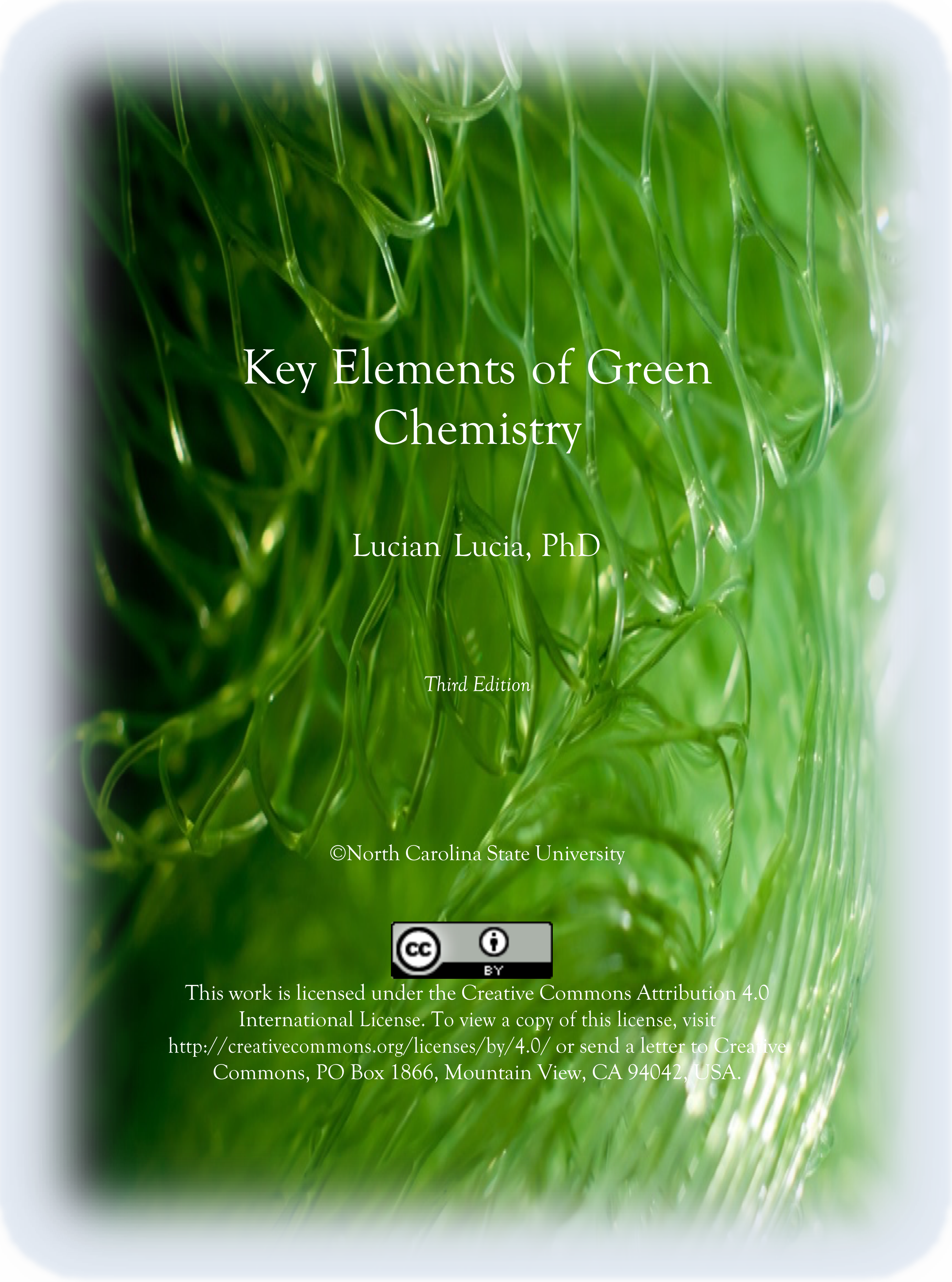

Key Elements of Green Chemistry

Lucian Lucia, PhD

Third Edition

Key Elements of Green Chemistry

Third Edition

Key Elements of Green Chemistry
Third Edition

Lucian Lucia
Departments of Forest Biomaterials, Chemistry,

North Carolina State University

In loving memory of

Agostino Lucia (1930–2003)

&

Maria Lucia (1936–2015)

Table of Contents

About the Author

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BioResources | http://www.bioresources.com

QR Code for ***Laboratory of Soft Materials & Green Chemistry***

Lucian Lucia currently serves as an Associate Professor in the Departments of Forest Biomaterials and Chemistry and as faculty in the programs of Fiber & Polymer Science and Environmental Sciences at North Carolina State University. His laboratory, *The Laboratory of Soft Materials & Green Chemistry*, probes fundamental materials chemistry of biopolymers. He received his Ph.D. in organic chemistry from the University of Florida under Professor Kirk Schanze for modeling photoinduced charge separation states of novel Rhenium (I)-based organometallic ensembles as a first order approximation of photosynthesis. He began his independent professional career as an Assistant Professor at the Institute of Paper Science and Technology at the Georgia Institute of Technology by examining the mechanism of singlet oxygen's chemistry with lignin & cellulose. A large part of his recent work has been focused on the chemical modification of cellulosics for biomedical applications. He teaches "From Papyrus to Plasma Screens: Paper & Society" (PSE 220), "Principles of Green Chemistry" (PSE / CH 335), and acts as graduate supervisor for the Forest Biomaterials Seminar Series (WPS 590 / 790) while providing workshops in Wood Chemistry and Green Chemistry at Qilu University of Technology in PR China. He co-founded and co-edits an open-access international research journal, *BioResources*, dedicated to original research articles, reviews, and editorials on the fundamental science & engineering and advanced applications of lignocellulosic materials.

Preface to the First Edition

Green chemistry is one of the most timely and popular chemistry courses taught in schools. In fact, this decade has been listed as the age of “Green Chemistry” according to a recent ACS compilation. First of all, thanks to Prof. Medwick Byrd, who gave me the chance five years ago to install my edition of green chemistry at North Carolina State University. As it evolved, I realized how scant the learning resources were for this wonderful chemistry that had its roots in 1990. Thus, I dedicated myself in the Fall of 2016 to compile a learning textbook specific to my teaching style and content. Its evolution occurred during the on-the-ground learning environment of this term, but it was truly based on the actual content that evolved since Fall of 2012 when it was first offered at North Carolina State University. My objective for this first edition was to make it a student-sourced learning text that would be essentially a living textual compendium on the nature of what we were learning and discussing. I wanted my students to put their ideas into thought, into practice, and into realization through this particular text. I was very happy with the interest that a contemporary, connected, and living text generated amongst the student population. I realized that I would do this every year and therefore appropriately recognize the Fall 2016 students who greatly contributed and enhanced this living and learning text (alphabetized by first name):

Alan May
Andrea Irving
Frederic Graumann
Millicent Blivin
Robert Wilson
Zack Ufland

Preface to the Second Edition

Since the online accessible version of the first edition, I have worked to add a final, sixth chapter that attempts to encapsulate (not unlike cyclodextrin!) the principles as neatly as possible. In reference to this edition, I ask the Fall 2017 student reader to actively participate in making this edition even more encompassing and thorough. In Fall of 2016, I had six active student participants engaged in reading, editing, and suggesting changes to the text. The class that had access to the first five chapters was on the order of sixty students. This class will have nearly ninety! I would very much like to get you all (no diphthong, really, even if I was born in Virginia!) to critically read and send me your suggestions for edits and additional information, questions, concepts, and suggested reading to include. I welcome your input.

Preface to the Third Edition

Since the second edition, we have been privileged to have our living text hosted at the Open Textbook Library (http://open.umn.edu/openTextbooks/BookDetail.aspx?bookId=538). We have also decided that all students, in the class or outside, have the opportunity to submit edits of our chapters and/or new chapters that we can capture in a classroom setting. All the chapters shown are part of our intended discussion within the boundaries of our weekly meetings. I encourage all students reading this text to submit their ideas to me so I can continue to update and reintegrate the key elements that make green chemistry one of the most fascinating and exciting sciences in our world.

Acknowledgments

I would be very remiss if I didn't acknowledge my Class of 2016 that inspired me to put this living text together. It has made a world of difference to me because it has stimulated me to think and pose what I think is of value. I am deeply indebted to Dr. Medwick Byrd for his commitment to this class by his original suggestion back in 2011 and his constant support of my teaching efforts in class and in the laboratory. His sizeable support of a CEM microwave has lent this class a level of world-class stature in its content and substance to our NC State students. I am very grateful, as well, to Ms. Rachel Scroggins, who was part of my Fall 2015 class and one of my very best students and protégés. She has returned to help me TA our current crop of students and also develop new laboratory exercises. I would be remiss if I didn't acknowledge that she received one of the most prestigious awards an undergraduate student can receive in the USA, the John J. McKetta Undergraduate Scholarship. I would also like to recognize my second home, the Chemistry Department, for their active support and input. Melinda Box, who coordinates our chemistry labs for the University, is a pleasure to work with. Drs. Feducia, Gallardo-Williams, and Neyhart have helped me in directing students to me and helping find TAs. A shout out to Dr. Lisa Bullard at Chemical & Biomolecular Engineering who has been so wonderfully involved in the course through the many fabulous engineering students who have taken it over the last five years. I am also deeply indebted to Dr. Laura Sremaniak who has been a marvelous supporter of our labs, especially the molecular mechanics lab. I am happy to acknowledge Dr. David Tilotta at Forest Biomaterials, who has been a co-instructor of this course over the last several years and has been instrumental in helping me to upgrade and improve the content. It is my hope that this living text is a springboard to future versions of enhanced content.

Chapter 1: Principles of Green Chemistry

"Great ambition is the passion of a great character. Those endowed with it may perform very good or very bad acts. All depends on the principles which direct them."

–Napoleon Bonaparte

Summary of Chapter

Green chemistry is a burgeoning field of heighted chemical consciousness that saw its inception in ~1990 through efforts spearheaded by Paul Anastas and John Warner. Indeed, the twentieth century was a magnificently fertile time for the course of human achievement that embodied the class-modified catchy jingle of DuPont:

"Better living through chemistry"

The opportunities afforded to humans for the rise of organized societies and improvements in lifestyles and quality/quantity of life were never greater in our history. This chapter therefore will introduce the field of green chemistry and how it has captured the public awareness as a force for good. We will begin to examine what constitutes "green" and how human perception of bad vs. good is actually a question rooted in quantity.

Introduction

The rise of the industrial complex and society's strong need to increase its quality of life, security, wealth, and future productivity have helped to relegate the discipline of chemistry and its work to a very lofty position of prominence. Our progress toward achieving a Utopia of human intellectual growth, freedom of choices, equality within classes, and wealth acquisition have been supplemented and encouraged by the fruits of chemical research & development efforts since the dawn of last century. For example, we have witnessed significant strides in the following facets of our lives:

- Water: the introduction of reagents such as chlorine and fluoride to not only reduce and eliminate microbial contamination, but to also improve dental health, respectively;
- Food: we have seen the ability to use fluoro, chlorocarbons (CFCs, "Freon") to help refrigerate foods for much longer "shelf life", packaging that has specific mechanical and antimicrobial properties, and preservatives/food processing aids for eliminating spoilage;
- Clothing: synthetic fibers such as rayon, nylon, polyester, and Kevlar have been indispensable to not only normal wear, but to military, geologic, agricultural, and packaging applications;
- Safety: materials chemistry has spurred the manufacture of lightweight, but tough materials such as helmets, resins, plastics, etc., that have helped save lives in a number of military and industrial sectors.

The chemical industry has played a vital role in the emergence of high quality life within our human societies in these latter areas as well as many others. In fact, the industry is among the top ten industrial sectors in terms of gross output and sales.
One of the most adverse realities and perceptions of the industry is its impact on the environment. Although it is a very safe industry as a whole, well publicized disasters have contributed to a poor public perception. For example, issues such as eutrophication, persistent organic pollutants, BOD, and the famous burning Cuyahoga River are typical of the calamities that damage the reputation and importance of our industry.

Please see http://clevelandhistorical.org/items/show/63#.V7NI5BWU2og

In fact, the morning of June 22, 1969 was witness to a fire from the burning of oil and debris that collected on the surface of the Cuyahoga River (Cleveland). The event roused up a media storm, captured national attention, and was featured in a commentary on the nation's environmental problems (*Time* magazine, Aug. 1). It was a clarion call to how calamitous the nation's environmental problems had become. The then EPA Administrator Lisa Jackson commented years later (2011) that the fire evidence of "the almost unimaginable health and environmental threats" from water pollution of the time. Clearly, as one environmentalist stated, "when rivers are on fire, you know things are bad."

The image was seared into the nation's emerging environmental consciousness and fueled a demand for greater regulation. In 1972, Congress passed the federal Clean Water Act (CWA). Today, the nation's waters are far cleaner, and many credit CWA with preventing other rivers from befalling a similar fate.

The reality is that the fire was a symbol of how bad river conditions in the US had once been. That fire was not the first time an industrial river had caught on fire, but it was the last. For example, the late 19th and early 20th century saw many river fires. At least 13 on the Cuyahoga occurred, whereas there were others on rivers in Detroit, Baltimore, Philadelphia, and elsewhere. Although industries, chemists, and governments do not ever intentionally wish to or contribute to cause harm, the law espoused by "Murphy" holds. The contemporary form of the law can be traced back to 1952 as an epigraph for a mountaineering book by Sack who described the adage as an "ancient mountaineering adage":

Anything that can possibly go wrong, does (Sack, 1952).

Thus, the challenge for contemporary chemists and allied workers in view of the law is to ensure that any and all reactions, processes, and designs keep this general philosophy in mind. Our goal in the twenty first century is to mitigate potential disasters that can occur from our chemistries and engineering.

Sustainable Development

The concept of "sustainable development" was articulated from a UN Commission on Environment and Development in 1987 (Brundtland Commission). It is simply stated:

'..meeting the needs of the present without compromising the ability of future generations to meet their own needs.'

Since the Brundtland Commission, a number of governments, NGOs, and societies have considered deeply what sustainable really means. Several of the key drivers heating up this discussion include:

1 – What is an acceptable rate of depletion of fossil fuels? Is there?
2 – Is there an acceptable level of pollution to release into the atmosphere and water?

Obviously, waste is a given in any industrial process, but the primary question is not its generation, but how it is handled. If we produce a waste stream, can it be recovered, recycled, or reused? If carbon dioxide is the waste stream, can we conclude that nature will sequester it or will it contribute to global warming (climate change)? These are questions that warrant intense analysis and follow-up. The overall fate of the planet (humanity, ecosystems, and our way of life) hang in the balance. Methods to address ensuring the continuation of our planet and its resources include:

- Not allowing for the accretion of toxics (e.g., heavy metals) from the earth's crust and other beds;
- Not continuously creating non-degradable/perishable compounds (e.g., CFCs, benzodioxocins) that can cause significant damage to the ozone and aquatic life, respectively;
- Ensuring that the natural processes in place on earth are not disrupted (e.g., ravaging rainforests, polluting watersheds);
- Not depleting or hoarding natural resources (e.g., water).

We as an educated community (students, teachers, government workers, industry workers, etc.) recognize and appreciate that the Earth is equipped to deal with hiccups and disturbances in its processes, but continuously pushing such boundaries of recovery will only lead to disasters. Indeed, a paradigm for ensuring that our chemical processes do not exceed the capacity of the Earth to engage in buffering and recovery is the following:

To promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture, and use of chemical products.

The above statement defines the concept of "Green Chemistry." The subject has now become a very well accepted and welcomed part of many chemistry curricula and industry philosophies. In fact, the concept of a triple bottom line, i.e., financial, social, and environmental owes its existence to green chemistry. Green chemistry has become an incredibly indispensable field within the panoply of chemistry subject matter. Its content and mission, however, are very unique in comparison to its sister courses because it embodies a social and environmental focus.

Concepts:

Agricultural Support

The growing of crops in different farming regions to feed the masses owes its potential greatly to harnessing the power of chemicals such as herbicides, pesticides, fungicides, etc. Although in general we tend to think of the benefits of pesticides, there are a number of issues associated with their use that go well beyond their ability to promote the cultivation and availability of food. For example, DDT (show below in **Figure 1-1**) is a chemical that has seen much use in the US. Over the period of 1950 to 1980, it was used in agriculture at the rate of more than 40,000 tons each year worldwide and it has been estimated that a total of 1.8 million tons have been produced around the world since the 1940s. In the United States, it was manufactured by numerous companies including Monsanto, Ciba, Montrose Chemical Company, and Pennwalt. More than 600,000 tons (1.35 billion pounds) were applied in the US before it was banned in 1972.

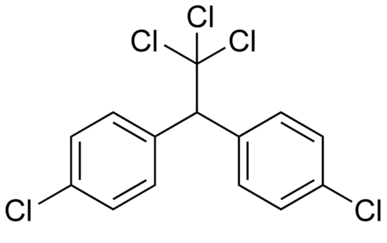


Figure 1-1 Shown above is a chemical representation of DDT or **D**icholoro**D**iphenyl**T**richloroethane, a colorless, crystalline, tasteless and nearly odorless organochlorine compound that displays insecticidal properties with huge environmental impacts. DDT has been formulated in multiple forms that include solutions in xylene or petroleum distillates, emulsifiable concentrates, water-wettable powders, including solutions in vaporizers and lotions. https://www.wikiwand.com/en/Dichlorodiphenyltrichloroethane

Nature's Best

The idea that nature produces chemicals that are "green" is a fallacy or a myth. The concept of green deserves some clarification at this point. What is green and what isn't is actually a matter of nature, quantity, human safety, long term effects, and acute toxicity. Green is generally a term associated with a sustainable (renewable) product or non-toxic process whose employment in society has no acute toxicity and a general favorable life cycle analysis. There are a number of documented chemicals in nature that are extremely toxic even at small doses thus invalidating the idea that nature is "green". For example, aflatoxin B_1, shown below in **Figure 1-2**, is a toxin produced by *Apsergillus flavus* and *A. parasiticus* that is one of the most potent carcinogens known. It is a common contaminant of a variety of foods including peanuts, cottonseed meal, corn, and other grains as well as animal feeds. According to the Food and Agriculture Organization, the worldwide maximum levels of aflatoxin B_1 is in the range of 1–20 μg/kg in food, and 5–50 μg/kg in dietary cattle feed.

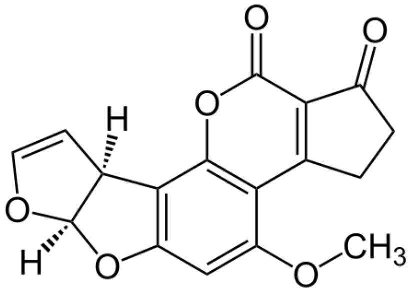


Figure 1-2. Shown above is a chemical representation of Aflatoxin B_1, one of the most notorious carcinogens available. And it is "natural"! The IUPAC name is: 6aR,9aS)-2, 3, 6a, 9a-Tetrahydro-4-methoxy-1H, 11H cyclopenta[c]furo[3',2':4,5]furo[2,3- h][1]benzopyran-1,11-dione. https://www.wikiwand.com/en/Aflatoxin_B1

Shown in **Figure 3** below is a derivative of lysergic acid. Lysergic acid, also known as D-lysergic acid and (+)-lysergic acid, is a precursor to a diverse array of ergoline alkaloids produced by the ergot fungus and found in the seeds of *Turbina corymbosa* (ololiuhqui), *Argyreia nervosa* (Hawaiian Baby Woodrose), and *Ipomoea tricolor* (morning glories, tlitliltzin). Amides of lysergic acid, lysergamides (see Fig. 3), are widely used as pharmaceuticals and as psychedelic drugs (LSD). Lysergic acid received its name from the lysis of various ergot alkaloids.

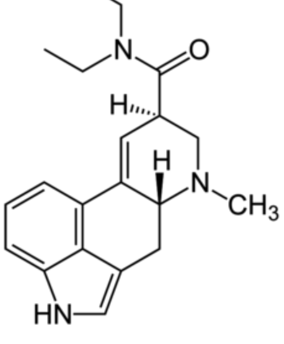


Figure 1-3. Shown above is the diethylamide version of lysergic acid. https://www.wikiwand.com/en/Lysergic_acid

Again, as already stipulated, nature's best does not necessarily imply that her products are "green". Green, by virtue of the product distribution found in nature (e.g., cocaine), can certainly pose serious if not lethal implications for human consumption. We all know that sodium chloride is ubiquitous within nature. It is a common salt that manifests a cubic crystal lattice structure that readily dissolves in water where it is mostly found. Humans consume it in great quantities as a flavorant, seasoning, and preservative. Nevertheless, its mass consumption especially in the US has led to > 65 million people afflicted with high blood pressure while numerous others have all other maladies associated from its overconsumption.

Accidents & Waste Minimization

Waste because of the nature of living processes is a natural consequence. Within the *schema* of living cell frameworks, the ability to generate waste is considered a clear indication of a "living" system. Waste is a necessary by-product of any work function even if it is heat, light, or some other form of energy by virtue of the intrinsic inefficiencies associated with the utilization of "fuel" or raw materials. For example, even a newborn that is fed on breast milk, a ideal natural food source for babies, does not simply produce a non-material, i.e., heat/energy dissipation, waste product. The problems associated with waste including inherent inefficiencies with using resources are how it builds up and affects the quality of the environment. In general, we cannot prevent waste because everything is subject to entropy (please see: https://prezi.com/lwp2rodqux3p/wasteful-chemical- reactions-8a/).

The crux of the problem associated with waste boils down to safety. As alluded to in the Prezi example above, rust can cause material fatigue or loss of integrity that can compromise functionality. Additionally, chemical processes that produce waste need to adhere to the three general "R"s of Green Chemistry:

- Reduce
- Reuse
- Recycle

Case Study – LeBlanc Process

The Leblanc process industrial factories were very damaging to the local environment. It was an early industrial process for producing *soda ash* (sodium carbonate) that was named after its inventor. It required two stages: sodium sulfate (salt cake) produced from sodium chloride (salt, we just discussed this!) followed by reaction with coal and calcium carbonate to produce sodium carbonate. It eventually became obsolete after development of the Solvay process.

The process of generating salt cake involved reacting salt with sulfuric acid which released hydrochloric acid gas, an acid that was industrially useless in the early 19th century and therefore vented into the atmosphere. Also, an insoluble, smelly solid waste (CaS, *galligu*) was produced. The inefficiency of the process was horrific! Each ton of soda ash, the process produced ~1.5 tons of hydrogen chloride and >1 ton of calcium sulfide, the useless waste product! Galligu had no economic value so it was piled in heaps and spread on fields where it weathered to release hydrogen sulfide (what a smell!).

Leblanc soda works then became targets of lawsuits and legislation. A lawsuit from 1839 alleged that, "the gas from these manufactories is of such a deleterious nature as to blight everything within its influence and is alike baneful to health and property. The herbage of the fields in their vicinity is scorched, the gardens neither yield fruit nor vegetables; many flourishing trees have lately become rotten naked sticks. Cattle and poultry droop and pine away. It tarnishes the furniture in our houses, and when we are exposed to it, which is of frequent occurrence, we are afflicted with coughs and pains in the head ... all of which we attribute to the Alkali works."

