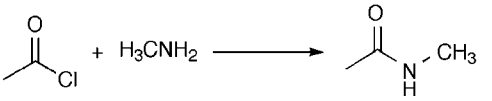
This reaction is a trimerization of acetaldehyde. The mechanism is based on the nucleophilicity of the carbonyl oxygen coupled with the

electrophilicity of the carbonyl carbon. The mechanism is illustrated below using arrow pushing.

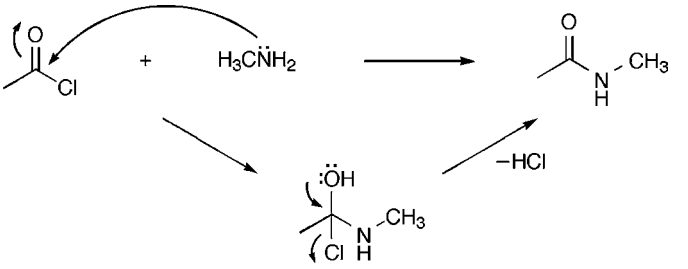


5. *Explain the following products resulting from the reaction of amines with carbonyls. Use arrow pushing and specify mechanistic types.*

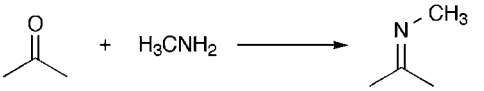
a.



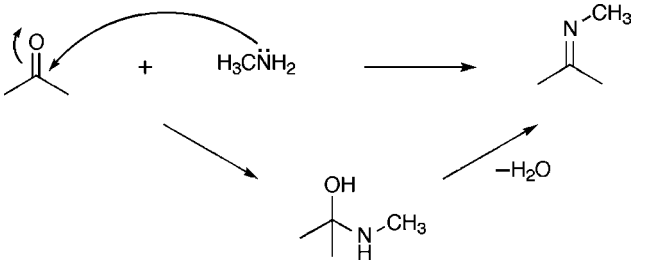
This is an addition–elimination reaction involving addition of methylamine to the acid chloride and elimination of hydrochloric acid. The mechanism is illustrated below using arrow pushing.



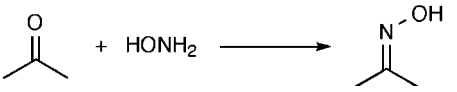
b.



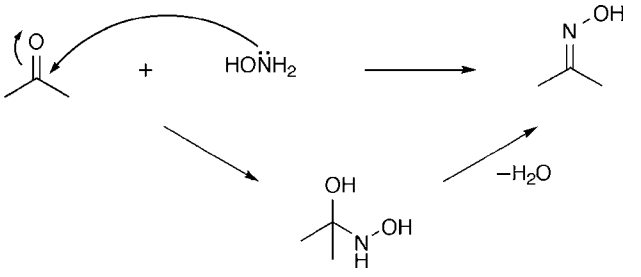
The product of this reaction is an imine resulting from 1,2-addition of methylamine to the carbonyl followed by dehydration. Please note that in the dehydration step, the amine contributes a hydrogen to match the leaving hydroxide group. The mechanism is illustrated below using arrow pushing.



c.

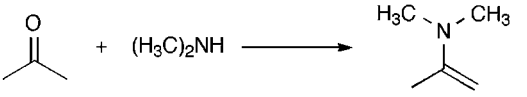


The product of this reaction is an oxime resulting from 1,2-addition of hydroxylamine to the carbonyl followed by dehydration. Please note that in the dehydration step, the amine contributes a hydrogen to match the leaving hydroxide group. The mechanism is illustrated below using arrow pushing.

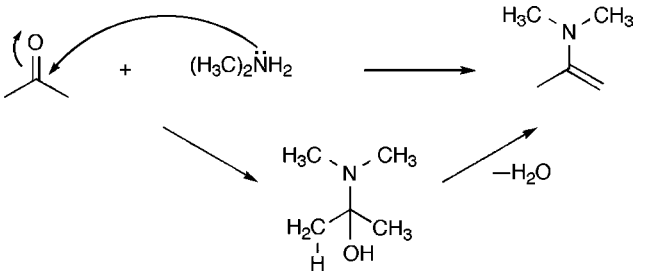


.

d.



The product of this reaction is an enamine resulting from 1,2-addition of dimethylamine to the carbonyl followed by dehydration. Please note that in the dehydration step, an adjacent methyl group contributes a hydrogen to match the leaving hydroxide group. The mechanism is illustrated below using arrow pushing.



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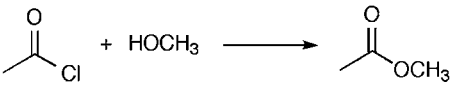
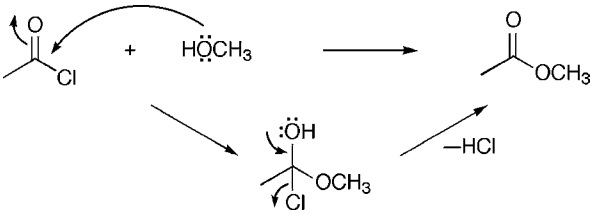
6. *Provide mechanisms for the following reactions. Show arrow pushing.*

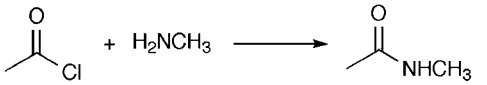
a.



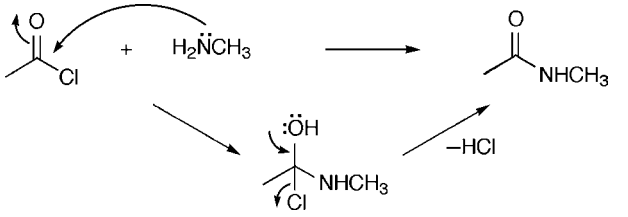
This is an addition–elimination reaction of methanol with acetyl chloride forming methyl acetate. As illustrated below using arrow pushing, methanol is being added while hydrochloric acid is being eliminated. The driving force behind this reaction lies with the relative electronegativities of chlorine and oxygen. Chlorine being more electronegative than oxygen translates to a chlorine anion (chloride) being a better leaving group than an oxygen anion (alkoxide).



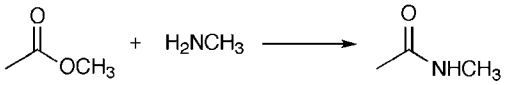
b.



This is an addition–elimination reaction of methylamine with acetyl chloride forming methyl acetamide. As illustrated below using arrow pushing, methylamine is being added while hydrochloric acid is being eliminated. The driving force behind this reaction lies with the relative electronegativities of chlorine and nitrogen. Chlorine being more electronegative than nitrogen translates to a chlorine anion (chloride) being a better leaving group than a nitrogen anion (amide).

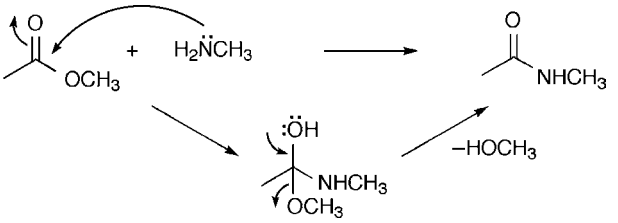


c.

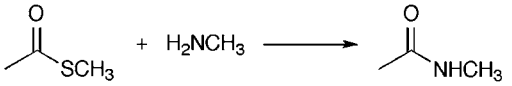


This is an addition–elimination reaction of methylamine with methyl acetate forming methyl acetamide. As illustrated below using arrow pushing, methylamine is being added while methanol is being eliminated. The driving force behind this reaction lies with the relative electronegativities of oxygen and nitrogen. Oxygen

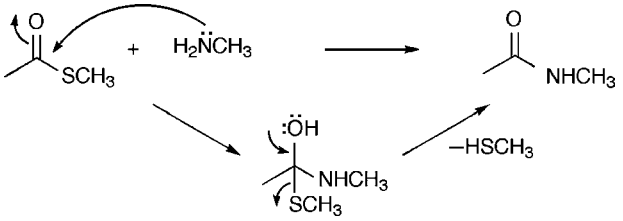
being more electronegative than nitrogen translates to an oxygen anion (alkoxide) being a better leaving group than a nitrogen anion (amide).



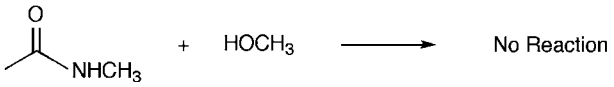
d.



This is an addition–elimination reaction of methylamine with methyl thioacetate forming methyl acetamide. As illustrated below using arrow pushing, methylamine is being added while methanethiol is being eliminated. The driving force behind this reaction lies with the relative polarizabilities of sulfur and nitrogen. Sulfur being more polarizable than nitrogen translates to a sulfur anion (sulfide) being a better leaving group than an nitrogen anion (amide).

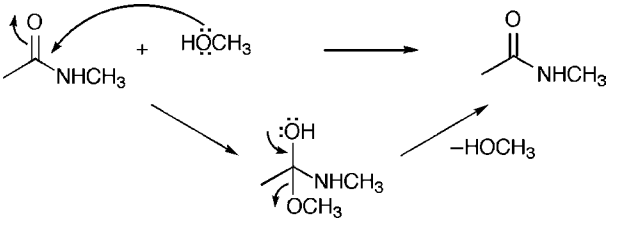


e.

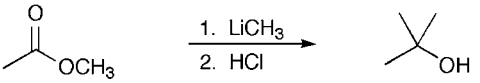


The failure of this attempted addition–elimination reaction is driven by the relative electronegativities of oxygen and nitrogen. Oxygen being more electronegative than nitrogen translates to an oxygen anion (alkoxide) being a better leaving group than a nitrogen anion (amide). Thus, while methanol may

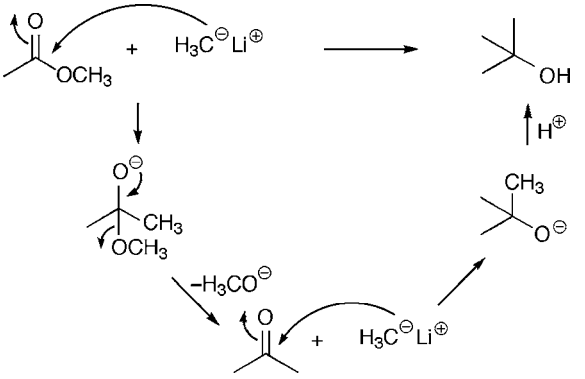
add to the amide, methanol will be the only group eliminated and there will be no net reaction.



