ORGANIC CHEMISTRY - MLC



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TABLE OF CONTENTS

Licensing

1: Introduction to Organic Chemistry and Structure

- 1.1: Introduction to Organic Chemistry
  - 1.1.1: History
- 1.2: Fractional Distillation and Alkanes
  - 1.2.1: Hydrocarbons and the Homologous Series
  - 1.2.2: Overview of Distillation
  - 1.2.3: Fractional Distillation
    - 1.2.3.1: Theory of Fractional Distillation
    - 1.2.3.2: Fractionating Columns
    - 1.2.3.3: Uses of Fractional Distillation
    - 1.2.3.4: Step-by-Step Procedures for Fractional Distillation
  - 1.2.4: Structural Formulas - Lewis, Kekule, Bond-line, Condensed, and Perspective
  - 1.2.5: Alkanes and Alkane Isomers
  - 1.2.6: Alkyl Groups
  - 1.2.7: Naming Alkanes
  - 1.2.8: Properties of Alkanes
- 1.3: Cyclic Hydrocarbons
  - 1.3.1: Naming Cycloalkanes
  - 1.3.2: Stability of Cycloalkanes - Ring Strain
- 1.4: Alkenes
  - 1.4.1: Bond Rotation
  - 1.4.2: Introduction to Alkenes
  - 1.4.3: Industrial Preparation and Use of Alkenes
  - 1.4.4: Naming Alkenes
  - 1.4.5: Polymerization of Alkenes
- 1.5: Alkynes and Benzene
  - 1.5.1: Naming Alkynes
  - 1.5.2: Introduction
  - 1.5.3: Naming Aromatic Compounds
  - 1.5.4: Structure and Stability of Benzene
- 1.6: Halides
  - 1.6.1: Introduction to Organohalides
  - 1.6.2: Names and Properties of Alkyl Halides
- 1.7: Isomers
  - 1.7.1: Isomerism Introduction
- 1.8: Polarity and Lewis Structures
  - 1.8.1: Atomic Structure - Orbitals
  - 1.8.2: Atomic Structure - Electron Configurations
  - 1.8.3: Development of Chemical Bonding Theory
  - 1.8.4: Describing Chemical Bonds - Valence Bond Theory

- 1.8.5: Polar Covalent Bonds - Electronegativity
- 1.9: Formal Charge and Resonance
  - 1.9.1: Lewis Structures and Formal Charges
  - 1.9.2: Resonance
- 1.10: Common Bonding Patterns for Organic Chemistry

2: Tools of Organic Chemistry

- 2.1: Intermolecular Forces (IMFs) - Review
  - 2.1.1: Intermolecular Forces and Relative Boiling Points (bp)
  - 2.1.2: Intermolecular Forces and Solubilities
  - 2.1.3: Chromatography
  - 2.1.4: Thin Layer Chromatography (TLC)
    - 2.1.4A: Overview of TLC
    - 2.1.4B: Uses of TLC
    - 2.1.4C: The Retention Factor
    - 2.1.4D: Separation Theory
    - 2.1.4E: Step-by-Step Procedures for Thin Layer Chromatography
    - 2.1.4F: Visualizing TLC Plates
  - 2.1.5: Gas Chromatography (GC)
    - 2.1.5A: Overview of GC
    - 2.1.5B: Uses of Gas Chromatography
    - 2.1.5C: Separation Theory
    - 2.1.5D: Quantitating with GC
    - 2.1.5E: GC Parameters
    - 2.1.5F: Sample Preparation for Gas Chromatography
- 2.2: Column Chromatography
  - 2.2.1: Macroscale Columns
  - 2.2.2: Microscale (Pipette) Columns
  - 2.2.3: 5.5 Polarimetry
  - 2.2.4: Crystallization
    - 2.2.4.1: Overview of Crystallization
    - 2.2.4.2: Uses of Crystallization
      - 2.2.4.2A: Reagent Purification
      - 2.2.4.2B: Purification of Product Mixtures
    - 2.2.4.3: Choice of Solvent
      - 2.2.4.3A: Ideal Temperature Profile
      - 2.2.4.3B: General Procedures for Removing Impurities
      - 2.2.4.3C: Determining Which Solvent to Use
      - 2.2.4.3D: Using Solubility Data
      - 2.2.4.3E: Experimentally Testing Solvents
      - 2.2.4.3F: Mixed Solvents
    - 2.2.4.4: Crystallization Theory
      - 2.2.4.4A: Purification
      - 2.2.4.4B: Cooling Slowly
      - 2.2.4.4C: Using the Minimum Amount of Hot Solvent
      - 2.2.4.4D: The Unavoidable Loss of Recovery
      - 2.2.4.4E: Quantitating Crystallization

- 2.2.4.4F: Second Crop Crystallization
- 2.2.4.5: Procedural Generalities
  - 2.2.4.5A: General Procedure
  - 2.2.4.5B: Heat Source and Bump Prevention
  - 2.2.4.5C: Charcoal
  - 2.2.4.5D: Cooling Slowly
  - 2.2.4.5E: Initiating Crystallization
- 2.2.4.6: Step-by-Step Procedures
  - 2.2.4.6A: Single Solvent Crystallization
  - 2.2.4.6B: Crystallization Summary
  - 2.2.4.6C: Using Solvents Other Than Water
  - 2.2.4.6D: Mixed Solvent Crystallization
  - 2.2.4.6E: Mixed Solvent Summary
  - 2.2.4.6F: Troubleshooting

3: Alcohols, Ethers, Thiols, Sulfides, and Amines

- 3.1: Alcohols and Phenols
  - 3.1.1: Introduction
  - 3.1.2: Naming Alcohols and Phenols
  - 3.1.3: Properties of Alcohols and Phenols
  - 3.1.4: Preparation of Alcohols- A Review
  - 3.1.5: Alcohols from Carbonyl Compounds- Reduction
  - 3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents
  - 3.1.7: Reactions of Alcohols
  - 3.1.8: Oxidation of Alcohols
  - 3.1.9: Protection of Alcohols
  - 3.1.10: Phenols and Their Uses
  - 3.1.11: Reactions of Phenols
  - 3.1.12: Spectroscopy of Alcohols and Phenols
  - 3.1.S: Alcohols and Phenols (Summary)
- 3.2: Ethers and Epoxides; Thiols and Sulfides
  - 3.2.1: Introduction
  - 3.2.2: Names and Properties of Ethers
  - 3.2.3: Preparing Ethers
  - 3.2.4: Reactions of Ethers- Acidic Cleavage
  - 3.2.5: Reactions of Ethers- Claisen Rearrangement
  - 3.2.6: Thiols and Sulfides
- 3.3: Amines and Heterocycles
  - 3.3.1: Naming Amines
  - 3.3.2: Structure and Properties of Amines
  - 3.3.3: Synthesis of Amines
  - 3.3.4: Reactions of Amines

4: Carbonyls

- 4.1: Aldehydes and Ketones- Nucleophilic Addition Reactions
  - 4.1.1: Chapter Objectives and Preview of Carbonyl Chemistry
  - 4.1.2: Naming Aldehydes and Ketones

- 4.1.3: Preparing Aldehydes and Ketones
- 4.1.4: Oxidation of Aldehydes and Ketones
- 4.1.5: Nucleophilic Addition Reactions of Aldehydes and Ketones
- 4.1.6: Nucleophilic Addition of Water- Hydration
- 4.2: Carboxylic Acids
  - 4.2.1: Chapter Objectives and Introduction to Carboxylic Acids
  - 4.2.2: Naming Carboxylic Acids and Nitriles
  - 4.2.3: Structure and Properties of Carboxylic Acids
  - 4.2.4: Reactions of Carboxylic Acids - An Overview
  - 4.2.5: Chemistry of Esters
  - 4.2.6: Chemistry of Amides

5: Biomolecules

- 5.1: Biomolecules- Carbohydrates
  - 5.1.1: Introduction
  - 5.1.2: Classification of Carbohydrates
  - 5.1.3: Depicting Carbohydrate Stereochemistry - Fischer Projections
  - 5.1.4: D, L Sugars
  - 5.1.5: Configurations of Aldoses
  - 5.1.6: Cyclic Structures of Monosaccharides - Anomers
  - 5.1.7: Reactions of Monosaccharides
  - 5.1.8: The Eight Essential Monosaccharides
  - 5.1.9: Disaccharides
  - 5.1.10: Polysaccharides and Their Synthesis
  - 5.1.11: Other Important Carbohydrates
  - 5.1.12: Cell-Surface Carbohydrates and Influenza Viruses
  - 5.1.S: Biomolecules- Carbohydrates (Summary)
- 5.2: Biomolecules- Amino Acids, Peptides, and Proteins
  - 5.2.1: Introduction
  - 5.2.2: Structures of Amino Acids
  - 5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points
  - 5.2.4: Synthesis of Amino Acids
  - 5.2.5: Peptides and Proteins
  - 5.2.6: Amino Acid Analysis of Peptides
  - 5.2.7: The Edman Degradation
  - 5.2.8: Peptide Synthesis
  - 5.2.9: The Merrifield Solid-Phase Technique
  - 5.2.10: Protein Structure
  - 5.2.11: Enzymes and Coenzymes
  - 5.2.12: How do Enzymes Work? Citrate Synthase
- 5.3: Biomolecules - Lipids
  - 5.3.1: Introduction to Lipids
  - 5.3.2: Waxes, Fats, and Oils
  - 5.3.3: Soap
  - 5.3.4: Phospholipids
  - 5.3.5: Prostaglandins and Other Eicosanoids
  - 5.3.6: Terpenoids
  - 5.3.7: Steroids

- 5.3.8: Biosynthesis of Steroids
- 5.3.S: Biomolecules - Lipids (Summary)
- 5.4: Biomolecules - Nucleic Acids
  - 5.4.1: Nucleotides and Nucleic Acids
  - 5.4.2: Base Pairing in DNA - The Watson-Crick Model
  - 5.4.3: Replication of DNA
  - 5.4.4: Transcription of DNA
  - 5.4.5: Translation of RNA - Protein Biosynthesis
  - 5.4.6: DNA Sequencing
  - 5.4.7: DNA Synthesis
  - 5.4.8: The Polymerase Chain Reaction

Index

Glossary

Detailed Licensing

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*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

CHAPTER OVERVIEW

1: Introduction to Organic Chemistry and Structure

1.1: Introduction to Organic Chemistry
1.1.1: History
1.2: Fractional Distillation and Alkanes
1.2.1: Hydrocarbons and the Homologous Series
1.2.2: Overview of Distillation
1.2.3: Fractional Distillation
1.2.3.1: Theory of Fractional Distillation
1.2.3.2: Fractionating Columns
1.2.3.3: Uses of Fractional Distillation
1.2.3.4: Step-by-Step Procedures for Fractional Distillation
1.2.4: Structural Formulas - Lewis, Kekule, Bond-line, Condensed, and Perspective
1.2.5: Alkanes and Alkane Isomers
1.2.6: Alkyl Groups
1.2.7: Naming Alkanes
1.2.8: Properties of Alkanes
1.3: Cyclic Hydrocarbons
1.3.1: Naming Cycloalkanes
1.3.2: Stability of Cycloalkanes - Ring Strain
1.4: Alkenes
1.4.1: Bond Rotation
1.4.2: Introduction to Alkenes
1.4.3: Industrial Preparation and Use of Alkenes
1.4.4: Naming Alkenes
1.4.5: Polymerization of Alkenes
1.5: Alkynes and Benzene
1.5.1: Naming Alkynes
1.5.2: Introduction
1.5.3: Naming Aromatic Compounds
1.5.4: Structure and Stability of Benzene
1.6: Halides
1.6.1: Introduction to Organohalides
1.6.2: Names and Properties of Alkyl Halides
1.7: Isomers
1.7.1: Isomerism Introduction
1.8: Polarity and Lewis Structures
1.8.1: Atomic Structure - Orbitals
1.8.2: Atomic Structure - Electron Configurations
1.8.3: Development of Chemical Bonding Theory
1.8.4: Describing Chemical Bonds - Valence Bond Theory

1.8.5: Polar Covalent Bonds - Electronegativity
1.9: Formal Charge and Resonance
1.9.1: Lewis Structures and Formal Charges
1.9.2: Resonance
1.10: Common Bonding Patterns for Organic Chemistry

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1.1.1: History



Berzelius

Jöns Jacob Berzelius, a physician by trade, first coined the term “organic chemistry” in 1806 for the study of compounds derived from biological sources. Up through the early 19th century, naturalists and scientists observed critical differences between compounds that were derived from living things and those that were not.

Chemists of the period noted that there seemed to be an essential yet inexplicable difference between the properties of the two different types of compounds. The **vital force theory**, sometimes called “vitalism” (vital means “life force”), was therefore proposed, and widely accepted, as a way to explain these differences, that a “vital force” existed within organic material but did not exist in any inorganic materials.

Synthesis of urea



Urea

Friedrich Wöhler is widely regarded as a pioneer in organic chemistry as a result of his synthesizing of the biological compound urea (a component of urine in many animals) utilizing what is now called “the Wöhler synthesis.”

Wöhler mixed silver or lead cyanate with ammonium nitrate; this was supposed to yield ammonium cyanate as a result of an exchange reaction, according to Berzelius’s dualism theory. Wöhler, however, discovered that the end product of this reaction is *not* ammonium cyanate (NH_4OCN), an inorganic salt, but urea ($(NH_2)_2CO$), a biological compound. (Furthermore, heating ammonium cyanate turns it into urea.) Faced with this result, Berzelius had to concede that $(NH_2)_2CO$ and NH_4OCN were *isomers*. Until this discovery in the year 1828, it was widely believed by chemists that organic substances could only be formed under the influence of the “vital force” in the bodies of animals and plants. Wöhler’s synthesis dramatically proved that view to be false.

Urea synthesis was a critical discovery for biochemists because it showed that a compound known to be produced in nature only by biological organisms could be produced in a laboratory under controlled conditions from inanimate matter. This “in vitro” synthesis of organic matter disproved the common theory (vitalism) about the *vis vitalis*, a transcendent “life force” needed for producing organic compounds.

Organic vs inorganic chemistry

Although originally defined as the chemistry of biological molecules, organic chemistry has since been redefined to refer specifically to carbon compounds — even those with non-biological origin. Some carbon molecules are not considered organic, with carbon dioxide being the most well known and most common inorganic carbon compound, but such molecules are the exception and not the rule.

Organic chemistry focuses on carbon and following movement of the electrons in carbon chains and rings, and also how electrons are shared with other carbon atoms and heteroatoms. Organic chemistry is primarily concerned with the properties of covalent bonds and non-metallic elements, though ions and metals do play critical roles in some reactions.

The applications of organic chemistry are myriad, and include all sorts of plastics, dyes, flavorings, scents, detergents, explosives, fuels and many, many other products. Read the ingredient list for almost any kind of food that you eat — or even your shampoo bottle — and you will see the handiwork of organic chemists listed there.

Major advances in the field of organic chemistry



Of course a chemistry text should at least mention Antoine Laurent Lavoisier. The French chemist is often called the “Father of Modern Chemistry” and his place is first in any pantheon of great chemistry figures. Your general chemistry textbook should contain information on the specific work and discoveries of Lavoisier — they will not be repeated here because his discoveries did not relate directly to organic chemistry in particular. Berzelius and Wöhler are discussed above, and their work was foundational to the specific field of organic chemistry. After those two, three more scientists are famed for independently proposing the elements of structural theory. Those chemists were August Kekulé, Archibald Couper, and Alexander Butlerov.

Kekulé was a German, an architect by training, and he was perhaps the first to propose that isomerism was due to carbon’s proclivity towards forming four bonds. Its ability to bond with up to four other atoms made it ideal for forming long chains of atoms in a single molecule, and also made it possible for the same number of atoms to be connected in an enormous variety of ways. Couper, a Scot, and Butlerov, a Russian, came to many of the same conclusions at the same time or just a short time after.