Therefore, in 1863, the British Parliament passed the first Alkali Act, a precursor to the first modern air pollution legislation. This Act dictated that no more than 5% of the hydrochloric acid produced by alkali plants could be vented. To comply, soda works passed it up a tower packed with charcoal where it was absorbed by water flowing in the other direction. Unfortunately, the chemical works usually dumped the resulting solution into nearby bodies of water where it promptly ended up killing fish and other aquatic life.

Conclusions

The greatest blight affecting the modern time is the apathy associated with ignorance. We tend to strongly adhere to wrongful beliefs—all manufacturing and industrial processes are failsafe in protecting humans and the environment. The truth is that Murphy's Law more often than not is RIGHT. Thus, the need for pre-emptive measures as embodied by the principles of green chemistry is of paramount significance. The principles as listed below will be constitute a future chapter in this book:

Prevention
It is better to prevent waste than to treat or clean up waste after it has been created.

Atom Economy
Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

Less Hazardous Chemical Syntheses
Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

Designing Safer Chemicals
Chemical products should be designed to affect their desired function while minimizing their toxicity.

Safer Solvents and Auxiliaries
The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

Design for Energy Efficiency
Energy requirements of chemical processes should be recognized for their environmental and

economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

Reduce Derivatives

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

Real-time analysis for Pollution Prevention

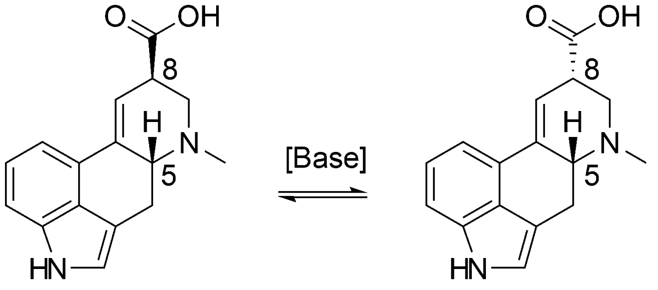
Analytical methodologies need to be further developed to allow for real-time, in- process monitoring and control prior to the formation of hazardous substances.

Inherently Safer Chemistry for Accident Prevention

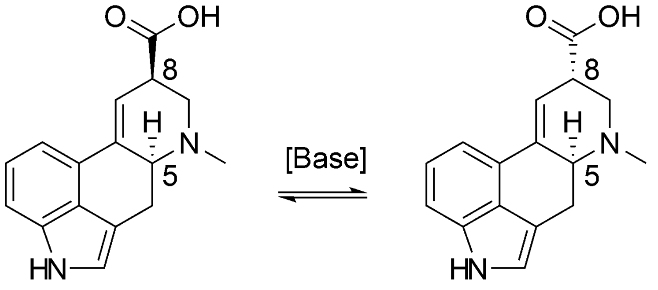
Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Review Questions

1. Using lysergic acid as a starting point, indicate the general type of chemistry (you can indicate in your own words what is happening) that would need to occur in order for the epimerization of lysergic and L-lysergic acid to occur shown below. https://www.wikiwand.com/en/Lysergic_acid



Lysergic acid **Isolysergic acid**



L-Lysergic acid **L-Isolysergic acid**

2. How does too much salt in a human's diet contribute to high blood pressure?
   a. What are two known chemical mechanisms (reactions) that enzymes can pursue for bonding to 4-hydroxy-2-nonenal?
   b. Come up with a way to quantify the inefficiency of a reaction; that is, derive a quantitative measure of the wastefulness of a reaction using the LeBlanc numerical process information contained in this chapter.

Further Reading

1. Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. By permission of Oxford University Press.
2. http://time.com/3921976/cuyahoga-fire/
3. https://www.theartof.com/articles/consumerism-mass-extinction-and-our-throw- away-society
4. Video on importance of green chemistry and some advances in the green chemistry field. https://www.youtube.com/watch?v=rIE4T2HLW7c
5. Reference: "EPA Green Chemistry". *YouTube*, 2016. Web. 29 Nov. 2016.

Chapter 2: Life-Cycle Analysis

"If you laugh, you think, and you cry, that's a full day. That's a heck of a day. You do that seven days a week, you're going to have something special".

–Jim Valvano

Summary of Chapter

Green chemistry relies on the implicit understanding that processes, reactions, and materials used by us as scientists are indeed sustainably driven and “green”. However, the notion of “green” is not well-established from a quantitative perspective. In fact, it tends to be blurred by a knee-jerk intuitive response to green; for example, if we use water as a solvent, well then, compared to benzene or most other petroleum-based solvents, it must be green. We will demonstrate in this chapter that this kind of “fuzzy” thinking is counterproductive to the field. We will show examples and provide skills to endow the student with a better sense of what is and what isn’t green.

Introduction

Green chemistry, in addition to being a science, it is also a philosophy and nearly a religion. Attendance at American Chemical Society Green Chemistry & Engineering Conferences will instill such an ideal into any attendant because of the universal appeal and possibilities in this novel approach to radicalizing the business of doing science and engineering.

Life Cycle Assessment (LCA) is a comprehensive life cycle approach that quantifies ecological and human health impacts of a product or system over its complete life cycle. It uses credible scientific methods to model steady-state, global environmental and human health impacts. It also helps decision-makers understand the scale of many environmental and human health impacts of competing products, services, policies or actions.

Please see for more information https://www.youtube.com/watch?v=NQTW7jjXVmE (*LCA: Intro to Life Cycle Assessment*. (2013).)

Triple bottom line (economic, social, and environmental)

Triple Bottom Line accounting enables enterprises to support sustainability analysis in their operations, products and services.

LCA contributes to the Triple Bottom Line reporting by quantifying the ecological and human health performance of competing products and services (**Figure 2-1**).

Adding the social and economic performance reporting of a product or service to the LCA results of the product or service is one way to deliver Triple Bottom Line reporting.

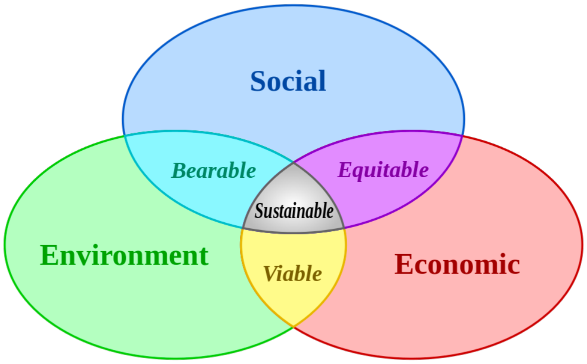


Figure 2-1. The triple bottom line in GC containing social, economic, and environmental Venn diagram whose intersection contributes to a valid sustainability analysis.

LCA for Decision Making

Who makes decisions

- Company product managers or planners
- Company procurement and purchasing
- Industrial sector consortia
- (example: aluminum manufacturers)

- Regional or national policy makers
- Consumers, customers and product users

Primary drivers and expectations for LCA:

- Learning about the environmental performance of products
- and services
- Minimizing production and regulatory costs
- Minimizing environmental and human health damage
- Understanding trade-offs between multiple impact categories
- and product phases
- Supporting equitable economic distribution
- and profitable operations

Types of decision situations

- strategic planning and capital investments
- (green building, waste management)
- eco-design, product development
- operational management
- (green procurement)
- communication and marketing
- (eco-labeling, product information)

Eco-labels:

Type 1)
Third-party certified multi-criteria environmental labeling Example: Forest
Stewardship Council label for wood products Type 2)
Environmental self-declaration claims
Example: Single issue claim such as the "bio-degradable" label Type 3)
Independently verified label with preset quantified indices Example:
Numerical water consumption rating for a dish washer

Eco-labels that require LCA:

Type 1) Third-party certified multi-criteria environmental labeling Type 3)
Independently verified label with preset quantified indices

Life Cycle Assessment (LCA) enables the creation of Type 1 and Type 3 eco-labels. These eco-labels can be powerful tools in obtaining larger shares of a specific market sector.

Life cycle assessment (LCA) is a standardized programmatic tool to determine the environmental impacts of products or services. It can be described by a four-part framework as outlined by the 14044 ISO standard, which includes:

1. Goal and scope definition

2. Life cycle inventory
3. Life cycle impact assessment
4. Interpretation

This integrated framework was inspired by earlier forms of life-cycle thought from life cycle financial analysis. Examining a product from origination to use and disposal provides more holistic analysis to identify where environmental impacts originate and guide efforts in reducing impacts.

The ISO standards (http://www.iso.org/iso/home/standards.htm) provides guidance on structure framework, reuse requirements of data, study assumptions, and methods. By using more standard LCA methodologies, studies are more comparable and of greater scientific rigor. A standardized method allows LCA practitioners to manage complex datasets, provide comparisons among products, and allow benchmarking. In the absence of a standardized method, the results of LCA studies are even more variable depending on study assumptions and methods. The ISO standards help reduce the influence of the practitioner influence on study results.

Concepts:

Goal, Scope, and Definition

Assumptions inherent in an LCA study are apt to change the results and conclusions derived from analysis. In addition, many different types of studies require various levels data collection and analysis. The goal and scope of a LCA defines its intent, targeted audience, and use. The intended use informs further decisions for scope, functional unit of comparison, and data collection. For example, if a LCA study is used internally, a full review panel of LCA experts is not required; however, when providing public environmental claims about a competing product, a review is required.

Inventory analysis

A life cycle inventory (LCI) is the most laborious step of a LCA: data is collected and organized. It often involves contacting companies, accumulating literature sources, and building models using life cycle assessment software. Materials flows, types of materials, product life time, and product energy requirements are collected in the LCI phase.

Life Cycle Impact Assessment

A life cycle impact assessment (LCIA) part of the analysis process collects life cycle inventory data and delivers environmental impacts values. This process greatly reduces the complexity of the data set from hundreds of inputs to 10 or fewer impact categories for decision-making. There are many different methods for LCIA based on location, goals, and scope.

Interpretation

The interpretation step derives from what was found in the other steps for the generation of new information. It is not the last step but iterative. When it is done, the study assumptions, goals, scope, and methods are refined to suit the needs of the study.

LCA goal, scope, and boundaries

Goal

The first step is defining the goal to give the aim and what it encompasses. There are two types of LCA objectives: (1) descriptive and (2) change-oriented. The descriptive types look at broader aspects of an issues, e.g., how much of the world's carbon dioxide emissions are derived from commuters (light duty vehicles). These broader environmental questions fall within the domain of descriptive LCAs. The second type of LCA is change-oriented, in which two options for fulfilling a function are compared. Typical examples of change-oriented LCAs are paper vs. plastic, flying vs. driving, and gas vs. electric heating. These types of studies can guide the choice of methods to reduce environmental impacts. The intended audience is another part of the goal and scope. The audience may include interest groups such as policy makers, company marketing groups, or product development teams. Additionally, interest groups should be identified. These include companies, funding sources, target audiences, and expert reviewers. It is noted that the intended use of the LCA may be different from the end use because the information may be relevant to other decisions and analyses beyond the original intent.

One specific LCA to compare two products is a "comparative assertion disclosed to the public". In this type of study, "environmental claims regarding the superiority or equivalence of one product vs a competing product which performs the same function" are communicated. These types of studies must follow ISO 14044 standards with the nine steps for a "comparative assertion".

Scope definition

The scope definition serves the purpose of communicating to the audience what is included and what is excluded. Depending on the goal, there are several types of scopes including cradle-to-gate, cradle-to-grave, and gate-to-gate. There are other words commonly used to describe these scopes:

- Cradle-to-grave: includes all flows and impacts from obtaining raw material to disposal and reuse
- Cradle-to-gate: includes all flows and impacts from raw material to production, but excludes product use and end of life
- Gate-to-gate: only includes flows from production or material processing steps of a product life cycle

The scope must be carefully selected in consideration of the potential implications not including product stages or phases in the scope of the work. For example, a product may have lower production emissions, but have a shorter lifetime than an alternative product that would not be considered if a cradle-to-gate boundary was used. The scope of the study is often best communicated in a process stage diagram as seen in **Figure 2-2**. These types of diagrams list the major unit steps considered and clearly show what is not included.

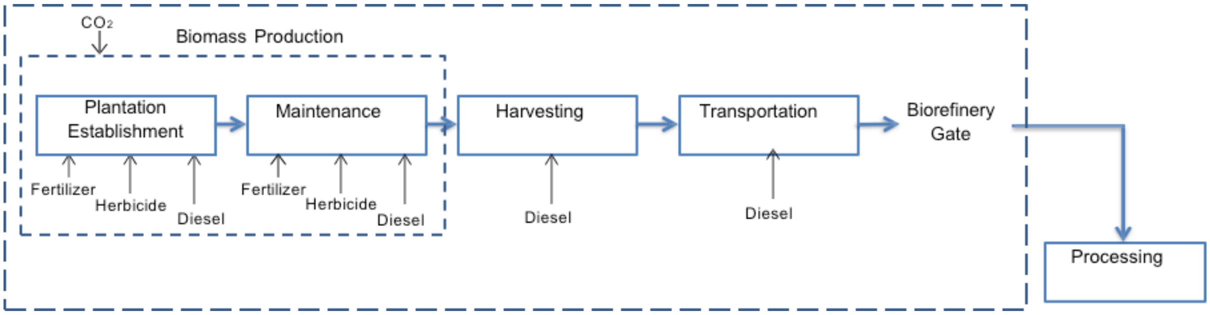


Figure 2-2. System boundary diagram of a cradle-to-grave biofuels process.

Temporal boundaries are also established in the scope. Assumptions relating to time can have a large influence on the results. A study timeframe should be picked which will best capture the impacts of the product or processes. A 100-year window is a common temporal boundary, for example, in global warming. In a 100-year temporal window, impacts occurring after 100 years are not part of the overall analysis.

Other aspects to be included in scope are technology and geographical regions. Many studies are spatially dependent so LCA results are not broadly applicable to other regions. Products or services from older technologies often have different impacts than current technologies. Thus, it is important to communicate the type and stage of the technology. In addition, allocation procedure impact assessment methods and should be reported.

Functional Unit

A functional unit is the primary measure of a product or service. ISO states that "the functional unit defines the quantification of the identified functions (performance characteristics) of the product. The primary purpose of a functional unit is to provide a reference to which the inputs and outputs are related. This reference is necessary to ensure comparability of LCA results. The functional unit can be a service, mass of material, or an amount of energy. Selecting appropriate functional units is critical to creating an unbiased analysis. For example, when comparing trains to cars for transportation, the comparison may suffer from the inability to correlate energy inputs and outputs. The real purpose of the train would be to deliver a larger number of people to a specific centralized location. For this example, a better functional unit may be impacts of a train delivering a specific number of people over a specified distance. The results will then be normalized to distance for more reasonable correlations and assessments.

Cut of Criteria

Data collection for an LCA is the most time-intensive and laborious step. Cut-off criteria are used to expedite the process. Cut-off criteria define a level of product content or other parameter to which the study will not consider. One example: materials contents less than 1% of the total product mass are not considered. This allows the LCA practitioner to focus on data from the main flows of the system while systematically eliminating flows which may not influence the results.

Life Cycle Inventory

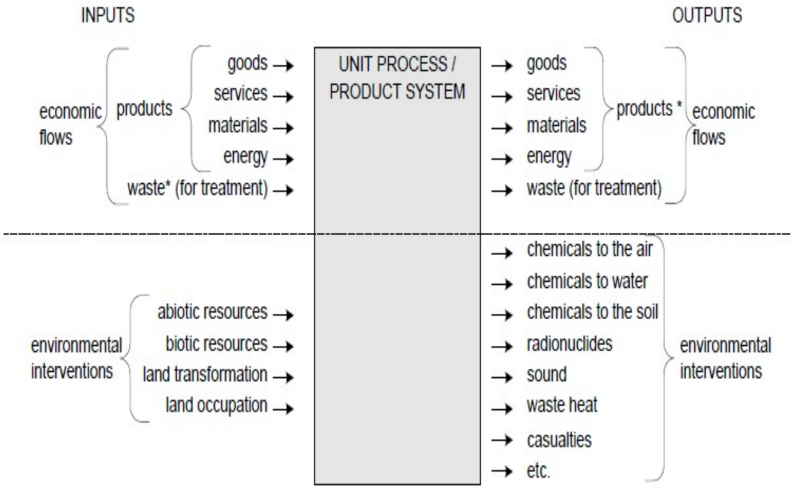
In addition to data collection, the life cycle inventory (LCI) step is a very laborious aspect of life cycle assessment. The data collected for the product, production process, and product life cycle are used in the impact assessment to determine the environmental impacts. Collecting consistent, transparent, and accurate LCI data is critical to the success of an overall LCA.

Primary and Secondary Data

Example data collected:

- Raw material use
- Energy use
- Transportation distances
- Chemical use
- Waste treatment information
- Process yields
- Life time
- Water use
- Product and co-product flows
- Other flows in or out of the system that are within the defined cut-of criteria.

Tracking the material flows into and out of the defined system is the first step of LCI. After the materials flows have been determined through interviews, literature searches, and measurement, LCA software can be used to track the material process's elementary flows to and from the environment. Elementary flows originate in the environment and are mined or retrieved for use in a process or flows that are released from processes to the environment and are not used by other processes. These elementary flows are the actual materials used and materials released to the environment as a result of the studied product system. In **Figure 2-3**, the two types of LCI data can be seen. On the top half of the figure, process flows such as products, services and other goods are listed. The lower half lists elementary flows such as chemicals released to soil or air.



* the functional flows of the process

Figure 2-3. System boundary diagram of a cradle-to-grave biofuels process.

Life Cycle Impact Assessment

Life cycle impact assessment (LCIA) is among the last steps of LCA. The purpose of a LCIA "is to provide additional information to assess life cycle inventory (LCI) results and help users better understand the environmental significance of natural resource use and environmental releases". The LCIA helps provide significance and results for easier decision making; however, it is important to understand it does not directly measure the impacts of chemical releases to the environment as an environmental risk assessment does. The third step of LCIA follows sequentially after the LCI using the many flows to and from the environment developed in the LCI. These LCI flows, without an impact assessment step, are not easily interpreted and understanding the significance of emissions is impossible.

The LCIA is different from a risk assessment measuring absolute values of environmental impacts in that the LCIA helps determine the significance of emissions and impacts in relation to the study scope. The absolute value of the impacts cannot be determined by the LCIA due to (Margni and Curran 2012):

- The relative expression of potential environmental impacts to a reference unit
- The integration of environmental data over space and time
- The inherent uncertainty in modeling environmental impact
- The fact that some possible environmental impact occurs in the future.

Even though the LCIA has limitations, it is useful in determining what impacts matter, what unit processes are contributing the most through hot spot analysis and identify best scenario options when environmental tradeoffs occur.

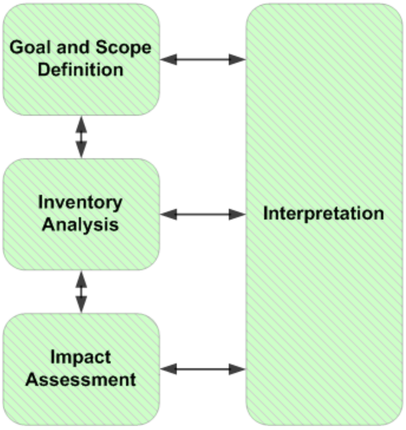


Figure 2-4. Life cycle assessment stages.
https://commons.wikimedia.org/w/index.php?curid=40862556

According to ISO there are three mandatory processes of a LCIA including Selection of impact categories, Classification, and Characterization, **Figure 2-5**.

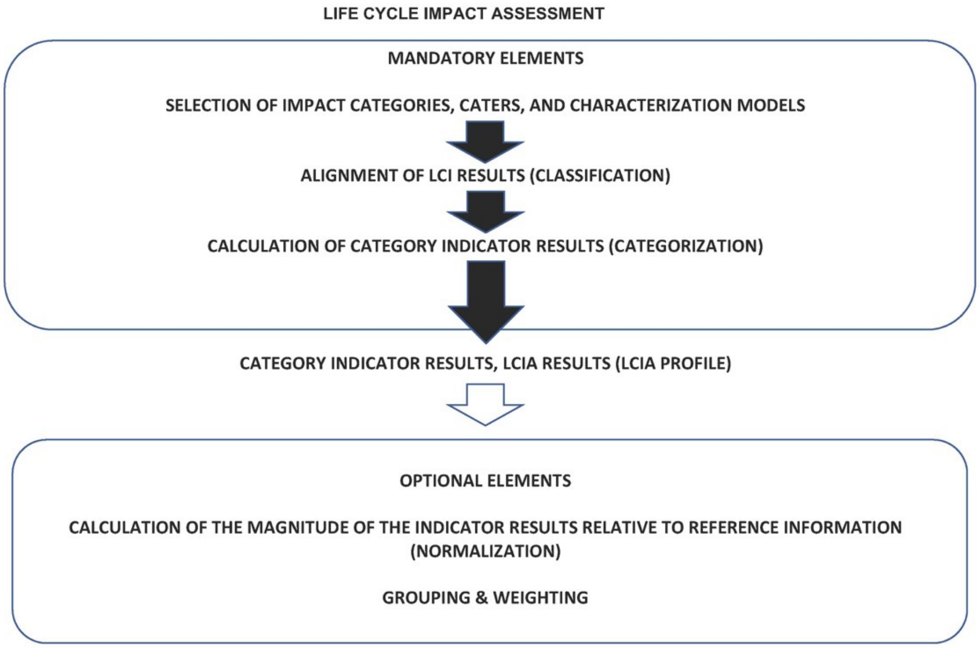


Figure 2-5. Impact assessment ISO mandatory and optional steps.

Conclusions

There are many tools to assist life cycle assessments. There are software and data packages designed for performing LCAs. No matter the form of the software, the use of some sort of LCA software and data management system is needed in LCAs. The life cycle inventory step of an LCA often requires a large data set listing hundreds of emissions to the environment. Keeping track of these flows manually is arduous, so LCA software is designed to manage these flows and perform specific functions such as impact assessments based on the inventory as well as uncertainty analysis.

There is a large list of LCA software emerging with various features. A basic overview of how data and LCA software will first be provided then a list of software packages.

Basic LCA Software Structure
LCA software can be split into several components:

- The software package
- Data sets
- Life cycle impact assessment (LCIA) methods

Software packages such as SimaPro, openLCA, and Gabi are frameworks or calculators that keep track of data and performs intensive numerical calculations. With the many flows and detailed data, much effort has been invested in creating efficient calculation methods to speed up analysis time. This framework, however, is not useful without inventory data. There are many premade datasets provided from sources such as Ecoinvent, Gabi and United States Department of Agriculture (USDA) that contain previous life cycle inventory results for various chemicals, materials, energy, services, and waste treatment processes. LCA software can access this previously developed data and include a chemical or other process from a dataset in their LCA without needing to perform an entire LCA on that particular material or process. This fundamental aspect of LCA, the leveraging of previous study results for new studies, is a key benefit of LCA software and can save countless hours on the LCI step. LCIA methods are procedures and conversions that are used in performing a LCIA such as global warming potential characterizations and weighting methods. There are many accepted LCIA methods that calculate LCA results using different impact categories, types of impacts, and weighting methods.

Figure 2-6 visually depicts how the different components of LCA software and data interact. The life cycle inventory step requires data from datasets (e.g., Ecoinvent) and primary data gathered by the LCA practitioner surrounding the process or product under analysis. The combination of these two types of data with the use of LCA software calculations gives an LCI. The LCI data can then be used to perform an impact assessment using the LCIA methods (e.g., TRACI).