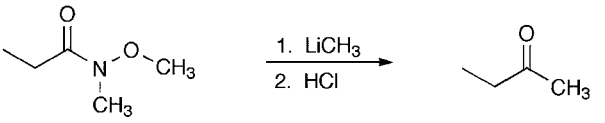
f.



This is a two-step transformation. The first step is an addition–elimination reaction of methyllithium with methyl acetate transiently forming acetone. The second step is a 1,2-addition of methyllithium to acetone forming the final *tert*-butyl alcohol. Hydrochloric acid is present only to quench the formed anions and liberate a neutral product. The steps of this transformation are illustrated below using arrow pushing. Please note that, for simplicity, association of the lithium cations with the anions of the illustrated mechanistic pathway is not shown.

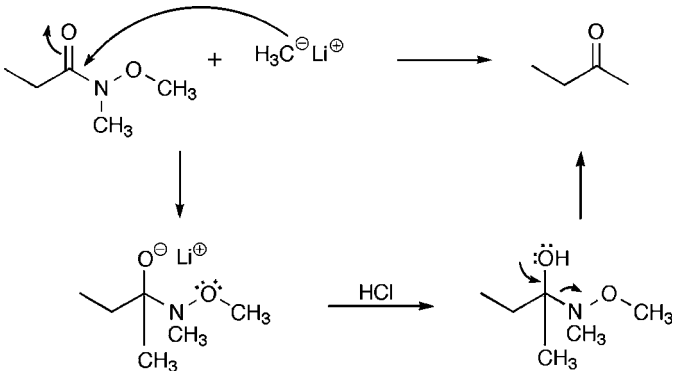


g.

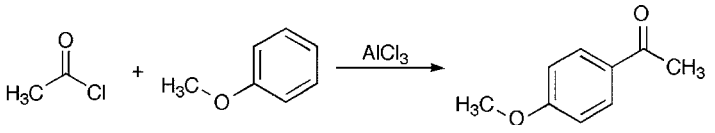


This is an addition–elimination reaction of methyllithium with *N*-methyl-*N*-methoxypropionamide forming 2-butanone. As illustrated below using arrow pushing, methyllithium initially adds to the amide. Unlike the process illustrated in Problem 6(f), a second methyllithium does not add and an alcohol is not formed. This is explained by the ability of lithium to coordinate between the two present oxygen atoms. The first is the oxygen of the former carbonyl and the second is the oxygen associated with the methoxy component of the illustrated amide. Due to the stability of this type of five-membered interaction, initial

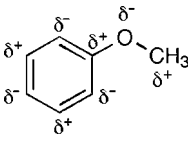
collapse of the anionic intermediate with loss of *N*-methyl-*N*-methoxyamine is prevented. In Problem 6(f), collapse of the anionic intermediate led to regeneration of a carbonyl capable of reacting with a second methyllithium. In this example, this does not happen, and quenching with hydrochloric acid allows exclusive formation of the ketone shown. This process is illustrated below using arrow pushing.



h.

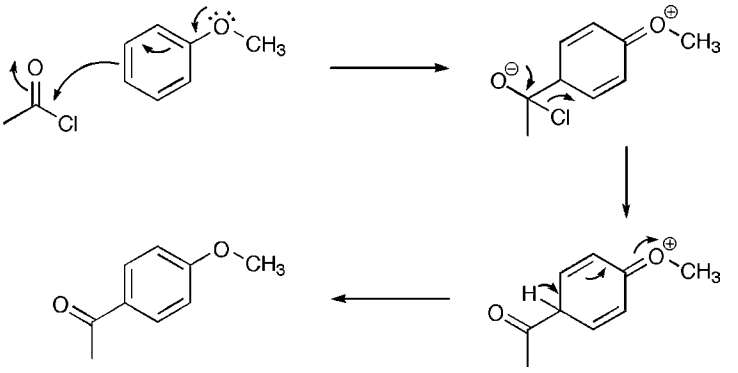


Just as double bonds possess nucleophilic characteristics, so do aromatic rings. By analyzing the charge distribution around an aromatic ring, sites of partial positive charge and sites of partial negative charge can be identified. The sites of partial positive charge are electrophilic in nature, and the sites of partial negative charge are nucleophilic in nature. The partial charge distribution for methoxybenzene was the subject of Problem 2(h) from Chapter 1 and is shown below.

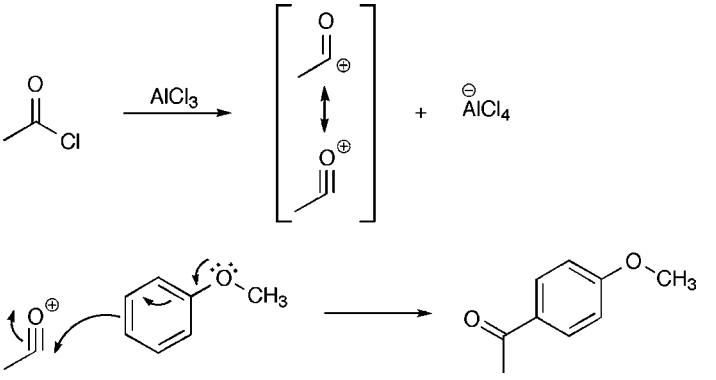


Having identified the nucleophilic sites, this mechanism now becomes an addition–elimination reaction between methoxybenzene and acetyl chloride where methoxybenzene is being added and chloride is being eliminated. As shown below, using arrow pushing, electron movement starts with the methoxy oxygen and moves through the aromatic ring. The addition–elimination steps occur as shown in Problem 6(a). Finally, due to the conjugated and charged system, the proton present on the reactive carbon atom of the phenyl ring becomes acidic. Loss

of this proton allows rearomatization and neutralization of the cationic intermediate, thus allowing conversion to the final product.

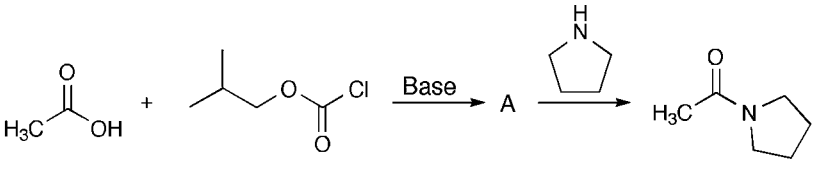


The reaction presented in this problem is known as a Friedel–Crafts acylation. Technically, this example belongs to a class of reactions referred to as electrophilic aromatic substitutions. Furthermore, the actual mechanism associated with this reaction, utilizing Lewis acid reagents as catalysts, proceeds through initial formation of an electrophilic acyl cation followed by reaction with an aromatic ring acting as a nucleophile. This mechanism, shown below, reflects distinct parallels to standard addition–elimination reaction mechanisms warranting introduction at this time.

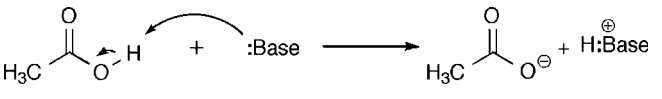


7. *Explain the following amide-forming reactions using arrow pushing. Specify the structures of* ***A***, ***B***, *and* ***C*** *and show all relevant mechanistic steps.*

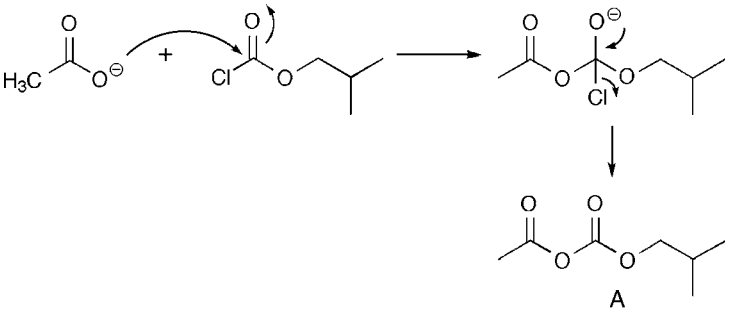
a.



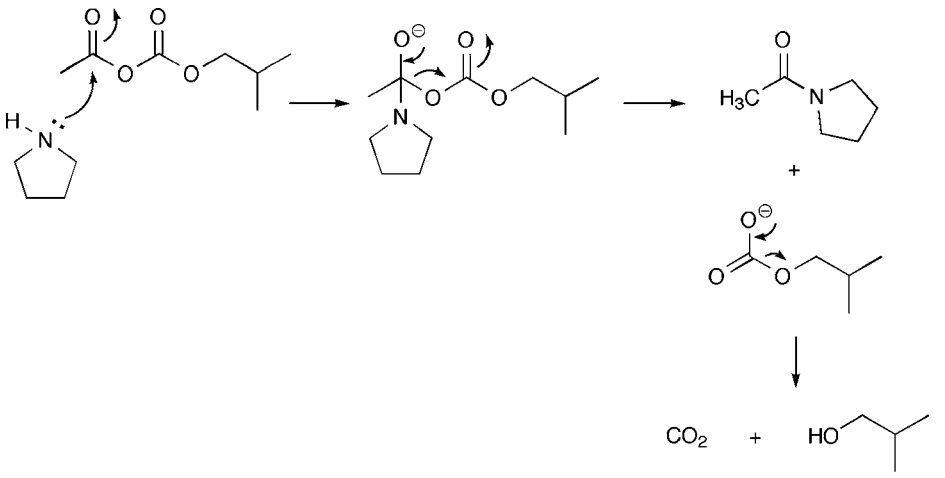
The first step of this sequence is deprotonation of the carboxylic acid by an amine base.