Through the nineteenth century and into the twentieth, experimental results brought to light much new knowledge about atoms, molecules, and molecular bonding. In 1916 it was Gilbert Lewis of U.C. Berkeley who described covalent bonding largely as we know it today (electron-sharing). Nobel laureate Linus Pauling further developed Lewis’ concepts by proposing resonance while he was at the California Institute of Technology. At about the same time, Sir Robert Robinson of Oxford University focused primarily on the electrons of atoms as the engines of molecular change. Sir Christopher Ingold of University College, London, organized what was known of organic chemical reactions by arranging them in schemes we now know as mechanisms, in order to better understand the sequence of changes in a synthesis or reaction.

The field of organic chemistry is probably the most active and important field of chemistry at the moment, due to its extreme applicability to both biochemistry (especially in the pharmaceutical industry) and petrochemistry (especially in the energy industry). Organic chemistry has a relatively recent history, but it will have an enormously important future, affecting the lives of everyone around the world for many, many years to come.

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1.2.1: Hydrocarbons and the Homologous Series

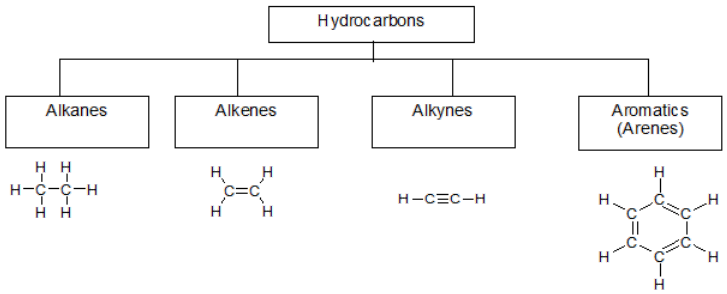
Learning Objective

- classify hydrocarbons as saturated or unsaturated
- classify hydrocarbons as alkanes, alkenes, alkynes, cycloalkanes, or aromatics (arenes)
- apply the homologous series to organic molecules with 1-10 carbons

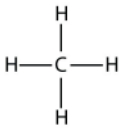
Hydrocarbon Classifications

Hydrocarbons are organic compounds that contain **only** carbon and hydrogen. The inherent ability of hydrocarbons to bond to themselves is known as catenation, and allows hydrocarbon to form more complex molecules, such as cyclohexane and benzene. Catenation comes from the fact that the bond character between carbon atoms is entirely non-polar.

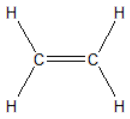
The four general classes of hydrocarbons are: alkanes, alkenes, alkynes and arenes. Aromatic compounds derive their names from the fact that many of these compounds in the early days of discovery were grouped because they were oils with fragrant odors. The classifications for hydrocarbons are summarized below.



Saturated hydrocarbons (alkanes) are the simplest of the hydrocarbon species. They are composed entirely of single bonds and are saturated with hydrogen. The general formula for saturated hydrocarbons is C_nH_{2n+2} (assuming non-cyclic structures). Saturated hydrocarbons are the basis of petroleum fuels and are found as either linear or branched species.The simplest alkanes have their C atoms bonded in a straight chain; these are called *normal* alkanes. They are named according to the number of carbon atoms in the chain. The smallest alkane is methane:



Unsaturated hydrocarbons have double and/or triple bonds between carbon atoms. Those with double bond are called alkenes and have the general formula C_nH_{2n} (assuming non-cyclic structures). Those containing triple bonds are called alkynes and have general formula C_nH_{2n-2}. The smallest alkene—ethene—has two C atoms and is also known by its common name ethylene and the smallest alkyne is ethyne, also known as acetylene.



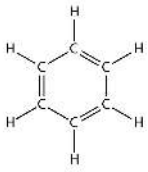
ethene
C_2H_4

ethyne (acetylene)
C_2H_2

Cycloalkanes are hydrocarbons containing one or more carbon rings to which hydrogen atoms are attached. The prefix "cyclo" is added to the name to communicate the ring structure. The general formula for a saturated hydrocarbon containing one ring is C_nH_{2n}.

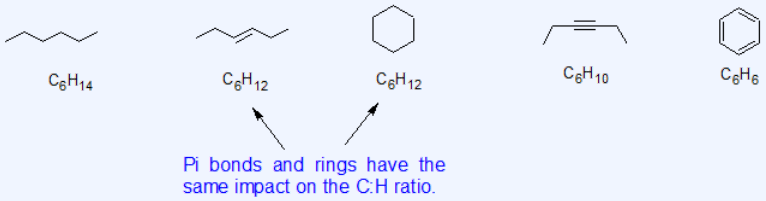


Aromatic hydrocarbons, also known as arenes, are hydrocarbons that have at least one aromatic ring. Aromatic compounds contain the benzene unit. Benzene itself is composed of six C atoms in a ring, with alternating single and double C–C bonds:



For most compounds, information beyond the chemical formula will be needed to elucidate their structure. However, the ratio of C:H in a chemical formula can provide insights into the chemical structure.

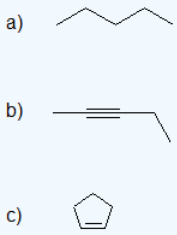
For example, let's look at some of the possible structures and chemical formulas for hydrocarbons containing six carbon atoms.



The saturated alkane has the highest ratio of hydrogen to carbon. The unsaturated alkene and the six membered alkane ring share the same chemical formula. It is important to remember this relationship. The unsaturated alkyne has a lower ratio of hydrogen to carbon than alkenes with a second pi bond. Benzene rings have the lowest hydrogen ratio to carbon at 1:1.

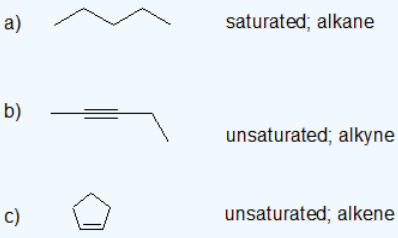
Exercise

1. Classify the following compounds are saturated or unsaturated. For unsaturated hydrocarbons, refine the classification by indicating whether the compound is an alkene, alkyne, or arene.



Answer

1.



The number of carbons continuously bonded together is an important structural feature and is described using the Homologous Series. In first year organic chemistry, the first ten names of the Homologous Series are usually all that need to be memorized.

Of course, your professor will set the standard. Most of the prefixes are familiar from the Greek prefixes for binary covalent compounds. It is the prefixes for the first four carbon chain lengths that may be unfamiliar. Interestingly, three of these hydrocarbons frequently appear in every day life. Methane gas is a primary component of flatulence and is the ingredient that ignites when farts are lit - don't try this at home. Propane and butane are gases at room temperature. They are stored under pressure to create the liquid state. Propane is the fuel for bbqs, while butane is used in lighters. The suffix "ane" is used to distinguish between the longest continuous carbon chain, while the shorter carbon branches (substituents) are indicated with "yl" as the suffix.

THE HOMOLOGOUS SERIES

# C's	Alkane Structure	Parent name	Substituent name
1	CH_4	methane	methyl
2	CH_3CH_3	ethane	ethyl
3	$CH_3CH_2CH_3$	propane	propyl
4	$CH_3CH_2CH_2CH_3$	butane	butyl
5	$CH_3CH_2CH_2CH_2CH_3$	pentane	pentyl
6	$CH_3CH_2CH_2CH_2CH_2CH_3$	hexane	hexyl
7	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	heptane	heptyl
8	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	octane	octyl
9	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	nonane	nonyl
10	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	decane	decyl

Exercise

2. Complete the table below.

Condensed Structural Formula	Chemical Name
	propane
C_6H_6	
$CH_3CH_2CH_2CH_2CH_2CH_3$	

Answer

2.

Condensed Structural Formula	Chemical Name
$CH_3CH_2CH_3$	propane
C_6H_6	benzene
$CH_3CH_2CH_2CH_2CH_2CH_3$	hexane

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1.2.2: Overview of Distillation

Several distillation variations are used in the organic laboratory depending on the properties of the mixture to be purified. The apparatus in Figure 5.1 is used to perform a simple distillation and is used if the components have widely different boiling points (greater than a 100 °C difference in boiling points). If a simple distillation is attempted on a mixture where the components have more similar boiling points (less than a 100 °C difference in boiling points), it will fail to purify the mixture completely. Instead, fractional distillation can be used to improve the chances of purification. Vacuum distillation may be used when the boiling points of the mixture's components are very high (>150 °C), or steam distillation if the components are very water insoluble. The distillation variations are summarized in Table 5.1, and are discussed in detail in this chapter.



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SECTION OVERVIEW

1.2.3: Fractional Distillation

A simple distillation is incapable of significant purification if the boiling points of the components are too close. When the difference in boiling points is less than 100 ˚C, a modification is necessary, namely insertion of a fractionating column between the distilling flask and three-way adapter.

1.2.3.1: Theory of Fractional Distillation

1.2.3.2: Fractionating Columns

1.2.3.3: Uses of Fractional Distillation

1.2.3.4: Step-by-Step Procedures for Fractional Distillation

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1.2.3.1: Theory of Fractional Distillation

A simple distillation is incapable of significant purification if the boiling points of the components are too close. When the difference in boiling points is less than 100°C, a modification is necessary, namely insertion of a fractionating column between the distilling flask and three-way adapter (Figure 5.37a).

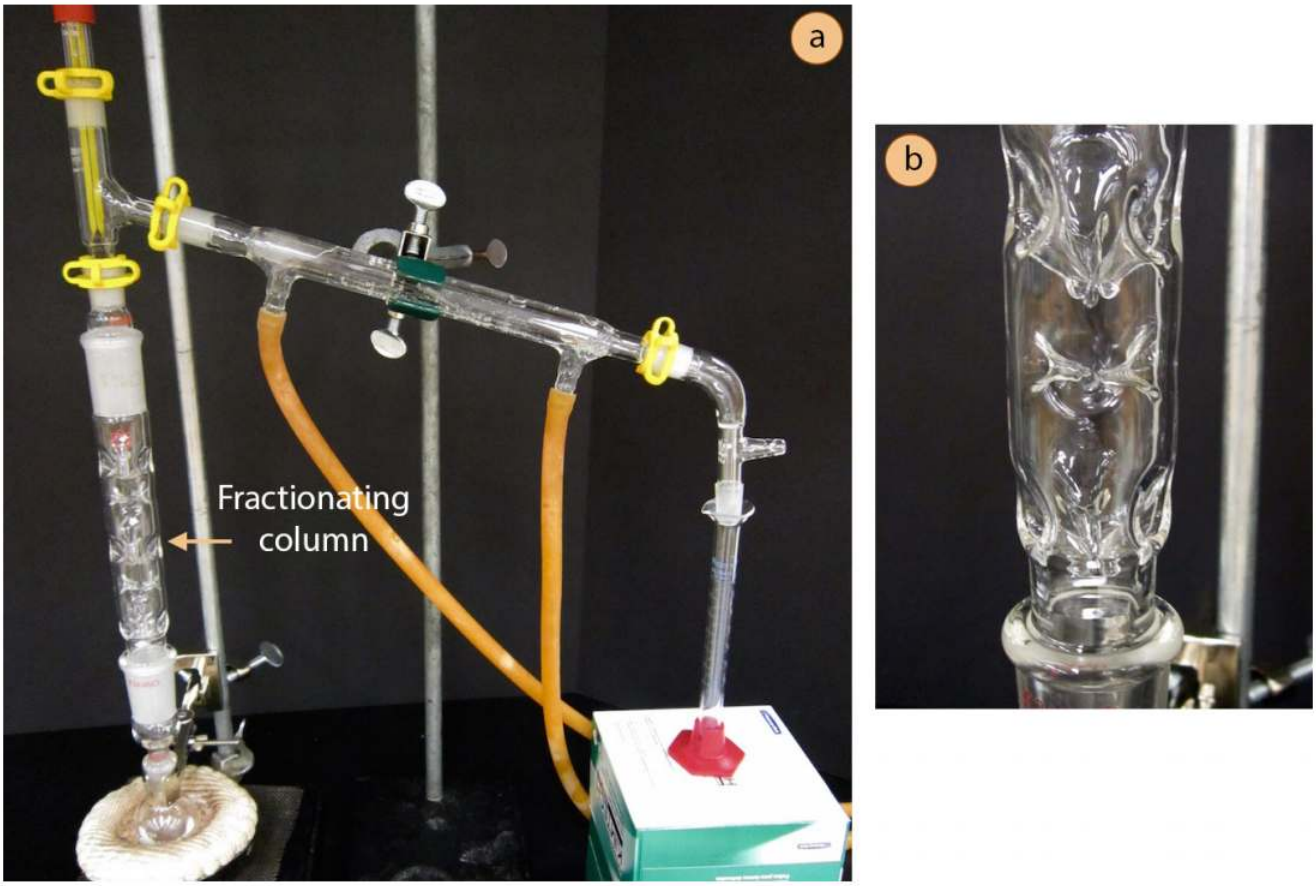


Figure 5.37: a) Fractional distillation setup, b) Zoom in of fractionating column during distillation, with condensation dripping from the glass indentations.

The distillate of a simple distillation is always enriched in the lower boiling compound. As previously discussed, the simple distillation of a 75 mol% ethylbenzene/25 mol% *p*-cymene mixture resulted in a distillate that was 90 mol% ethylbenzene (ethylbenzene had the lower boiling point). Imagine if a subsequent distillation were performed on the 90 mol% solution: the distillate of *that* process would contain an even higher percentage of ethylbenzene.

A fractionating column essentially allows for many successive distillations to take place at once, without dismantling the apparatus. A fractionating column contains indentations (a Vigreux column, Figure 5.37) or a packing material with lots of surface area. The vapors temporarily condense on these surfaces (see Figure 5.37b) and the heat of the distillation allows those pools of liquid to vaporize again. Every vaporization-condensation event (called a "theoretical plate") is similar to a simple distillation, and each event enriches the distillate in the lower boiling component.

The concepts of a fractional distillation can be shown through a distillation curve. In the distillation of an equimolar mixture of compounds A + B (which is described by the distillation curve in Figure 5.38), one vaporization-condensation event is represented in Figure 5.38 by following points *a* to *b* to *c*. This process represents one theoretical plate, and would produce a distillate that is 81% A and 19% B. A second vaporization-condensation event is represented in Figure 5.38 by following points *c* to *d* to *e*, and would produce a distillate that is 96% A and 4% B.

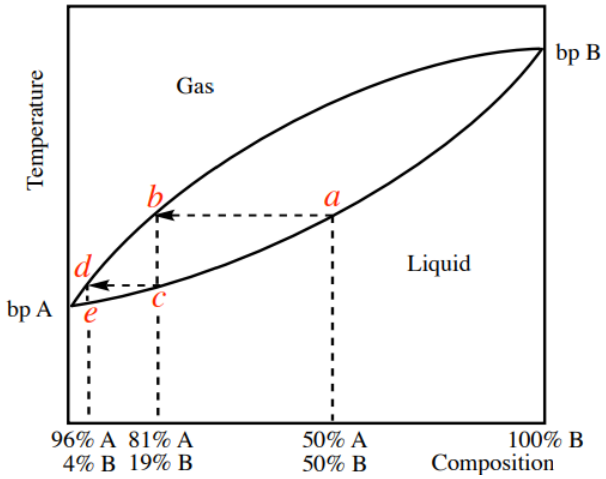


Figure 5.38: Distillation curve of a two-component system of A+B, showing two theoretical plates.

A 50%/50% mixture of two components whose boiling points differ by only 20-30°C would require at least three theoretical plates to obtain a distillate with $>$ 95% purity. In practice, fractional distillations still often produce mixtures. The best chance of obtaining purity via fractional distillation is when there is very little impurity to begin with.

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1.2.3.2: Fractionating Columns

The choice of what fractionating column to use for which application depends in part on availability and the task at hand. Several columns are shown in Figure 5.39: a) Vigreux column with glass indentations, b) Steel wool column made simply be loosely inserting steel wool into the cavity of a fractionating column (similar to a West condenser, but wider), c) Glass beads filled in the cavity of a fractionating column.



Figure 5.39: Different fractionating columns: a) Vigreux, b) Steel wool, c) Glass beads.