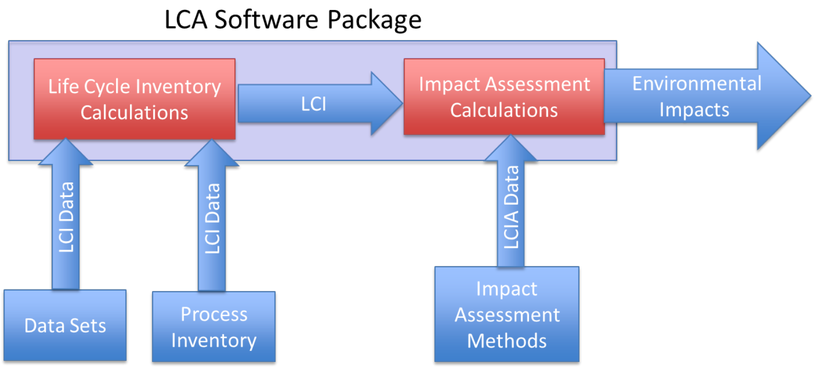


Figure 2-6. Life cycle assessment software structure.

Table 1: Three common LCA software package options.

Software	Licensing	Datasets	Software Features	Website
openLCA	Open source and free	Ecoinvent, Gabi, USLCI, CML and others	Fast calculation engine, easily share models, no yearly subscription, process based with transparent data, used for USDA digital commons LCA data development	www.openlca.org

SimaPro	Paid licensing	Ecoinvent, USLCI, CML and others	Process based with transparent data, good customer support, robust uncertainty analysis	www.pre-sustainability.com/simapro
Gabi	Paid licensing	Gabi Dataset, Ecoinvent, USLCI	Robust dataset, visual process flow based modeling, ease of use	www.gabi-software.com

Review Questions

1. Define the opportunities that could benefit from an LCA and why?
2. Is LCA going to be completely exhaustive in any of the various gate scenarios for determination of impacts?
3. What software is available for LCA?
4. Come up with a process and define 10 or less flows to allow you to calculate impacts.

Further Reading

1. Margni and Curran 2012 (See “Chapter 2 Supplementary Material in Moodle site)
2. Novel Screening Technique: Integrated Combinatorial Green Chemistry & Life Cycle Analysis (CGC-LCA): http://ojs.cnr.ncsu.edu/index.php/BioRes/article/view/BioRes_08_2_1513_Reeb_Editorial_Novel_Screening_Technique

Chapter 3: Hazards

"The world is a dangerous place to live; not because of the people who are evil, but because of the people who don't do anything about it".

–Albert Einstein

"Poison is in everything, and no thing is without poison. The dose makes it either a poison or a remedy".

–Paracelsus, 1564

Summary of Chapter

This chapter focuses our attention on the essential importance of green chemistry: the need to address in a safe and satisfactory way hazards. Hazards are ubiquitous relative to our experiences as human beings. There are not localized to mills, factories, waste dumps, and hockey arenas (please note feeble attempt at humor). As a species, we often attempt to downplay their role in governing our behavior, but no human enterprise is free of such an exemption. In this key third chapter, we begin to appreciate the significance and magnitude of hazards through a walk-through history from the infamous anti-nausea medications used in the middle part of the twentieth century to the very recent Flint River crisis. We categorize their effects and their nature, attempt to understand their effects, and offer strategies to avoid or mollify the potential enormity of their impacts.

Introduction

What we as a population must realize is that no substance in and of itself is a poison or a remedy. It is the dosage that defines the activity of the substance. For example, let's look at the concept of "hormesis" as a precursor to the concept of poison/remedy by dosage.

We all have heard at one time or another the phrase, "What doesn't kill you makes you stronger". This phrase contains truth and contains at its essence the theory of *hormesis*: when organisms are exposed to low levels of stressors or toxins, they become more resistant to larger levels of stressors or toxins. This theory has been met with skepticism. Recently, however, biologists have put together a molecular explanation of its function and it has finally been accepted as a fundamental principle of biomedicine.

For example, exposing mice to low levels of gamma ray radiation before irradiating them with high levels actually decreases their likelihood of cancer. Similarly, when dioxin is given to rats we find the same situation. However, the biochemical mechanisms are not well understood. It is believed that a low dose of a toxin can trigger repair mechanisms that are efficient enough to not only neutralize the toxin, but repair other defects not caused by the toxin.

Thus, hormesis is nature's way of dealing with harmful agents; in fact, antibodies are a natural consequence of hormesis. However, the toxins/poisons that were once absolute, are NO LONGER. For example, thalidomide was found to be a very dangerous chemical for embryo development, but has recently found great promise in a number of ailments according to the Mayo Clinic including HIV, skin lesions, and multiple myeloma (please see: http://www.mayoclinic.org/diseases-conditions/cancer/in- depth/thalidomide/art-20046534). Such a fact is outstanding considering the horrific aftermath (a few photographs shown below) of its use in the middle part of last century:

https://www.flickr.com/photos/22719239@N04/2241322031

https://www.flickr.com/photos/bowbrick/3525018934

In fact, the list of former "pure" toxins is extremely interesting: snake venom, bacteria (botulin), fungi (penicillin), leeches (Hirudin), maggots (gangrene), etc. The toxic aspect notwithstanding, we all live in the wake of a world and society that is rife with potential hazards.

Types of hazards

A hazard is "threat" to life, health, property, or environment. These can come in many forms, but they are classified according to their modalities or nature of operation. The modalities of hazards are the following:

- Dormant: Has the potential, but nothing currently can be affected. This modality is typified by the "volcano" scenario – a volcano that is no longer showing any signs of activity or imminent threat but is lying "dormant". *There is no immediate and pressing issue based on human perception.*
- Armed: Has the potential, and something can be affected. This modality is given by a person holding a gun in the midst of a war or other aggressive situation. The gun has the potential to affect life, limb, or other vital function, but it is not yet doing so, *although the intention is there.*
- Active: Currently on-going event (something is being affected). Finally, this is the modality that is actually affecting life, limb, or some other vital function. A volcano that is spewing, a gun that is being fired, a fire that is consuming a building, radiation that is leaking, etc. These are the situations that are causing harm.

Within these modalities of hazards, hazards can be further refined as to their types. The following types of hazards classify the threats to life:

- Physical: Condition or situations that cause the body physical harm, e.g., a bullet that is entering into a human being.
- Chemical: Substances that cause harm or damage to the body, property or the environment, e.g., liquid oxygen converting to gaseous oxygen within a closed container (bomb).
- Biological: Biological agents that cause harm to the body, e.g., anthrax bacteria.
- Psychological: Stress affecting the mental state, e.g., the knowledge that the trajectory of a five-mile wide asteroid coincides with earth.

- Radiation: Electromagnetic radiation that harms or damages biological organisms.

Concepts

Globally Harmonized System

Tobest classify hazards, the concept of GHS (Globally Harmonized System) has been introduced. **Figure 3-1** demonstrates the categories of hazards:

Figure 3-1. The globally harmonized system (GHS) that attempts to specifically categorize the general types of threats in society. Please see http://emergency.cdc.gov/agent/agentlistchem-category.asp for more information; https://commons.wikimedia.org/wiki/File:GHS_HAZCOM_Safety_Labels.jpg

Notice that each logo attempts to demonstrate pictorially the type of hazard represented by a specific chemical or material. For example, notice **Figure 3-2** below. This particular chemical's hazard level could be listed as "gases under pressure" and "explosives". The intensity of its peculiar hazards is evaluated according to the pressure and the explosive nature of the gas.

Figure 3-2. A tank of propane gas. https://commons.wikimedia.org/wiki/File:FoamFatale_in_details_foam_storage_in_FoamFatale_Pressure_Vessel.jpg

Exposure and Categories of Hazardous Substances

Our overall sensitivity to hazards, again, depends on a number of factors that not only include the typical factors of levels, LDs, type of toxin, modality, etc., but also to our idiosyncratic immunity or responsiveness.

We have been accustomed to a number of wonderful creature comforts in life that have only come about because of the power, versatility, and creativity inherent in the chemical enterprise. For example, phosgene, a notorious chemical warfare agent in the Great War, is now used as a precursor for the manufacture of a number of items including polyurethane. Shown below in **Figure 3-3** is a representation of phosgene:

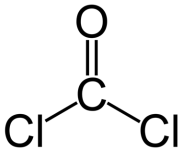


Figure 3-3. A chemical representation of phosgene.
http://www.toxipedia.org/display/toxipedia/Phosgene

In the realm of hazards, phosgene is very dangerous, but these hazards are classified within the following categories:

- Carcinogen cancer causing. Example: benzo[a]pyrene, a PAH. Cancer-suspect agent. Example: flat polyaromatics
- Mutagen changes genetic information (likely a carcinogen). Example: bis (2- chloroethyl) sulfide or 2,2'-dichlorodiethyl sulfide
- Teratogen causes malformed embryo. Example: thalidomide
- Tumor Promotors not necessarily carcinogenic. Examples: DDT, phenobarbital, arsenic trioxide
- Corrosives "Gnaws" tissue. Examples: Acids, Bases
- Neurotoxins Adversely affects nerve tissue. Examples: CO, CO_2, Pb, Hg, Mn, CH_2Cl_2, etc.
- Lachrymators Damages/irritates mucous membranes. Example: 2-chloro-1-phenylethanone (or chloroacetophenone or mace)

Lab Safety

Lab safety is an essential part of working with hazardous materials. It is important to follow good lab practice techniques and to know how to deal with situations should they occur. In the following video by Chemistry crash courses, some good lab techniques and safety guidelines are discussed. Lab Techniques and safety by crash course: https://www.youtube.com/watch?v=VRWRmIEHr3A

Reference: Green, H. Crashcourse. (2013, July 8). *Lab Techniques & Safetey: Crash Course Chemistry#21*. Retrieved from https://www.youtube.com/watch?v=VRWRmIEHr3A

Lethal Dose

Lethal dose (LD_{50}) is the amount of any ingested or interfering substance that kills 50% of a test sample. It is expressed in mg/kg, or milligrams of substance per kilogram of body weight. In toxicology, it is also referred to as the median lethal dose that refers specifically to a toxin, radiation, or pathogen. The lower the LD_{50}, the more toxic is the item being measured for toxicity. It can be considered a pragmatic approach to toxicity exposure levels because in general, toxicity does NOT always scale with body mass. The choice of 50% lethality as the gold standard avoids ambiguity because it measures in the extremes and reduces the amount of testing. However, such a fact also means that LD_{50} is *not* the lethal dose for all subjects; in other words, some may be killed by much less. Measures such as "LD_1" and "LD_{99}" (dosages required to kill 1% or 99%, respectively, of the test population) are sometimes used. Shown below is a chart of sample LD_{50} taken from Wikipedia (https://en.wikipedia.org/wiki/Median_lethal_dose) with active links to allow further investigation of the substances whose measurements are given.

Substance	**LD_{50} {LC_{50}}**	**LD_{50} : g/kg {LC_{50} : g/L} standardized**
Water	>90g/kg	>90
Pentaborane	<50 mg/kg	<0.05
Cobalt(II) chloride	80 mg/kg	0.08
Metallic Arsenic	763 mg/kg	0.763
Cadmium oxide	72 mg/kg	0.072
Sucrose (table sugar)	29,700 mg/kg	29.7
Monosodium glutamate (MSG)	16,600 mg/kg	16.6
Vitamin C (ascorbic acid)	11,900 mg/kg	11.9
Urea	8,471 mg/kg	8.471

Cyanuric acid	7,700 mg/kg	7.7
cadmium sulfide	7,080 mg/kg	7.08
ethanol (Grain alcohol)	7,060 mg/kg	7.06
sodium isopropyl methylphosphonic acid (IMPA, metabolite of sarin)	6,860 mg/kg	6.86
Melamine	6,000 mg/kg	6
Melamine cyanurate	4,100 mg/kg	4.1
Venom of the Brazilian wandering spider	134 μg/kg	0.000134
Venom of the Inland Taipan (Australian snake)	25 μg/kg	0.000025
Ricin	22 μg/kg 20–30 mg/kg	0.000022 0.02
2,3,7,8-Tetrachlorodibenzodioxin (TCDD, a dioxin)	20 μg/kg	0.00002

https://commons.wikimedia.org/w/index.php?curid=3325271

Notice that the venom of the Brazilian Wandering Spider is particularly potent. A ten thousandth of a g/kg or ~5 mg would kill a normal sized female. Luckily, the venom discharged/bite is quite small. Nevertheless, the point is that the vector (or venom) represents a toxin that is of sufficient lethality that it can cause great harm/injury to a human being.

Sources for toxicity information:

http://www.atsdr.cdc.gov/; http://cfpub.epa.gov/ecotox/
http://toxnet.nlm.nih.gov/

Case Study for Hazardous Waste

Badger Army Ammunition Plant (BAAP)

https://dma.wi.gov/DMA/news/2015news/15042

Environmental cleanup of the 7,400-acre Badger Army Ammunition Plant will be greater than $250 million. This is one of the 40 contaminated military sites in Wisconsin which the Defense Environmental Restoration Account cites as the most contaminated. In fact, 32 areas are polluted with dangerous levels of solvents, metals and explosive/incendiary waste. The water beneath the plant is contaminated with mutagenic chemicals that include carbon tetrachloride, trichloroethylene and dinitrotoluenes. One part of the site, known as the Propellant Burning Grounds, is the source of a three-mile plume of contaminated groundwater that has migrated offsite, completely contaminating private drinking water wells in addition to the Wisconsin River.

Elevated Cancer Rates

In 1990, the Wisconsin Division of Health conducted a health survey. It concluded that communities near the Badger plant have a significantly higher incidence of cancer and deaths. In spite of these alarming findings, the State refused to take any action. In 1995, the Division of Health responded because of pressure from CSWAB (Citizens for Safe Water Around Badger) and reopened the community health study.

On October 26, 1998, CSWAB concluded "there was entirely inadequate contact with our community – the population being studied." Prior to September 1998, no press releases were published, no public meetings were held, and no interviews were conducted. Despite several requests, virtually no resources were devoted to interviewing residents about current health problems and concerns regarding their exposure to air, dust, emissions, and surface soils. Assessment of risk from cleanup activities was also absent. CSWAB also determined that the Wisconsin DOH focused on death studies when many health problems and community concerns have been nonlethal, such as respiratory illnesses or reproductive problems.

CSWAB appealed to ATSDR (Agency for Toxic Substances and Disease Registry in D.C.) to discuss the lack of adequate community participation in this and similar health assessments across the nation. The Wisconsin Department of Health conducted the assessment under a cooperative agreement with ATSDR.

Cleanup Plans Abandoned

The U.S. Army proposed to abandon and severely reduce cleanup of two priority areas within the plant. The Settling Ponds and Spoils Disposal area — a series of lagoons that run the length of the 7,000-acre facility — is contaminated with high levels of lead and dinitrotoluenes.

Maintenance of the Badger plant costs in excess of $17 million per year. In 1991, only $3 million was allocated for environmental studies. Since 1975, there have been over 56 chemical spills and incidents. Moreover, there is no national strategic need for maintaining the Badger plant. A February 20, 1997 Government Accounting Office report concludes BAAP and three other military plants could be eliminated "because alternative sources exist...to provide the capabilities these plants provide."

Green Technologies for Safer Chemical Production of Sevin

Since the fallout from the Bhopal tragedy, efforts have centered on avoiding storage of methyl isocyanate (MIC). The final product, Sevin, is no longer being manufactured by a two-step process. The process now consists of no longer reacting naphthol with MIC (one step), but sequentially with phosgene and methyl amine. The basis for the Bhopal tragedy was the reaction shown in **Figure 3-4**.

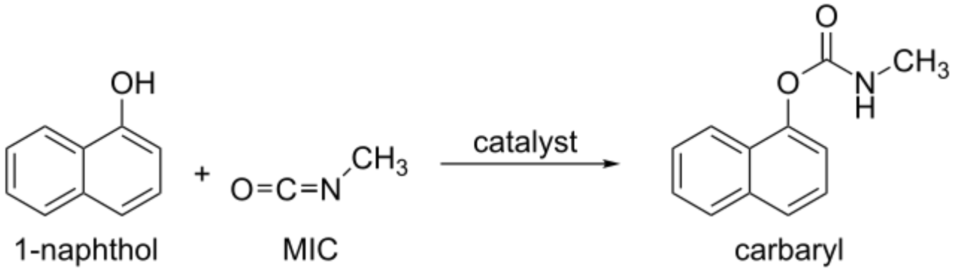
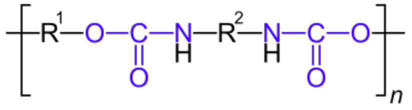


Figure 3-4. The original process that DuPont had in place to make Sevin (the commercial pesticide) through methyl isocyanate (MIC). http://www.wikiwand.com/en/Methyl_isocyanate

Polyurethanes

Polyurethane is a polymer composed of carbamate (urethane) linkages. Polyurethanes are traditionally formed by reacting a di- or polyisocyanate with a polyol (alcoholic polymer such as PEG, polyethylene glycol). Both the isocyanates and polyols used to make polyurethanes contain, on average, two or more functional groups (either on termini or within the molecule, hence being telechelic, *i.e.*, a di-end-functional polymer where both ends possess the same functionality) per molecule. Recent efforts have been dedicated to minimizing the use of isocyanates to synthesize polyurethanes because isocyanates are toxic. Non-isocyanate-based polyurethanes (NIPUs), especially made from soybean oils, have recently been targeted as a new greener class of polyurethanes. Shown in **Figure 3-5** is a molecular representation of polyurethane linkages (highlighted in blue). The carbamate linkages are composed of a central carbonyl moiety that has two heteroatoms attached to it – a nitrogen and an oxygen. From an organic perspective, it is an ester/amide hybridized molecular system. Interestingly, telechelic monomers such as adipic acid chloride (left telechelic monomer) and hexamethylene diamine (right telechelic monomer) such as shown in **Figure 3-6.**



$$\left[-R^1-O-\underset{\|}{\overset{}{C}}(=O)-\underset{H}{N}-R^2-\underset{H}{N}-\underset{\|}{C}(=O)-O-\right]_n$$

Figure 3-5. A simplified representation of urethane (carbamate) linkages in polyurethane polymers. https://de.wikipedia.org/wiki/Polyurethane#/media/File:Polyurethane-allg.svg

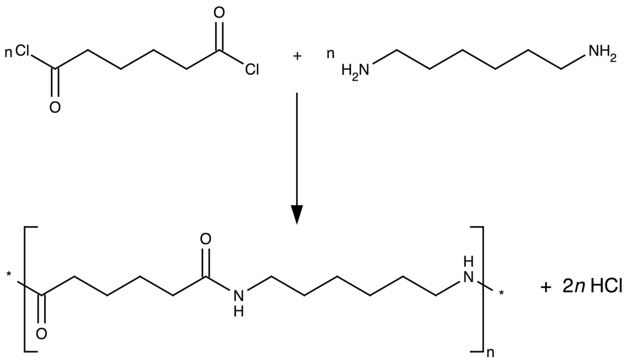


Figure 3-6. A simplified representation of the telechelic nature of the starting materials (monomers) that upon coupling form a telechelic polymer.
https://commons.wikimedia.org/wiki/File:Nylon_synthesis_from_chloride_and_amine.s vg

What is immediately noticeable is that the final polymer is a blend of two distinct monomers; thus, the final properties can be tailored by judicious (and discrete) choice of the monomers. More specifically, prepolymers (> 10-12 monomer units) of each monomer may be coupled to provide distinct segments having specific properties. For example, polyethylene glycol (PEG) is a polymer that is hydrophilic, soft, rubbery, and flows well. However, the phenyl-based di-isocyanate segment is much more rigid, tough, and non-stretchable. Therefore, the overall final physical and thermal properties of the polyurethane can be tuned. The opportunity to enhance the polymerization reactivity inherent for polyurethanes can be catalyzed by a non-nucleophilic base (such as DABCO – diazabicyclooctane) shown in **Figure 3-7**.

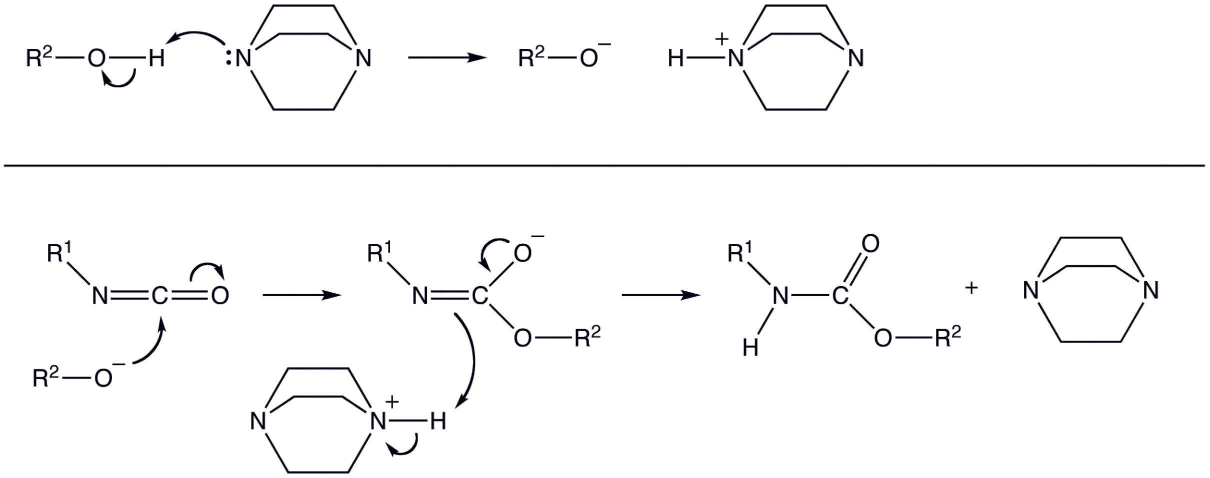


Figure 3.7. The molecular steps in the formation of a urethane bond by base catalysis. http://www.wikiwand.com/en/Polyurethane

In **Figure 3-7**, DABCO is able to abstract a proton from an alcohol (say ethylene glycol) to allow for the nucleophilic reactivity at the cumulated carbon of the isocyanate.

Curtius Rearrangement to Form Isocyanates

An additional "greener" approach to forming isocyanates, an important class of starting material in the formation of many highly important materials, is through the Curtius Rearrangement (RAR) Reaction, an example of which is shown in **Figure 3-8**.