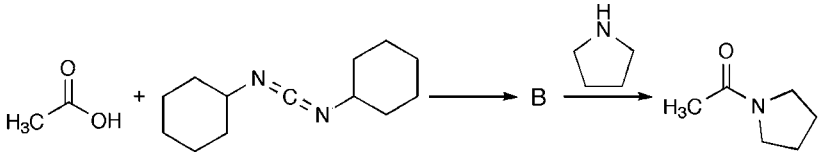
Next, the carboxylate anion participates in an addition–elimination reaction with isobutyl chloroformate. Elimination of a chloride anion results in formation of intermediate **A**. These reactions are generally facilitated by the introduction of an amine base such as triethylamine (not shown in this problem). The mechanism is illustrated below using arrow pushing, and the illustrated product belongs to a class of compounds known as mixed carbonic anhydrides.



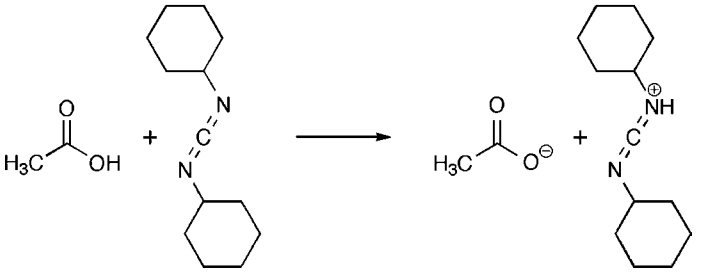
Mixed carbonic anhydrides are a form of activated esters that can react with amines to form amides. The addition–elimination mechanism, illustrated below using arrow pushing, involves addition of an amine followed by an elimination step driven by the release of carbon dioxide.



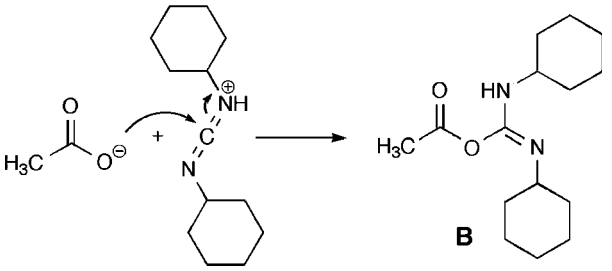
b.



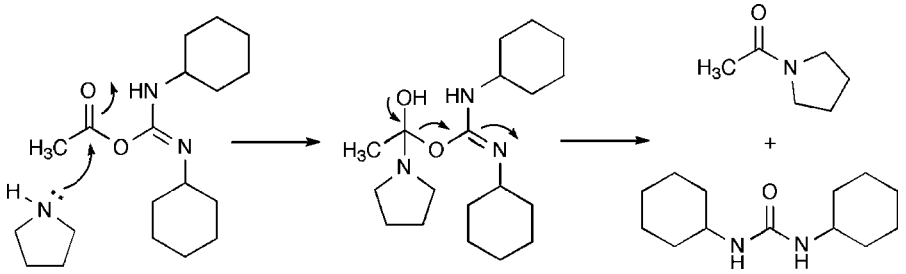
As with Problem 7(a), the first step in this reaction is a proton transfer. In this case, the base is a nitrogen atom present on dicyclohexylcarbodiimide.



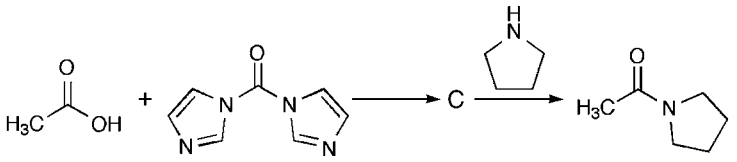
Following proton transfer, the resulting carboxylate anion adds to the protonated dicyclohexylcarbodiimide.



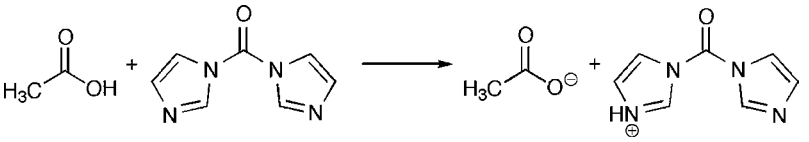
Like the mixed carbonic anhydride (intermediate **A** from Problem 7(a)), intermediate **B** is an active ester that can react with amines to form amides. The addition–elimination mechanism, illustrated below using arrow pushing, involves addition of an amine followed by elimination of dicyclohexylurea.



c.

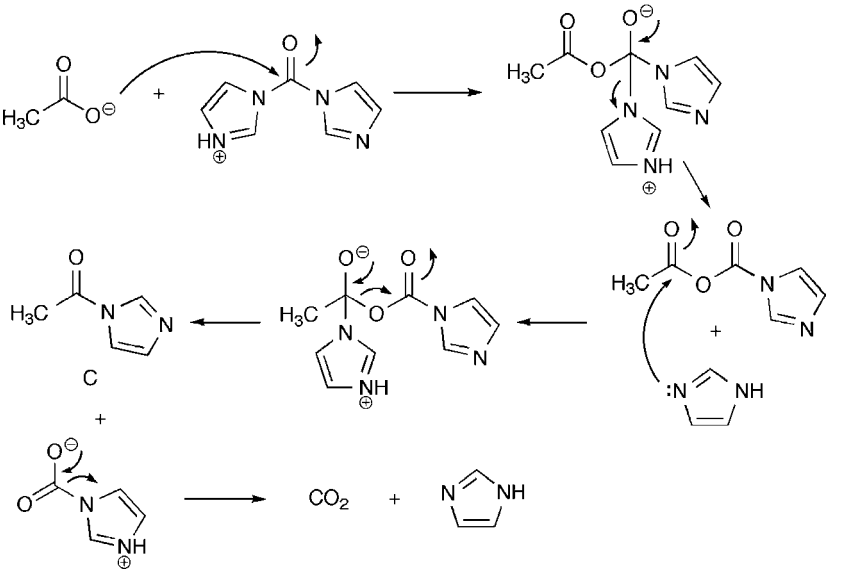


Like Problems 7(a) and 7(b), the first step of this reaction is a proton transfer. In this case, the basic nitrogen is a nitrogen atom present on carbonyl diimidazole.

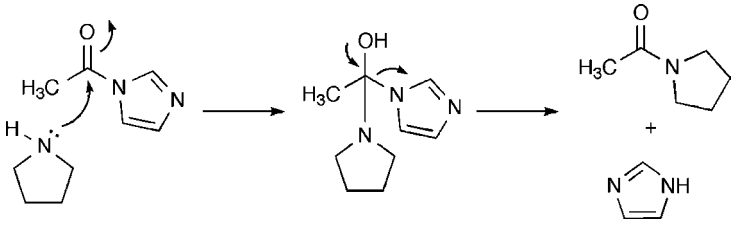


Following proton transfer, the carboxylate anion participates in an addition–elimination reaction where the carboxylate anion adds to the carbonyl of carbonyl

diimidazole and imidazole is eliminated. Intermediate **C** then results from a second addition–elimination step where imidazole adds to the resulting anhydride species, and the group being eliminated decomposes to carbon dioxide and imidazole. This sequence of events is illustrated below using arrow pushing.



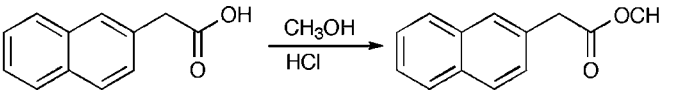
Like the mixed carbonic anhydride (intermediate **A** from Problem 7(a)), the intermediate imidazolide (intermediate **C**) is an activated carboxy group that can react with amines to form amides. The addition–elimination mechanism, illustrated below using arrow pushing, involves addition of an amine followed by elimination of imidazole.



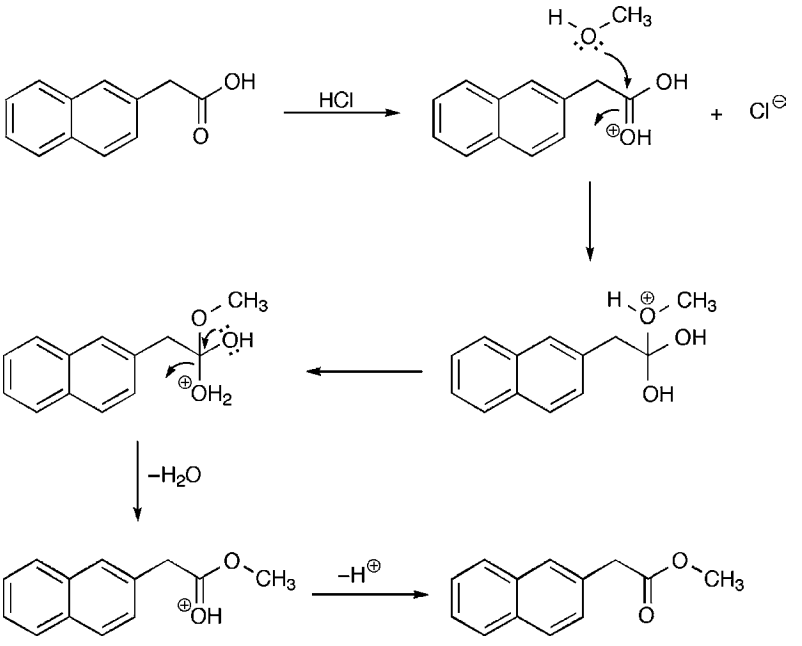
CHAPTER 8 SOLUTIONS

1. *Describe the following functional group transformation in mechanistic terms. Show arrow pushing.*

a.

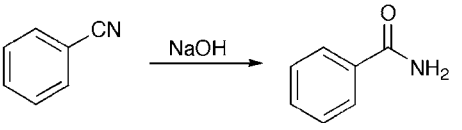


This is an addition–elimination reaction between methanol and a protonated carboxylic acid. As illustrated below, hydrochloric acid protonates the carboxylic acid. Methanol then adds to the protonated carboxylic acid. Elimination of water liberates the methyl ester.