These columns have different surface areas and numbers of theoretical plates, and thus differ in their ability to separate close-boiling components. They also differ somewhat in the quantity of compound that will be sequestered through wetting the column. A Vigreux column has the least surface area, making it the least capable of separating close-boiling components. And yet with the lowest surface area, it can have the highest recovery, making it the optimal choice if a separation is not particularly difficult. Glass beads have a high surface area, so are a good choice for separation of close-boiling components. And yet, beads will suffer the greatest loss of material. Steel wool columns have intermediate surface areas and their effectiveness can depend on how tightly the wool is packed in the column. Steel wool columns also cannot be used with corrosive vapors like those containing acid.

To demonstrate the effectiveness of different fractionating columns, a mixture containing $75\ \text{mol\%}$ ethylbenzene (normal b.p. $136°\text{C}$) and $25\ \text{mol\%}$ *p*-cymene (normal b.p. $177°\text{C}$) was distilled using several methods. The first two mL of distillate was collected in each process (Figure 5.40).

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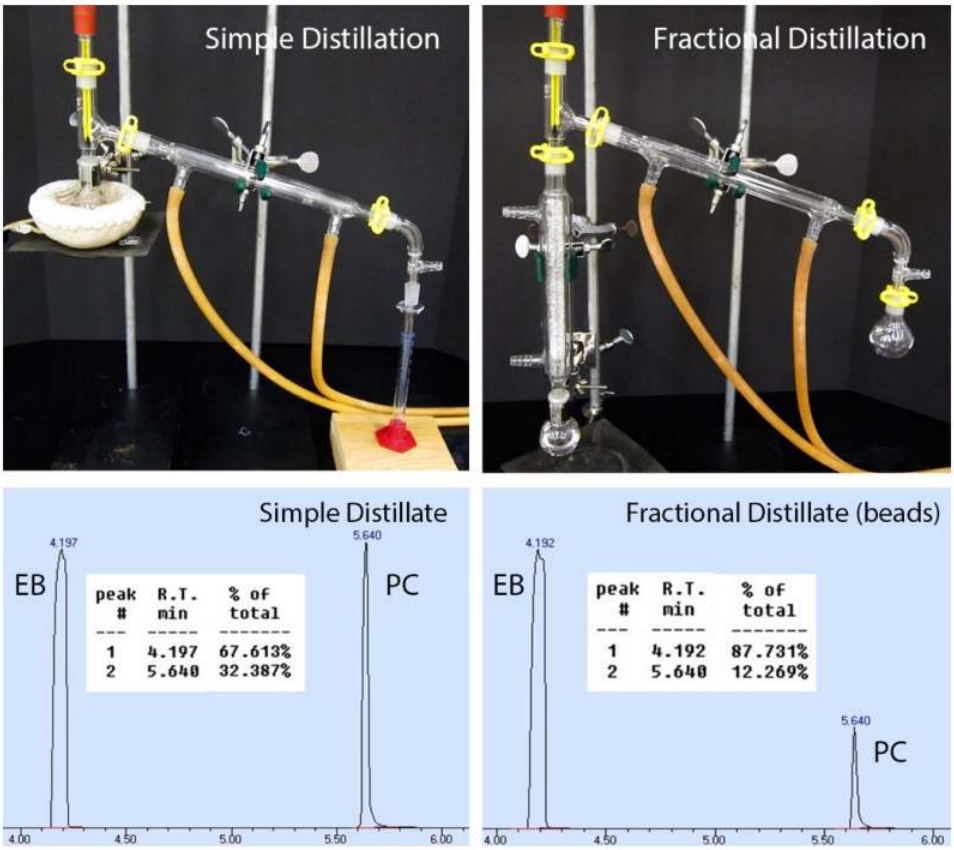


Figure 5.40: Simple and fractional distillation of a 75 mol% ethylbenzene/25 mol% p-cymene mixture, with GC analysis. In each GC spectrum, ethylbenzene is the peak at 4.192 min and p-*cymene is the peak at* 5.640 min.

Gas chromatograph analysis of the initial mixture and distillates allowed for quantitation of the mixtures, although a calibration curve was necessary to translate the reported percentages into meaningful values. As the two components had only a 41°C difference in boiling points, a fractional distillation was more effective than a simple distillation, although in some cases only slightly (see Table 5.7). The distillate was never $> 98\%$ pure with any method as there was a large quantity of the minor component in the distilling pot.

Table 5.7: GC results for various distillations of a 75 mol% ethylbenzene (EB) and 25 mol% p-cymene (PC) mixture. The actual percentage values were estimated from the calibration curve in Figure 5.11.

Method	Components	GC%	Actual %
Initial Solution	ethylbenzene	55.6%	75%
	p-cymene	44.4%	25%
Simple Distillation	ethylbenzene	67.6%	90%
	p-cymene	32.4%	10%
Fractional (Beads)	ethylbenzene	87.7%	97%
	p-cymene	12.3%	3%
Fractional (Steel Wool)	ethylbenzene	71.4%	92%
	p-cymene	28.6%	8%
Fractional (Vigreux)	ethylbenzene	70.4%	92%
	p-cymene	29.6%	8%

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1.2.3.3: Uses of Fractional Distillation

Oil Refining

Crude oil (petroleum) is composed of mostly hydrocarbons (alkanes and aromatics), and is a tremendous mixture of compounds consisting of between 5 and 40 carbon atoms.[11] The components in oil are incredibly useful as fuels and lubricants, but not when they are mixed together. Fractional distillation is used in oil refineries (Figure 5.41) to separate the complex mixture into fractions that contain similar boiling points and therefore similar molecular weights and properties. Gasoline, diesel fuel, kerosene, and jet fuel are some of the different fractions produced by an oil refinery.



Figure 5.41: San Francisco Refinery in Rodeo, California.

Purification of Reagents and Products

Cyclopentadiene is used in many chemical reactions, including Diels-Alder reactions and polymerizations. The reagent is so reactive, however, that it undergoes a Diels-Alder reaction with itself in the reagent bottle to form dicyclopentadiene (Figure 5.42a). Therefore, chemical companies do not sell cyclopentadiene, and chemists are instead required to distill commercial dicyclopentadiene (Figure 5.42b) to reverse the dimerization reaction and obtain cyclopentadiene (Figure 5.42c).

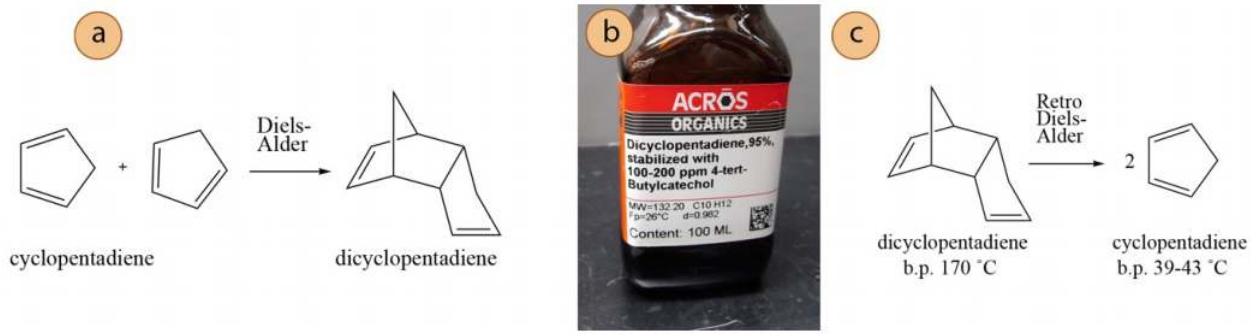


Figure 5.42: a) Dimerization reaction of cyclopentadiene, b) Dicyclopentadiene reagent, c) Retro Diels-Alder reaction.

At temperatures above $150°C$ the dimer reverts to the monomer through a retro Diels-Alder reaction (driven by the favorable change in entropy, Figure 5.42c). Distillation can be used to remove the monomer as it forms. Although the two components (dimer and monomer) have dramatically different boiling points, the temperature required for the reverse reaction is too similar to the boiling point of the dicyclopentadiene that its vapor pressure cannot be ignored. Therefore, a fractional distillation is required for this process.

[11] About 6% of crude oil contains hydrocarbons with greater than 40 carbon atoms, a fraction that eventually becomes used for asphalt.

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1.2.3.4: Step-by-Step Procedures for Fractional Distillation

Fractional Distillation Procedure

An assembled fractional distillation apparatus is shown in Figure 5.43, using glass beads in the fractionating column. Other columns may be substituted. It is assumed that readers have previously performed a simple distillation, so in this section are described differences between simple and fractional distillation.

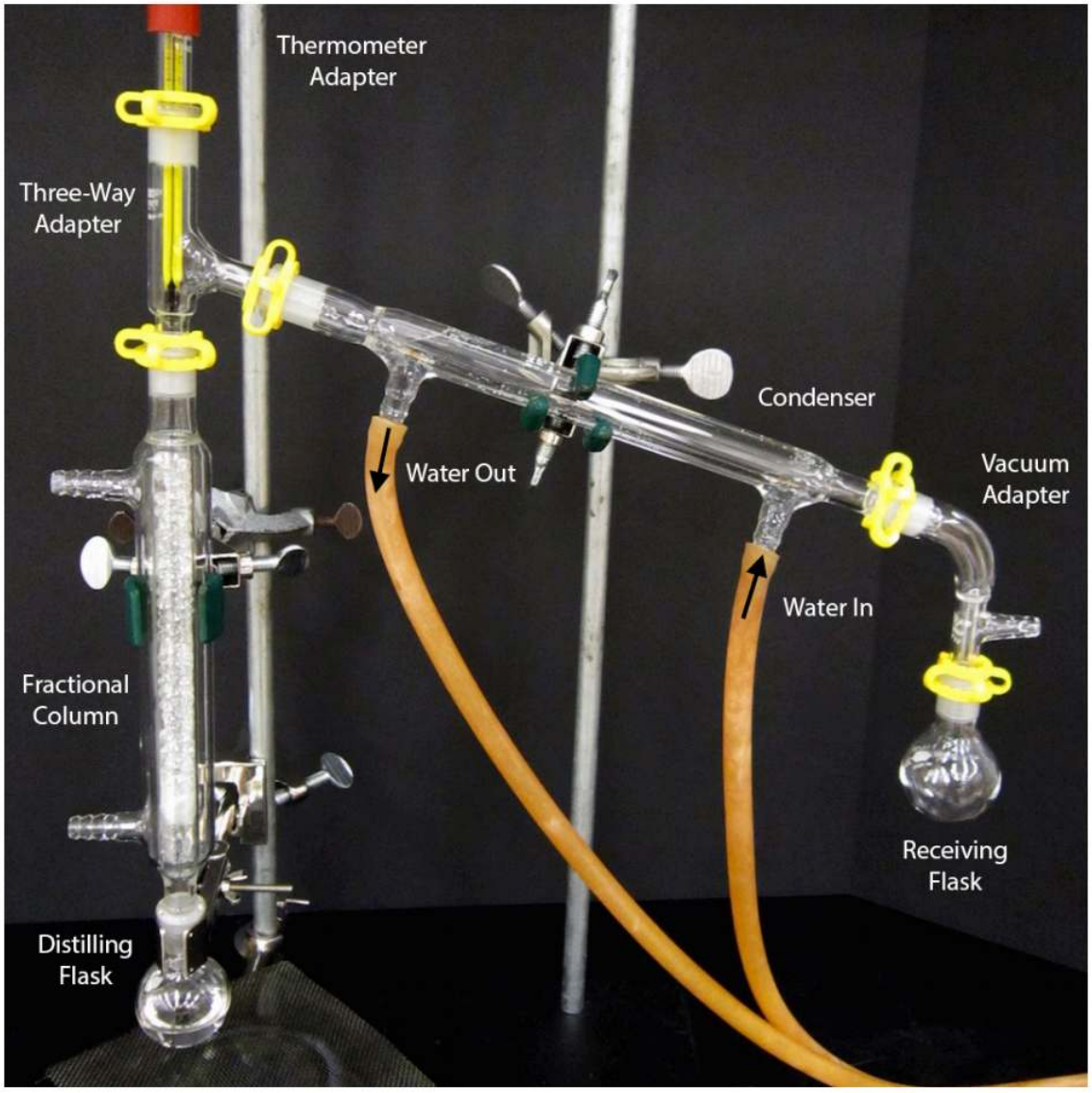


Figure 5.43: Fractional distillation apparatus.

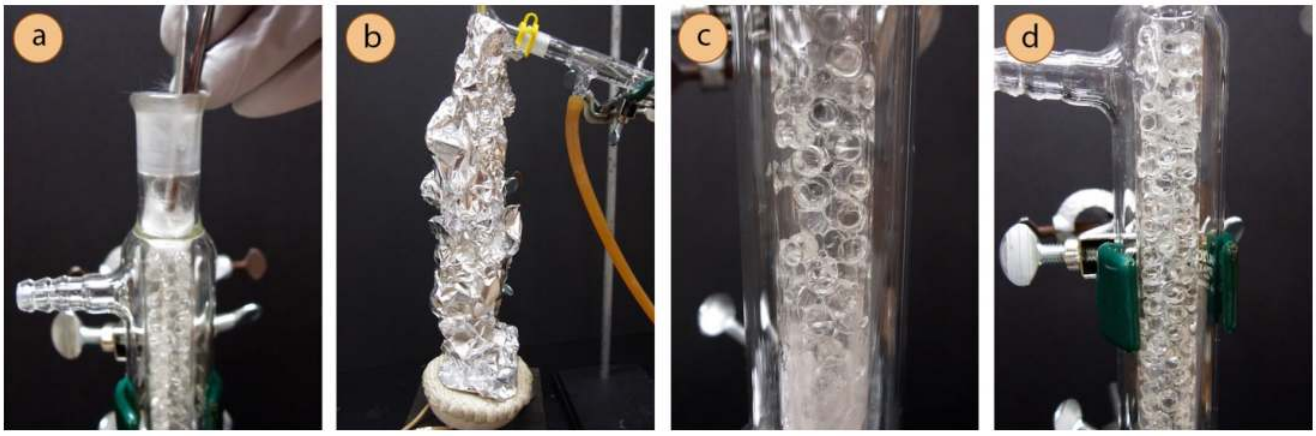


Figure 5.44: a) Removal of glass wool plug on a beaded fractionating column, b) Insulating the column with foil, c+d) Condensation on the beads of a fractionating column.

1. If a beaded fractionating column is used, sometimes a wad of glass wool is inserted into the top so that the beads do not spill out. Before using the column, remove this wad as it may interfere with the passage of vapors (Figure 5.44a). If using a Vigreux column, check for broken glass indentations (which would case a leak in the column).
2. The distilling pot will need to be heated much more vigorously than with a simple distillation, as there is a greater distance for the vapors to travel before reaching the condenser. The vapors will tend to reflux in the column (condense and drip back into the distilling pot) unless stronger heating is applied.

   A rule of thumb is that the distilling pot needs to be **30°C** hotter than the top of the column in order for material to ascend the column. If it is difficult to achieve more than a reflux, the column can be insulated by wrapping it with glass wool then aluminum foil (Figure 5.44b). This allows the column to maintain heat and the sample to remain in the gas phase longer. A small gap can be left in the foil or glass wool if desired to "peek in" on the activity in the column.
3. Ideally both liquid and gas should be seen in the fractionating column, as the sample needs to undergo many vaporization-condensation events (Figures 5.44 c+d). Droplets of liquid *should* be seen on the surfaces of the packing material, but there should never by a large pool of liquid. A "river" of liquid traveling up the column is called **flooding** (Figure 5.45). If a column floods, remove the heat until the liquid drains back into the distilling flask, then resume heating at a gentler rate.



Figure 5.45: Flooding of a fractionating column.

4. Cleaning of a fractionating column:
   a. Vigreux column: rinse with acetone. Don't use a scrub brush or the glass indentations may break.
   b. Steel wool column. rinse with large amounts of acetone. Don't rinse with water as wet steel will rust over time.
   c. Glass bead column: rinse with acetone, then replace the glass wool wad to prevent the beads from pouring out when horizontal. Alternatively, pour out the glass beads to be cleaned separately. Be delicate when using a scrub brush on the

fractionating column as there are fragile indentations near the bottom joint which can break.