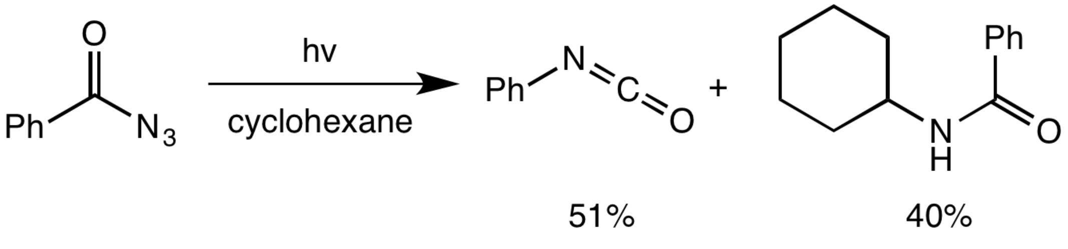
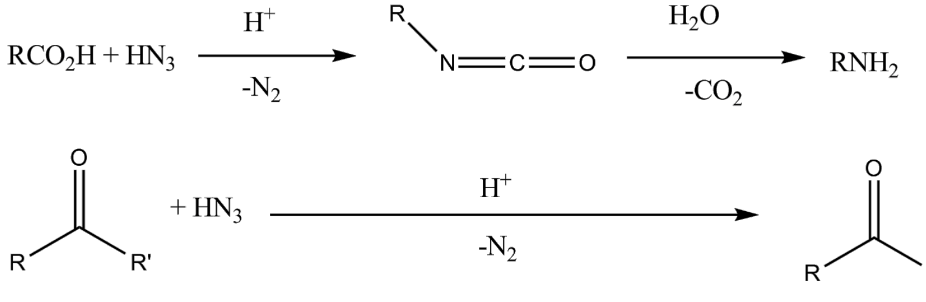


Figure 3-8. The Curtius RAR reaction. http://www.wikiwand.com/en/Curtius_rearrangement

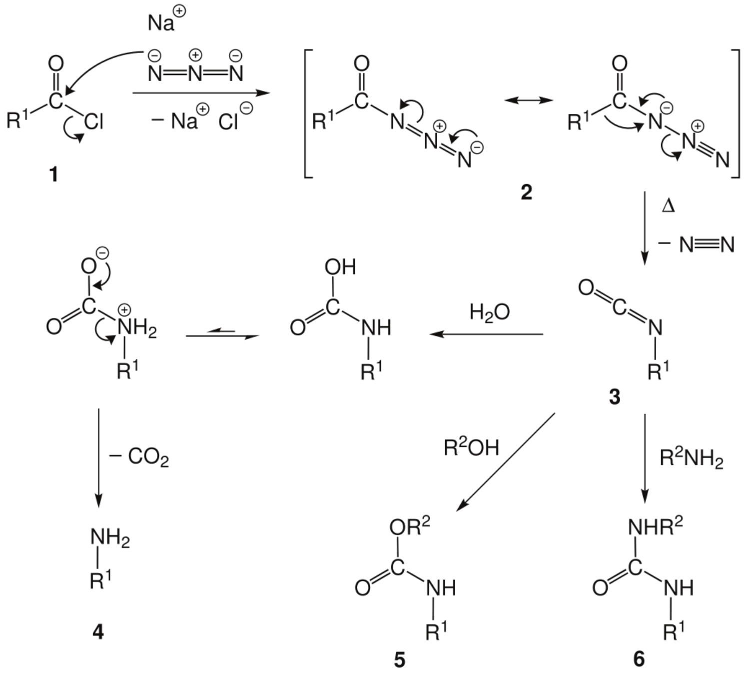
The Curtius Rearrangement is a thermal or photochemical decomposition starting from carboxylic azides (left structure in reaction above) to an isocyanate (first product in reaction above). In the above reaction, the solvent also plays the role of a reactant as shown by N atom insertion into cyclohexane via a radicaloid mechanism. These intermediates may be isolated, or their reaction or hydrolysis products can be obtained.

The reaction sequence that includes the subsequent reaction with water that leads to amines is called the Curtius Reaction. This reaction is similar to the Schmidt Reaction, shown below (https://www.wikiwand.com/en/Schmidt_reaction), with acids that differs in that the acyl azide is prepared from the acyl halide and an azide salt.

Schmidt Reaction:



Mechanism of the Curtius Rearrangement:



For the Curtius RAR, the following steps take place: Starting Reagent **1** undergoes an electrophilic attack by an anionic azide molecule to produce an azide whose mesomerism is shown in brackets **2**. It then undergoes decomposition under the appropriate stressor (heat, pressure, etc.), which leads to the isocyanate **3** with the loss of nitrogen (denitrogenation). This can react with water to yield a carbamate-like molecule (carbamic acid, urethane-like) which can spontaneously decompose thru decarboxylation to a primary amine **4**. In the presence of an alcohol or an amine, **3** can yield an ester, **5**, and an amide, **6**, respectively. http://www.wikiwand.com/en/Curtius_rearrangement

Conclusions

The opportunity to apply green chemistry to reducing the toxicity in industrial processes is of paramount importance for a sustainable future. In this chapter, we investigated the concept of hazards from the perspective of their meaning, nature, implications, control, and ultimate re-engineering. Green chemical principles hold the key to ensuring that society provides a viable channel for all of our physical needs and maintains the environment.

Review Questions

1. Think about the additive impact of hazards from a LD_{50} perspective. Why would materials with different values not be additive in their cumulative effects on lethality? Can you think of two chemicals, however, whose lethality may be more than the sum of their individual values?
2. Would phosgene be more or less reactive as a function of relative humidity? Why or why not? In a wartime situation, for example, would an opposing army to whom phosgene is being directed favor a low humidity?
3. Can phosgene be reacted with sodium azide in a 1:2 molar ratio? If so, what would be the reaction and product? If not, why not?
4. What do these GHS labels tell us about ammonia?

Components Of A GHS-Compliant Label

AMMONIA

DANGER

TOXIC IF INGESTED

Wash hands thoroughly after handling. Keep container tightly closed when not in use Keep away from heat, sparks and open flames - may explode when exposed to high heat. Use in an open area that is well-ventilated. Breathing in ammonia is irritating and corrosive. Wear protective gloves and safety goggles to prevent burns and irritation.

If swallowed: Immediately call Poison Control or doctor/physician. Drink water or milk to dilute ammonia.

See Safety Data Sheet (SDS) for further details regarding safe use of this product.

ABC Chemicals - 123 Main Street - Cincinnati, OH - www.abcchem.com - 800-733-5252

https://www.general-data.com/about/blog/ghs-compliant-labels-what-are- essential-components

Further Reading

- http://blogs.ei.columbia.edu/2014/12/08/toxic-chemicals-all-around-us-is-green- chemistry-the-answer/
- https://play.google.com/books/reader?id=4_PJCgAAQBAJ&printsec=frontcover&output=reader&hl=en_US&pg=GBS.PP1 (Bretherick's Handbook of Reactive Chemical Hazards: Edition 4, L. Bretherick, October 22, 2013, Elsevier)
- http://ccc.chem.pitt.edu/wipf/Web/HCH.pdf (Hazardous Chemicals Handbook)

Chapter 4: Alternative Solvents

“Two roads diverged in a wood and I – I took the one less traveled by, and that has made all the difference”.

–Robert Frost

“The solution to pollution is dilution”.

–Sherry Rogers

Summary of Chapter

This chapter focuses our attention on the pre-eminence of alternative solvents. The topics covered include the following:

- Auxiliary substances
- Transition state
- Michael Reaction
- Ball Milling
- Graft Polymerization
- Supercritical Fluids

We attempt to ensure that their significance to the field of green chemistry is well elucidated because of their universal nature in chemistry, biology, and engineering.

Introduction

In a very general sense, solvents are a class of chemical compounds that allow chemistry to occur. The concept of a solvent has significant ramifications because they serve as the matrix, medium, or carrier for solutes. They are necessary in a number of processes, reactions, and systems. We tend to think of a substance like "water" as a universal solvent because it is so useful in so many disciplines. Water cleans up everything, allows biochemical reactions to occur, is used in paints, coatings, and films, allows cooking to occur (or else everything would catch fire), and provides lubrication and ease of movement for a great many devices.

Interestingly, in the business world, the word "solvent" has another meaning: A state of financial soundness characterized by the ability of an entity to meet its monetary obligations when they fall due. This latter definition does indeed apply in a certain sense to the solvent concept we are espousing in this chapter. A solvent ($olvent) carries materials for a reaction or specific function in the same sense that solvent from a financial sense carries funding/money to meet its obligations. Thus, using an analogy:

Solvent : Solute :: $olvent : Money

Chemically, a solvent will dissolve or "solvate" a solute. What does that mean? It means that solvent molecules will surround the solute in such a way that a solution is formed; in other words, a homogeneous system is generated in which the solute is part of/indistinguishable from the solvent network. A solute/solution concept can be visualized in the Figure below:

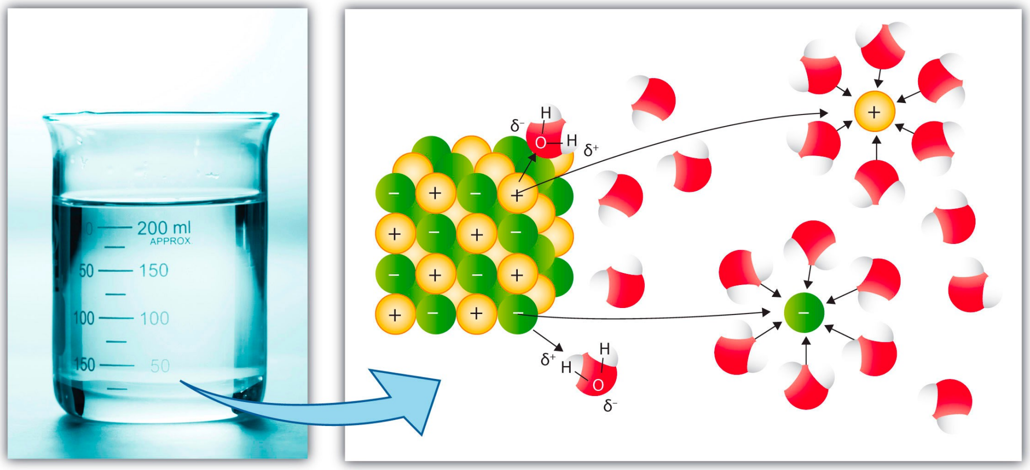


Figure 4-1. Shown is a simplified representation of how a solvent such as water can "encapsulate" or cause a solute to go into solution (or be washed away).
https://commons.wikimedia.org/wiki/File:Sodium_chloride_dissolution.jpg

Solubility

The ability of one a compound to dissolve in some other (likely different) compound is termed "solubility". Miscibility is another term that characterizes the facility of compound A to dissolve in compound B. When the two compounds can completely dissolve or combine to form a homogeneous solution, the two liquids are said to be *miscible*. Two that can never blend well enough to form a solution are called *immiscible*.

All solutions have a positive entropy of mixing whereas the interactions between different compounds may or may not be energetically favored. If interactions are unfavorable, then the free energy decreases with increasing solute concentration. The energy loss may at some point in time outweighs the entropy gain, and no more solute can be dissolved – this is a condition solution in which the solution is said to be saturated. This condition can change with different environmental factors, such temperature, pressure, and purity of the system. A supersaturated solution can be prepared by raising the solubility (e.g., increasing temperature) to dissolve more solute, and then lowering it by cooling. However, most gases and several compounds exhibit solubilities that tend to drop with raised temperatures. The solubility of liquids in liquids, however, is less temperature-sensitive than solids or gases.

Concepts

According to GC Principle No. 5, "*The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary wherever possible, and innocuous when used.*" This statement signifies or upholds the dogma in GC that simplification to execute a specific transformation should be observed. In other words, if we can find a way to not use a solvent, let's not use it! Although in our modern society such a stance is almost untenable, the ideal nevertheless is what we as a society should contend to achieve. For example, as shown in **Figure 4-2**, we have an overwhelming influx of medicines, drugs, etc., within our society to promote our health. We typically take these concoctions with water, in emulsions, in solutions, in suspensions, etc.

Figure 4-2. The gamut of medicines and its varieties in our culture and life is staggering. https://pixabay.com/en/health-medicine-tablets-846862/

Of course, taking a medicine without solution is a difficult proposition, but there are a number of ways to do it:

- Dry swallowing or sublingually (e.g., nitroglycerin tablets for angina);
- Patch application (microneedles or high concentration, usually done dermally);
- Inhaled by a mist/spray (e.g., gaseous phase);
- Via a tube (e.g., stomach tube or intravenous).

Nevertheless, the use of solvents and solvent-based systems are deeply ingrained in our culture and society. The reasons are many, but they tend to be tradition, ease of use, reduced cost, and convenience. Doing without solvents tends to require much more creativity and overall planning.

Reaction Energy Coordinate

Typically, a reaction profile or surface (where and how a reaction proceeds according to an energy perspective) provides sufficient information to understand the pathways (independent of final energy states) necessary to achieve a forward reaction. For example, the coordinate shown below illustrates the S_N2 reaction between *t*-butyl chloride and hydroxide. Note that most of the variables shown relate to the energy constraints or parameters associated with the reaction. The reaction has an inherent activation barrier for the forward direction. This barrier characterized by an energy differential input (DE_1^1), relates to the difficulty to accessing a transition state (^{1}) that must be accessed for the forward reaction.

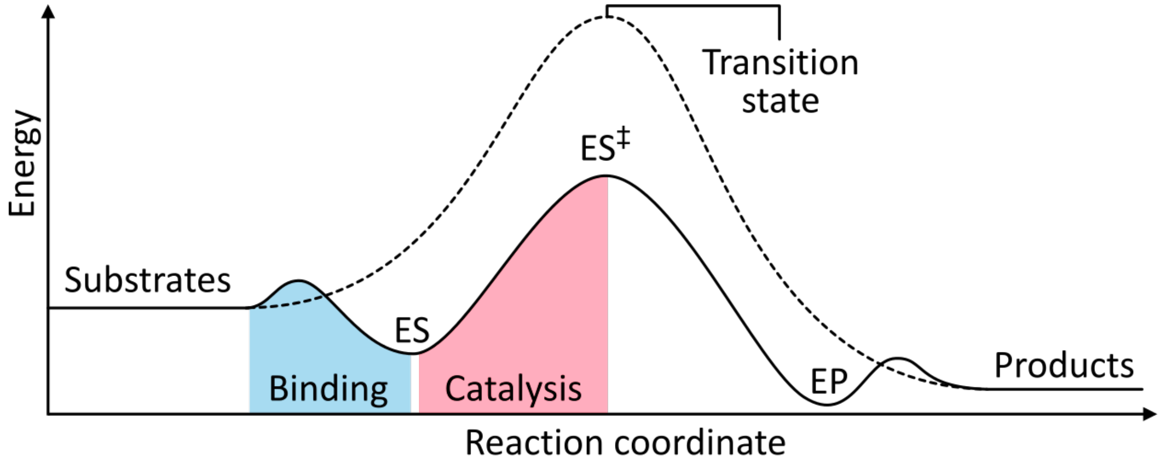


Figure 4-3. A typical representation of the energy surfaces obtained during the transformation of an organic halide in a classic S_N2 (bimolecular nucleophilic substitution) reaction. https://commons.wikimedia.org/wiki/File:Enzyme_catalysis_energy_levels_2.svg

Such an energy input, however, can be accommodated or lessened by a number of factors, *viz.*, the use of a catalyst which in general has shown the ability to reduce the energetic considerations to access that state by virtue of its capacity to engage in structural or energetic interactions with the starting material and strongly encourage the formation of the transition state. The downhill nature of the coordinate surface is akin to rolling a ball whose potential energy conversion to kinetic energy is extremely facile. Thus, an intermediate is achieved (the trialkyl carbocation in **Figure 4-3**) that has a measurable lifetime and properties. Although it is by its fundamental character unstable, it nevertheless exists to then engage in further reactions. Notice that it still at an energy surface that is much higher to the starting energy state. Such a phenomenon is then predictive of its future course. In fact, as you move closer to the product along the abscissa of the reaction coordinate surface, the intermediate resembles in a number of properties the nature of the final product. In this case, the intermediate has to a great extent a number of the features of both the starting materials and the product. Indeed, the next activation barrier that must be crossed to access the final product is much lower in height than the normal activation barrier indicating the gradual easing of the transition of starting material(s) to product(s).

Solvent Categories

There are a number of solvents that from a green chemistry perspective must be dealt with judiciously. The following are representative solvent classes:

- Hydrocarbons
- Halogenated hydrocarbons
- Aromatic hydrocarbons
- Alcohols
- Ethers
- Aprotic Solvents

Each of the above have their pros & cons in terms of environmental benefit/issue, economics, and social justice. Each may do different things; for example, the aprotic solvent class is one where there is no chance for the solvent to provide a proton to a reaction it is hosting. Alcohols, on the other hand, can easily do that and should not be used in reactions where water/protons could quench a reaction or trigger a violent reaction.

Methyl Soyate

Methyl soyate is a biobased solvent that is a mixture of long-chain fatty acid methyl esters. More information on its specific properties and potential uses can be found in the following tract:

https://www.yumpu.com/en/document/view/10362159/the-formulary-guide-for-methyl-soyate- soy-new-uses

In general, it can be used to clean countertops, pretreat fabric stains, clean concrete, degreaser, graffiti remover (with ethyl lactate and surfactants), paint stripper, mastic remover, varnish remover, deinker, asphalt remover, and waterless hand cleaner. In addition to the soyate, there are a number of other emerging biobased cleaners/solvents such as shown below:

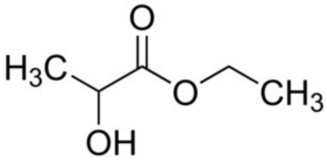


Figure 4-4. A representation of ethyl lactate, also known as lactic acid ethyl ester, which is a monobasic ester formed from lactic acid and ethanol, that can be used as a solvent. It is considered biodegradable and can be used as a water-rinseable degreaser.
https://www.wikiwand.com/en/Ethyl_lactate

Please see http://pubs.rsc.org/en/Content/ArticleLanding/2011/GC/c1gc15523g#!divAbstract for more information on this marvelous solvent.

Additional Alternative Solvent Systems or Modes

Gas Phase

The gas phase is a very useful modality to allow reactions to occur because (like the hydrophobic effect) it forces reactions or processes to occur through non-solvent- mediated channels. For example, the production of methanol can be done in the gas phase by reaction of "syn" gas (hydrogen and carbon monoxide) with ZnO as the solid catalyst for the reaction to occur.

No Solvents

It is altogether possible and highly desirable to use the starting materials themselves for the reaction of interest. This is doable if one of the reactants is a liquid that can allow the other(s) to dissolve into it. This has been shown by taking a *p*-xylene and reacting it with oxygen to make the terephthalic acid:

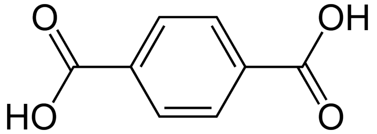


Figure 4-5. A molecular representation of terephthalic acid. https://www.wikiwand.com/en/Terephthalic_acid

The acid in **Figure 4-5** can then be used directly with ethylene glycol to synthesize polyethylene terephthalate:

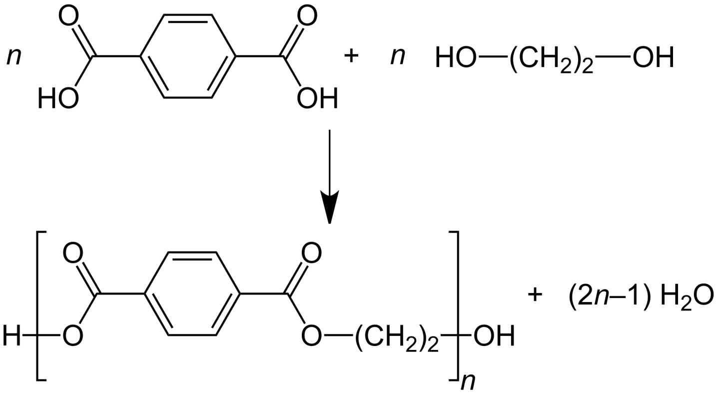


Figure 4-6. The reaction of terephthalic acid with ethylene glycol leading to the production of the polymer. https://www.wikiwand.com/en/Polyethylene_terephthalate

Melt State

It is possible to combine two solids to provide a composition that can achieve a eutectic point, or melts/solidifies at a single temperature lower than the melting points of the separate constituents or of any other mixture of them. At the eutectic point, you can achieve an isotropic blend of dissolved materials such as evidence in **Figure 4-7.**

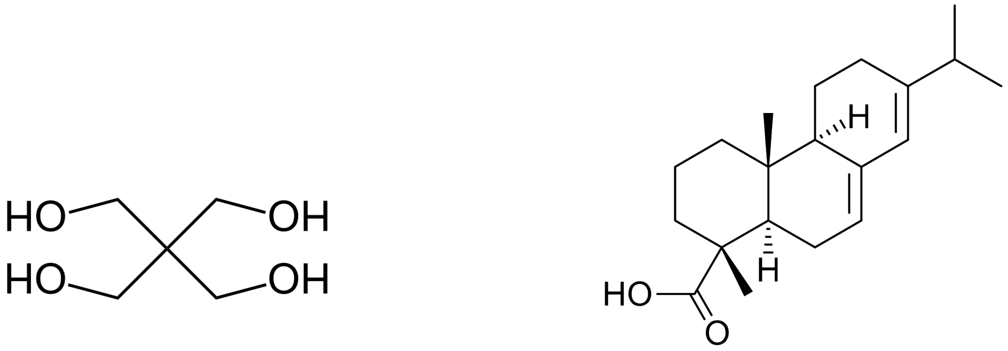


Figure 4-7. A mixture of pentaerythritol (left) and abietic acid (right) can blend in a melt (eutectic) that can provide a pentaester product. https://www.wikiwand.com/pt/Pentaeritritol; https://www.wikiwand.com/en/Abietic_acid

Triggered Solid State Reactions.