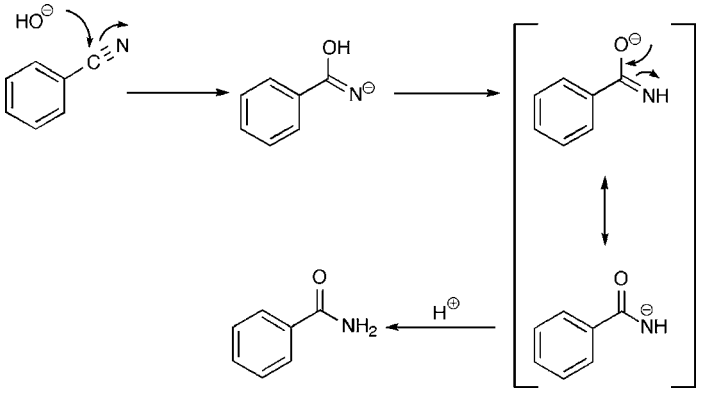
Please note that this reaction is generally run with methanol as the solvent. Under these circumstances, the reverse reaction, ester hydrolysis, does not proceed because the water being liberated during the reaction is so dilute in the methanol that water molecules never interact with the forming ester.

b.

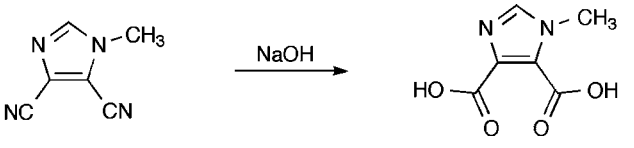


This is a hydrolysis reaction where a hydroxide anion adds to a nitrile. As illustrated below, the hydroxide anion adds to the nitrile carbon atom. Proton

transfer from the hydroxyl group to the nitrogen anion is followed by charge transfer through resonance. This charge transfer results in formation of a carbonyl and a nitrogen anion. The nitrogen anion is neutralized when the reaction is quenched with acid.

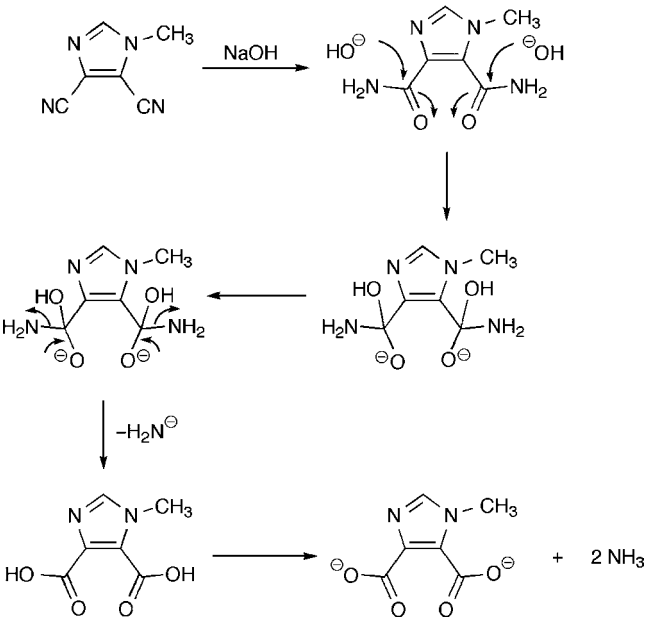


c.



The first step in this reaction is the hydrolysis of two nitrile groups to form amides. The mechanism for the amide formation is identical to that illustrated in the previous example. Continuing from the amides, hydroxide anions add to the carbonyls, generating negative charges on each functional group. Following the addition–elimination mechanistic sequence, the negative charges residing on the oxygen atoms displace amine anions (amide ions), liberating the illustrated carboxylic acids. However, since ammonia is less acidic than a carboxylic acid, the amine anions deprotonate the carboxylic acids, generating

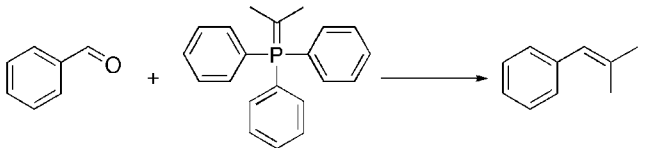
carboxylate anions and ammonia. These carboxylate anions become neutralized on treatment with acid. In order to simplify the presentation of this mechanism, associated sodium cations are omitted. It is understood that each negative charge is associated with a sodium cation.



Please note that this reaction generally requires strongly basic conditions and high temperatures and that the hydrolyses probably occur one at a time.

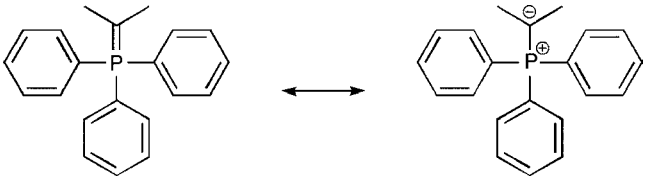
2. *Explain the following reactions in mechanistic terms. Show arrow pushing and describe the reaction as a name reaction.*

a.

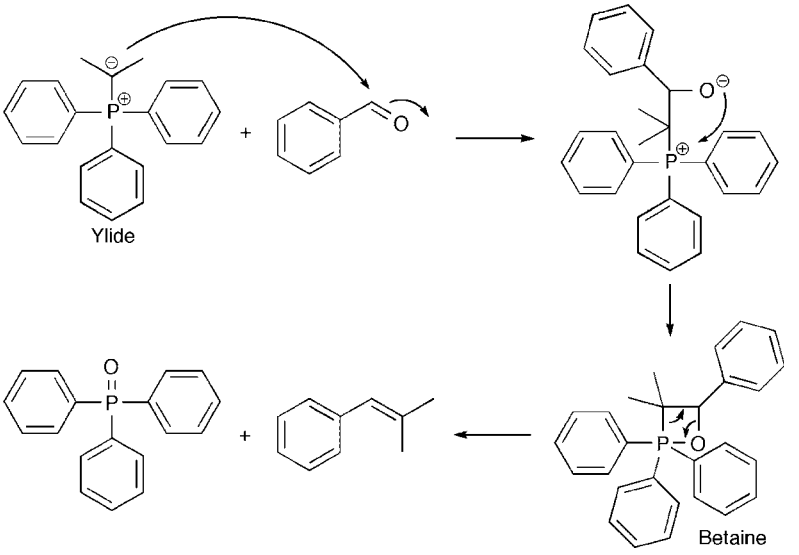


This is an example of the Wittig reaction which occurs when a phosphorus ylide reacts with an aldehyde or a ketone. An ylide is a molecule in which there exists a natural state of charge separation. In this case, the ylide is

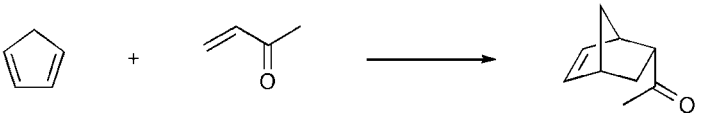
isopropylidene triphenylphosphorane, illustrated below. Note that the phosphorus possesses a positive charge and is electrophilic while the negative charge resides on a carbon atom, rendering it nucleophilic.



The Wittig reaction mechanism involves addition of the anionic carbon atom to the carbon atom of an aldehyde. As illustrated below, the now negatively charged oxygen atom adds to the positively charged phosphorus atom, forming a four-membered ring. This ring, known as a betaine, then decomposes to form an olefin and triphenylphosphine oxide.

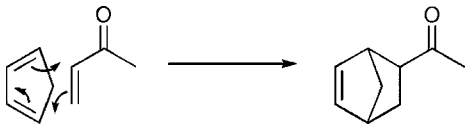


b.

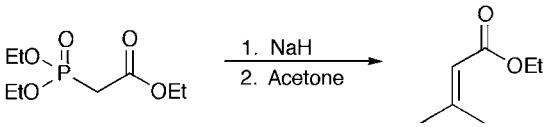


This is an example of a Diels–Alder reaction. This is an electrocyclic reaction where no charges are involved. While no charges are involved, electron pairs do move and their movement can be illustrated using arrow pushing. The mechanism, illustrated below, involves aligning cyclopentadiene (a diene) with methyl vinyl ketone (a dienophile) such that all three double bonds define a six-membered

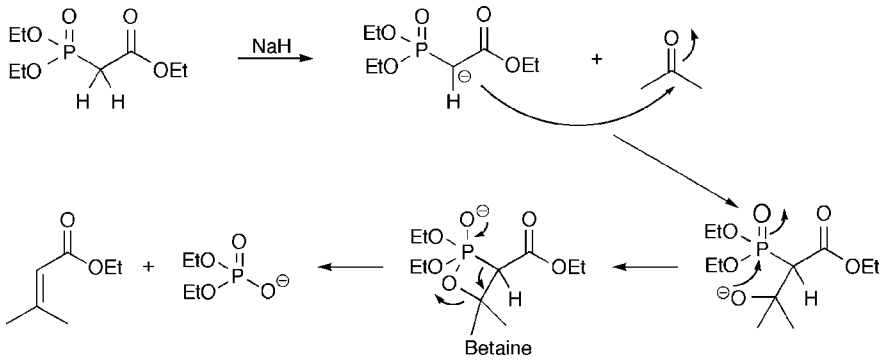
ring. Once the six-membered ring is defined, the electrons simply move to form two new carbon–carbon bonds with a net conversion of two carbon–carbon double bonds to carbon–carbon single bonds. It is important to recognize that in electrocyclic reactions, the total number of bonds never changes. Specifically, seven bonds are involved in the reaction where six of the seven bonds are incorporated in double bonds. Upon conclusion of the reaction, these seven bonds comprise five carbon–carbon single bonds and one carbon–carbon double bond.



c.

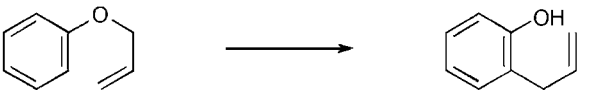


This is an example of a Horner–Emmons reaction. The mechanism, illustrated below, is similar to that discussed for Problems 7(n) and 7(o) from Chapter 4. As shown, the first step involves deprotonation of triethyl phosphonoacetate with sodium hydride. The resulting anion then participates in an addition reaction with acetone. The product of this addition reaction possesses a negatively charged oxygen. This negatively charged oxygen adds into the phosphorus–oxygen double bond, forming a four-membered ring known as a betaine. The betaine, on decomposition as illustrated with arrow pushing, liberates the product.