Fractional Distillation Summary

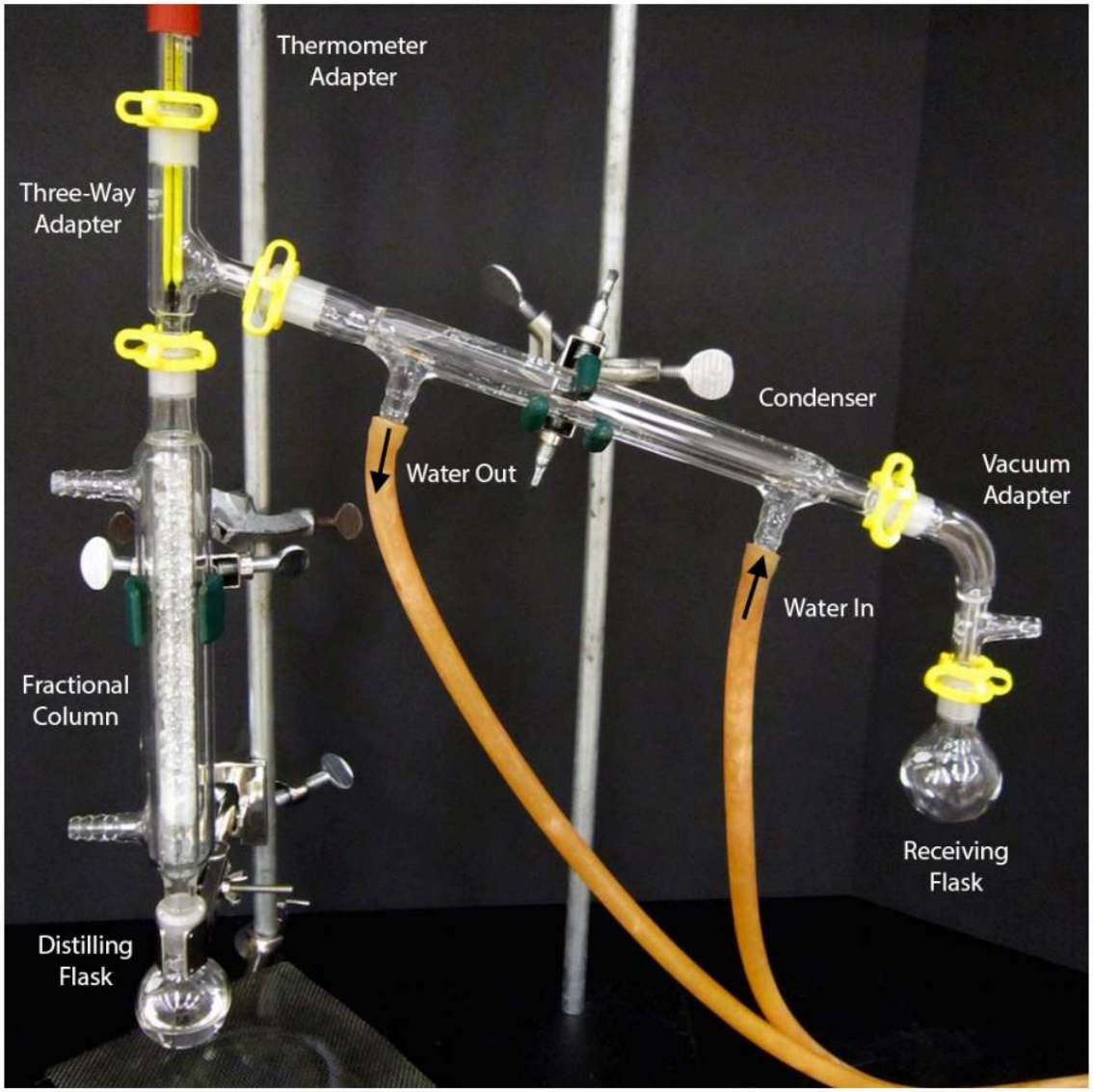


Figure 5.46: Fractional distillation setup.

Table 5.8: Procedural summary of fractional distillation.

Most comments for a simple distillation apply to fractional as well. The distilling pot will need to be heated more vigorously than with a simple distillation, as there is a greater distance for the vapors to travel before reaching the condenser.	Commonly the column will need to be insulated to maintain heat: wrap the column (and three-way adapter if desired) in glass wool followed by an outer layer of aluminum foil.	Droplets of liquid should be seen in the fractional column, but there should never be a large pool of liquid (flooding). If the column floods, allow the liquid to drain back into the distilling flask and heat at a gentler rate.

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1.2.4: Structural Formulas - Lewis, Kekule, Bond-line, Condensed, and Perspective

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

Shorthand notations to represent organic molecules rely on our knowledge of common neutral bonding patterns. Knowing these patterns, we can fill in the missing structural information. Some of these shorthand ways of drawing molecules give us insight into the bond angles and relative positions of atoms in the molecule, while some notations eliminate the carbon and hydrogen atoms and only indicate the heteroatoms (the atoms that are NOT carbon or hydrogen).

There are three primary methods to communicate chemical structure of organic molecules:

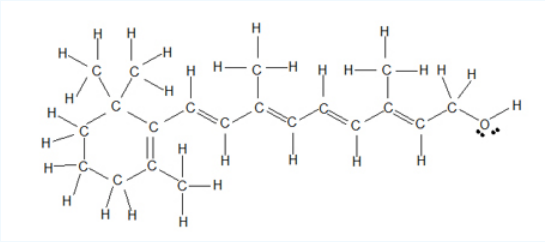
Kekule: Lewis structures using lines to represent covalent bonds and showing all atoms and lone pair electrons

Bond-line (Skeletl-line): shows bonds between carbon atoms and heteroatoms) (with lone pair electrons when requested)

Condensed: all atoms are written to communicate structure without drawing any chemical bonds based on the carbon backbone

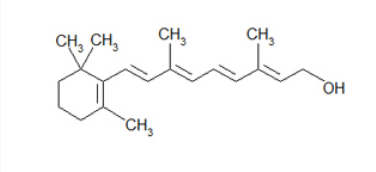
Introduction

Observe the following drawings of the structure of Retinol, the most common form of vitamin A. The first drawing follows the straight-line (a.k.a. Kekulé) structure which is helpful when you want to look at every single atom; however, showing all of the hydrogen atoms makes it difficult to compare the overall structure with other similar molecules and makes it difficult to focus in on the double bonds and OH group.



Retinol: Kekulé straight-line drawing

The following is a bond-line (a.k.a. zig-zag) formula for retinol. With this simiplified representation, one can easily see the carbon-carbon bonds, double bonds, OH group, and CH_3 groups sticking off of the the main ring and chain. Also, it is much quicker to draw this than the one above. You will learn to appreciate this type of formula writing after drawing a countless number of organic molecules.



Retinol: Bond-line or zig-zag formula

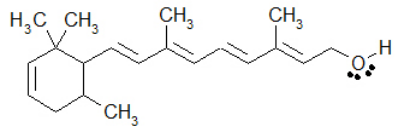
Importance of Structure

Learning and practicing the basics of Organic Chemistry will help you immensely in the long run as you learn new concepts and reactions. Some people say that Organic Chemistry is like another language, and in some aspects, it is. At first it may seem difficult or overwhelming, but the more you practice looking at and drawing organic molecules, the more familiar you will

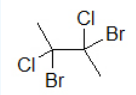
become with the structures and formulas. Another good idea is to get a model kit and physically make the molecules that you have trouble picturing in your head.

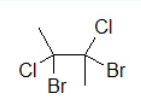
Through general chemistry, you may have already experienced looking at molecular structure. The different ways to draw organic molecules include Kekulé (straight-line), Condensed Formulas, and Bond-Line Formulas (zig-zag). It will be more helpful if you become comfortable going from one style of drawing to another, and look at drawings and understanding what they mean, than knowing which kind of drawing is named what.

An example of a drawing that incorporates all three ways to draw organic molecules would be the following additional drawing of Retinol. The majority of the drawing is Bond-line (zig-zag) formula, but the -CH_3 are written as condensed formulas, and the -OH group is written in Kekulé form.



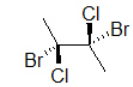
A widely used way of showing the 3D structure of molecules is the use of dashes, wedges, and straight lines. This drawing method is essential because the placement of different atoms could yield different molecules even if the molecular formulas were exactly the same. Below are two drawings of a 4-carbon molecule with two chlorines and two bromines attached.

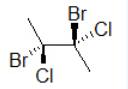




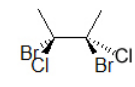
4-carbon molecule with 2 chlorines and 2 bromines 4-carbon molecule with 2 chlorines and 2 bromines

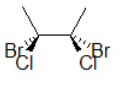
Both drawings look like they represent the same molecule; however, if we add dashes and wedged we will see that two different molecules could be depicted:





The two molecules above are different, prove this to yourself by building a model. An easier way to compare the two molecules is to rotate one of the bonds (here, it is the bond on the right):



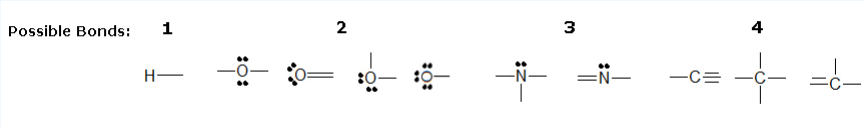


Notice how the molecule on the right has both bromines on the same side and chlorines on the same side, whereas the first molecule is different. Read about Dashed-Wedged Line structures, bottom of page, to understand what has been introduced above. You will learn more about the importance of atomic connectivity in molecules as you continue on to learn about Stereochemistry.

Drawing the Structure of Organic Molecules

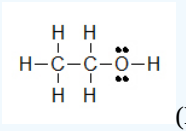
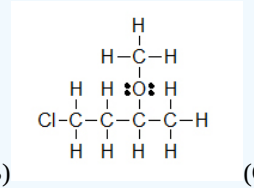
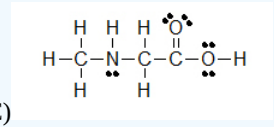
Although larger molecules may look complicated, they can be easily understood by breaking them down and looking at their smaller components.

All atoms want to have their valence shell full, a "closed shell." Hydrogen wants to have 2 e^- whereas carbon, oxygen, and nitrogen want to have 8 e^-. When looking at the different representations of molecules, keep in mind the Octet Rule. Also remember that hydrogen can bond one time, oxygen can bond up to two times, nitrogen can bond up to three times, and carbon can bond up to four times.



Kekulé (a.k.a. Lewis Structures)

Kekulé structures are similar to Lewis Structures, but instead of covalent bonds being represented by electron dots, the two shared electrons are shown by a line.

(A)  (B)  (C) 

Lone pairs remain as two electron dots, or are sometimes left out even though they are *still there*. Notice how the three lone pairs of electrons were not draw in around chlorine in example B.

Condensed Formulas

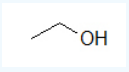
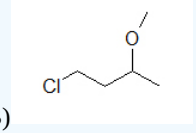
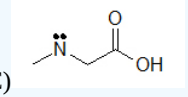
A condensed formula is made up of the elemental symbols. The order of the atoms suggests the connectivity. Condensed formulas can be read from either direction and H_3C is the same as CH_3, although the latter is more common because Look at the examples below and match them with their identical molecule under Kekulé structures and bond-line formulas.

(A) CH_3CH_2OH (B) $ClCH_2CH_2CH(OCH_3)CH_3$ (C) H_3CNHCH_2COOH

Let's look closely at example B. As you go through a condensed formula, you want to focus on the carbons and other elements that aren't hydrogen. The hydrogen's are important, but are usually there to complete octets. Also, notice the $-OCH_3$ is in written in parentheses which tell you that it not part of the main chain of carbons. As you read through a a condensed formula, if you reach an atom that doesn't have a complete octet by the time you reach the next hydrogen, then it's possible that there are double or triple bonds. In example C, the carbon is double bonded to oxygen and single bonded to another oxygen. Notice how COOH means C(=O)-O-H instead of CH_3-C-O-O-H because carbon does not have a complete octet and oxygens.

Bond-Line (a.k.a. zig-zag) Formulas

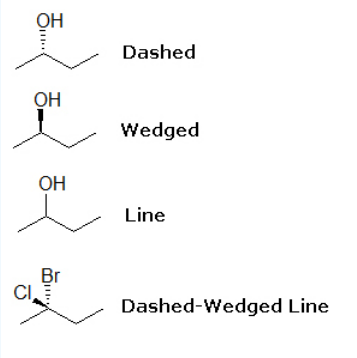
The name gives away how this formula works. This formula is full of bonds and lines, and because of the typical (more stable) bonds that atoms tend to make in molecules, they often end up looking like zig-zag lines. If you work with a molecular model kit you will find it difficult to make stick straight molecules (unless they contain sp triple bonds) whereas zig-zag molecules and bonds are much more feasible.

(A)  (B)  (C) 

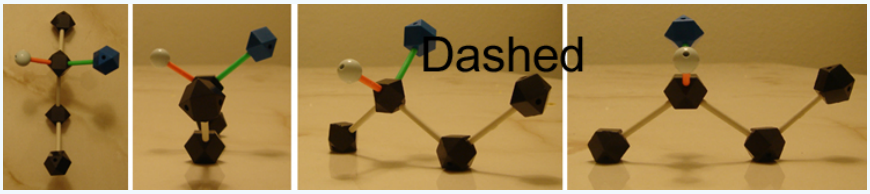
These molecules correspond to the exact same molecules depicted for Kekulé structures and condensed formulas. Notice how the carbons are no longer drawn in and are replaced by the ends and bends of a lines. In addition, the hydrogens have been omitted, but could be easily drawn in (see practice problems). Although we do not usually draw in the H's that are bonded to carbon, we do draw them in if they are connected to other atoms besides carbon (example is the OH group above in example A) . This is done because it is not always clear if the non-carbon atom is surrounded by lone pairs or hydrogens. Also in example A, notice how the OH is drawn with a bond to the second carbon, but it does not mean that there is a third carbon at the end of that bond/ line.

Dashed-Wedged Line Structure

As you may have guessed, the Dashed-Wedged Line structure is all about lines, dashes, and wedges. At first it may seem confusing, but with practice, understanding dash-wedged line structures will become like second nature. The following are examples of each, and how they can be used together.

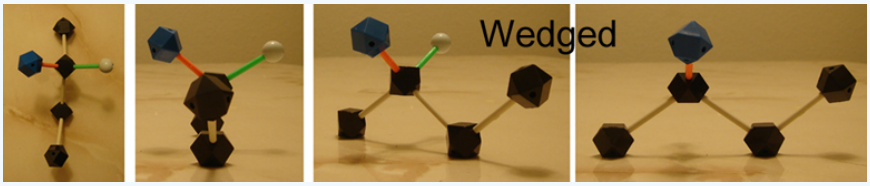


Above are 4-carbon chains with attached OH groups or Cl and Br atoms. Remember that each line represents a bond and that the carbons and hydrogens have been omitted. When you look at or draw these structures, the straight lines illustrate atoms and bonds that are in the same plane, the plane of the paper (in this case, computer screen). **Dashed lines** show atoms and bonds that go into the page, behind the plane, away from you. In the above example, the OH group is going into the plane, while at the same time a hydrogen comes out (wedged).



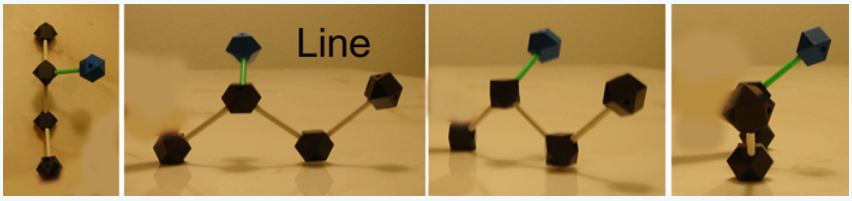
Blue bead= OH group; White bead=H

Wedged lines illustrate bonds and atoms that come out of the page, in front of the plane, toward you. In the 2D diagram above, the OH group is coming out of the plane of the paper, while a hydrogen goes in (dashed).