It is possible to induce a chemical reaction outside of the melt by introducing a trigger such as acid, ultrasound, grinding, light, etc. Such triggers take the place of solvent- mediated reaction stabilization. For example, the following reactions are amenable to such triggers:

Michael Reaction:

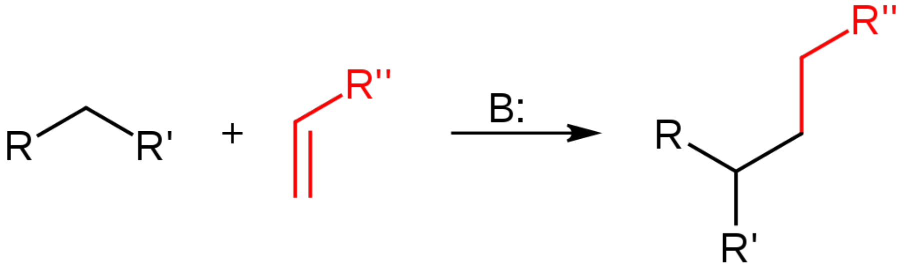


Figure 4-8. A simplified representation of the Michael reaction. The conjugation of alkanes to unsaturated substrates (is a key step for the synthesis of various complex natural products, antibiotics, and chiral compounds. http://www.wikiwand.com/en/Michael_reaction

In addition, it is possible to do the reaction using a catalyst such as alumina with microwave induction as shown in **Figure 4-9**:

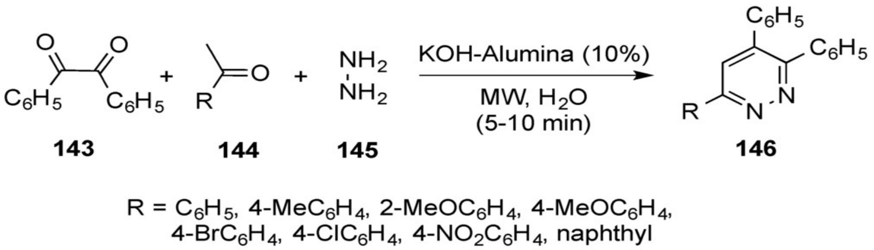
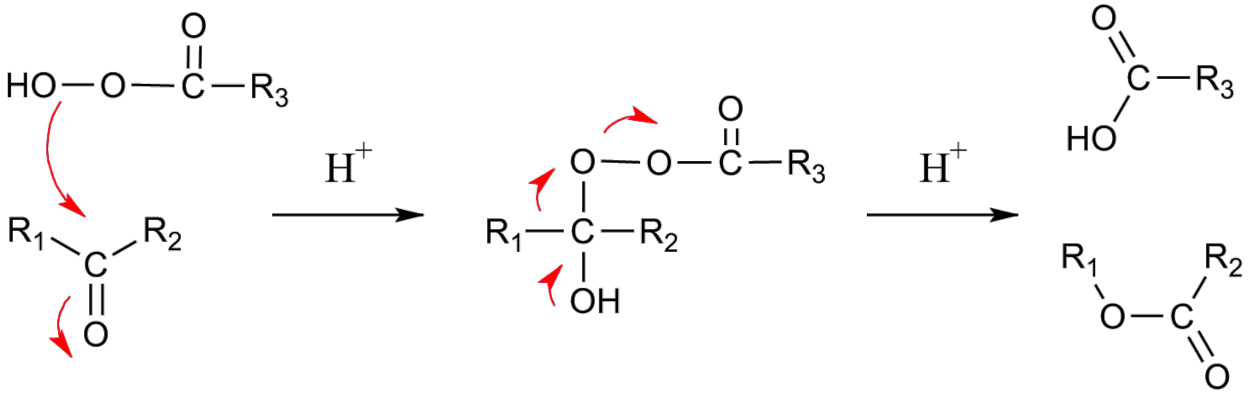


Figure 4-9. Michael reaction of a gem ketone to a 3,4-Di(phenyl)-5-(R) pyridazine (**146**) in the presence of alumina under microwave irradiation is shown. Reproduced from *Molecules* **2016**, *21*(4), 492; doi: 10.3390/molecules21040492. The solvent-free Michael addition reaction of **143** to the 3,4,6-triarylpyridazine **146** shown in **Figure 4-9** proceeded very efficiently using potassium hydroxide on alumina (KOH-alumina) as a mild, efficient, and recyclable catalyst. This approach gave pyridazines with high yields (73%–89%) after only several minutes.

There are a number of other reactions that are similar in their reactivity as a function of triggers in water (non-organic) and without catalysts.

Baeyer-Villiger:

For example, the Baeyer-Villiger Reaction is an important reaction in making an ester or lactone.



The Baeyer-Villiger Oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl to converts ketones to esters and cyclic ketones to lactones. It may vw carried out with peracids, such as m-CBPA, or with hydrogen peroxide and a Lewis acid.
https://commons.wikimedia.org/wiki/File:Baeyer- Villiger_oxidation_(mechanism).png

Benzilic Acid Rearrangement

1,2-Diketones undergo a rearrangement in the presence of a strong base to yield α-hydroxycarboxylic acids. The best yields are obtained when the diketones do not have enolizable protons. Shown below in **Figure 4-10** is a representation of the mechanism of the reaction.

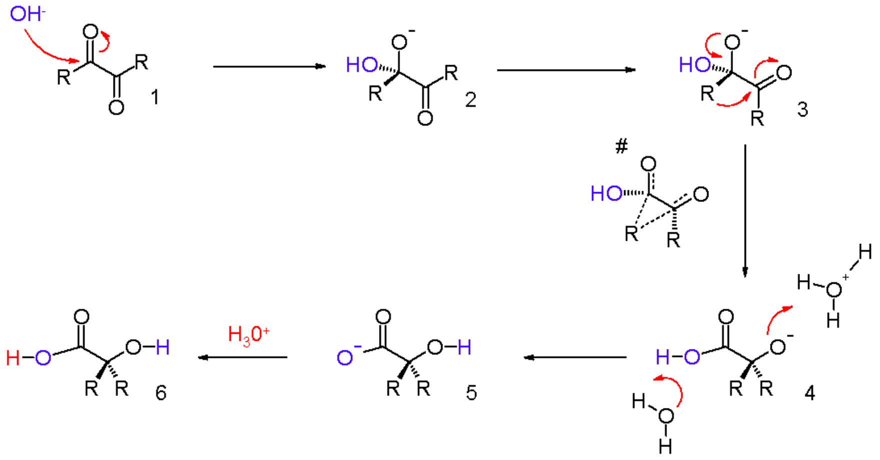


Figure 4-10. The mechanism of the Benzilic Acid Rearrangement.
https://commons.wikimedia.org/wiki/File:Benzilicacidrearrangement.png

Benzilic acid rearrangement has traditionally been conducted by heating benzyl derivatives and alkali metal hydroxides (KOH) in aqueous organic solvent. However, the rearrangements proceed more efficiently and quickly in the solid state.

Williamson Ether Synthesis

The Williamson Ether Synthesis is an organic reaction forming an ether from an organohalide and a deprotonated alcohol (alkoxide) that is done in organic solvents. However, a very rapid synthesis of symmetrical and asymmetrical ethers in "dry" media under microwave radiation has been reported (http://www.cyfronet.krakow.pl/~pcbogdal/alcohol/). The reaction was carried out by mixing an alcohol with 50% excess of an alkyl halide and catalytic amount of tetrabutylammonium bromide, adsorbed onto potassium carbonate or a mixture of potassium carbonate and potassium hydroxide, and irradiated in open conditions in a domestic microwave oven for 45-100 s. In the absence of the ammonium salt, ethers were not detected or were very low yield.

Friedel-Crafts Reaction

The opportunity to perform acylation or alkylation of an aromatic nucleus is a very important transformation in organic chemistry. The principal tool we have for such a transformation is the Friedel-Crafts, a classical reaction dating back to the 19th century, can be done in a green way to avoid the need for acid chlorides, Lewis acids, and hydrochloric acid waste products. Shown below in **Figure 4-11** is a representation of the photo-Friedel-Crafts, a mild and greener alternative to the classical analogue.

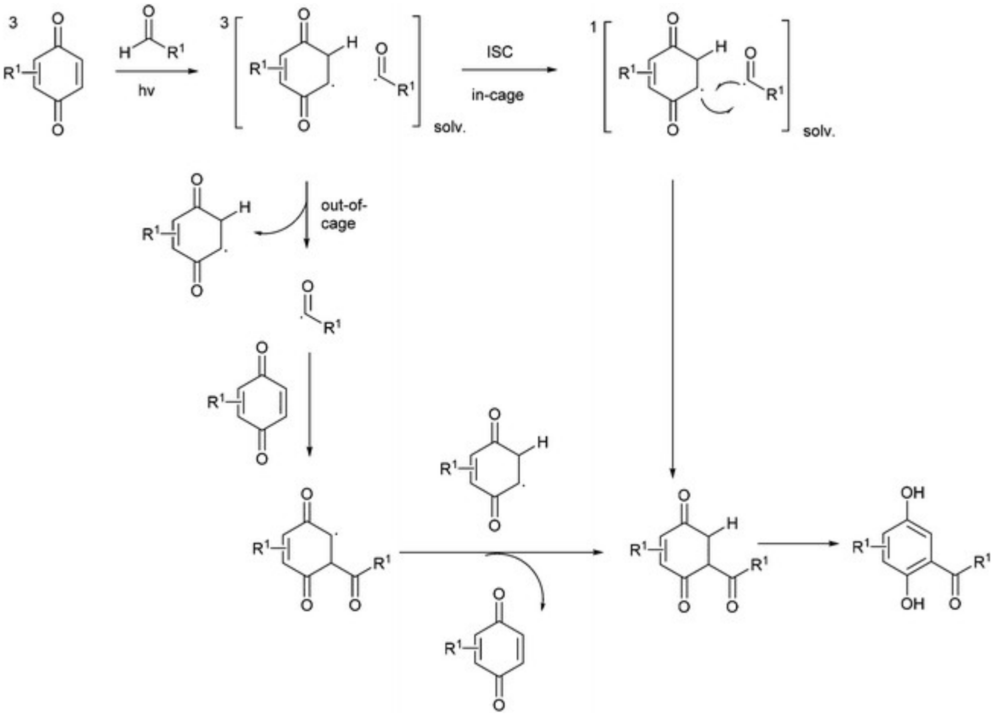


Figure 4-11. The solar-induced Friedel-Crafts reaction in which the elegance of the photoreaction is revealed by its simplicity, atom economy, and efficiency. Reproduced from *Green Chemistry* **2013**, *15*, 2830-2842. DOI:10.1039/C3GC41477A.

Ball Milling

Ball milling works on the principle of impact and attrition; size reduction results from impact as the balls drop from near the top of the shell. A ball mill is made up of a hollow cylindrical shell rotating about its axis. The axis may be either horizontal or at an acute angle to the horizontal. The shell is partially filled with balls whose grinding by action of balls, made of steel (chrome steel), stainless steel, ceramic, or rubber, results in much finer particles. The inner surface of the cylindrical shell is usually lined with an abrasion-resistant material such as manganese steel or rubber whereas less wear takes place in a rubber-lined mill. One of the reactions that is done in this manner is polymerization of MMA (methylmethacrylic acid) to PMMA (poly-) shown in **Figure 4-12**. Below is a video resource that shows the process of ball milling. In this video it is possible to see how larger materials could be broken down and ground to specific sizes based on the size of grinding ball used.

https://www.youtube.com/watch?v=L6sgGXXYdEU&t=118s

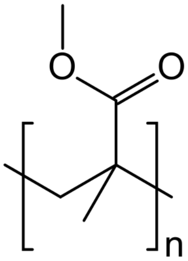


Figure 4-12. The opportunity to make one of the world's most abundant synthetic materials shown above (PMMA) through ball milling addresses fundamental green chemistry principles. https://www.wikiwand.com/en/Poly(methyl_methacrylate)

The polymerization of MMA is normally done through one of several chemical-initiated approaches. In the ball milling approach, the application of mechanical energy is sufficient to conduct the reaction, a significant finding! The same type of approach can be used to extract lignin, the third or fourth most abundant polymer on the planet. A generic molecular representation of the structure of lignin is shown in **Figure 4-13**.

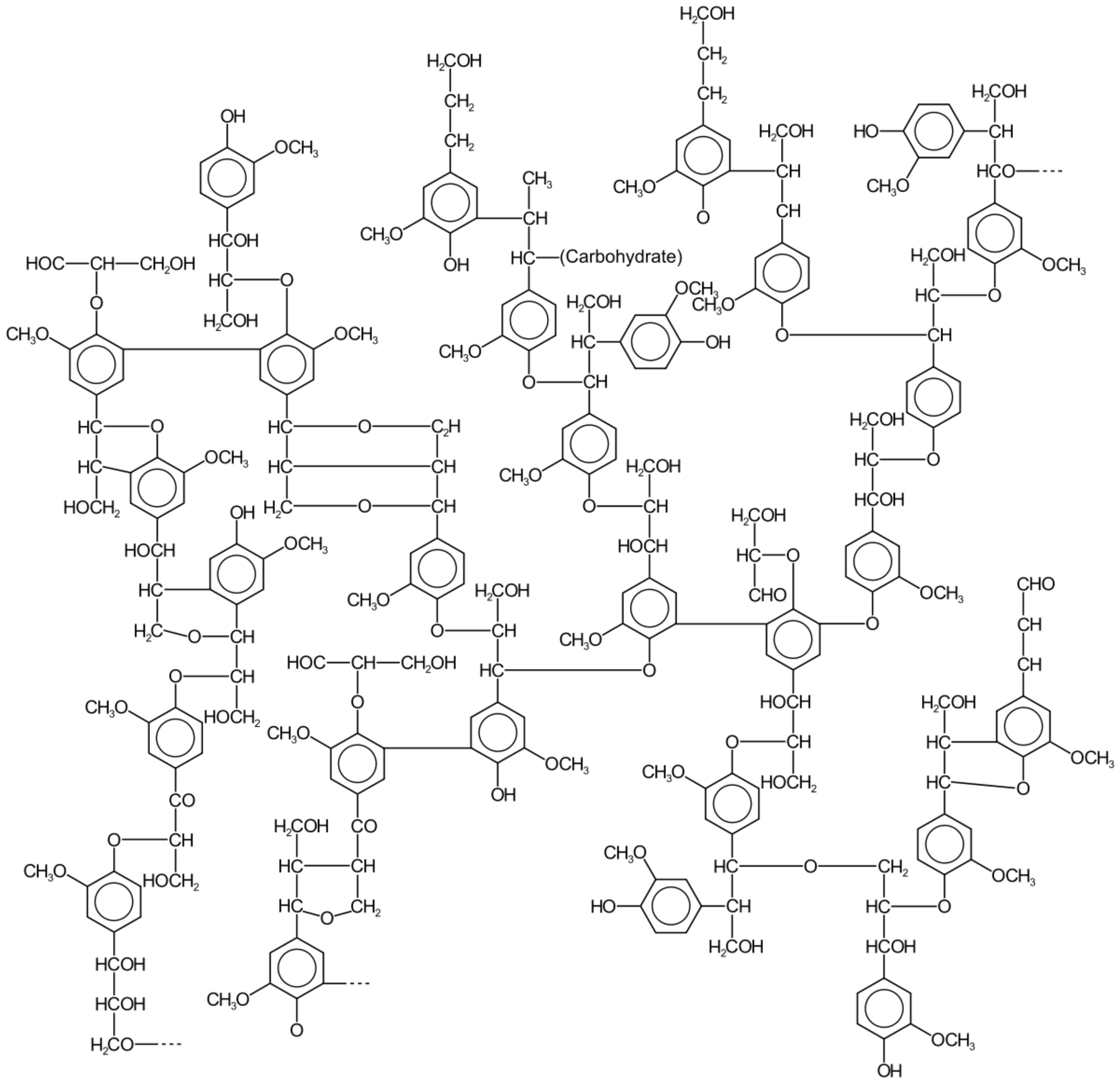


Figure 4-13. A chemical representation of the two-dimensional structure of lignin as it is known from gymnosperms (softwoods). https://en.wikipedia.org/wiki/Lignin

Process Intensification

Process intensification can be defined as a strategy for introducing dramatic reductions in the footprint of a chemical plant to reach a given production objective. These reductions may consist of shrinking the size of pieces of equipment and reducing the number of unit operations or apparatuses. Such reductions tend to be significant because the objective is to dramatically reduce energy, materials waste, and process efficiency. Several of its most salient characteristics are:

- http://tinyurl.com/bpwpah9
- Continuous, short contact times
- Minimizes further reaction
- Higher, purer yields

- Mixing & heat transfer are very good! No explosive limits reached!

Reactive Extrusion

Reactive extrusion is a chemical engineering process characterized by the forced mixing of one or more components under high pressure conditions for a specific end goal. Hot melt extrusion is one example of this. It is defined as the application of heat and/or pressure to melt a polymer and force it though a small space (extruder) as part of a continuous process. It is a well-known process that was developed to make polymer products of uniform shape and density. It is widely applied in the plastic, rubber and food industries to prepare more than half of all plastic products including bags, films, sheets, tubes, fibers, foams, and pipes.

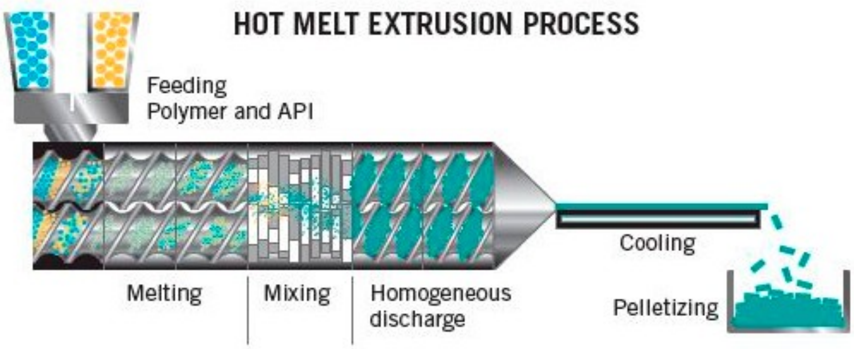


Figure 4-14. A simple idealization of the hot melt extrusion process in which the feed (polymer and API or Anionic Polymerization Initiator) go into a melting and mixing stage to ultimately yield pellets upon cooling. http://www.particlesciences.com/news/technical-briefs/2011/hot-melt-extrusion.html

Supercritical Fluids

A supercritical fluid (sCF) is a substance at a temperature and pressure that are above the critical point, at which distinct liquid and gas phases do not exist. It is a very unique phase that can effuse through solids like a gas, and dissolve materials like a liquid.

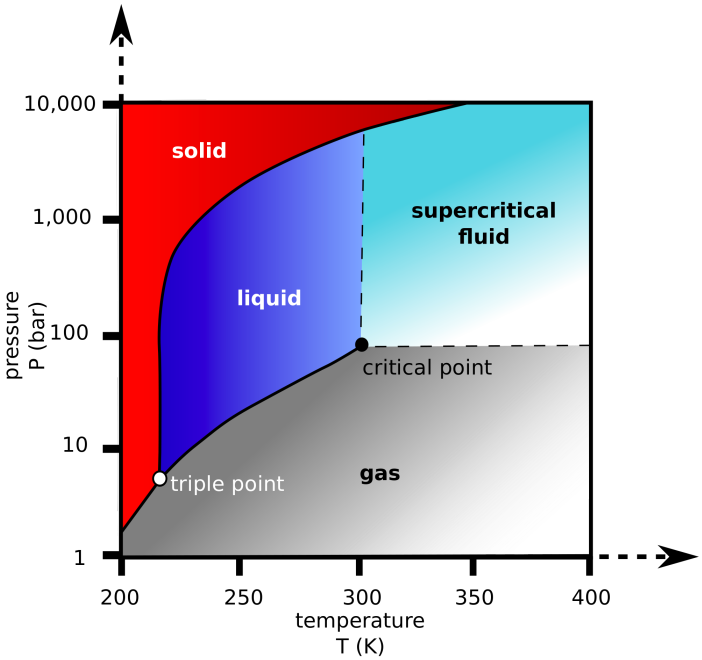


Figure 4-15. A phase diagram for the various states a substance can exhibit as a function of pressure and temperature. Notice that the upper right "quadrant" is the so-called supercritical fluid state. https://en.wikipedia.org/wiki/Supercritical_fluid

sCFs are extremely useful in green chemistry because they can be derived from environmentally friendly materials such as water and carbon dioxide with little to no impact on the carbon footprint of the planet.

Water as a Solvent

Water can behave as an exquisite solvent in a host of typical organic reactions by virtue of its ability to encourage reactivity via the "hydrophobic effect".

Microemulsions

Microemulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and a surfactant that are frequently in combination with a co-surfactant. The aqueous phase likely contains salt(s) or other ingredients, whereas the "oil" may actually be a complex mixture of different hydrocarbons and olefins.

Conclusions

The opportunity to use alternatives to typical organic solvents to do the same transformations with the same or better efficiencies has never been better than today. We are learning that we can do a lot of chemistry in a green way because we are putting our efforts into it. Although we still have a long way to go before solventless, gas phase, etc., are the mode of doing chemistry, the range of available reactions and processes is superb.

Review Questions

1. What are the implications of using alternative solvents from a life cycle analysis perspective?
2. What are the energetic considerations for allowing polymerization to occur by ball milling?
3. What is the difference between a “critical point” and the “triple point” as defined in standard phase diagrams?

Further Reading

1. Cagniard de la Tour C. 1822 Exposé de quelques résultats obtenu par l'action combinée de la chaleur et de la compression sur certains liquides, tels que l'eau, l'alcool, l'éther sulfurique et l'essence de pétrole rectifiée. Ann. Chim.
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7. P, Licence P. 2010 Photoelectron spectroscopy of ionic liquid-based interfaces. Chem. Rev. 110, 5158–5190.
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Chapter 5: Alternative Reagents

James Bond: *007 reporting for duty.*

M: *Where the hell have you been?*

James Bond: *Enjoying death.*

"Skyfall"

Summary of Chapter

This chapter focuses our attention on the pre-eminence of alternative reagents that supplant petroleum-derived reagents. The general GC principles covered in this chapter are 2 (low or no toxic substance synthesis), 7 (sustainable feedstocks), and 10 (biodegradability). The topics covered include:

- Reagent
- Ion-exchange resin
- Combinatorial Chemistry
- Cyclodextrins
- Parenteral delivery

As we indicated for solvents, we again attempt to ensure that their significance to the field of green chemistry is elucidated because of their universal nature in chemistry, biology, and engineering.

Introduction

"A reagent ain't supposed to make you faint!"

–Lucian Lucia

Reagents, not unlike solvents in the previous chapter, are the chemical materials or reactants used in a chemical conversion to product. When we think of a "reagent", we tend to think of a chemical used in a reaction, although there are numerous examples of chemicals throughout our world that do not neatly fit that mold. Dirt, water, air, etc., can all be reagents in terms of transformations to products. For example, the humic and fulvic acids found in dirt can act as exquisite reagents in separation, uptake, and cellular metabolic processes. Fulvics display a sorptive interaction with environmental chemicals before or after they reach concentrations that are toxic. The toxic herbicide Paraquat is rapidly detoxified, as are other organic compounds applied to the soil as pesticides. It is also vital to aid in the formation of new species of metal ions that bind with pesticides and herbicides to catalyze their breakdown.

We must think of a reagent as a means to an end. How can we use ingenious chemistry to take an otherwise invaluable or low-value item (commodity) to a valuable end product? This is the secret to enhancing the appeal and utility of green chemistry.

Concepts

The opportunity to do chemistry by means of, for example, a fixed substrate is very much in keeping with the concepts that we are learning. We explored the functionality and power of packed-bed columns that do chemistry normally done in solution with dissolved solutes. A packed-bed reactor can provide a source of protons, ions, or other chemicals that can affect chemistry. An ion-exchange system can perform ion *metathesis*, i.e., substitute the anion (X^{-m}) in dilute salt system $(M^{+n})_m(X^{-m})_n$ for the anion enriched on the packed bed. Shown below is an example of the process of interest. The solute (a mixture of proteins) is loaded onto the exchanger and subsequently adsorbs to the carboxymethyl anion substrate (a porogen). This process is typically characterized as a facile equilibrium process in which the protein mixture can replace the sodium cations. UV absorbance can follow the overall displacement as shown in the graph at the lower right (1st: Mes anion peak; 2nd and 3rd peaks are the desired protein chloride substance).

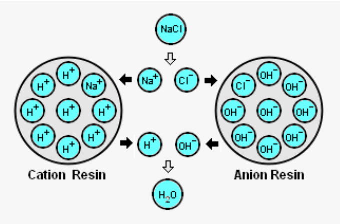


Figure 5-1. Shown is a simplified representation of the way metathesis occurs on cation and anion exchanging beds. The steps of the process are replacing the sodium cations for the positively charged hydrogens while simultaneously the chloride is replaced by the negatively charged hydroxides to lead to water. http://www.pharmaguideline.com/2014/09/mixed-bed-ion-exchanger-in-purified-water- system.html

Replacing Hazardous Substances

A common misconception in chemistry is that we should be vigilant only when we know we are working with a hazardous compound. In fact, all substances should be treated with the level of respect that they deserve. Even salt can be an irritant when used incorrectly. The most importance criteria to consider in the evaluation of the hazards of substances are the following:

- **Efficacy**: the alternative must carry out desired transformation with comparable or superior efficiency
- **Safety**: the alternative reagent should display reduced volatility, flammability, toxicity, and/or reactivity, as well as increased stability
- **Environmental impacts**: the alternative reagent should represent a reduced environmental impact

Each of the above three criteria may be used in the assessment of a compound with respect to hazard level. Obviously, efficacy must be emphasized or else there is no need to go any further with the replacement.