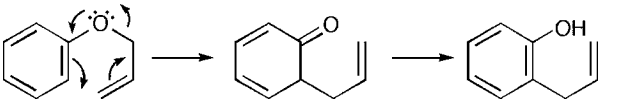


When considering the Horner–Emmons reaction, it is important to recognize that the mechanism and products are similar to those observed during a Wittig reaction. In fact, the Horner–Emmons reaction is a recognized and viable alternative to the Wittig reaction.

d.

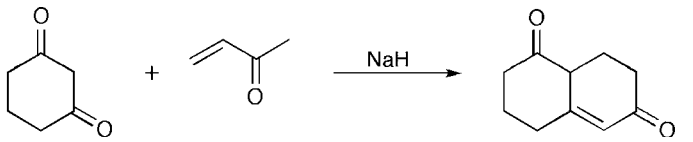


This is an example of a Claisen rearrangement which is an electrocyclic reaction where no charges are involved. While no charges are involved, like the Diels–Alder reaction, electron pairs do move and their movement can be illustrated using arrow pushing. The mechanism, illustrated below, involves moving a lone pair of electrons from the oxygen into the aromatic ring. The aromatic ring then adds electrons to the double bond. The double bond then migrates and the carbon–oxygen bond is cleaved. While the expected product may be the illustrated ketone, spontaneous conversion to the enol form is facilitated by the stability of the resulting aromatic ring. Thus the illustrated product is formed.



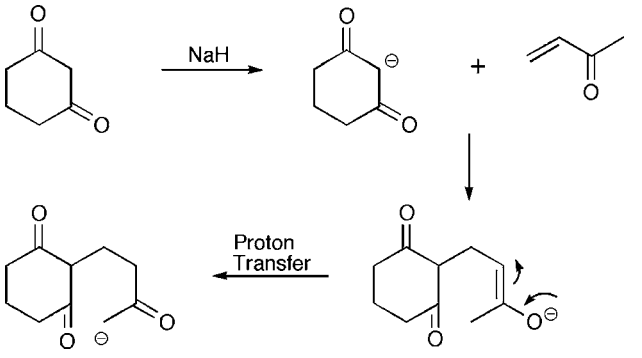
When considering the above mechanistic description, it is important to recognize that all of these steps occur concurrently. Furthermore, like the Diels–Alder reaction (and all electrocyclic reactions), there is no net loss or gain of bonds.

e.

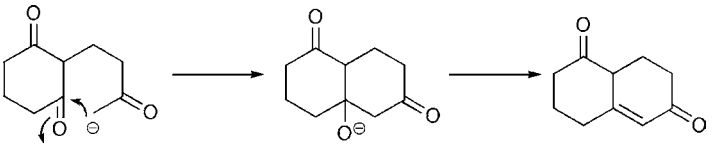


This is an example of a Robinson annulation. The mechanism for the Robinson annulation involves a sequence of conjugate addition reactions and aldol condensations. As illustrated, the first step is deprotonation of cyclohexanedione with sodium hydride. The resulting anion then participates in a 1,4-addition to methyl vinyl ketone. The resulting enolate anion then tautomerizes through

resonance, placing the anion adjacent to a carbonyl. Proton transfer migrates this negative charge to the terminal methyl group.

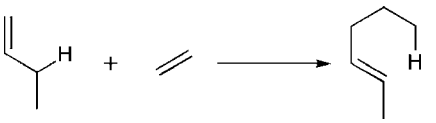


Following formation of a negative charge at the terminal methyl group, the terminal methyl group participates in an aldol condensation with one of the cyclohexanedione carbonyl groups. This aldol condensation involves initial addition of the anion to the carbonyl followed by subsequent dehydration of the resulting alkoxide. This dehydration usually occurs under acidic conditions during isolation of the product and through mechanistic pathways already presented (consider protonation of a hydroxyl group followed by an E1 elimination under solvolytic conditions).



3. *Explain the following name reactions in mechanistic terms. Show arrow pushing.*

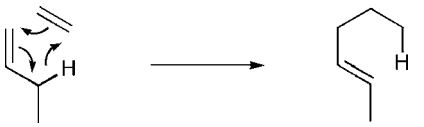
a. *The ene reaction*



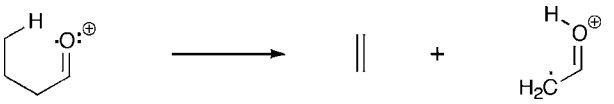
Note: Only the hydrogen involved in the reaction is shown.

The ene reaction is an electrocyclic reaction similar to the Diels–Alder reaction and the Claisen rearrangement. In this reaction, a hydrogen atom is participating in the electrocyclic process. The mechanism, illustrated below using arrow pushing,

involves no charges. Note that there is no net gain or loss of bond count between the starting materials and the product.

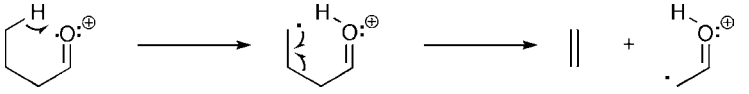


b. *The McLafferty rearrangement*

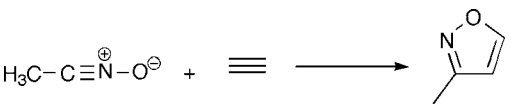


Note: The radical cation present in the starting material is the result of the carbonyl oxygen losing a single electron. This reaction is generally observed during electron impact mass spectrometry.

The McLafferty rearrangement is a reaction generally seen as part of the fragmentation processes observed during mass spectrometry. It is, in fact, during electron impact mass spectrometry that the illustrated starting radical cation is formed. Since this is a radical mediated process, there are no charges involved in the progression of the reaction mechanism other than the positive charge that remains on the oxygen atom. As shown below, using arrow pushing, the first step of this rearrangement involves transfer of a hydrogen atom to the carbonyl oxygen. This occurs through homolytic bond cleavage and bond formation. The second step, also progressing through a homolytic process, involves cleavage of a carbon–carbon bond and liberation of ethylene.

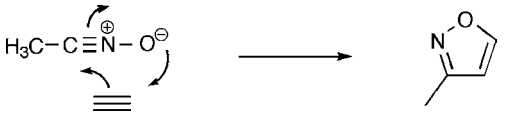


c. *1,3-Dipolar cycloaddition*

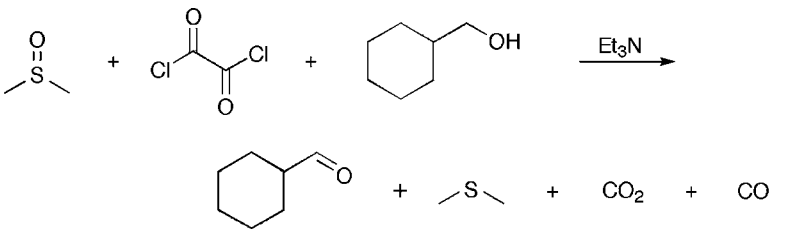


1,3-Dipolar cycloadditions are electrocyclic reactions where one of the starting materials is charged. In fact, the charges on the starting material define the dipole. Like all electrocyclic reactions, there is no net gain or loss of bond count. However, in this case, while the starting material is charged, there are no charges

present on the product. The mechanism of this reaction is illustrated below using arrow pushing.

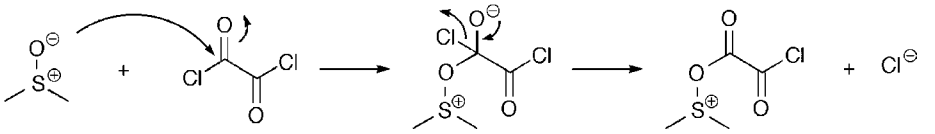


d. *The Swern oxidation*

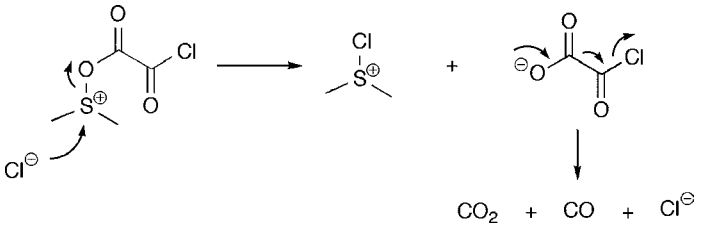


Hint: The oxygen atom in dimethyl sulfoxide is nucleophilic.

In this book, there have been many references to oxidation and reduction reactions. While these reactions are not within the scope of the discussions of this book, their mechanisms do involve the processes presented herein. In the case of the Swern oxidation, the first step is an addition–elimination reaction between dimethyl sulfoxide and oxallyl chloride. This process, illustrated below using arrow pushing, involves addition of the sulfoxide oxygen to a carbonyl with subsequent elimination of a chloride anion.

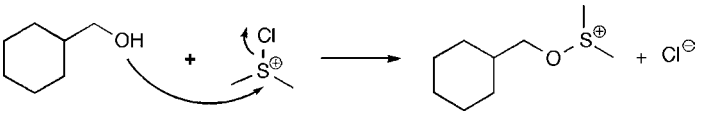


The second stage of the Swern oxidation, illustrated below, involves a nucleophilic displacement of the oxallyl group from the sulfur. In this step, the nucleophile is a chloride anion, and the reaction is facilitated by the decomposition of the leaving group into carbon dioxide gas, carbon monoxide gas, and a chloride anion.

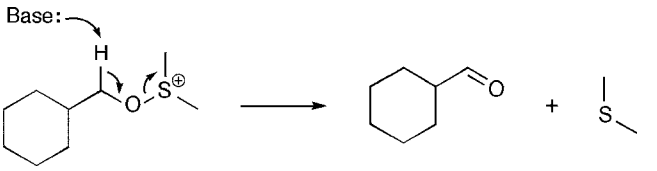


The third stage of this reaction involves another nucleophilic displacement. In this step, the nucleophile is an alcohol and the leaving group is a chloride anion. This

step, illustrated below, involves protonation of the leaving chloride anion forming hydrochloric acid.