Blue bead= OH group; White bead=H

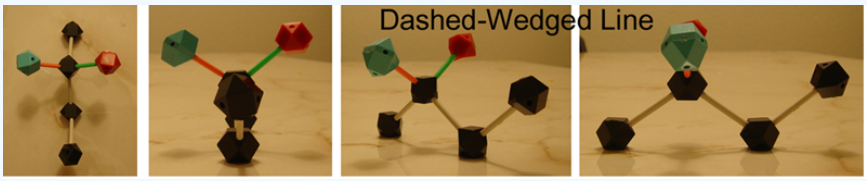
As stated before, straight lines illustrate atoms and bonds that are in the same plane as the paper, but in the 2D example, the straight line bond for OH means that it it unsure or irrelevant whether OH is going away or toward you. It is also assumed that hydrogen is also connected to the same carbon that OH is on.



Blue bead= OH group; H is not shown

Try using your model kit to see that the OH group cannot lie in the same plane at the carbon chain (don't forget your hydrogens!). In the final 2Dexample, both dashed and wedged lines are used because the attached atoms are not hydrogens

(although dashed and wedged lines *can* be used for hydrogens).The chlorine is coming out the page while bromine is going into the page.



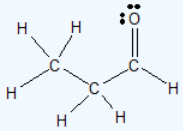
Blue bead=Cl; Red bead=Br

Example: Converting between Structural Formulas

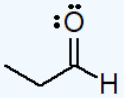
Throughout the course, it will be helpful to convert compounds into different structural formulas (Kekule (Lewis Structures), Bond-line, and Condensed) depending on the type of question that is asked. Standardized exams frequently include a high percentage of condensed formulas because it is easier and cheaper to type letters and numbers than to import figures. Initially, it can be tricky writing a bond-line structure directly from a condensed formula. First write the Kekule structure from the condensed formula and then draw the bond-line structure from the Kekule. Practice will quickly allow you to convert directly between condensed and bond-line structures.

The condensed formula for propanal is CH_3CH_2CHO. Can you visualize the bond-line structure of propanal? If yes, excellent, If no, the following practice will help.

The Kekule structure for propanal is shown below.

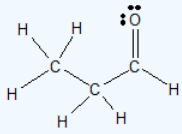


The bond-line structure for propanal is shown below.

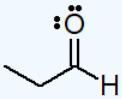


All three structures represent the same compound, propanal.

CH_3CH_2CHO =

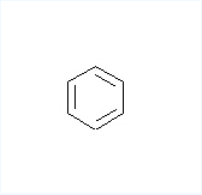


=

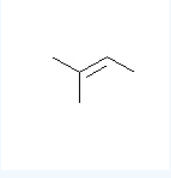


Exercises

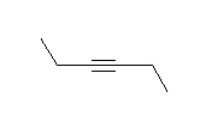
1. How many carbons are in the following drawing? How many hydrogens?



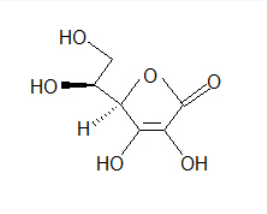
2. How many carbons are in the following drawing? How many hydrogens?



3. How many carbons are in the following drawing? How many hydrogens?



4. Look at the following molecule of vitamin A and draw in the hidden hydrogens and electron pairs.

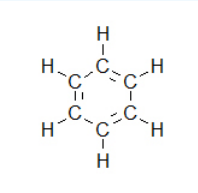


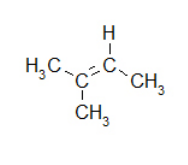
(hint: Do all of the carbons have 4 bonds? Do all the oxygens have a full octet?)

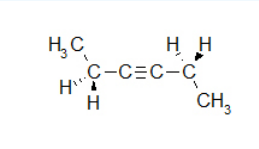
5. How many bonds can hydrogen make?
6. How many bonds can chlorine make?
7. Dashed lines means the atomic bond goes _____(away/toward) you.
8. Draw $ClCH_2CH_2CH(OCH_3)CH_3$ in Kekuléand zig-zag form.
9. Extra practice problems can be found _____?

Solutions

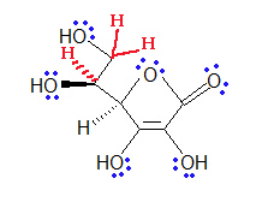
1. Remember the octet rule and how many times carbons and hydrogens are able to bond to other atoms.



2. 

3. 

4. Electron pairs drawn in blue and hydrogens draw in red.



5. Hygrogen can make one bond.
6. Chlorine can make one bond.
7. Away
8. See (B) under Kekulé and Bond-line (zig-zag) formulas.
9. Extra practice problems can be found: in your textbook, homework, lecture notes, online, reference books, and more. Try making up some of your own molecules, they may exist!

References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W. H. Freeman Company, 2007. 38-40.
2. Klein, David R. Organic Chemistry I As a Second Language. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc, 2007. 1-14.

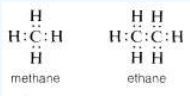
Outside Links

- Stereochemistry: en.Wikipedia.org/wiki/Stereochemistry
- Retinol: http://en.Wikipedia.org/wiki/Retinol
- Octet Rule: http://en.Wikipedia.org/wiki/Octet_rule
- Lewis Structures: chemwiki.ucdavis.edu/index.ph...wis+structures
- sp hybrid orbitals: chemwiki.ucdavis.edu/index.ph...s&highlight=sp
- For drawing organic molecules on the computer: http://bkchem.zirael.org/download_en.html

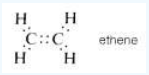
Contributors and Attributions

- Choo, Ezen (2009, UCD '11)

The building block of structural organic chemistry is the tetravalent carbon atom. With few exceptions, carbon compounds can be formulated with four covalent bonds to each carbon, regardless of whether the combination is with carbon or some other element. The two-electron bond, which is illustrated by the carbon-hydrogen bonds in methane or ethane and the carbon-carbon bond in ethane, is called a **single bond**. In these and many related substances, each carbon is attached to four other atoms:



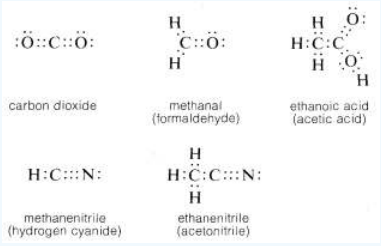
There exist, however, compounds such as ethene (ethylene), C_2H_4, in which two electrons from each of the carbon atoms are mutually shared, thereby producing *two* two-electron bonds, an arrangement which is called a **double bond**. Each carbon in ethene is attached to only three other atoms:



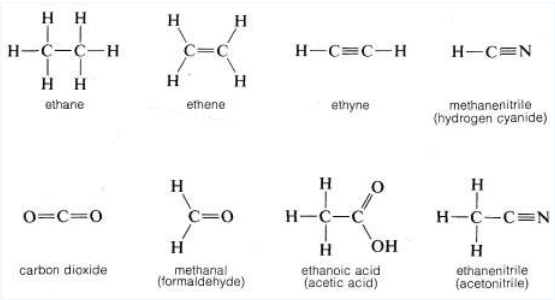
Similarly, in ethyne (acetylene), C_2H_2, three electrons from each carbon atom are mutually shared, producing *three* two-electron bonds, called a **triple bond**, in which each carbon is attached to only two other atoms:



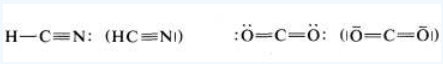
Of course, in all cases each carbon has a full octet of electrons. Carbon also forms double and triple bonds with several other elements that can exhibit a covalence of two or three. The carbon-oxygen (or carbonyl) double bond appears in carbon dioxide and many important organic compounds such as methanal (formaldehyde) and ethanoic acid (acetic acid). Similarly, a carbon-nitrogen triple bond appears in methanenitrile (hydrogen cyanide) and ethanenitrile (acetonitrile).



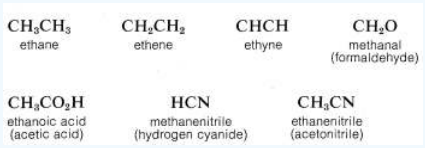
By convention, a single straight line connecting the atomic symbols is used to represent a single (two-electron) bond, two such lines to represent a double (four-electron) bond, and three lines a triple (six-electron) bond. Representations of compounds by these symbols are called **structural formulas**; some examples are



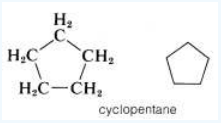
A point worth noting is that structural formulas usually do not indicate the *nonbonding* electron pairs. This is perhaps unfortunate because they play as much a part in the chemistry of organic molecules as do the bonding electrons and their omission may lead the unwary reader to overlook them. However, when it is important to represent them, this can be done best with pairs of dots, although a few authors use lines:



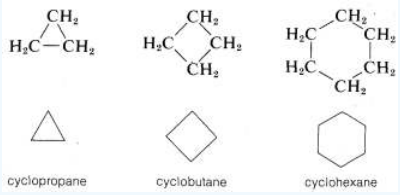
To save space and time in the representation of organic structures, it is common practice to use "condensed formulas" in which the bonds are not shown explicitly. In using condensed formulas, normal atomic valences are understood throughout. Examples of condensed formulas are



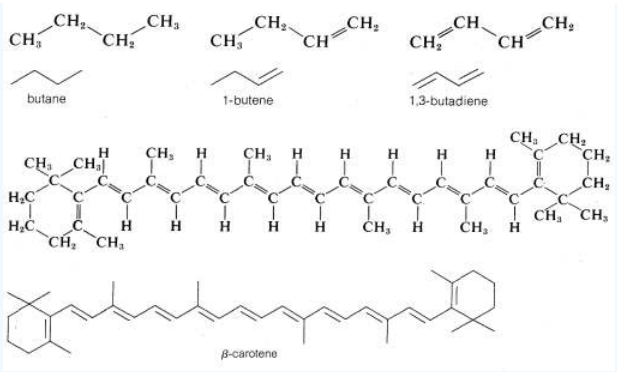
Another type of abbreviation that often is used, particularly for ring compounds, dispenses with the symbols for carbon and hydrogen atoms and leaves only the lines in a structural formula. For instance, cyclopentane, C_5H_{10}, often is represented as a regular pentagon in which it is understood that each apex represents a carbon atom with the requisite number of hydrogens to satisfy the tetravalence of carbon:



Likewise, cyclopropane, C_3H_6; cyclobutane, C_4H_8; and cyclohexane, C_6H_{12}, are drawn as regular polygons:



Although this type of line drawing is employed most commonly for cyclic structures, its use for open chain (acyclic) structures is becoming increasingly widespread. There is no special merit to this abbreviation for simple structures such as butane, C_4H_{10}; 1-butene, C_4H_8; or 1,3-butadiene, C_4H_6, but it is of value in representing more complex molecules such as β-carotene, $C_{40}H_{56}$:



Line structures also can be modified to represent the three-dimensional *shapes* of molecules, and the way that this is done will be discussed in detail in Chapter 5. At the onset of you study of organic chemistry, you should write out the formulas rather completely until you are thoroughly familiar with what these abbreviations stand for.

Contributors and Attributions

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1.2.5: Alkanes and Alkane Isomers

Objectives

After completing this section, you should be able to

1. draw the Kekulé structure, condensed structure and shorthand structure of each of the first ten straight-chain alkanes.
2. name each of the first ten straight-chain alkanes, given its molecular formula, Kekulé structure, condensed structure or shorthand structure.
3. explain the difference in structure between a straight- and a branched-chain alkane, and illustrate the difference using a suitable example.
4. explain why the number of possible isomers for a given molecular formula increases as the number of carbon atoms increases.
5. draw all the possible isomers that correspond to a given molecular formula of the type $C_n H_{2n+2}$, where n is ≤ 7.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- branched-chain alkane
- constitutional or structural isomer
- homologous series
- isomer
- saturated hydrocarbon
- straight-chain alkane (or normal alkane)

Study Notes

A series of compounds in which successive members differ from one another by a CH_2 unit is called a homologous series. Thus, the series CH_4, C_2H_6, C_3H_8 . . . C_nH_{2n+2}, is an example of a homologous series.

It is important that you commit to memory the names of the first 10 straight-chain alkanes (i.e., from CH_4 to $C_{10}H_{22}$). You will use these names repeatedly when you begin to learn how to derive the systematic names of a large variety of organic compounds. You need not remember the number of isomers possible for alkanes containing more than seven carbon atoms. Such information is available in reference books when it is needed. When drawing isomers, be careful not to deceive yourself into thinking that you can draw more isomers than you are supposed to be able to. Remember that it is possible to draw each isomer in several different ways and you may inadvertently count the same isomer more than once.

Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes are often called saturated hydrocarbons because they have the maximum possible number of hydrogens per carbon. In Section 1.7, thealkane molecule, ethane, was shown to contain a C-C sigma bond. By adding more C-C sigma bond larger and more complexed alkanes can be formed. Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. Any family of compounds in which adjacent members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner.

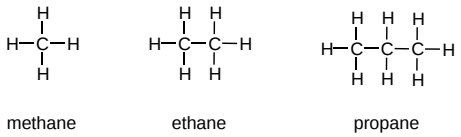


Figure 25.3.1 : The Three Simplest Alkanes

Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. Consider the series in Figure 25.3.3. The sequence starts with C_3H_8, and a CH_2 unit is added in each step moving up the series. Any family of compounds in which adjacent members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner.

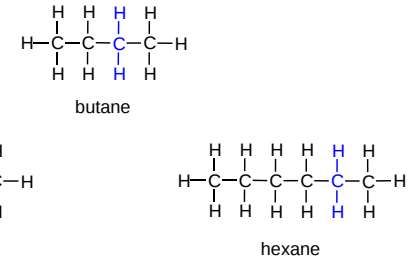


Figure 25.3.2: Members of a Homologous Series. Each succeeding formula incorporates one carbon atom and two hydrogen atoms more than the previous formula.

The homologous series allows us to write a general formula for alkanes: $C_nH_{2n\ +\ 2}$. Using this formula, we can write a molecular formula for any alkane with a given number of carbon atoms. For example, an alkane with eight carbon atoms has the molecular formula $C_8H_{(2\ \times\ 8)\ +\ 2} = C_8H_{18}$.

Molecular Formulas

Alkanes are the simplest family of hydrocarbons - compounds containing carbon and hydrogen only. Alkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The first six alkanes are as follows:

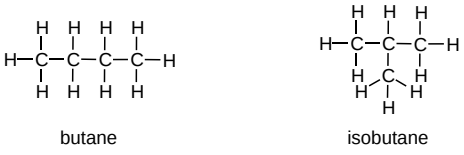
Table 1.2.5.1: Molecular formulas for small alkanes

methane	CH_4
ethane	C_2H_6
propane	C_3H_8
butane	C_4H_{10}
pentane	C_5H_{12}
hexane	C_6H_{14}

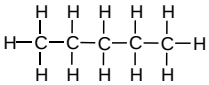
You can work out the formula of any of the alkanes using the general formula C_nH_{2n+2}

Isomerism

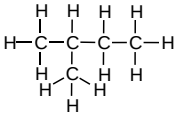
All of the alkanes containing 4 or more carbon atoms show structural isomerism, meaning that there are two or more different structural formulas that you can draw for each molecular formula. Isomers (from the Greek *isos* + *meros*, meaning "made of the same parts") are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. Alkanes with 1-3 carbons, methane (CH_4), ethane (C_2H_6), and propane (C_3H_8,) do not exist in isomeric forms because there is only one way to arrange the atoms in each formula so that each carbon atom has four bonds. However, C_4H_{10}, has more than possible structure. The four carbons can be drawn in a row to form butane or the can branch to form isobutane. The two compounds have different properties—for example, butane boils at −0.5°C, while isobutane boils at −11.7°C.