Inorganic and Organic Supports

Supports or scaffolds or templates represent a fixed medium for the express purpose of a targeted transformation. We will use the following paper (shown are title, authors, and abstract) for our discussion in this part of the chapter.

"Paper-immobilized enzyme as a green microstructured catalyst" Hirotaka Koga, Takuya Kitaokabc and Akira Isogaia; DOI: 10.1039/c2jm30759f

The facile and direct introduction of methacryloxy groups into cellulose paper was carried out using a silane coupling technique, leading to the improvement of hydrophobicity and both dry and wet physical strengths of the paper. Immobilization of lipase enzymes onto the methacrylate- modified paper was then accomplished, possibly due to hydrophobic interaction. The as-prepared immobilized lipase on methacrylate-modified paper possessed paper-specific practical utility. During a batch process for the nonaqueous transesterification between 1 phenylethanol and vinyl acetate to produce 1- phenylethylacetate, the paper-immobilized lipase showed high catalytic activity, selectivity and reusability, suggesting that the methacryloxy groups introduced into the cellulose paper played a key role in the hyperactivation of lipases. In addition, a higher productivity of 1-phenylethylacetate was achieved in a continuous flow reaction system than in the batch system, indicating that the interconnected porous microstructure of the paper provided favorable flow paths for the reactant solution. Thus, the paper-immobilized enzyme is expected to offer a green catalytic material for the effective production of useful chemicals.

What we note in this "paper" is the "smart" exploitation of paper as a porous microreaction chamber (interconnected paths) for a transesterification reaction between 1-phenylethanol and vinyl acetate to produce 1-Phenylethylacetate, as shown below:

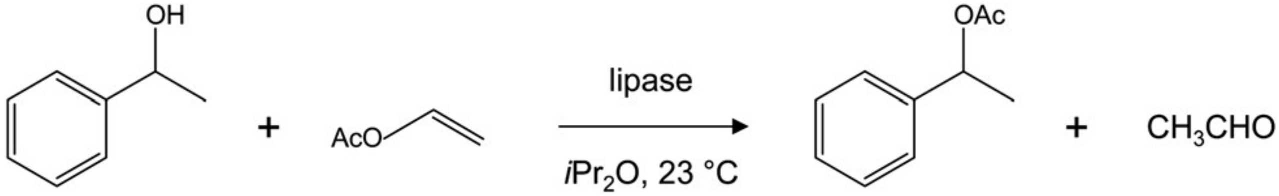


Figure 5-2. The reaction of interest (transesterification) on a solid support (cellulosic paper) between 1 phenylethanol and vinyl acetate that leads to the production of 1-phenylethylacetate. Reproduced from "Paper-immobilized enzyme as a green microstructured catalyst" Hirotaka Koga, Takuya Kitaokabc and Akira Isogaia; DOI: 10.1039/c2jm30759f

This research effort explores the opportunity to catalyze reactions of interest using natural catalysts (enzymes). In this case, lipase-catalyzed reactions (e.g., esterification, transesterification, aminolysis, acylation, and thio-transesterification) that can be carried out in nonaqueous media have been examined in the synthesis of many useful chemicals for food, cosmetic, pharmaceutical and biodiesel.

However, lipases are typically unstable in nonaqueous media due to aggregation, denaturation, or some other form of deactivation. Enzymes are often immobilized on supporting materials (silica, ceramics, carbon, resins) to provide reusability, isolation advantages, and stability in nonaqueous media. Their study offered a number of advantages for the use of this green system including the asymmetry of the final product composition:

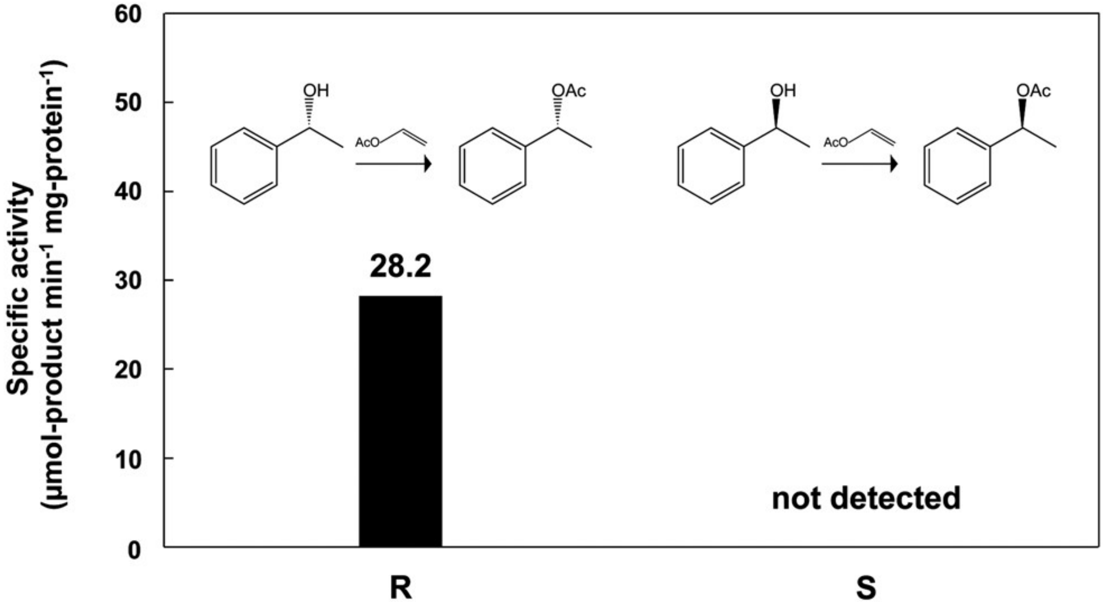
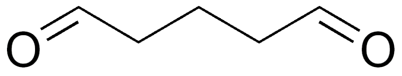


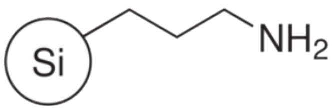
Figure 5-3. Enantioselectivity of immobilized lipase on methacrylate-modified Cellulose Whatman paper. Reaction temperature = 23 °C; stirring rate =150 rpm. Reproduced from "Paper-immobilized enzyme as a green microstructured catalyst" Hirotaka Koga, Takuya Kitaokabc and Akira Isogaia, DOI: 10.1039/c2jm30759f

Figure 5-3 shows that the paper-based system encourages the formation of the "R" enantiomer as opposed to the S (non-detected). Such a finding signals the value of a simple, facile, and highly conserved approach to an enantioselective and high yield (50%, 5 hrs.).

Removal of Lactose

The opportunity to remove lactose through a separation process can be achieved by attaching glutaraldehyde (two terminal-ended aldehyde group below, left) to an aminated silica particle (image on right) which is then covalently linked to a galactosidase enzyme that can be used to remove lactose from milk products followed by coupling with galactosidase and reaction with milk.





Quaternization of Amines

Quaternary ammonium cations, **quats**, are positively-charged ions of the structure shown below:

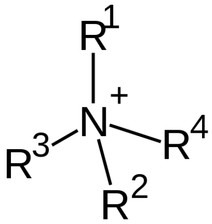


Figure 5-4. A simple representation of a quaternized amine or ammonium cation. https://www.wikiwand.com/en/Quaternary_ammonium_cation

The R group can be an alkyl group or an aryl group. Unlike ammonium (NH_4^+), quaternary ammonium cations are permanently charged, independent of pH.

Combinatorial Chemistry

Combinatorial chemistry is an approach to chemical synthesis that makes possible the preparation of a large number (e.g., millions) of compounds in a single sweep. These libraries can be mixtures, individual compounds, or computational structures.

Combinatorial chemistry can be used for small molecules, as well as for biomacromolecules such as peptides. Synthesis can quickly lead to large numbers of products. As an example, a molecule with three points of functionality or diversity (R_1, R_2, and R_3) can generate structures, where $N_{R\#}$ = the numbers of different substituents utilized. The basic principle of combinatorial chemistry is the preparation of large numbers of compounds that are then used to identify the useful components of the libraries.

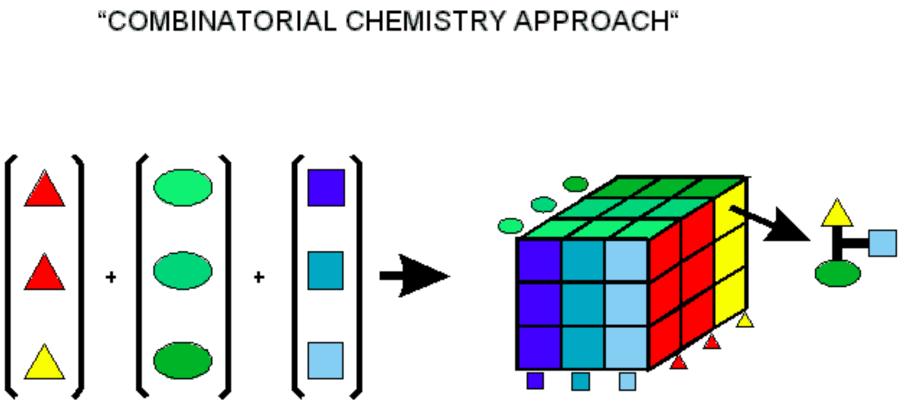


Figure 5-5. A simplified accounting of the process involved in the combinatorial chemistry approach toward developing a library of 3x3x3 indexed combinations. http://chem3513-2007.pbworks.com/w/page/15648417/Combinatorial%20Chemistry

Although combinatorial chemistry has been in play over the last 25 years, its roots go to the 1960s when a Rockefeller researcher, Bruce Merrifield, started investigating solid phase synthesis of peptides. It has had its biggest impact in the drug industry where researchers optimize the activity profile of a compound by creating a library of many different but related compounds.

Starch

Starch is an energy storage biomaterial generated from carbon dioxide and water during photosynthesis. Among the panoply of natural polymers, starch is of considerable interest because of its biodegradability, low cost, renewability, and biocompatibility. It is therefore considered a promising candidate for the sustainable development of new functional materials.

Starch is composed of two homopolymers of D-glucose: amylase, a virtually linear α-D- (1, 4')-glucan, and branched amylopectin, with many α-1, 6'-linked branch points (**Figure 5-6**).

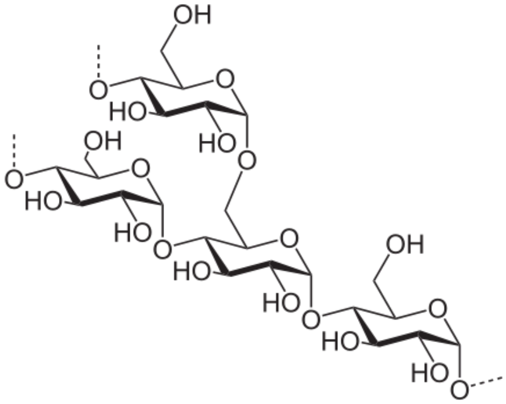


Figure 5-6. A simplified representation of the amylopectin macromolecule with the characteristic 1,6-linked branching. https://www.wikiwand.com/en/Amylopectin

Starch is a polyol: it has therefore, two secondary hydroxyl groups at C-2 and C-3, and one primary hydroxyl at C-6 when it is not linked. It is also quite hydrophilic and can be oxidized and reduced for the formation of ethers and esters and many other functional molecules. Starch has various proportions of amylose and amylopectin from about 10–20% amylose and 80–90% amylopectin based on the source. It forms a helical structure and occurs naturally as discrete granules because the short- branched amylopectin chains can form helical structures to crystallize. It has a MW of 500-20K consisting of *a*-(1à4)-D-glucose units whose extended shape has a 7-22 nm hydrodynamic radius range. The helical form of the molecule usually forms a stiff left- handed single helix whose structure, not unlike DNA, is supported by H-bonding between O2 and the O6 atoms. Amylose can undergo syneresis (dehydration synthesis) between vicinal (neighboring) glucan residues to form the cyclodextrin cavity in which the interior maintains a hydrophobicity. Interestingly, it can form double-stranded crystallites that are resistant to amylase (the putative enzyme for its deconstruction), and H-bonding and solubility. The crowing macromolecule from starch, CD, is a veritable green chemist's dream owing to a number of wonderful properties. Shown below is the toroidal structure of CD and dimensions:

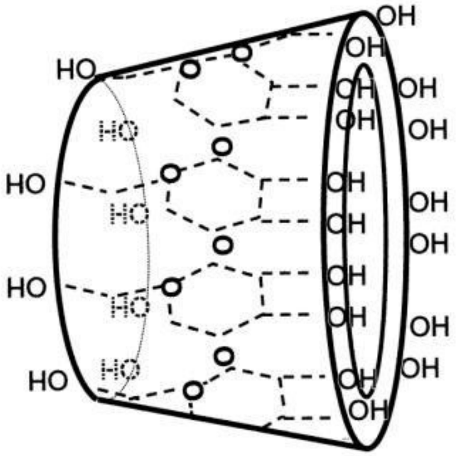


Figure 5-7. A representation of the CD macromolecule. https://commons.wikimedia.org/wiki/File:Gamma_CD_cone_shape.jpg

How do Cyclodextrins Work?? https://www.youtube.com/watch?v=UaEes6cJu7k (*How do Cyclodextrins work?* (1980). Cyclolab.)

Specifically, it is a cyclic oligomer of *a*-D-glucopyranose held together by glycosidic bonds very much like what is seen in all polysaccharides. It was discovered in 1891 by Villiers who synthesized by the enzymatic conversion of amylose followed by a selective precipitation. The precipitation can be done with several solvents, albeit organic in nature and not sustainable, but with varying degrees of yields. Note that we look at three forms of the CDs as shown in the graph below:

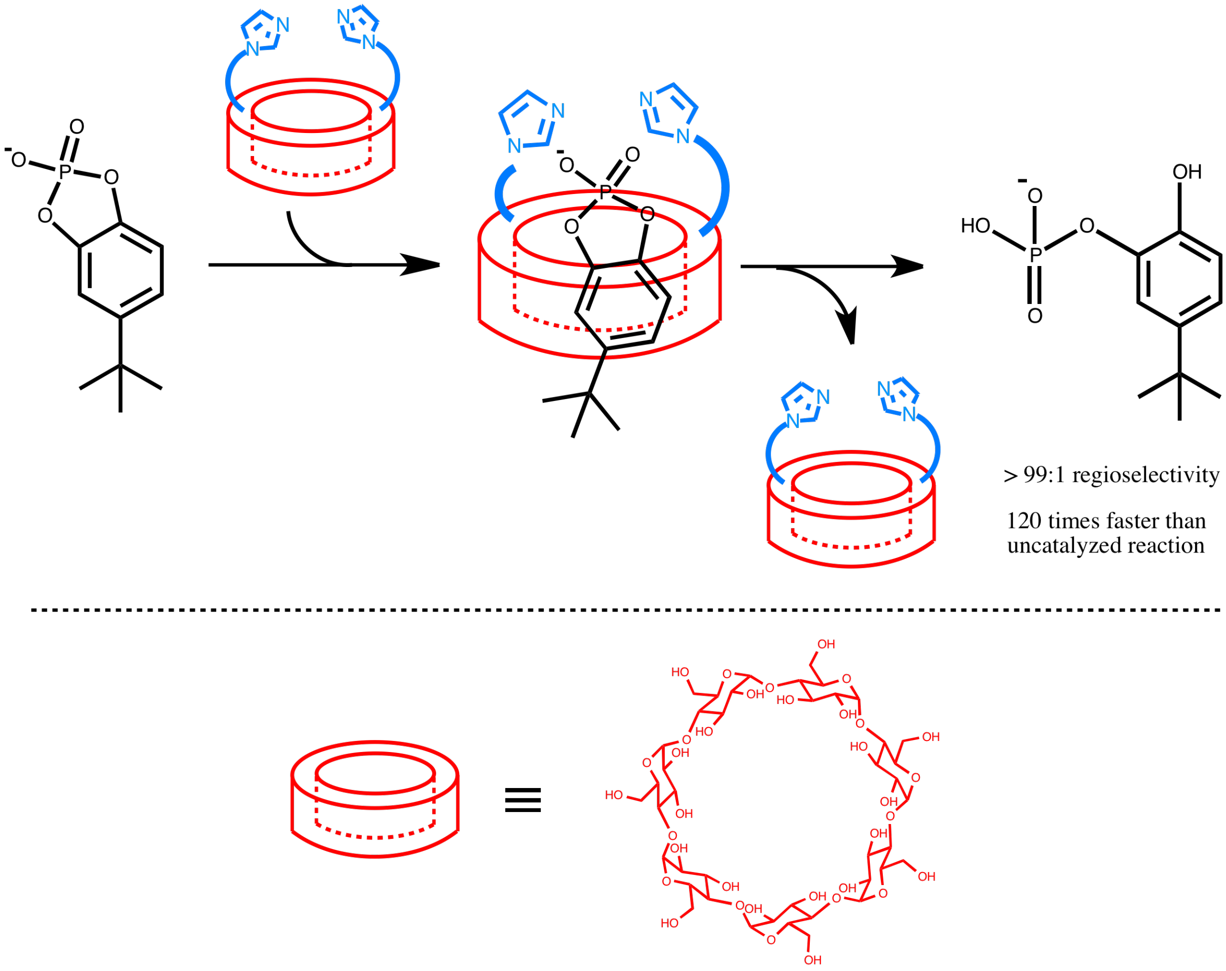
	Precipitating Agent	Yield (%)
a-CD	1-decanol	40

b-CD	toluene	50-60
g-CD	Cyclohexadec-8-en-1-ol	40-50

What is remarkable about the CDs is their ability to form host/guest inclusion complexes owing to their unique HLB (Hydrophilic Lipophilic Balance) criteria. These are quite literally molecular-scale reactors that can do many things. In the context of biomedical applications, the focus for our particular discussion, the following are among their benefits.

- To increase aqueous solubility of drugs.
- To increase chemical stability of drugs.
- To enhance drug delivery to and through biological membranes.
- To increase physical stability of drugs.
- To convert liquid drugs to microcrystalline powders.
- To prevent drug-drug and drug-excipient interactions.
- To reduce local irritation after topical or oral administration.
- To prevent drug absorption into skin or after oral administration.

The nanoreactors have an uncanny capacity to encapsulate and/or do chemistry with a number of chemicals that are hydrophobic or low polarity. Shown in **Figure 5-8** is a cartoon that depicts the hydrolytic action of CD with a phosphate molecule.



> 99:1 regioselectivity

120 times faster than uncatalyzed reaction

β-cyclodextrin

Figure 5-8. A simplified representation of the encapsulating and chemical reactivity behavior of a CD macromolecule for phosphate hydrolysis. https://commons.wikimedia.org/wiki/File:Brewslow_Cyclodextrin_Ribonuclease_Mimi c.png

CD can by virtue of the varieties in its sizes accommodate relatively small to large guest molecules. Shown below in **Figure 5-9** is a pictorial description of a 1:2 guest:host complex that engages in photophysical behavior.

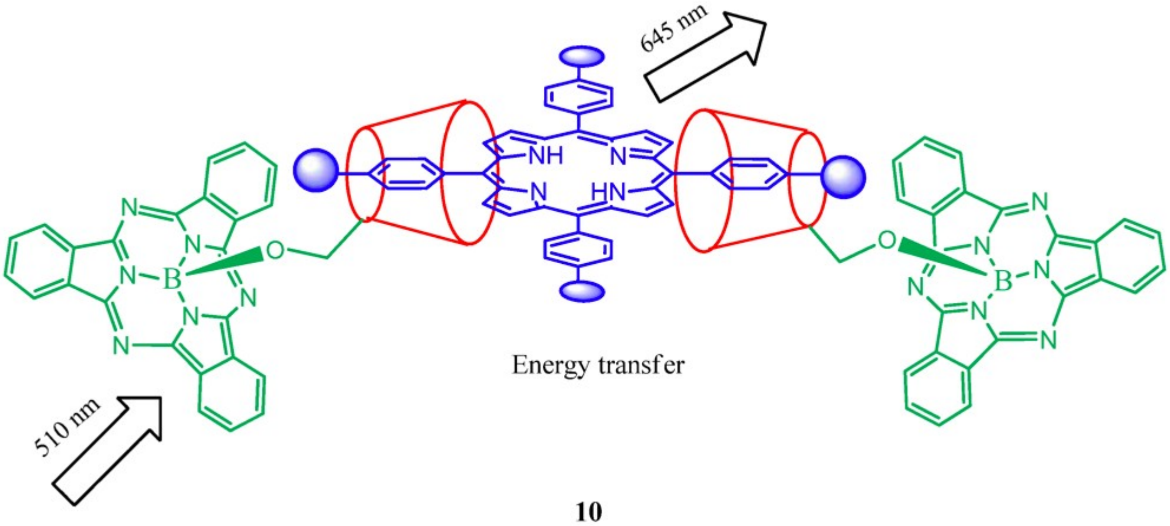


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Figure 5-9. Pictorial description of a 2:1 host-guest complex formed by β-cyclodextrin- conjugated subphthalocyanine and tetrasulfonated porphyrin (4 outside blue spheres) as part of an energy transfer system. Reproduced from *Molecules* **2012**, *17*(10), 11763- 11799; doi:10.3390/molecules171011763.

The system is engaging in an energy transfer from the peripheral boron- containing molecules to the encapsulated porphyrin molecules which releases a photon of light upon resonant energy transfer (645 nm) from the peripheral molecules.

Phase Solubility Diagrams

Phase solubility studies are carried out in aqueous systems at different temperatures to calculate stability (equilibrium) constants, (K_c) and thermodynamic values for the formation of inclusion complexes. It is known that if phase solubility diagrams show that the solubility of a guest molecule increases linearly along with the concentration of CD, then they can be considered as AL-type phase diagrams [1], suggesting the formation of 1:1 complexes, which are the most common and best understood of these types of interactions. When the phase solubility data are collected at different temperatures, we can obtain valuable additional information such as the thermodynamic parameters for the formation of the complex.

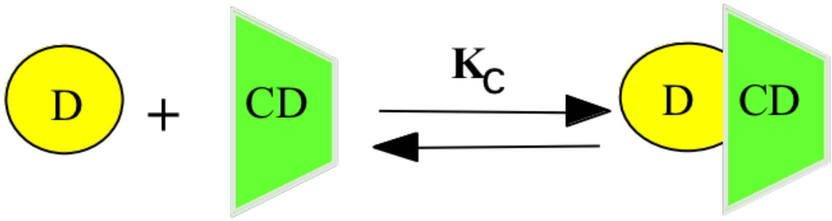
The integrated form of the Van't Hoff Equation allows for the calculation of the enthalpy (ΔH) and entropy changes (ΔS) depending on the variations of the stability constants with temperature [2]:

$$ln\,K_c = {}^{D \times H}/_{R \times T} + {}^{D \times S}/_{R}$$

The Kc can also be expressed as the following relationship:

$$K = \frac{[D - CD]}{[D]} = [D] \times [CD]$$

that can be pictorially described as:



in which there is a complexation with D (the substrate or drug in this case) and the CD. The above represents an A_L-type complex which is first order with respect to the CD and the drug (D).