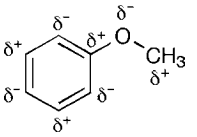


The final stage of this reaction involves an E2 elimination. In this step, illustrated below, a proton adjacent to the oxygen is removed by a base such as triethylamine. The negative charge then forms a double bond with the oxygen and dimethylsulfide is eliminated. The overall oxidation process converts an alcohol into an aldehyde.



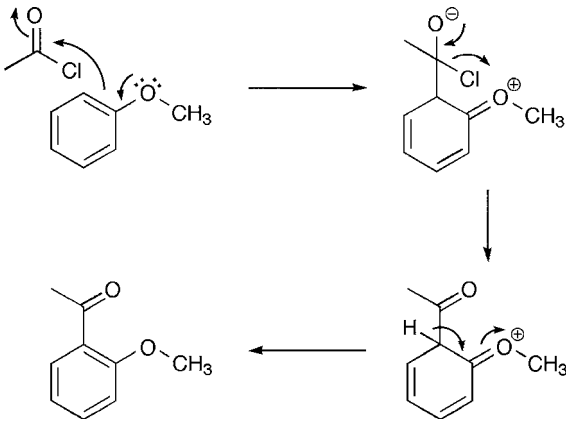
4. *The Friedel–Crafts acylation, illustrated in Scheme 8.12, shows the formation of one product. However, the reaction, as illustrated, actually forms a mixture of two products. Using the arguments presented in the solution set for Chapter* 7, *identify the second product. Show partial charges and arrow pushing.*

Just as double bonds possess nucleophilic characteristics, so do aromatic rings. By analyzing the charge distribution around an aromatic ring, sites of partial positive charge and sites of partial negative charge can be identified. The sites of partial positive charge are electrophilic in nature and the sites of partial positive charge are nucleophilic in nature. The partial charge distribution for methoxybenzene was the subject of Problem 2(h) from Chapter 1 and is shown below.



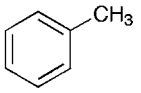
Having identified the nucleophilic sites, this mechanism now becomes an addition–elimination reaction between methoxybenzene and acetyl chloride where methoxybenzene is being added and chloride is being eliminated. As shown below, using arrow pushing, electron movement starts with the methoxy oxygen and moves through the aromatic ring. The addition–elimination steps occur as shown in Problem 6(a). Finally, due to the conjugated and charged system, the proton present on the reactive carbon atom of the phenyl ring becomes acidic. Loss of this proton allows

rearomatization and neutralization of the cationic intermediate, thus allowing conversion to the final product.

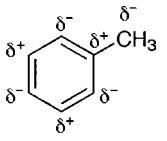


Please note that while the Friedel–Crafts acylation reaction is presented in discussions of addition–elimination reaction mechanisms, this reaction is actually an electrophilic aromatic substitution reaction. The correct mechanisms for a Freidel–Crafts acylation was presented in the solution for Problem 6 (h) from Chapter 7.

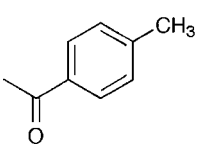
5. *Predict all products formed from a Friedel–Crafts acylation on the following compounds with acetyl chloride. Rationalize your answers using partial charges.*

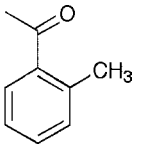
a. 

Identification of the partial charges on toluene (methylbenzene), illustrated below, was the subject of Problem 2(g) in Chapter 1.

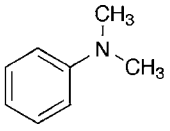


Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the two structures shown below.

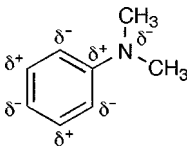




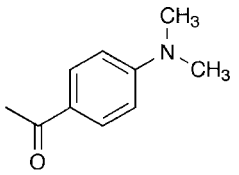
b.

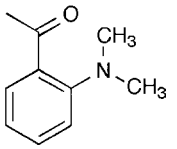


Like methoxybenzene (see Problem 4 in this chapter and Problem 2(h) from Chapter 1), the partial charges of dimethylaniline (dimethylaminobenzene) are dependent upon the electron-donating properties of nitrogen. Thus, the partial charges are distributed as shown below.

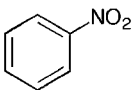


Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the two structures shown below.

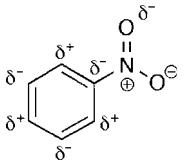




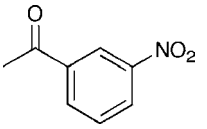
c.



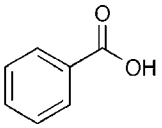
Identification of the partial charges on nitrobenzene, illustrated below, was the subject of Problem 2(j) in Chapter 1.



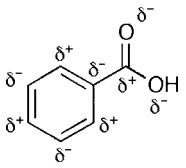
Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the structure shown below. Please note that while there are two carbon atoms bearing partial negative charges, acylation of each of these leads to the formation of identical products.



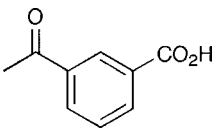
d.



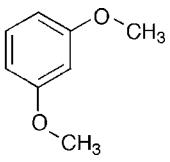
Identification of the partial charges on benzoic acid, illustrated below, was the subject of Problem 2(k) in Chapter 1.



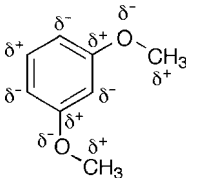
Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the structure shown below. Please note that while there are two carbon atoms bearing partial negative charges, acylation of each of these leads to the formation of identical products.



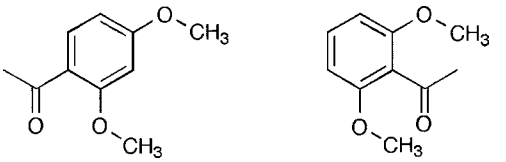
e.



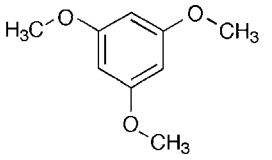
Extrapolating from the arguments presented in Problem 2(h) of Chapter 1, the partial charge distribution of 1,3-dimethoxybenzene is as shown below.



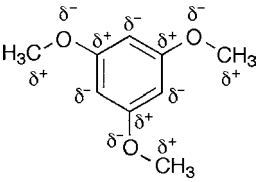
Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the two structures shown below. Please note that while there are three carbon atoms bearing partial negative charges, acylation of two of these leads to the formation of identical products.



f.

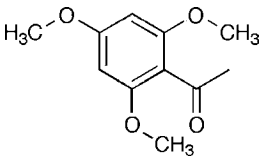


Extrapolating from the arguments presented in Problem 2(h) of Chapter 1, the partial charge distribution of 1,3,5-trimethoxybenzene is as shown below.

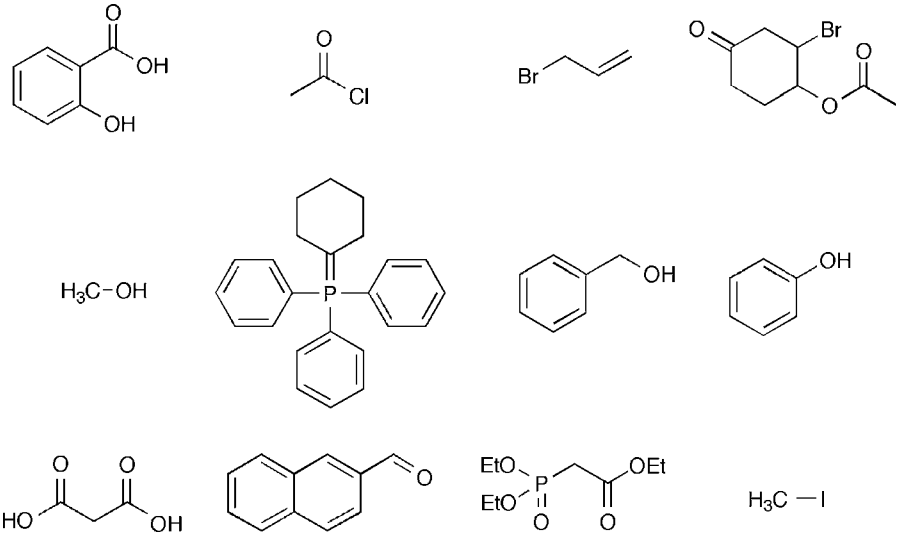


Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the structure shown below. Please note that

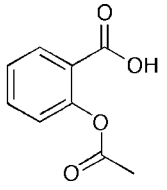
while there are three carbon atoms bearing partial negative charges, acylation of each of these leads to the formation of the same product.



6. *From the following list of compounds propose a synthetic strategy for the specified compounds. Up to four synthetic steps may be required. Any chemical reagents may be used. Show all arrow pushing.*

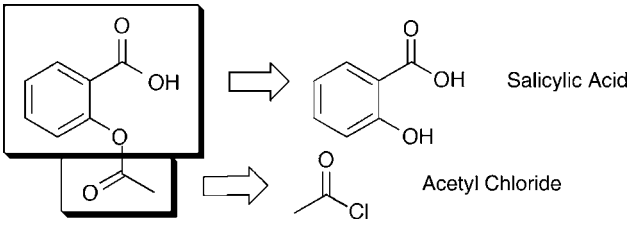


a.

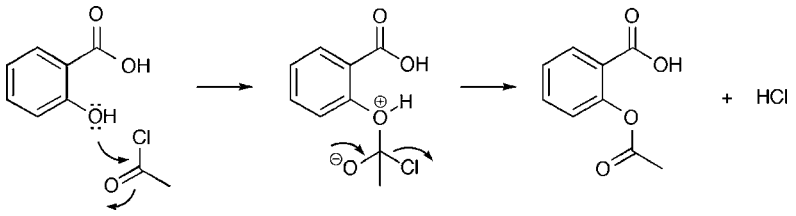


(Acetylsalicylic acid, aspirin)

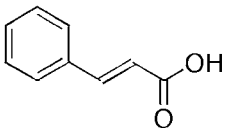
Acetylsalicylic acid, a common pain reliever, is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to salicylic acid and acetyl chloride.