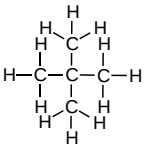
Likewise the molecular formula: C_5H_{12} has three possible isomer. The compound at the far left is pentane because it has all five carbon atoms in a continuous chain. The compound in the middle is isopentane; like isobutane, it has a one CH_3 branch off the second carbon atom of the continuous chain. The compound at the far right, discovered after the other two, was named neopentane (from the Greek *neos*, meaning "new"). Although all three have the same molecular formula, they have different properties, including boiling points: pentane, 36.1°C; isopentane, 27.7°C; and neopentane, 9.5°C.



pentane



isopentane



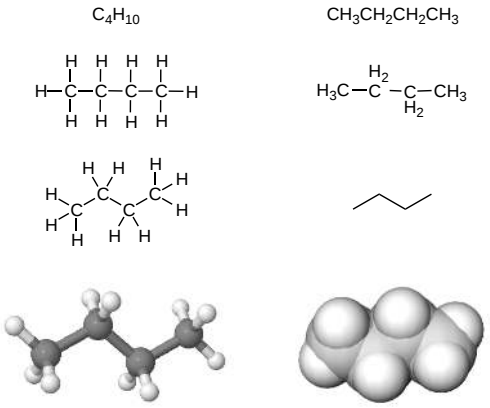
neopentane

Of the structures show above, butane and pentane are called **normal alkanes** or **straight-chain alkanes**, indicating that all contain a single continuous chain of carbon atoms and can be represented by a projection formula whose carbon atoms are in a straight line. The other structures, isobutane, isopentane, and neopentane are called called branched-chain alkanes. As the number of carbons in an akane increases the number of possible isomers also increases as shown in the table below.

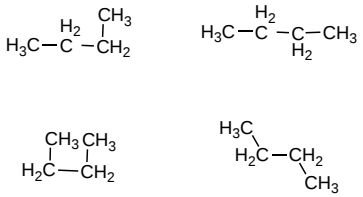
Table 1.2.5.2: Number of isomers for hydrocarbons

Molecular Formula	Number of Structural Isomers
CH_4	1
C_2H_6	1
C_3H_8	1
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{14}H_{30}$	1858
$C_{18}H_{38}$	60,523
$C_{30}H_{62}$	4,111,846,763

Akanes can be represented in many different ways. The figure below shows some of the different ways straight-chain butane can be represented. Most often chemists refer to butane by the condensed structure $CH_3CH_2CH_2CH_3$ or *n*-C_4H_{10} where n denotes a normal straight alkane.



Note that many of these structures only imply bonding connections and do not indicate any particular geometry. The bottom two structures, referred to as "ball and stick" and "space filling" do show 3D geometry for butane. Because the four-carbon chain in butane may be bent in various ways the groups can rotate freely about the C–C bonds. However, this rotation does not change the identity of the compound. It is important to realize that bending a chain does *not* change the identity of the compound; all of the following represent the same compound, butane:



The nomenclature of straight alkanes is based on the number of carbon atoms they contain. The number of carbons are indicated by a prefix and the suffix -ane is added to indicate the molecules is an alkane. The prefix for three carbons is prop so adding -ane, the IUPAC name for C_3H_8 is propane. Likewise, the prefix for six is hex so the name for the straight chain isomer of C_6H_{14} is called hexane. The first ten prefixes should be memorized, because these alkane names from the basis for naming many other organic compounds.

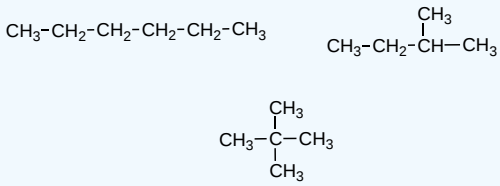
9.2.1" role="presentation" style="position:relative;" tabindex="0">

Table **1.2.5.3**: The First 10 Straight-Chain Alkanes

Molecular Formula	Prefix	Condensed Structural Formula	Name
CH_4	Meth	CH_4	methane
C_2H_6	Eth	CH_3CH_3	ethane
C_3H_8	Prop	$CH_3CH_2CH_3$	propane
C_4H_{10}	But	$CH_3CH_2CH_2CH_3$	butane
C_5H_{12}	Pent	$CH_3CH_2CH_2CH_2CH_3$	pentane
C_6H_{14}	Hex	$CH_3(CH_2)_4CH_3$	hexane
C_7H_{16}	Hept	$CH_3(CH_2)_5CH_3$	heptane
C_8H_{18}	Oct	$CH_3(CH_2)_6CH_3$	octane
C_9H_{20}	Non	$CH_3(CH_2)_7CH_3$	nonane
$C_{10}H_{22}$	Dec	$CH_3(CH_2)_8CH_3$	decane

Example 1.2.5.1: Chain Isomers in Pentane

Pentane, C_5H_{12}, has three chain isomers. If you think you can find any others, they are simply twisted versions of the ones below. If in doubt make some models.

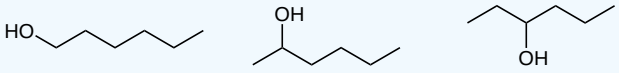


Exercises

Exercise 1.2.5.1

Draw all of the isomers for $C_6H_{14}O$ that contain a 6 carbon chain and an alcohol (-OH) functional group.

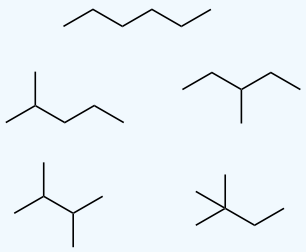
Answer



Exercise 1.2.5.2

Draw all possible isomers for C_6H_{14} (There are five total).

Answer



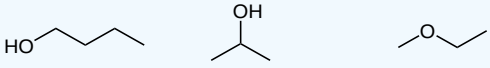
The top structure is when it is a 6 carbon chain. The middle row contains the 5 carbon chained isomers with branching at the 2nd and 3rd carbon. The bottom row contains the two 4 carbon chain isomers that can be drawn.

Exercise 1.2.5.3

Draw all possible isomers for C_3H_8.

Answer

The first structure is when an alcohol comes off the first carbon. The second structure is when the alcohol is coming off the central carbon. The third structure is the only possible ether form of C_3H_8.

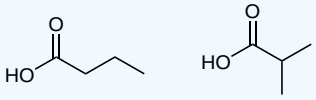


Exercise 1.2.5.4

Draw all possible isomers for $C_4H_8O_2$ that contain a carboxylic acid.

Answer

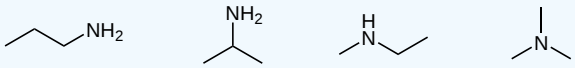
There are only 2 possibilities.



Exercise 1.2.5.5

Draw all possible isomers for C_3H_9N and indicate whether each amine is primary, secondary, or tertiary.

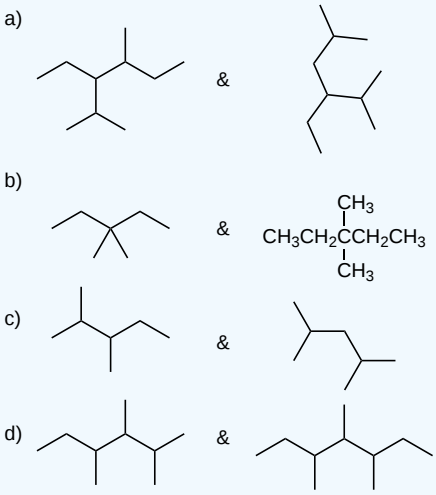
Answer



The first and second structures are primary amines. The third structure is a secondary amine. The last structure is a tertiary amine.

Exercise 1.2.5.6

Indicate whether each of the following sets are constitutional isomers, the same compound, or different compounds.



Answer

a) Both structures have formulas of $C_{10}H_{22}$ and have different connectivity which makes these **constitutional isomers**.

b) Both structures have formulas of C_7H_{16} and have the same connectivity which makes these the **same compound**.

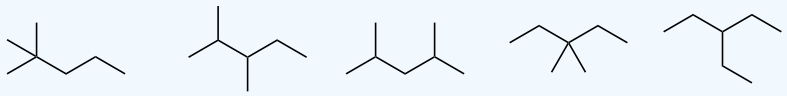
c) Both structure have formulas of C_7H_{16} and have different connectivity which makes these **constitutional isomers**.

d) The structure on the left has a formula of C_9H_{20} and the structure on the right has a formula of $C_{10}H_{22}$ so these are **different compounds**.

Exercise 1.2.5.7

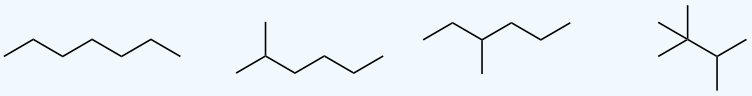
Draw the 5 constitutional isomers of C_7H_{16} (of the 9 total isomers possible) that have 5 carbons as the longest carbon chain length.

Answer



The 5 constitutional isomers with a 5 carbon chain length are shown above. Since there needs to be 7 carbons total, the 2 extra carbons are added as substituents. From left to right, the methyl group substitution pattern is 2,2, 2,3, 2,4, and 3,3, and the last one (on right) has a 3-ethyl substituent.

The other 4 possible constitutional isomers (with different length carbon chains) are shown below.



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1.2.6: Alkyl Groups

Objectives

After completing this section, you should be able to

1. recognize and name any alkyl group that can be considered to have been formed by the removal of a terminal hydrogen atom from a straight-chain alkane containing ten or fewer carbon atoms.
2. explain what is meant by a primary, secondary, tertiary or quaternary carbon atom.
3. represent the various types of organic compounds using the symbol “R” to represent any alkyl group.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkyl group
- methyl group
- isopropyl group
- *sec*-butyl group
- isobutyl group
- *tert*-butyl group
- primary carbon
- secondary carbon
- tertiary carbon
- quaternary carbon

Study Notes

The differences among primary, secondary, tertiary and quaternary carbon atoms are explained in the following discussion. A convenient way of memorizing this classification scheme is to remember that a primary carbon atom is attached directly to only one other carbon atom, a secondary carbon atom is attached directly to two carbon atoms, and so on.

The **IUPAC** system requires first that we have names for simple unbranched chains and second, that we have names for simple alkyl groups that may be attached to the chains. An **alkyl group** is formed by removing one hydrogen from the alkane chain. The removal of this hydrogen results in a stem change from **-ane** to **-yl** to indicate an alkyl group. The removal of a hydrogen from methane, CH_4, creates a methyl group -CH_3. Likewise, the removal of a hydrogen from ethane, CH_3CH_3, creates an ethyl group -CH_2CH_3. The nomenclature pattern can continue to provide a series of straight-chain alkyl groups from straight chain alkanes with a hydrogen removed from the end. Note, the letter **R** is used to designate a generic (unspecified) alkyl group.

CH_4	⟹	$\mathbf{CH_3}$–R
methane		methyl
$CH_3CH_2CH_3$	⟹	$\mathbf{CH_3CH_2CH_2}$–R
propane		propyl

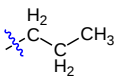
Table **1.2.6.2**: Straight chain alkane and alkyl group names

Alkane	Name	Alkyl Group	Name (Abbreviation)
CH_4	Methane	$-CH_3$	Methyl (Me)
CH_3CH_3	Ethane	$-CH_2CH_3$	Ethyl (Et)
$CH_3CH_2CH_3$	Propane	$-CH_2CH_2CH_3$	Propyl (Pr)
$CH_3CH_2CH_2CH_3$	Butane	$-CH_2CH_2CH_2CH_3$	Butyl (Bu)
$CH_3CH_2CH_2CH_2CH_3$	Pentane	$-CH_2CH_2CH_2CH_2CH_3$	Pentyl
$CH_3CH_2CH_2CH_2CH_2CH_3$	Hexane	$-CH_2CH_2CH_2CH_2CH_2CH_3$	Hexyl

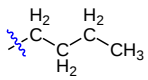
Prior to the systematic nomenclature developed for organic chemistry, prefixes were used to specify the connection point of straight-chain and branched-chain alkyl groups. Although the modern nomenclature system, discussed in the next section, is preferred these older terms are still often used, especially in solvents and reagents. Thus, an understanding of these prefixes is important to understanding organic chemistry. Notice that the total number of carbons in the alkyl subsistent is still indicated with the **prefix + yl**. For methyl and ethyl alkyl groups there is only one possible connection point so connection prefixes are not necessary. Starting with a three carbon alkyl group (propyl) the possibility of multiple connection points necessitates connection prefixes. These prefixes are often abbreviated with a letter which is italicized.

Normal (*n*)

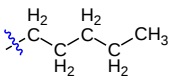
The prefix "n" is used to indicate a connection at the end of a straight-chain alkane. This prefix is not commonly used to just indicate alkyl subsistent as discussed above. However it is sometime used to indicate the connection of a functional group onto a straight alkane.



n-propyl
or propyl



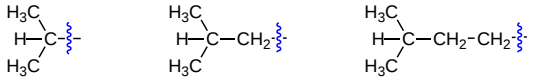
n-butyl
or butyl



n-pentyl
or pentyl

Iso (*i*)

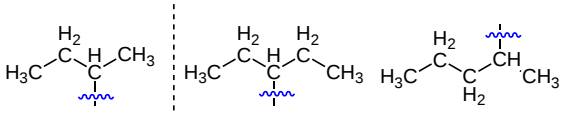
Starting with propyl alkyl groups there is the possibility of a connection other than the very end. The prefix "iso" implies that the connection ends with a $(CH_3)_2CH$- group.



isopropyl or *i*-propyl | isobutyl or *i*-butyl | isopentyl or *i*-pentyl

Secondary (*Sec*)

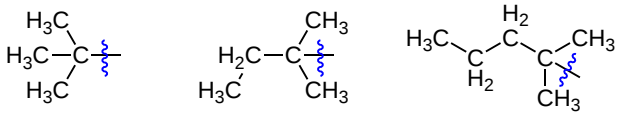
With butyl straight-chain alkyl groups there is the possibility of a connection on the second carbon from the end of the chain. These alkyl groups are given the prefix "*Sec*." This is not used for pentyl or hexyl groups because there is more than one structure that are not identical that could be named as sec-pentyl or sec-hexyl.



sec -butyl | NOT *sec* -pentyl

Tertiary (*tert* or *t*)

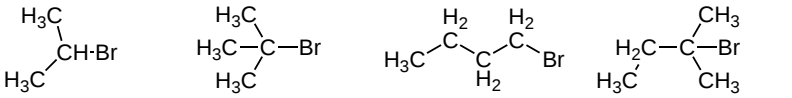
Starting with four carbon alkyl groups, there is an isomer which can have a connection to a tertiary carbon. These alkyl groups get the prefix "*t*."



tert-butyl or *t*-butyl | *tert*-pentyl or *t*-pentyl | *tert*-hexyl or *t*-hexyl

Example:

The naming system described above is often used to describe halogens which contain only a few carbons. The halogen is shown as bonded to the connection point of the alkyl group.



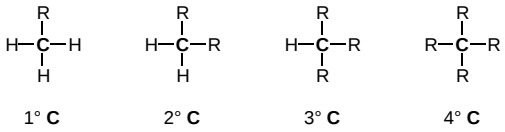
isopropyl bromide | *t*-butyl bromide | *n*-butyl bromide | *tert*-pentyl bromide

Classification of carbon atoms

Carbons have a special terminology to describe how many other carbons they are attached to. This allows for an easy description of branching in alkanes. Also, we will find that the number of carbons attached to a given atom will have subtle effects on its chemistry.

- Primary carbons (1°) attached to one other C atom.
- Secondary carbons (2°) are attached to two other C's.
- Tertiary carbons (3°) are attached to three other C's.
- Quaternary carbons (4°) are attached to four C's.

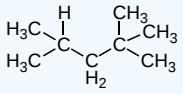
The figure below use the group "R" to represent an alkyl group of unspecified length. R typically used to represent alkyl groups but an also represent a part of a molecule which is either unspecified or not germane to the discussion.



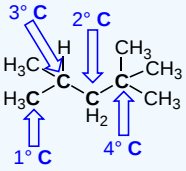
This terminology will be used repeatedly in organic chemistry to describe the number of carbons attached to a specific atom, however, the atom will not always a carbon.

Example 1.2.6.1

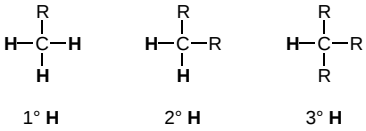
Please indicate the the number of 1°, 2°, 3°, and 4° carbons in the following molecule:



- The molecule has five Primary carbons (1°).
- The molecule has one Secondary carbon (2°).
- The molecule has one Tertiary carbon (3°).
- The molecule has one Quaternary carbon (4°)



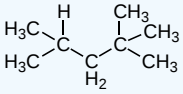
Hydrogen atoms are also classified in this manner. A hydrogen atom attached to a primary carbon atom is called a primary hydrogen ect.