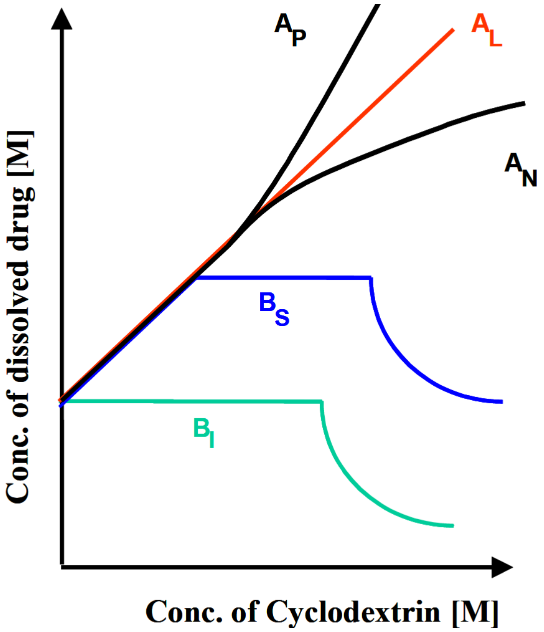


Figure 5-10. A mathematical profiling of the various phase solubility regimes available to substrate (drug) and ligand (CD) complexes as a function of CD concentration.
Reproduced from Drug Discovery Today 2016, 21, 356-362.
https://doi.org/10.1016/j.drudis.2015.11.017

A-type phase-solubility profiles are defined by the solubility of the substrate (drug) increasing with increasing ligand (cyclodextrin) concentration. When the complex is first order relative to the ligand and first or higher order with respect to substrate then A_L-type phase-solubility profiles are obtained. If the complex is first order with respect to the substrate but second or higher order with respect to ligand, A_P-types are obtained. A_N-type phase-solubility profiles are difficult to interpret. B-type phase- solubility profiles indicate formation of complexes with limited solubility in the aqueous medium. The water-soluble cyclodextrin derivatives form A-type phase- solubility profiles while less soluble cyclodextrins form B-type profiles. A number of drug/cyclodextrin complexes form inclusion complexes, but cyclodextrins form non- inclusion complexes and aggregates that dissolve drugs through micelle-like structures. The phase-solubility profiles do not verify inclusion complexes, but only describe how increasing cyclodextrin concentration influences drug solubility. As we already discussed, the most common type of cyclodextrin complexes are the 1:1 where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD). In an A_L-type phase-solubility diagram where the slope is less than unity, the stability constant ($K_{1:1}$) of the complex can be calculated from the slope and the intrinsic solubility (S_0) of the drug in the aqueous media (i.e., drug solubility when no cyclodextrin is present):

$$K_{1:1} = \frac{Slope}{S \times (1 - Slope)}$$

The value of $K_{1:1}$ is typically 50 < 2000 M^{-1} with a mean value of 129, 490, and 355 M^{-1} for α-, β- and γ-cyclodextrin, respectively [3].

Conclusions

Advances in drug development such as high throughput have increased the total and variety of drug candidates whose clinical usefulness is principally limited to a great degree by the following:

- Water insolubility;
- Chemical or physical instability;
- Local irritation after administration.

Cyclodextrins alleviate many of these issues. As evidence, there are currently around 30 different cyclodextrin pharmaceutical products on the market that include different types of pills, capsules, parenteral solutions, nasal sprays, suppositories, eye drops, and skin products. Cyclodextrins tend to replace organic solvents, enhance oral bioavailability, reduce gastrointestinal irritation, and increase dermal availability. In addition, animal and human studies have demonstrated that cyclodextrins improve drug delivery.

Addition of cyclodextrins to existing formulations will seldom result in acceptable outcome. We still lack deep knowledge of the physical factors involved in complex formation. Cyclodextrins form both inclusion and non-inclusion complexes in aqueous solutions. It has also been shown that cyclodextrins form aggregates that are able to solubilize in a micellar-like fashion; their exact structures are not known, nor is the way they influence drug delivery.

Review Questions

1. What are ways that ion exchange columns can be improved to ensure maximum efficiency? In other words, what is the principle that governs their functionality?
2. Why is paper such a good medium for chemical reactions?
3. Does a practical limit exist for the variations of combinatorial chemical processes that can be studied?
4. Can you envision a way that CD systems can aggregate in human circulatory systems?

Further Reading

1. Cagniard de la Tour C. 1822 Exposé de quelques résultats obtenu par l’action combinée de la chaleur et de la compression sur certains liquides, tels que l’eau, l’alcool, l’éther sulfurique et l’essence de pétrole rectifiée. Ann. Chim. Phys. **21**, 127– 132.
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Chapter 6: Reaction Types, Design, and Efficiency

“A positive attitude causes a chain reaction of positive thoughts, events and outcomes. It is a catalyst and it sparks extraordinary results”.

–Wade Boggs

Summary of Chapter

This chapter focuses our attention on the greenest types of reactions relevant to this course and how and why they are germane for us. The topics covered include:

- Rearrangement
- Resonance
- Canonical structures
- Yield
- Specificity

We will focus on a variety of reactions whose character is in line with the first two GC principles (prevent waste and maximize incorporation of all materials in final product).

Introduction

"What has one voice, and is four-footed in the morning, two-footed in the afternoon and three- footed at night"?

–The Sphinx (Oedipus)

In any reaction, a transformation from a starting material to a final product is the basis. In other words, a budding green chemist such as yourself will investigate how a chemical will undergo one or more treatments to produce a needed product in a manner consistent with the dogmas of GC. Typically, any chemist is chiefly interested in the concepts of yield and specificity, namely, how efficiently is the conversion done based on a theoretical yield and how exactingly is it done (with respect to a series of products). These latter terms have long been the "mantras" of organic, synthetic, and biochemical studies. The secret to any successful transformation is ensuring that we get high yield and maximum specificity no matter what else is generated. A successful chemical transformation for a green chemist, however, must go beyond these staid concepts and introduce the concepts of safety, waste, energy, and number of steps (which are reflected in the first three terms).

The history of chemistry has been one of neglecting such concepts because of the lack of environmental consciousness, low regard for safety, and lack of understanding of economics or life cycle. When we approach the riddle of doing chemistry, we have not done so with an eye to mimicking nature. We have always approached it anthropomorphically, that is to say, with the resolute conviction that we can do it better, but we fail.

Concepts

Reaction types are significant to all fields of chemistry because they are what characterize any transformation from starting materials to products. In the pantheon of reactions, we tend to focus on functional group creation and atom transformation, both of which can be accomplished through the menu of reaction types shown below:

- Rearrangement (RAR)
- Addition
- Substitution
- Elimination
- Pericyclic reaction
- Ox/Red
- Reaction design
- Atom economy

The above six (6) general reaction categories simplify the panoply of reactivity paradigms in the discipline of chemistry. We can nearly list every pertinent reaction within one or more of the listings shown. Indeed, even acid/base chemistry can fall under Addition or Elimination reactions based on their precise reactivity patterns. We will delve deeply into each type in the following sections.

Rearrangements (RARs)

A **rearrangement reaction** covers a broad swath of chemistry which is principally characterized by the rearrangement of the skeletal configuration of a molecular system to yield a structural isomer (a swapped-out form of the original structure while retaining the original atoms). Oftentimes, a substituent moves from one backbone atom to another backbone atom. In the classical organic chemistry example shown below, we witness the Wagner-Meerwein RAR.

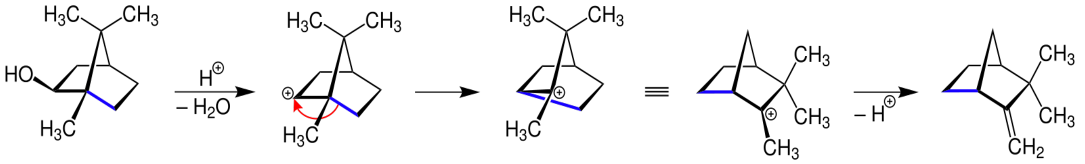


Figure 6-1. Shown is a simplified representation of the mechanistic pathway involving acid catalyzed transformation of the bicyclic tetra-substituted norbornane to an exo vinylic-substituted norbornane. The first step of the process is expulsion of water (dehydration) that leads to a reactive carbocation (albeit secondary) that lead to a 1,3- sigmatropic shift and delocalization of the carbocation to the bridgehead carbon (tertiary – hence, more stable). https://commons.wikimedia.org/wiki/File:Wagner- Meerwein_Camphene_Mech1.svg

A rearrangement is not exactly well depicted by discrete electron transfers shown by curly arrows. The actual mechanism of alkyl groups moving in **Figure 6-1** involves a fluid transfer of the alkyl group along a bond that is not described by simple ionic bond-breaking and reformation. Explanation by orbital interactions provides a better approximation although it is possible to draw the curved arrows for a sequence of discrete electron transfers to give the same result as a RAR reaction.

There are other types of RARs besides the chemically induced one shown above: we can have thermal or photo-induced as well. In these latter cases, heat or light can act as the triggers to actuate the transformation.

Thermal RARs

The isomerization of unsubstituted azulene to naphthalene was the first reported and hence most studied thermal transformation for an aromatic hydrocarbon. Many mechanisms have been suggested, yet not a one has been unequivocally confirmed.

Five mechanisms were proposed: reversible ring-closure, shown above, a norcaradiene- vinylidene, diradical, methylene walk, and a spiran mechanism. The reversible ring- closure mechanism is inaccurate despite its overall scientific appeal and evidence, and as such, multiple reaction pathways were deemed occurring simultaneously. This idea was widely accepted. It was thought that at high temperatures one mechanism would be energetically favored although energetic studies displayed similar activation energies for all mechanisms [1].

Four mechanisms for thermal isomerizations are warranted: dyotropic, diradical, and two benzene ring contractions. A 1,2-carbon shift to a carbene preceding a 1,2-hydrogen shift, and a 1-2-hydrogen shift to a carbene followed by a 1,2-carbon shift. The dyotropic mechanism shows the 1,2-shift displayed in **Figure 6-2**.

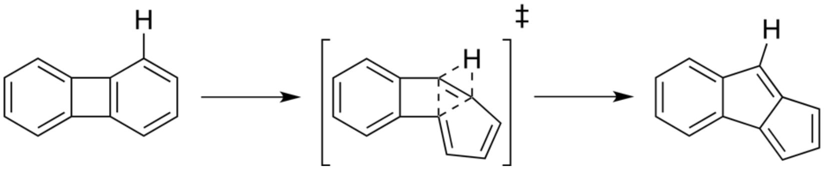


Figure 6-2. Shown is a simplified representation of the mechanistic pathway involving the thermal transformation of the above tricyclic aromatic.
http://www.wikiwand.com/en/Thermal_rearrangement_of_aromatic_hydrocarbons

Photoinduced RARs

The mechanisms of organic photochemical reactions are a treasure trove for photochemists and physicists because they provide tremendous insight into fundamental electronic behavior as a function of energy-matter interactions. The absorption of ultraviolet light by organics may lead to a number of reactions. Over the last century, an immense quantity of photochemical reactions have become unearthed; it has been found that reactions that are unlikely in ground-states are accessible in electronic excited-state configurations. One of the earliest photochemical studies was on the natural product santonin. Ciamician (1857-1922) observed that under sunlight exposure, santonin gave several photoproducts. The structure of santonin (molecule on left in **Figure 6-3**) was first described by Clemo and Hayworth in 1929 whose initial photoproduct is lumisantonin. As depicted, the photoreaction involves a C-3 carbonyl group movement to C-2, the C-4 methyl has moved to C-1, and the C-10 carbon has been inverted.

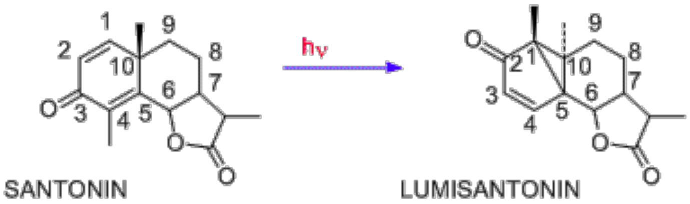


Figure 6-3. The photochemical transformation of santonin to lumisantonin as first discovered by Ciamician is represented above.
https://en.wikipedia.org/wiki/Mechanistic_organic_photochemistry

Beckmann RAR

This reaction is named after the German chemist Ernst Otto Beckmann (1853–1923). It is representative of an acid-catalyzed rearrangement of an oxime to an amide (when the oximes are cyclic, they yield “lactams”).

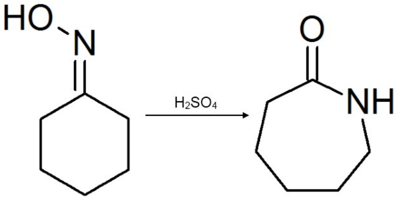


Figure 6-4. The classical transformation of a cyclic oxime to a lactam via the Beckmann RAR. http://www.wikiwand.com/en/Beckmann_rearrangement

Caprolactam, in this example, is a very important chemical because it is the feedstock in the production of Nylon 6, a material used extensively in the manufacture of textiles, clothes, carpets, cushions, bulletproof vests, etc. The reaction includes acetic acid, hydrochloric acid, sulfuric acid, and acetic anhydride, to catalyze the rearrangement. Sulfuric acid is the most commonly used acid for commercial lactam production because it forms ammonium sulfate (a common agricultural fertilizer) as a by-product when neutralized with ammonia.

In general, rearrangements tend to have no waste of atoms because they are a type of isomerization. They are hence *very atom economical and hence very efficient modes of chemical transformations. At this point, we will delve into a series of rearrangements to further illustrate the point.*

Addition Reactions

This type of reaction occurs when in general two molecules covalently bind to form a larger one referred to as the adduct. These reactions are limited to chemical compounds that have multiple bonds, such as molecules with carbon–carbon double bonds (alkenes), triple bonds (alkynes) hetero double bonds like carbonyl (C=O) groups, or imine (C=N) groups. An addition reaction is typically the reverse of an elimination reaction. For example, the hydration of an alkene to an alcohol is the reverse of dehydration which leads to an oxidative product (alkene). Electrophilic and nucleophilic additions are the main types of polar addition. The non-polar additions can be free radical and cycloaddition.

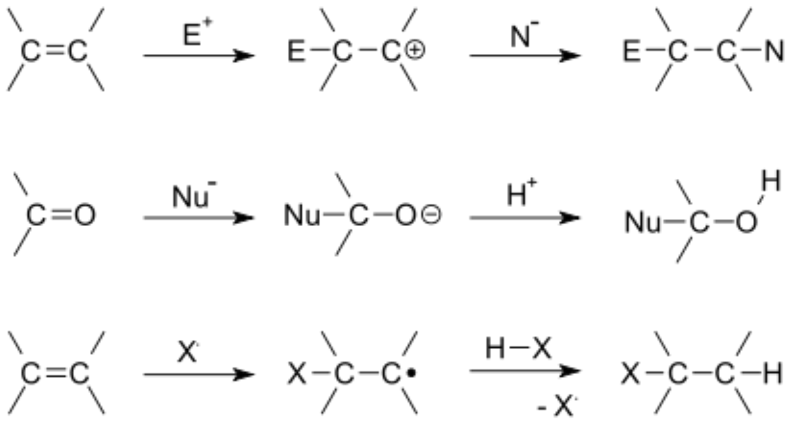


Figure 6-5. A generic depiction of the three major schemes of addition reactions. The top

represents an electrophilic addition reaction (as shown in electrophilic aromatic addition reaction such as nitration, sulfonation, etc., catalyzed by Lewis acids); the middle represents a nucleophilic addition reaction (as represented by S_N2 reactions); the bottom represents a radical-induced addition reaction which as opposed to the top two, requires an activation step (development of a radical from the olefin) that then allows for an addition (in the second step). https://www.wikiwand.com/en/Addition_reaction

In general, addition reactions are very common because they are simple, very powerful, robust, and preserve/conserve atom economy during the reaction sequence (think of the mathematical operation of addition – all numbers sum!). Thus, in general, no additional by-products are generated allowing for a clean and straight forward reaction scheme that in the final analysis may require little to no purification steps.

Substitution Reactions

These types of reactions are also known as single displacement reaction or single substitution reaction). One functional group is replaced by a more reactive functional group or else it would not happen (the reverse would be faster or more thermodynamically stable). Substitution reactions are classified either electrophilic or nucleophilic depending upon the reagents. A good example of a substitution reaction is halogenation. When chlorine gas (Cl-Cl) is irradiated with the appropriate light energy, several of the molecules photolyze into two chlorine radicals ($Cl^\cdot$) whose electrons are very nucleophilic. In **Figure 6-6**, one of radicals can rupture (homolytically) a C-H bond through abstraction of one of the equivalent protons on methane to form electrically neutral H-Cl. The other radical reforms a covalent bond with the $CH_3^\cdot$ to form CH_3Cl.

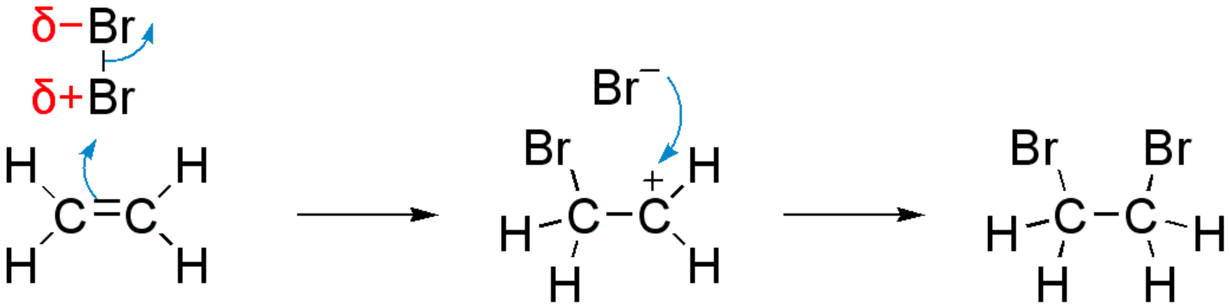


Figure 6-6. An electrophilic substitution reaction is shown in which chlorine electrophilically attacks a double bond that results in the activation of two C-H bonds. https://commons.wikimedia.org/wiki/File:Electrophilic_reaction_of_bromine_with_ethe ne.png

Elimination Reactions

An elimination reaction typically involves the removal of two substituents a substrate in either a one or two-step mechanism. The one-step mechanism is the **E2 reaction**, and the two-step mechanism is the **E1 reaction**. The numbering scheme relates to the kinetics of the reaction, i.e., bimolecular and unimolecular, respectively.

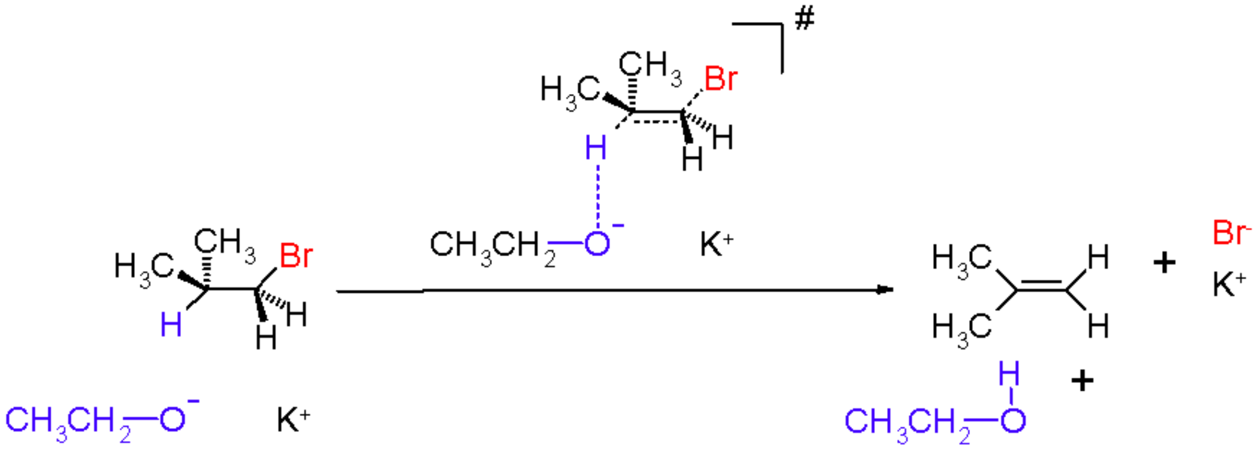


Figure 6-7. A representation of an E2 reaction (bimolecular) in which ethoxide acts as a base in a 1,2-atom removal to provide an olefin.
https://commons.wikimedia.org/wiki/File:E2_Elimination_Reaction.png

Elimination reactions are important because they are among a very few set of useful reactions that generate unsaturation within organic molecules. They are the opposite of addition reactions and involve homolytic or heterolytic dissociation of molecular groups on adjacent (vicinal) atoms leading to increased bond order on these vicinal atoms.

For example, $RCH_2CH_2OH \rightarrow R\text{-}CH{=}CH_2 + H_2O$. This latter reaction requires the expulsion of a water to lead to one degree of unsaturation. The presence of a leaving group is a pre-requisite for these types of reactions.

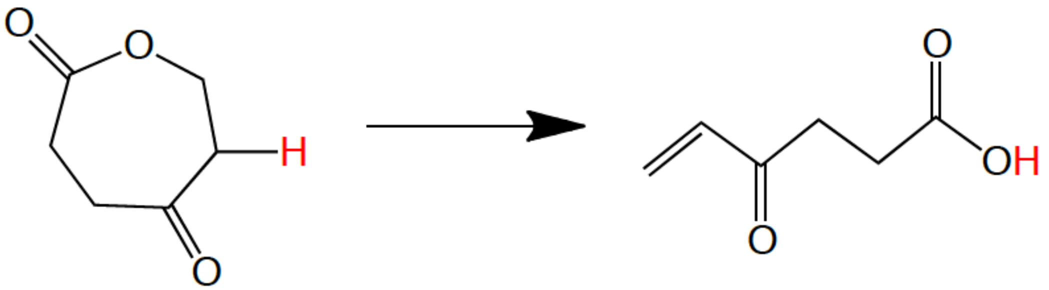


Figure 6-8. The 100% atom economic transformation of a lactone to an α,β-unsaturated carbonyl carboxylic acid in which the proton in red is conserved.

In **Figure 6-8**, the opportunity to retain a hydrogen on the final structure is an unusual mechanistic phenomenon. The conversion relies on a strict orbitally conserved concerted mechanism in which the degree of unsaturation (terminal vinyl group) is generated in tandem with the abstraction of the proton by the lactonic ring oxygen.

Such a sigmatropic shift would be over 3 atoms (hence, an unusual 1,3-hydride shift).

Pericyclic Reactions

A pericyclic reaction (**Figure 6-9**) is a reaction in which the transition state of the molecule has a cyclic geometry and progresses in a concerted manner. They are typically rearrangement reactions. The major classes of pericyclic reactions are electrocyclic, cycloaddition, sigmatropic, group transfer, cheletropic, and dyotropic, all of which are considered to be equilibrium processes.