The reaction between salicylic acid and acetyl chloride is an addition–elimination reaction where the hydroxyl group of salicylic acid adds to the carbonyl of acetyl chloride. This addition is followed by the elimination of hydrochloric acid as shown below.

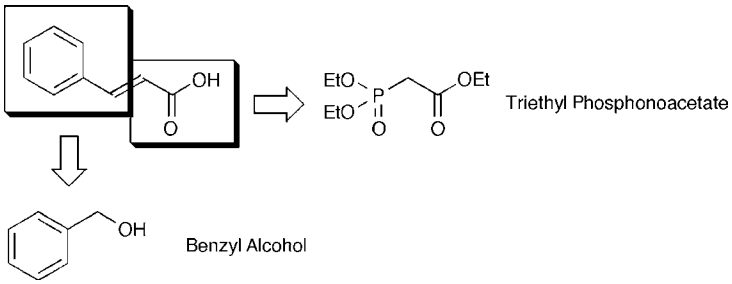


b.



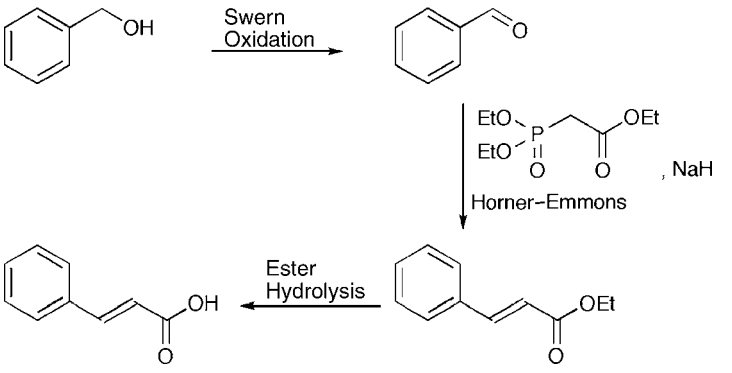
(*Cinnamic acid*)

Cinnamic acid, the active flavor compound in cinnamon, is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to benzyl alcohol and triethyl phosphonoacetate.

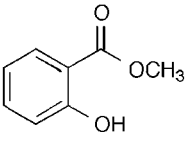


The combination of these compounds will generate cinnamic acid through the synthetic sequence illustrated below. As shown, benzyl alcohol is oxidized to benzaldehyde using the Swern oxidation. Next, the aldehyde is reacted with triethyl phosphonoacetate by applying the Horner–Emmons reaction. Finally, the ester is hydrolyzed to a carboxylic acid. With arrow pushing, the mechanism for the

Swern oxidation is shown in Problem 3(d) of this chapter, the mechanism for the Horner–Emmons reaction is shown in Problem 2(c) of this chapter, and the mechanism for base-mediated ester hydrolysis was highlighted in Scheme 7.19.

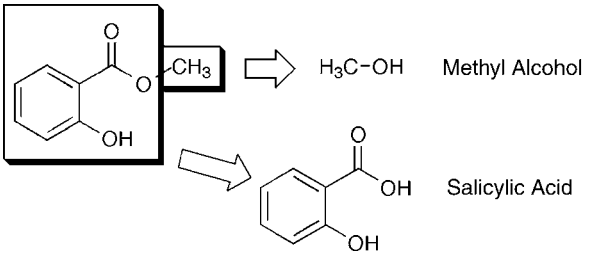


c.



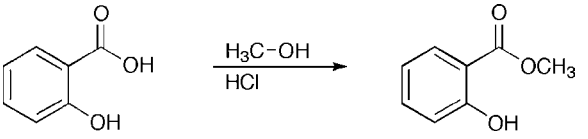
(Methyl Salicylate, oil of Wintergreen)

Methyl salicylate, the active flavor compound in wintergreen candy, is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to salicylic acid and methyl alcohol.

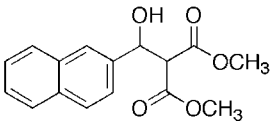


The combination of these compounds will generate methyl salicylate when conditions for an acid-mediated esterification, illustrated below, are applied. The

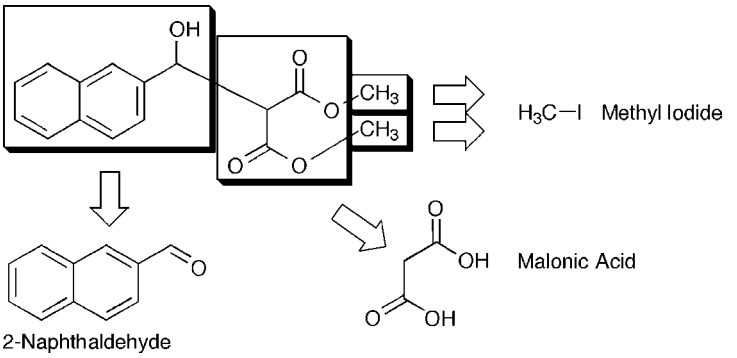
mechanism for this type of ester-forming reaction is shown in Problem 1(a) of this chapter.



d.

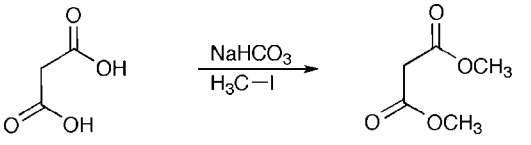


This molecule is composed of three fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to 2-naphthaldehyde, malonic acid, and methyl iodide.



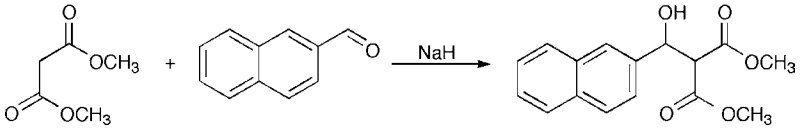
The combination of these compounds will generate the target compound through a two-step synthetic sequence. In the first step, illustrated below, malonic acid is converted to dimethyl malonate under mild basic conditions. This esterification reaction proceeds through an S_N2 reaction between a carboxylate anion and methyl iodide. The mechanism for an S_N2 reaction was presented in detail in Chapter 4. In this reaction it is important to use a base that is sufficient to deprotonate a carboxylic acid but not strong enough to remove a proton from the methylene group of malonic acid. Sodium bicarbonate is generally sufficient

to affect this deprotonation. Please note that this same esterification can proceed under acidic conditions in methyl alcohol.

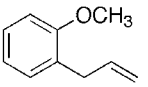


Dimethyl Malonate

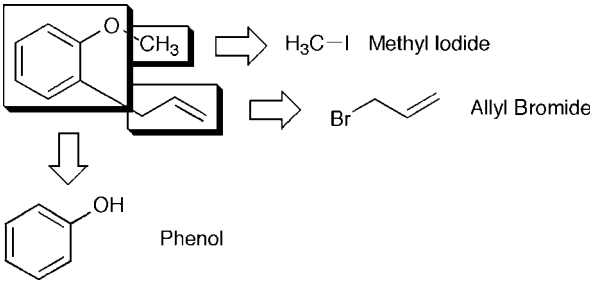
The second step in this sequence, illustrated below, is a 1,2-addition reaction between a dimethyl malonate anion and 2-naphthaldehyde. The mechanism for 1,2-addition reactions was discussed in detail in Chapter 7. In order for this reaction to proceed, it is important to use a base that is sufficient to deprotonate the methylene group of dimethyl malonate. Furthermore, it is important to use a base that will not hydrolyze the methyl esters. Sodium hydride is generally sufficient to affect this deprotonation.



e.

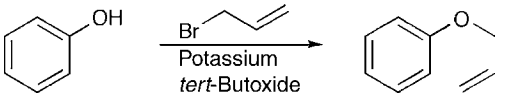


This molecule is composed of three fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to phenol (hydroxybenzene), allyl bromide, and methyl iodide.

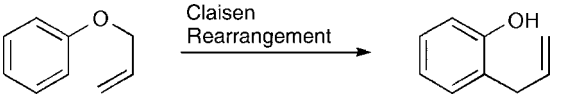


The combination of these compounds will generate the target compound through a three-step synthetic sequence. In the first step, illustrated below, phenol is alkylated with allyl bromide through an S_N2' mechanism. The mechanism for an S_N2' reaction was presented in detail in Chapter 4. In this reaction it is important to

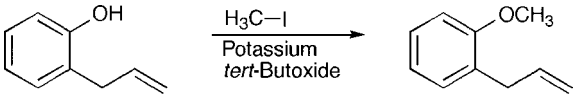
use a base that is sufficient to deprotonate a phenolic hydroxyl group. Potassium *tert*-butoxide is generally sufficient to affect this deprotonation.



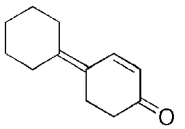
The second step of this sequence, illustrated below, is a Claisen rearrangement where the allyl group is migrated from the oxygen onto the aromatic ring. The mechanism for the Claisen rearrangement was presented in Problem 2(d) of this chapter.



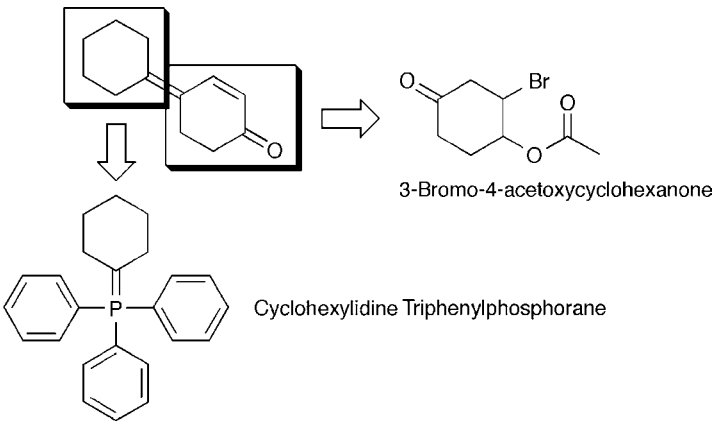
The third step of this sequence, illustrated below, is an S_N2 reaction between a phenol anion and methyl iodide. The mechanism for an S_N2 reaction was presented in detail in Chapter 4. In this reaction it is important to use a base that is sufficient to deprotonate a phenolic hydroxyl group. Potassium *tert*-butoxide is generally sufficient to affect this deprotonation.