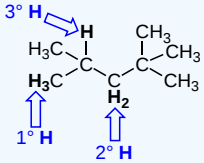
- Primary hydrogens (1°) are attached to carbons bonded to one other C atom
- Secondary hydrogens (2°) are attached to carbons bonded to two other C's
- Tertiary hydrogens (3°) are attached to carbons bonded to three other C's
- It is not possible to have a quaternary hydrogen (4°).

Example 1.2.6.2

Please indicate the the number of 1°, 2°, and 3°, hydrogens are in the following molecule:



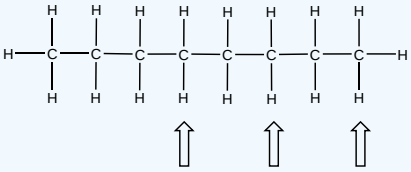
- The molecule has fifteen Primary (1°) hydrogens.
- The molecule has two Secondary (2°) hydrogens.
- The molecule has one Tertiary (3°) hydrogen.



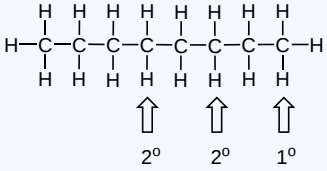
Exercises

Exercise 1.2.6.1

Determine whether the H's indicated in the following structure are 1°, 2°, or 3°.

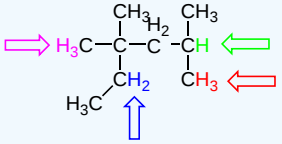


Answer

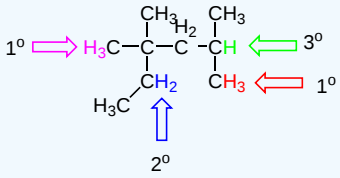


Exercise 1.2.6.2

Determine whether the H's indicated in the following structure is 1°, 2°, or 3°.

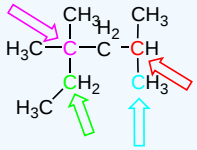


Answer

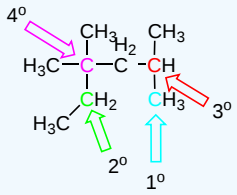


Exercise 1.2.6.3

Determine whether the carbons indicated in the structure below are 1°, 2°, 3°, or 4°.

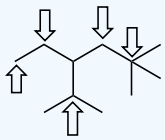


Answer

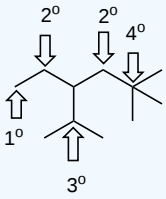


Exercise 1.2.6.4

Determine whether the carbons indicated in the structure below are 1°, 2°, 3°, or 4°.

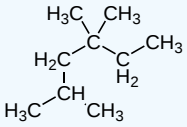


Answer



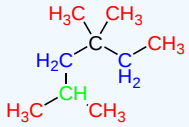
Exercise 1.2.6.5

Please indicate the total number of each type 1°, 2°, 3°, and 4° carbons in the following molecule.



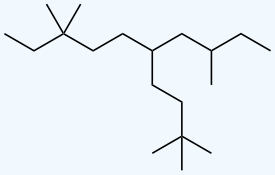
Answer

There are 5 primary (1°) C's, 2 secondary (2°) C's, 1 tertiary (3°) C and 1 quaternary (4°) C in the structure (seen color coded below).



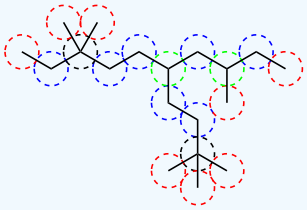
Exercise 1.2.6.6

Please indicate the total number of each type 1°, 2°, 3°, and 4° carbons in the following molecule.



Answer

There are 8 primary (1°) C's, 7 secondary (2°) C's, 2 tertiary (3°) C's and 2 quaternary (4°) C's in the structure (seen color coded below).



1.2.6: Alkyl Groups is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

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1.2.7: Naming Alkanes

Objectives

After completing this section, you should be able to

1. provide the correct IUPAC name for any given alkane structure (Kekulé, condensed or shorthand).
2. draw the Kekulé, condensed or shorthand structure of an alkane, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key term below.

- IUPAC system

Study Notes

The IUPAC system of nomenclature aims to ensure

1. that every organic compound has a unique, unambiguous name.
2. that the IUPAC name of any compound conveys the structure of that compound to a person familiar with the system.

One way of checking whether the name you have given to an alkane is reasonable is to count the number of carbon atoms implied by the chosen name. For example, if you named a compound 3-ethyl-4-methylheptane, you have indicated that the compound contains a total of 10 carbon atoms—seven carbon atoms in the main chain, two carbon atoms in an ethyl group, and one carbon atom in a methyl group. If you were to check the given structure and find 11 carbon atoms, you would know that you had made a mistake. Perhaps the name you should have written was 3-ethyl-4,4-dimethylheptane!

When naming alkanes, a common error of beginning students is a failure to pick out the longest carbon chain. For example, the correct name for the compound shown below is 3-methylheptane, not 2-ethylhexane.

Remember that every substituent must have a number, and do not forget the prefixes: di, tri, tetra, etc.

You must use commas to separate numbers, and hyphens to separate numbers and substituents. Notice that 3-methylhexane is one word.

Hydrocarbons having no double or triple bond functional groups are classified as **alkanes** or **cycloalkanes**, depending on whether the carbon atoms of the molecule are arranged only in chains or also in rings. Although these hydrocarbons have no functional groups, they constitute the framework on which functional groups are located in other classes of compounds, and provide an ideal starting point for studying and naming organic compounds. The alkanes and cycloalkanes are also members of a larger class of compounds referred to as **aliphatic**. Simply put, aliphatic compounds are compounds that do not incorporate any aromatic rings in their molecular structure.

The following table lists the IUPAC names assigned to simple continuous-chain alkanes from C-1 to C-10. A common **"ane"** suffix identifies these compounds as alkanes. Longer chain alkanes are well known, and their names may be found in many reference and text books. The names **methane** through **decane** should be memorized, since they constitute the root of many IUPAC names. Fortunately, common numerical prefixes are used in naming chains of five or more carbon atoms.

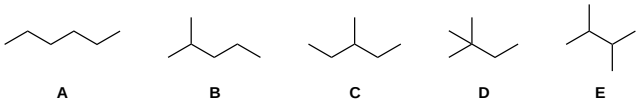
Table 3.4.1 : Simple Unbranched Alkanes

Name	Molecular Formula	Structural Formula	Isomers		Name	Molecular Formula	Structural Formula	Isomers
meth**ane**	CH_4	CH_4	1		hex**ane**	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
eth**ane**	C_2H_6	CH_3CH_3	1		hept**ane**	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
prop**ane**	C_3H_8	$CH_3CH_2CH_3$	1		oct**ane**	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
but**ane**	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2		non**ane**	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pent**ane**	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3		dec**ane**	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

Some important behavior trends and terminologies

1. The formulas and structures of these alkanes increase uniformly by a CH_2 increment.
2. A uniform variation of this kind in a series of compounds is called **homologous**.
3. These formulas all fit the $\mathbf{C_nH_{2n+2}}$ rule. This is also the highest possible H/C ratio for a stable hydrocarbon.
4. Since the H/C ratio in these compounds is at a maximum, we call them **saturated** (with hydrogen).

Beginning with butane (C_4H_{10}), and becoming more numerous with larger alkanes, we note the existence of alkane isomers. For example, there are five C_6H_{14} isomers, shown below as abbreviated line formulas (**A** through **E**):



Although these distinct compounds all have the same molecular formula, only one (**A**) can be called hexane. How then are we to name the others?

The **IUPAC** system requires first that we have names for simple unbranched chains, as noted above, and second that we have names for simple alkyl groups that may be attached to the chains. Examples of some common **alkyl groups** are given in the following table. Note that the "ane" suffix is replaced by "**yl**" in naming groups. The symbol **R** is used to designate a generic (unspecified) alkyl group.

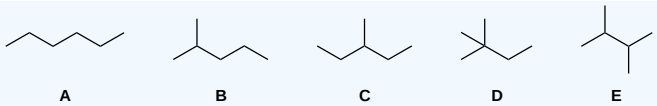
Table 3.4.2 : Alkyl Groups Names

Group	$CH_3–$	$C_2H_5–$	$CH_3CH_2CH_2–$	$(CH_3)_2CH–$	$CH_3CH_2CH_2CH_2–$	$(CH_3)_2CHCH_2–$	$CH_3CH_2CH(CH_3)–$	$(CH_3)_3C–$	R–
Name	Methyl	Ethyl	Propyl	Isopropyl	Butyl	Isobutyl	sec-Butyl	tert-Butyl	Alkyl

IUPAC Rules for Alkane Nomenclature

1. Find and name the longest continuous carbon chain.
2. Identify and name groups attached to this chain.
3. Number the chain consecutively, starting at the end nearest a substituent group.
4. Designate the location of each substituent group by an appropriate number and name.
5. Assemble the name, listing groups in alphabetical order.
6. The prefixes di, tri, tetra etc., used to designate several groups of the same kind, are not considered when alphabetizing.

Example 3.4.1 : Alkanes



The IUPAC names of the isomers of hexane are: **A** hexane **B** 2-methylpentane **C** 3-methylpentane **D** 2,2-dimethylbutane **E** 2,3-dimethylbutane

Halogen Groups

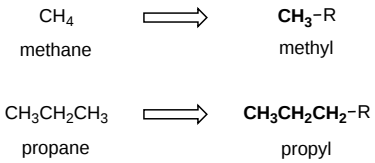
Halogen substituents are easily accommodated, using the names: fluoro (F-), chloro (Cl-), bromo (Br-) and iodo (I-).

Example 3.4.2 : Halogen Substitution

For example, $(CH_3)_2CHCH_2CH_2Br$ would be named 1-bromo-3-methylbutane. If the halogen is bonded to a simple alkyl group an alternative "alkyl halide" name may be used. Thus, C_2H_5Cl may be named chloroethane (no locator number is needed for a two carbon chain) or ethyl chloride.

Alkyl Groups

Alkanes can be described by the general formula C_nH_{2n+2}. An alkyl group is formed by removing one hydrogen from the alkane chain and is described by the formula C_nH_{2n+1}. The removal of this hydrogen results in a stem change from **-ane** to **-yl**. Take a look at the following examples.



The same concept can be applied to any of the straight chain alkane names provided in the table below.

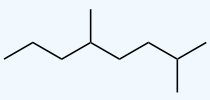
Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
Tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
Tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
Pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
Hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
Heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
Octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$
Nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
Eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

Three Rules for Naming Alkanes

1. Choose the longest, most substituted carbon chain containing a functional group.
2. A carbon bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number.
3. Take the alphabetical order into consideration; that is, after applying the first two rules given above, make sure that your substituents and/or functional groups are written in alphabetical order.

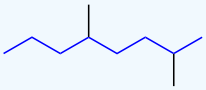
Example 3.4.3

What is the name of the follow molecule?

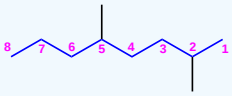


Solution

Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example does not contain any functional groups, so we only need to be concerned with choosing the longest, most substituted carbon chain. The longest carbon chain has been highlighted in blue and consists of eight carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. Because this example does not contain any functional groups, we only need to be concerned with the two substitutes present, that is, the two methyl groups. If we begin numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown below. This gives the methyl groups the lowest possible numbering.

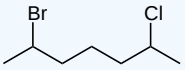


Rule 3: In this example, there is no need to utilize the third rule. Because the two substitutes are identical, neither takes alphabetical precedence with respect to numbering the carbons. This concept will become clearer in the following examples.

The name of this molecule is **2,5-dimethyloctane**

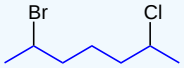
Example 3.4.4

What is the name of the follow molecule?



Solution

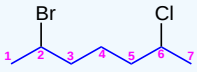
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number. In this example, numbering the chain from either the left or the right would satisfy this rule. If we number the chain from the left, bromine and chlorine would be assigned the second and sixth carbon positions, respectively. If we number the chain from the right, chlorine would be assigned the second position and bromine would be assigned the sixth position. In other words, whether we choose to number from the left or right, the functional groups occupy the second and sixth positions in the chain. To select the correct numbering scheme, we need to utilize the third rule.



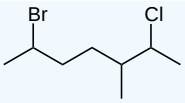
Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



The name of this molecule is: **2-bromo-6-chloroheptane**

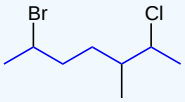
Example 3.4.5

What is the name of the follow molecule?

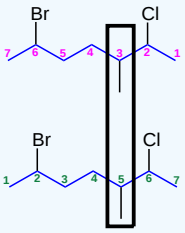


Solution

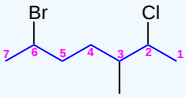
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. After taking functional groups into consideration, any substitutes present must have the lowest possible carbon number. This particular example illustrates the **point of difference principle**. If we number the chain from the left, bromine, the methyl group and chlorine would occupy the second, fifth and sixth positions, respectively. This concept is illustrated in the second drawing below. If we number the chain from the right, chlorine, the methyl group and bromine would occupy the second, third and sixth positions, respectively, which is illustrated in the first drawing below. The position of the methyl, therefore, becomes a **point of difference**. In the first drawing, the methyl occupies the third position. In the second drawing, the methyl occupies the fifth position. To satisfy the second rule, we want to choose the numbering scheme that provides the lowest possible numbering of this substitute. Therefore, the first of the two carbon chains shown below is correct.



Therefore, the first numbering scheme is the appropriate one to use.



Once you have determined the correct numbering of the carbons, it is often useful to make a list, including the functional groups, substitutes, and the name of the parent chain.

Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.

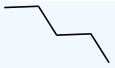
Parent chain: heptane Substitutents: 2-chloro 3-methyl 6-bromo

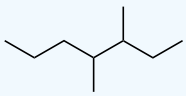
The name of this molecule is: **6-bromo-2-chloro-3-methylheptane**

Exercises

? Exercise 3.4.1

Give the proper IUPAC names of the following compounds.

a) 

b) 

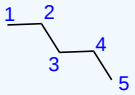
c) 

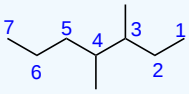
Answer

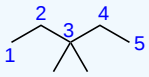
a) Since this structure is an unbranched alkane (all single bonds) with a 5 carbon chain length, its name would be **pentane**.

b) This alkane has a 7 carbon longest continuous chain length that we number from right to left to get the first methyl substituent we encounter to have the lowest possible number (3 versus being 4 if numbering from left to right). This causes it to have 2 methyl substituents at positions 3 & 4 so we would name it indicating those numbers and the prefix dimethyl which gives a proper IUPAC name of **3,4-dimethylheptane**.

c) This alkane has a 5 carbon longest continuous chain length (which could be numbered from left to right or right to left due to the symmetry at C-3). It has two methyl substituents off of C-3 so the proper IUPAC name is **3,3-dimethylpentane.**

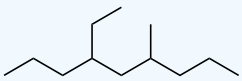
a) 

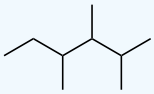
b) 

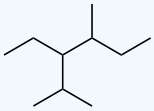
c) 

Exercise 3.4.2

Give the proper IUPAC names of the following compounds.

a) 

b) 

c) 

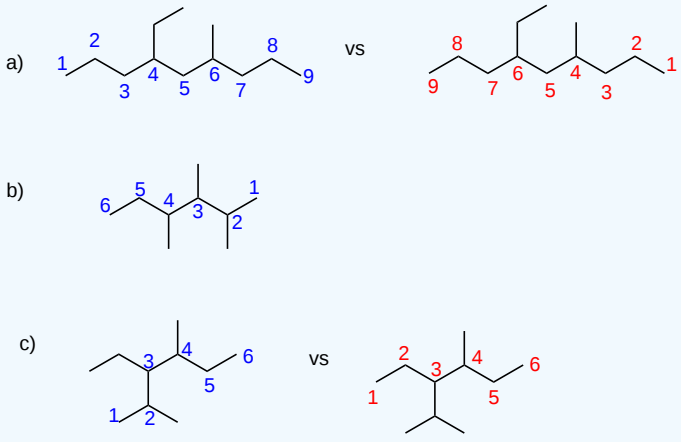
Answer

a) This alkane has a 9 carbon longest continuous chain length that we number from left to right (structure on left numbered in blue) to make the ethyl substituent be number 4. For the structure on the right (numbered in red) going from right to left,

the methyl substituent is number 4. Since ethyl is higher in the alphabetical order, you want to make it have the lower number so the structure on the left (blue numbering) takes priority and the name is **4-ethyl-6-methylnonane**.

b) This alkane has a 6 carbon longest continuous chain length that we number from right to left to make the first methyl be C-2 (versus the opposite direction which would make the first methyl C-3). Since there are 3 methyl substituents at positions 2,3, & 4, this compound would have the name **2,3,4-trimethylhexane**.

c) This 6 carbon alkane can be numbered along different chains (see below) as well as in the opposite directions. This shows the two different chains that can be drawn (making the first substituent in that chain the lowest number). The structure on the left (numbered in blue) is the correct choice since it causes more substituents to be on the longest continuous chain (3 vs 2 in the structure on the right). This would make the IUPAC name of the structure **3-ethyl-2,4-dimethylhexane**. (Notice how ethyl takes priority over methyl and the di- is not considered for alphabetizing.)