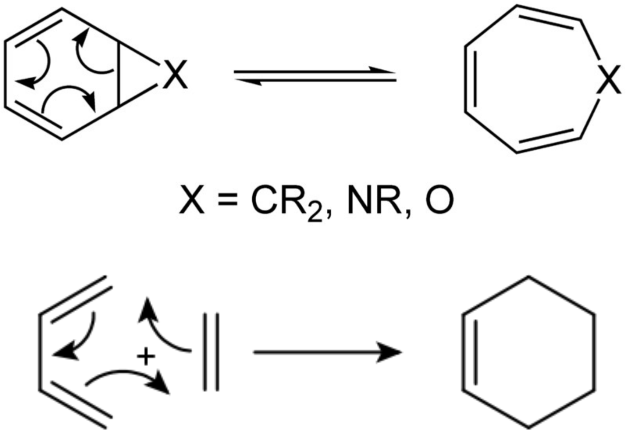


Figure 6-9. Classic examples of a pericyclic reaction that is bimolecular in nature as opposed to the preponderance of entropically-favored unimolecular pericyclic reactions. The above reactions are the classical [4+2] cycloaddition known universally as the **Diels-Alder** Reaction. https://commons.wikimedia.org/wiki/File:Diels_Alder_Mechanismus.svg

These types of reactions are governed by Frontier Molecular Orbital (FMO) Theory. Frontier molecular orbitals for a molecule are so called because the orbitals are the “frontier” or vanguard (leaders) of electron occupation. These are known classically as the highest-energy occupied (HOMO) and lowest-energy unoccupied (LUMO) molecular orbitals. The HOMO is characterized by nucleophilic or electron donation, whereas the LUMO is the opposite. Chemical reactions and resonance are very successfully described by the overlap between a filled HOMO and an empty LUMO.

Acidity and basicity are terms used in FMO Theory very broadly. Acidity refers to a ligand, metal center, or orbital ability to accept electron density (from electron sources that include Brønsted bases). Basicity refers to a ligand, metal center, or orbital ability to donate electrons (to electron sinks that include Brønsted acids). The theory distinguishes among σ-acids, σ-bases, π-acids, and π-bases. The first two, σ-X, accept or donate electrons in a σ manner, aligned head on with another orbital, whereas the latter two, π-X, accept or donate electrons in a π manner, aligned side by side with another orbital.

A pericyclic reaction typically is unimolecular and zero order with respect to kinetics. As shown below, the bicyclic on the left is highly strained because of the 1,2 bridging and undergoes an electrocyclic RAR to relieve the steric stress associated with the heterocyclic cyclopropanoid moiety.

Diels-Alder

This is a [4+2] cycloaddition as already mentioned that occurs between a conjugated diene and a substituted alkene known as a dienophile to form a substituted cyclohexene. It was first described by Otto Diels and Kurt Adler in 1928 that lead to the Nobel Prize in Chemistry in 1950. It is a reliable method for forming 6- membered systems with good regio- and stereochemical control. The concept has been applied to other π-systems to provide the corresponding heterocycles (hetero-Diels–Alder reaction).

1,3-Dipolar Cycloaddition

This reaction occurs between a 1,3-dipole and a dipolarophile to form a five-membered ring (**Figure 6-10**). The reaction is sometimes referred to as the Huisgen cycloaddition which specifically describes the 1,3-dipolar cycloaddition between an organic azide and an alkyne to generate 1,2,3-triazole. Currently, this reaction is an important route to the region- and stereospecific synthesis of five-
membered heterocycles.

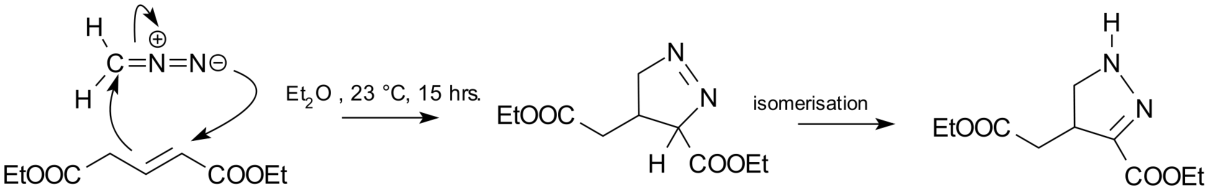


Figure 6-10. A representation 1,3-dipolar cycloaddition to yield a simple diazoalkane is shown above. http://www.wikiwand.com/en/1,3-Dipolar_cycloaddition

Cope Rearrangement (RAR)

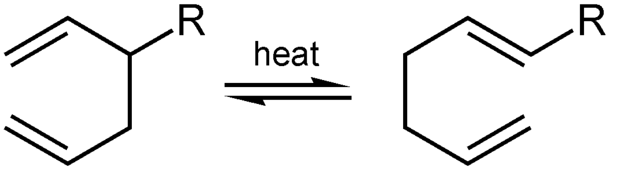


Figure 6-11. The Cope depicted for 3-alkyl-1,5-hexadiene.
http://www.wikiwand.com/en/Cope_rearrangement

The Cope RAR is an extensively studied [3,3]-sigmatropic RAR of 1,5-dienes developed by Arthur Cope. For example, 3-methyl-1,5-hexadiene heated to 300 °C yields 1,5- heptadiene (see **Figure 6-11**).

Oxidation/Reduction Reactions

The term “redox”, short for **red**uction–**ox**idation reaction, is used to describe the complete set of chemical reactions occurring for electron transfers leading to changes in oxidation states. Redox reactions require a reduction and complementary oxidation processes. The chemical species (reductant) where the electron is removed is oxidized, while the counter species (oxidant) to where it is added is reduced:

- Oxidation is the *loss* of electrons or *increase* in oxidation state;
- Reduction is the *gain* of electrons or a *decrease* in oxidation state.

As an example, in an electrolytic cell (shown in **Figure 6-12**), a complete redox (cycle) is shown.

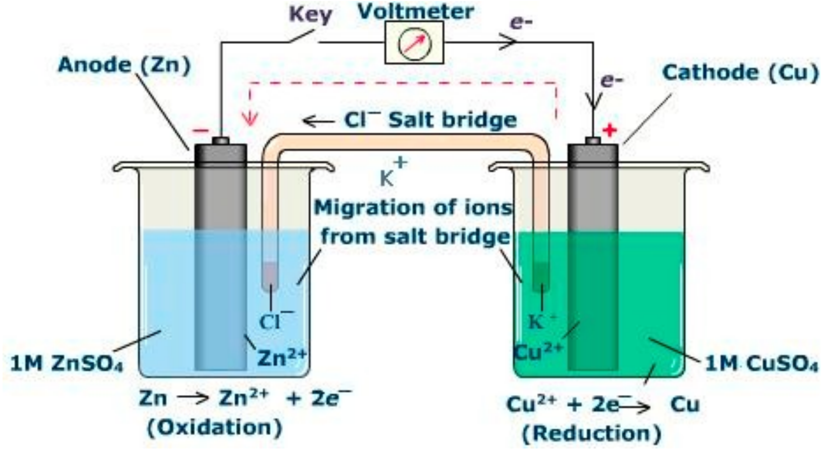


Figure 6-12. A representation of the electron flow occurring during a redox cycle in which zinc is the reductant and copper the oxidant.
https://commons.wikimedia.org/wiki/File:Half_cell_example.jpeg

In the example, zinc is being oxidized from $\text{Zn}^0 \rightarrow \text{Zn}^{+2}$ which is a net loss of two electrons per atom. The oxidized zinc solubilizes in the anodic solution and proceeds to pull over an anion from the cathodic solution through the electromotive force of the two electrons that it lost. In other words, the zinc cation is balanced by the anions (likely two chloride anions) in the cathodic solution. Simultaneously, copper sulfate cations (cupric cations) are reduced by the net influx of the two electrons. A redox reaction can occur relatively slowly, for example, in the case of rust, or more rapidly, as in fires.

Reaction design and efficiency

Green chemistry is all about increasing the overall efficiency of a reaction in terms of numerous criteria. In general, we try to mimic biological reactions because they are among the most efficient, low energy, and atom conserving reactions at our disposal. In terms of the "perfect" chemical reaction, we are talking about:

Selectivity: we want to make one thing and one thing only to ensure that we don't have contamination or other issues to content with the require cleanup, purification, or multi- step pathways.

Efficiency: This term refers to the overall energy, time, and material inputs relative to the final product required. How intense is the process needed to obtain a final product? Obviously, a more efficient process/reaction will require much less inputs. In an ideal scenario, a product occurs spontaneously without very little input.

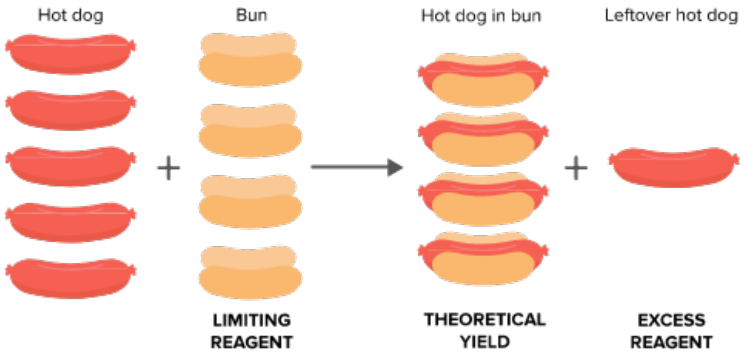
Safety: Although we don't talk about it much, the criterion of safety for a reaction or process must be paramount and very redundant given "Murphy's Law". Green chemistry is truly a discipline that is framed in the overall theme of safe performance and operation for a process or else it insists upon a no-go juncture point.

Solventless: Again, the overall inputs are minimized in any reaction, and this is just one of the many criteria to ensuring efficiency and lowest impact. To do a reaction solventless means allowing self-reaction to occur with or a bimolecular reaction with other reagents in the absence of a solvent. Although many biological reactions occur in a solvent, ideally, it would be best to avoid if possible because of the many issues surrounding solvents: disposal, clean up, concentration-based reactions (depend on kinetics), and in the case of water, its precious nature for food, drinking, washing, etc.

Low or no energetics: Here we try to approach an ideality for energy conservation in which we reduce the need for high heat, high pressure, long times, etc. Ideally, we would use the energy available to us without attempting to burn gas, coal, employ electricity (power grids), etc.

Chemical yield: In most standard chemistry reaction descriptions, we tend to emphasize the "yield" of a reaction as the chief parameter for assessing the reaction efficiency or utility. A low yield reaction would be undesirable because of the lack of return on the process. Chemical yield is defined as the moles of desired products obtained as a ratio to the possible moles (theoretical) possible expressed as a percentage.

Let's give an excellent intuitive example from the Khan Academy (https://www.khanacademy.org/science/chemistry/chemical-reactions- stoichiome/limiting-reagent-stoichiometry/a/limiting-reagents-and-percent-yield): Let's assume you have five hot dogs and four hot dog buns. Obviously, you will have one hot dog in excess.



In terms of chemical reactions, the hot dog buns are the limiting reagent and the leftover single hot dog is the excess reagent; thus, four complete hot dogs are the theoretical yield, assuming the hot dogs and buns combine in a one-to-one ratio (you've got to balance the reaction first). In any chemical reaction, the **limiting reagent** is the reactant that determines how much of the products can be made. The other reactant(s) is/are *in excess*.

How do we measure yield more efficiently?

Typically, chemical yield focuses on a part of the reaction, i.e., our desired product based on the complete reaction of the limiting reagent. However, in many cases, the overall efficiency from a green chemical perspective is compromised despite high chemical yields.

Consider the "Gabriel Synthesis":

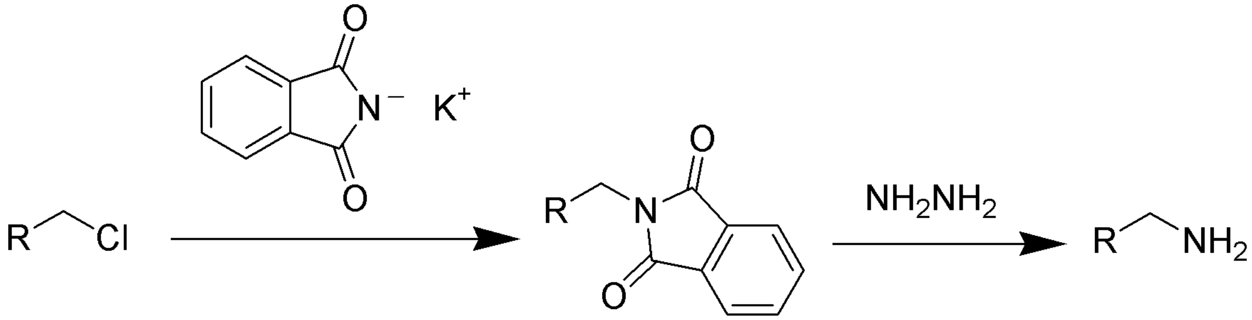


Figure 6-13. A representation of part of the classical Gabriel Synthesis whose product is a primary amine. http://www.wikiwand.com/en/Gabriel_synthesis

The reaction transforms primary alkyl halides into primary amines. In **Figure 6-13**, only the latter half of the reaction/synthesis is shown! Traditionally, the reaction uses potassium phthalimide (an –NH_2 synthon) to homologate the alkyl which is later coupled to the amine. In the Gabriel Synthesis, the phthalimide anion is employed as a surrogate of H_2N^-. The entirety of the reaction is shown in **Figure 6-14**:

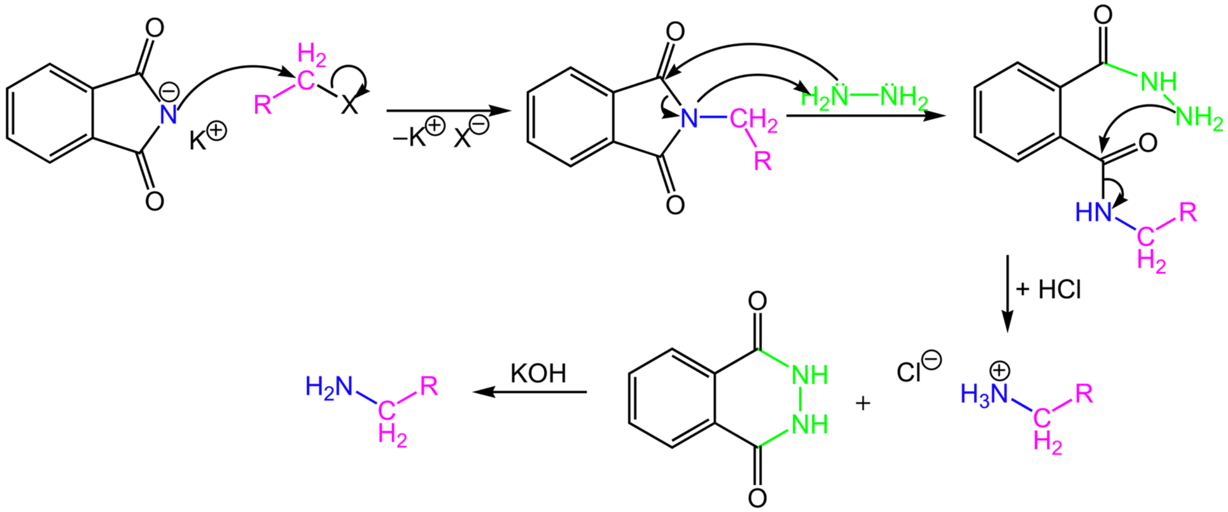


Figure 6-14. The Gabriel Synthesis that starts with the amine synthon (the first reactant at the left) that after four steps yields the desired primary amine. https://commons.wikimedia.org/wiki/File:Gabriel_synthesis_mechanism.png

In chemical yield methodologies, we do NOT account for the stream of by-products that amass during a reaction or set of reactions. In the above case, we have the following waste products: potassium halide (K-X), potassium chloride (KCl), and phthalhydrazide (see **Fig. 6-13** for the structure – the aromatic compound, second from right). Unbelievably, this array (especially the hydrazide) make up a huge fraction of wasted atoms that do not contribute in any way to the efficiency of the reaction. Because of the incredible "atomic" waste, we have a reaction with a very poor "atom economy".

Atom economy

This is a concept that was first formalized by Trost.[1] Atom economy (atom efficiency) is the conversion efficiency of a chemical process in terms of all atoms and the desired product(s). It is one of the most singularly powerful definitions for understanding the "greenness" of a reaction and its potential usefulness.

Atom economy can be written as:

$$Atom\ Economy\ (\%) = \frac{Molecular\ Mass\ (MW) of\ Desired\ Product}{Molecular\ Mass\ (MW) of\ all\ Reactants} \times 100$$

As we already alluded, in an ideal chemical process, the amount of starting materials equals the amount of all products generated and no atom is wasted. If this is not the case, this is a genuine concern for raw materials that have a high cost or due to economic and environmental costs of disposal of the waste.

In addition to high-yielding process such as the Gabriel Synthesis that result in substantial byproducts, we also have the Cannizzaro Reaction[2] where 50% of the reactant aldehyde becomes the other oxidation state of the target and the Wittig,[3] where high-mass phosphorus reagents are used but become waste.

A Diels-Alder reaction is an example of a very atom efficient reaction that also can be chemo-, regio-, diastereo- and enantioselective. Catalytic hydrogenation comes closest to being an ideal reaction that is extensively practiced both industrially and academically.[4] Poor atom economy is common in drug (pharmaceutical) synthesis, and in research. For example, during the synthesis of an alcohol by reduction of an ester with lithium aluminum hydride, the reaction produces a huge amount of aluminum salts. The cost can be considerable.

Experimental atom economy

In this derivative calculation of atom economy, we account for the actual quantities of reagents used in a ratio of theoretical yield of product total mass of reactants used as a percentage. Or equivalently, we can calculate the mass of reactants utilized in the desired product divided by the total mass of all reactants as a percentage.

Percentage yield x experimental atom economy

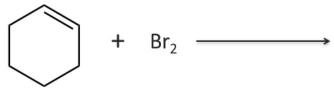
This is considered the ultimate measure of the efficiency of a reaction. In this case, you multiply the chemical yield of the product by the experimental atom economy to obtain a true measure of the atom efficiency of the reaction.

Conclusions

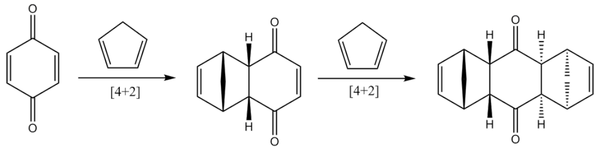
In this final chapter, we became very familiar with the concepts of reaction efficiency and design from a green chemistry perspective. We more or less employed the totality of the green chemistry principles to understanding what goes into maximizing the environmental, social, and economic benefits associated with scientific enterprises. We thoroughly explored the nature of the various types of reactions done in both fundamental and applied settings and how to evaluate them using very useful mathematical constructs. This chapter serves to cement the concepts we learned in this magnificent discipline and to provide a platform for understanding how to best approach the chemistry, chemical engineering, and the biological transformations of reactions and processes.

Review Questions

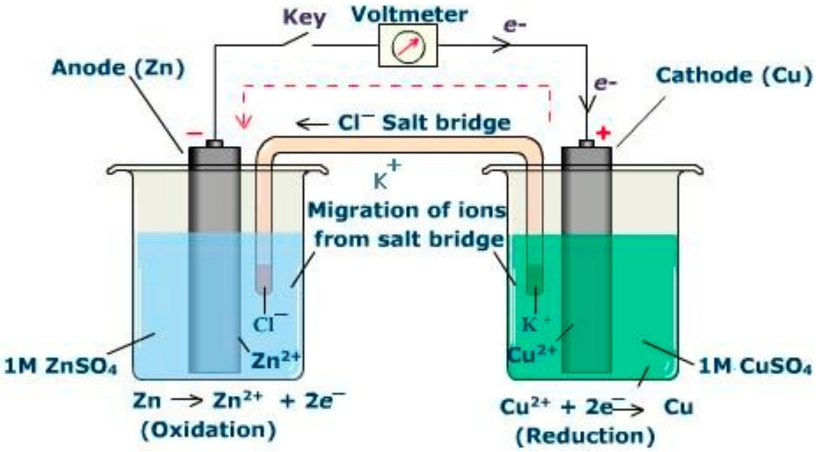
1. Indicate by drawings what the addition products are for the following reaction and what type of reaction it is:



2. Please indicate what the products are of the reaction of 2-phenyl isopropyl iodide with sodium methoxide.
3. Does the non-salt product in (2) retain its stereochemical configuration? Why?
4. Please explain how the minor product is formed in the E2 reaction below and why it is minor?
5. Using the Diels-Alder Reaction shown below, draw the transition state that will lead to the adduct.



6. Using the redox diagram below, indicate why the process cannot go on forever.

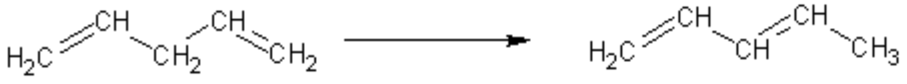


7. Define the following terms
   a. atom economy
   b. %-atom economy
   c. % yield (PE)
   d. % experimental atom economy (EAE)
   c) %PE x EAE
8. Which of the terms in question 7 are only meaningful with experimental results? What experimental result is necessary to make these terms meaningful?
9. Consider the following four (4) reactions shown below:
   a. Label each reaction as a substitution, elimination, addition or rearrangement.

b. Rewrite each reaction making sure that the reaction is balanced. Show all the reactant atoms that are incorporated into the desired product, and the atoms of the desired product in green, and all other atoms in brown.
c. Set up a table of atom economy whose headings are: formula, formula weight, number of utilized atoms, weight of utilized atoms, unutilized atoms, and weight of unutilized atoms.
d. Calculate the %-atom economy of each reaction.

$$H_3C{-}CH_2{-}Br \quad + \quad KOH \longrightarrow H_2C{=}CH_2 \quad + \quad KBr$$

$$H_3C{-}Cl \quad + \quad NaOH \longrightarrow H_3C{-}OH \quad + \quad NaCl$$



$$H_2C{=}CH_2 \quad + \quad Br{-}Br \longrightarrow Br{-}CH_2{-}CH_2{-}Br$$

10. In the *Further Reading* section (#3), Roger Sheldon has developed a term very similar to the %-atom economy termed % atom utilization. The % atom utilization can be calculated according to the following equation: % **Atom Utilization** = (MW of desired product/MW of all products) X 100
   a. Compare and contrast this with the %-atom economy.
   b. What concept that you learned in freshman chemistry makes the actual percentages calculated for the % atom utilization, and % atom economy equal (in most circumstances). Prove this by calculating the % atom utilization for each of the reactions in questions 9—13 and comparing your results to the %-atom economy that you calculated in question 9.

Further Reading

1. Williamson, Kenneth L., Macroscale and Microscale Organic Experiments, 2nd ed., D. C. Heath and Co., 1994, 247-252.
2. Trost, Barry M., The Atom Economy-A Search for Synthetic Efficiency. Science 1991, 254, 1471-1477.
3. Cann, Michael C.; Connelly, Marc E. Real-World Cases in Green Chemistry; ACS, Washington, 2000. Roger Sheldon of Delft University has developed a very similar concept called % atom utilization. Sheldon, Roger A. Organic Synthesis- Past, Present and Future. *Chem. Ind. (London)*, **1992,** (Dec), 903-906.
4. Anastas, Paul T., and Warner, John C. Green Chemistry Theory and Practice, Oxford University Press, New York, 1998.
5. Westheimer, T. The Award Goes to BHC. *Chem. Eng.* **1993**, (Dec.), 84-95.

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Index of Terms