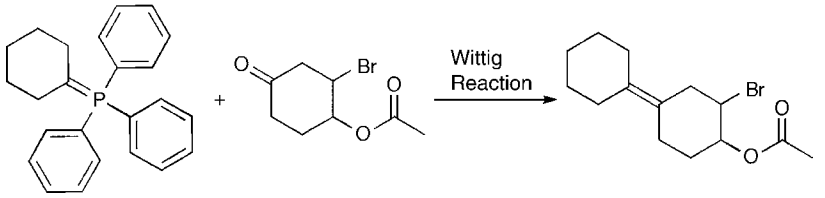
f.



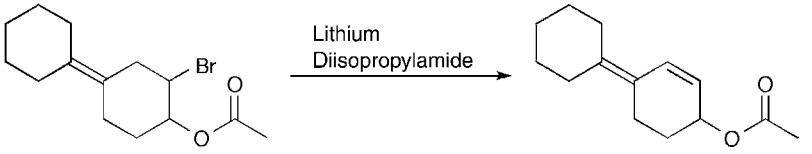
This molecule is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to cyclohexylidine triphenylphosphorane and 3-bromo-4-acetoxycyclohexanone.



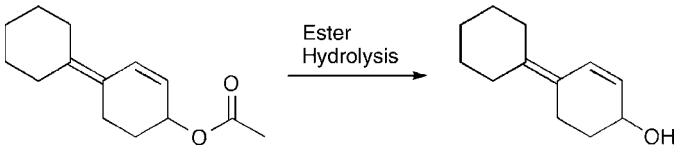
The combination of these compounds will generate the target compound through a four-step synthetic sequence. The first step, illustrated below, is a Wittig reaction between cyclohexylidine triphenylphosphorane and 3-bromo-4-acetoxycyclohexanone. The mechanism for the Wittig reaction was presented in Problem 2(a) of this chapter.



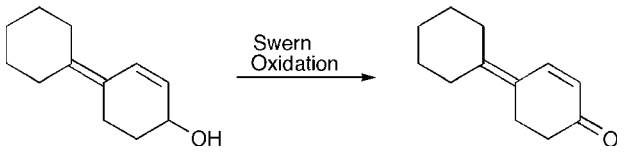
The second step of this sequence is an E2 elimination reaction generating a diene. The mechanism for an E2 elimination was presented in detail in Chapter 6. For this reaction to proceed, it is important to chose a base that is not nucleophilic and strong enough to remove an allylic proton. Lithium diisopropylamide is generally sufficient to affect this transformation.



The third step of this sequence, illustrated below, is an ester hydrolysis reaction. The mechanism for a base-mediated ester hydrolysis was highlighted in Scheme 7.19.



The fourth and final step of this sequence, illustrated below, is an oxidation of an alcohol to a ketone. This transformation can be accomplished utilizing the Swern oxidation. The mechanism for the Swern oxidation is shown in Problem 3(d) of this chapter.



Appendix 3

Student Reaction Glossary

The premise of this book is based on the presumption that introductory organic chemistry entails very little memorization. As presented in the chapters contained herein, this presumption is valid provided the student adheres to the philosophy that the study of organic chemistry can be reduced to the study of interactions between organic acids and bases. At this point, use of the principles presented in this book, in conjunction with more detailed coursework, allows students a broader understanding of organic chemistry reactions as described using combinations of fundamental organic mechanistic subtypes.

The mechanistic subtypes presented throughout this book include those related to the acid–base properties of organic molecules. These are protonations, deprotonations, and proton transfers. Mechanistic types based on solvation effects include solvolysis reactions, S_N1, and E1 processes. Additional mechanisms utilizing ionic interactions include S_N2, S_N2', E2, 1,2-additions, 1,4-additions, and addition–elimination processes. Finally, those mechanistic types dependent upon the presence of cationic species include alkyl shifts and hydride shifts.

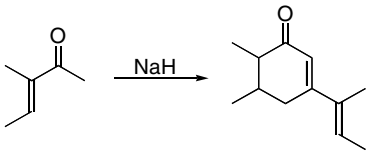
On the following pages, forms are provided that are designed to aid students in summarizing the various mechanistic components of reactions presented during introductory organic chemistry coursework. The forms are designed to allow students to summarize the name of a reaction in conjunction with its flow from starting material to product and its mechanism. To aid in the description of a reaction's mechanism, mechanistic subtypes are listed at the bottom of the table. Additional spaces are provided for students to add in more advanced mechanistic components presented throughout the subject.

As an example, the first form is filled out using the Robinson annulation. In completing this example, each mechanistic step was numbered in order to relate the appropriate mechanistic subtype to those listed in the form. Following this format, students are encouraged to complete additional pages using the reactions described in this book. Students are then encouraged to continue using these forms as an aid in the study of mechanistic organic chemistry.

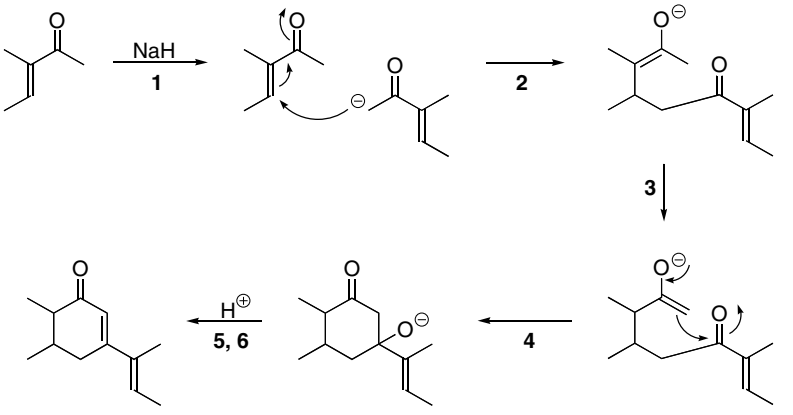
Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

Reaction Name: Robinson Annulation	Homolytic ☐ Heterolytic ☑ Concerted ☐

Summary:



Mechanism:



Mechanistic Types	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*
Deprotonation	1	S_N2		Hydride shift	
Protonation	5	S_N2'		Alkyl shift	
Solvolysis		E1	6	1,2-Addition	4
Proton transfer	3	E2		1,4-Addition	2
S_N1		Addition–elimination			

Reaction Name:	Homolytic ☐ Heterolytic ☐ Concerted ☐

Summary:

Mechanism:

Mechanistic Types	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*
Deprotonation		S_N2		Hydride shift	
Protonation		S_N2'		Alkyl shift	
Solvolysis		E1		1,2-Addition	
Proton transfer		E2		1,4-Addition	
S_N1		Addition–elimination			

*This page may be reproduced as necessary.

Index

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

PERIODIC TABLE OF THE ELEMENTS

1A												3A	4A	5A	6A	7A	8A
1 H 1.008	2A																2 He 4.003
3 Li 6.939	4 Be 9.0122											5 B 10.811	6 C 12.011	7 N 14.007	8 O 15.999	9 F 18.998	10 Ne 20.183
11 Na 22.99	12 Mg 24.312	3B	4B	5B	6B	7B		----------8B----------		1B	2B	13 Al 26.982	14 Si 28.086	15 P 30.974	16 S 32.064	17 Cl 35.453	18 Ar 39.948
19 K 39.102	20 Ca 40.08	21 Sc 44.956	22 Ti 47.9	23 V 50.942	24 Cr 51.996	25 Mn 54.938	26 Fe 55.847	27 Co 58.933	28 Ni 58.71	29 Cu 63.546	30 Zn 65.37	31 Ga 69.72	32 Ge 72.59	33 As 74.922	34 Se 78.96	35 Br 79.904	36 Kr 83.8
37 Rb 85.47	38 Sr 87.62	39 Y 88.905	40 Zr 91.22	41 Nb 92.906	42 Mo 95.94	43 Tc [97]	44 Ru 101.07	45 Rh 102.91	46 Pd 106.4	47 Ag 107.87	48 Cd 112.4	49 In 114.82	50 Sn 118.69	51 Sb 121.75	52 Te 127.6	53 I 126.9	54 Xe 131.3
55 Cs 132.91	56 Ba 137.34	57* La 138.91	72 Hf 178.49	73 Ta 180.95	74 W 183.85	75 Re 186.2	76 Os 190.2	77 Ir 192.2	78 Pt 195.09	79 Au 196.97	80 Hg 200.59	81 Tl 204.37	82 Pb 207.19	83 Bi 208.98	84 Po 210	85 At 210	86 Rn 222
87 Fr 215	88 Ra 226.03	89** Ac 227.03	104 Rt [261]	105 Db [262]	106 Sg [266]	107 Bh [264]	108 Hs [269]	109 Mt [268]	110 [271]	111 [272]	112 [277]		114 [289]		116 [289]		

*Lanthanides	58 Ce 140.12	59 Pr 140.91	60 Nd 144.24	61 Pm 145	62 Sm 150.35	63 Eu 151.96	64 Gd 157.25	65 Tb 158.92	66 Dy 162.5	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.04	71 Lu 174.97
**Actinides	90 Th 232.04	91 Pa 231	92 U 238.03	93 Np 237.05	94 Pu 239.05	95 Am 241.06	96 Cm 244.06	97 Bk 249.08	98 Cf 252.08	99 Es 252.08	100 Fm 257.1	101 Md 258.1	102 No 259.1	103 Lr 262.11

Gaseous at room temperature
Liquid at room temperature
Gallium melts at 29.78 °C
Synthetic elements
All other elements are solid at room temperature