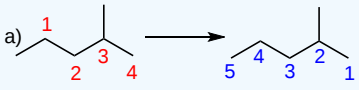
Exercise 3.4.3

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

a. 1,3-dimethylbutane
b. 4-ethylpentane
c. 2-ethyl-3-methylpentane

Answer

a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), the correct name should be **2-methylpentane**.

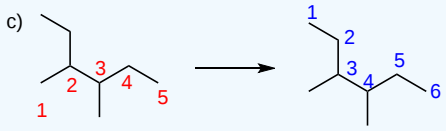


b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and we start the numbering on the end to the right to make the methyl substituent come off at C-3 (instead of beong at C-4 if we numbered it the opposite direction) the correct name should be **3-methyl hexane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and since this molecule is symmetrical (between carbon 3 &

4), you can start the numbers from either end. In this case, we have methyl substituents coming off of carbons 3 & 4 so the proper name is **3,4-dimethyl hexane**.



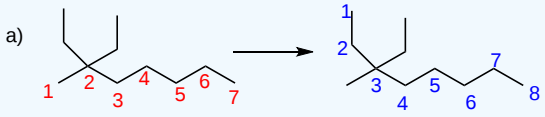
Exercise 3.4.4

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

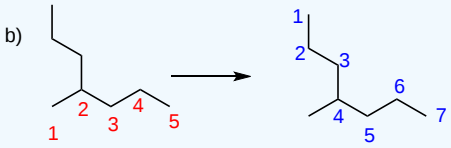
a. 2,2-diethylheptane
b. 2-propylpentane
c. 4,4-diethylbutane

Answer

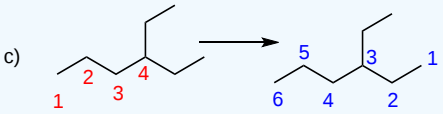
a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 8 C's and you have an ethyl substituent at C-3 and a methyl substituent also at C-3 so the proper name is **3- ethyl-3-methyloctane**.



b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 7 C's and since this molecule is symmetrical (at carbon 4), you can start the numbers from either end. There is a methyl substituent at C-4 so the proper name is **4-methylheptane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right) going from right to left (to make the ethyl substituent have the lowest number possible), the correct name is **3-ethylhexane**



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1.2.8: Properties of Alkanes

Objectives

After completing this section, you should be able to

1. arrange a number of given straight-chain alkanes in order of increasing or decreasing boiling point or melting point.
2. arrange a series of isomeric alkanes in order of increasing or decreasing boiling point.
3. explain the difference in boiling points between a given number of alkanes.

Key Terms

Make certain that you can define, and use in context, the key term below.

- van der Waals force (also known as London Dispersion force)

Alkanes are not very reactive and have little biological activity; all alkanes are colorless and odorless non-polar compounds. The relative weak London dispersion forces of alkanes result in gaseous substances for short carbon chains, volatile liquids with densities around 0.7 g/mL for moderate carbon chains, and solids for long carbon chains. For molecules with the same functional groups, there is a direct relationship between the size and shape of molecules and the strength of the intermolecular forces (IMFs) causing the differences in the physical states.

Boiling Points

Table **1.2.8.1** describes some of the properties of some straight-chain alkanes. There is not a significant electronegativity difference between carbon and hydrogen, thus, there is not any significant bond polarity. The molecules themselves also have very little polarity. A totally symmetrical molecule like methane is completely non-polar, meaning that the only attractions between one molecule and its neighbors will be Van der Waals dispersion forces. These forces will be very small for a molecule like methane but will increase as the molecules get bigger. Therefore, the boiling points of the alkanes increase with molecular size.

For isomers, the more branched the chain, the lower the boiling point tends to be. Van der Waals dispersion forces are smaller for shorter molecules and only operate over very short distances between one molecule and its neighbors. It is more difficult for short, fat molecules (with lots of branching) to lie as close together as long, thin molecules.

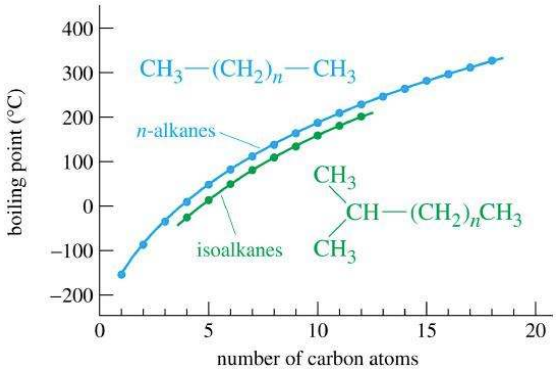
The boiling points shown are for the "straight chain" isomers of which there is more than one. The first four alkanes are gases at room temperature, and solids do not begin to appear until about $C_{17}H_{36}$, but this is imprecise because different isomers typically have different melting and boiling points.

Table **1.2.8.1**: Physical Properties of Some Alkanes

Molecular Name	Formula	Melting Point (°C)	Boiling Point (°C)	Density (20°C)*	Physical State (at 20°C)
methane	CH_4	–182	–164	0.668 g/L	gas
ethane	C_2H_6	–183	–89	1.265 g/L	gas
propane	C_3H_8	–190	–42	1.867 g/L	gas
butane	C_4H_{10}	–138	–1	2.493 g/L	gas
pentane	C_5H_{12}	–130	36	0.626 g/mL	liquid
hexane	C_6H_{14}	–95	69	0.659 g/mL	liquid
octane	C_8H_{18}	–57	125	0.703 g/mL	liquid
decane	$C_{10}H_{22}$	–30	174	0.730 g mL	liquid

*Note the change in units going from gases (grams per liter) to liquids (grams per milliliter). Gas densities are at 1 atm pressure.

The boiling points for the "straight chain" isomers and isoalkanes isomers are shown to demonstrate that branching decreases the surfaces area, weakens the IMFs, and lowers the boiling point.



Example 1.2.8.1: Boiling Points of Alkanes

For example, the boiling points of the three isomers of C_5H_{12} are:

- pentane: 309.2 K
- 2-methylbutane: 301.0 K
- 2,2-dimethylpropane: 282.6 K

The slightly higher boiling points for the cycloalkanes are presumably because the molecules can get closer together because the ring structure makes them better able!

Exercise 1.2.8.1

For each of the following pairs of compounds, select the substance which you expect to have the higher boiling point:

a. octane and nonane.
b. octane and 2,2,3,3-tetramethylbutane.

Solution

a. nonane, since it has more atoms it will have greater IMF
b. octane, since it is not branched, the molecules can pack closer together increasing IMF

Solubility

Alkanes are virtually insoluble in water, but dissolve in organic solvents. However, liquid alkanes are good solvents for many other non-ionic organic compounds.

Solubility in Water

When a molecular substance dissolves in water, the following must occur:

- break the intermolecular forces within the substance. In the case of the alkanes, these are the Van der Waals dispersion forces.
- break the intermolecular forces in the water so that the substance can fit between the water molecules. In water, the primary intermolecular attractions are hydrogen bonds.

Breaking either of these attractions requires energy, although the amount of energy to break the Van der Waals dispersion forces in something like methane is relatively negligible; this is not true of the hydrogen bonds in water.

As something of a simplification, a substance will dissolve if there is enough energy released when new bonds are made between the substance and the water to compensate for what is used in breaking the original attractions. The only new attractions between the alkane and the water molecules are Van der Waals forces. These forces do not release a sufficient amount of energy to compensate for the energy required to break the hydrogen bonds in water. The alkane does not dissolve.

> This is a simplification because entropic effects are important when things dissolve.

Solubility in organic solvents

In most organic solvents, the primary forces of attraction between the solvent molecules are Van der Waals. Therefore, when an alkane dissolves in an organic solvent, the Van der Waals forces are broken and are replaced by new Van der Waals forces. The two processes more or less cancel each other out energetically; thus, there is no barrier to solubility.

? Exercise 1.2.8.1

For each of the following pairs of compounds, select the substance you expect to have the higher boiling point.

a. octane and nonane.
b. octane and 2,2,3,3-tetramethylbutane.

Answer

Nonane will have a higher boiling point than octane, because it has a longer carbon chain than octane. Octane will have a higher boiling point than 2,2,3,3-tetramethylbutane, because it branches less than 2,2,3,3-tetramethylbutane, and therefore has a larger “surface area” and more van der Waals forces.

Note: The actual boiling points are:

- nonane, 150.8°C
- octane, 125.7°C
- 2,2,3,3-tetramethylbutane, 106.5°C

Reactions of Alkanes

Alkanes undergo very few reactions. There are two important reactions that are still possible, combustion and halogenation. The halogenation reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

Combustion

Complete combustion (given sufficient oxygen) of any hydrocarbon produces carbon dioxide, water, and a significant amount of heat. Due to the exothermic nature of these combustion reactions, alkanes are commonly used as a fuel source (for example: propane for outdoor grills, butane for lighters). The hydrocarbons become harder to ignite as the molecules get bigger. This is because the larger molecules don't vaporize as easily. If the liquid is not very volatile, only those molecules on the surface can react

with the oxygen. Larger molecules have greater Van der Waals attractions which makes it more difficult for them to break away from their neighbors and become a gas. An example combustion reaction is shown for propane:

$$C_3H_8 + O_2 \longrightarrow 3\,CO_2 + 4\,H_2O + 2044\,kJ/mol$$

Halogenation

Halogenation is the replacement of one or more hydrogen atoms in an organic compound by a halogen (fluorine, chlorine, bromine or iodine). Unlike the complex transformations of combustion, the halogenation of an alkane appears to be a simple **substitution reaction** in which a C-H bond is broken and a new C-X bond is formed.

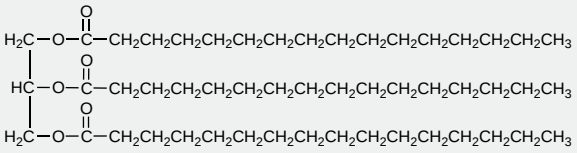
Since only two covalent bonds are broken (C-H & Cl-Cl) and two covalent bonds are formed (C-Cl & H-Cl), this reaction seems to be an ideal case for mechanistic investigation and speculation. However, one complication is that all the hydrogen atoms of an alkane may undergo substitution, resulting in a mixture of products, as shown in the following unbalanced equation. The relative amounts of the various products depend on the proportion of the two reactants used. In the case of methane, a large excess of the hydrocarbon favors formation of methyl chloride as the chief product; whereas, an excess of chlorine favors formation of chloroform and carbon tetrachloride.

$$CH_4 + Cl_2 \rightarrow CH_3Cl + CH_2Cl + CHCl_3 + CCl_4 + HCl$$

Looking Closer: An Alkane Basis for Properties of Other Compounds

An understanding of the physical properties of alkanes is important since petroleum and natural gas and the many products derived from them—gasoline, bottled gas, solvents, plastics, and more—are composed primarily of alkanes. This understanding is also vital because it is the basis for describing the properties of other organic and biological compound families. For example, large portions of the structures of lipids consist of nonpolar alkyl groups. Lipids include the dietary fats and fat like compounds called phospholipids and sphingolipids that serve as structural components of living tissues. These compounds have both polar and nonpolar groups, enabling them to bridge the gap between water-soluble and water-insoluble phases. This characteristic is essential for the selective permeability of cell membranes.

(a)



(b)

Tripalmitin (a), a typical fat molecule, has long hydrocarbon chains typical of most lipids. Compare these chains to hexadecane (b), an alkane with 16 carbon atoms.

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1.3: Cyclic Hydrocarbons

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1.3.1: Naming Cycloalkanes

Objectives

After completing this section, you should be able to:

- Name a substituted or unsubstituted cycloalkane, given its Kekulé structure, shorthand structure or condensed structure.
- Draw the Kekulé, shorthand or condensed structure for a substituted or unsubstituted cycloalkane, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

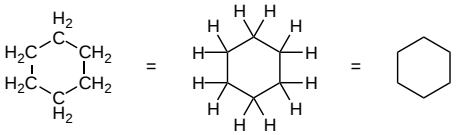
- cycloalkane

Study Notes

Provided that you have mastered the IUPAC system for naming alkanes, you should find that the nomenclature of cycloalkanes does not present any particular difficulties.

Many organic compounds found in nature contain rings of carbon atoms. These compounds are known as **cycloalkanes**. Cycloalkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The simplest examples of this class consist of a single, un-substituted carbon ring, and these form a homologous series similar to the unbranched alkanes.

Like alkanes, cycloalkane molecules are often drawn as skeletal structures in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens. Cyclohexane, one of the most common cycloalkanes is shown below as an example.



Cyclic hydrocarbons have the prefix "cyclo-". The IUPAC names, molecular formulas, and skeleton structures of the cycloalkanes with 3 to 10 carbons are given in Table **1.3.1.1**. Note that the general formula for a cycloalkane composed of **n** carbons is $\mathbf{C_nH_{2n}}$, and not $\mathbf{C_nH_{2n+2}}$ as for alkanes. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so are still considered to be **saturated** with hydrogen.

Table **1.3.1.1**: Examples of Simple Cycloalkanes

Cycloalkane	Molecular Formula	Skeleton Structure
Cyclopropane	C_3H_6	
Cyclobutane	C_4H_8	
Cyclopentane	C_5H_{10}	
Cyclohexane	C_6H_{12}	
Cycloheptane	C_7H_{14}	
Cyclooctane	C_8H_{16}	
Cyclononane	C_9H_{18}	
Cyclodecane	$C_{10}H_{20}$	

IUPAC Rules for Nomenclature

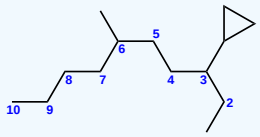
The naming of substituted cycloalkanes follows the same basic steps used in naming alkanes.

1. Determine the parent chain.
2. Number the substituents of the ring beginning at one substituent so that the nearest substituent is numbered the lowest possible. If there are multiple choices that are still the same, go to the next substituent and give it the lowest number possible.
3. Name the substituents and place them in alphabetical order.

More specific rules for naming substituted cycloalkanes with examples are given below.

1. Determine the cycloalkane to use as the parent. If there is an alkyl straight chain that has a greater number of carbons than the cycloalkane, then the alkyl chain must be used as the primary parent chain. Cycloalkanes substituents have an ending "-yl". If there are two cycloalkanes in the molecule, use the cycloalkane with the higher number of carbons as the parent.

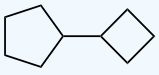
Example 1.3.1.1



The longest straight chain contains 10 carbons, compared with cyclopropane, which only contains 3 carbons. The parent chain in this molecule is decane and cyclopropane is a substituent. The name of this molecule is 3-cyclopropyl-6-methyldecane.

Example 1.3.1.2

Name the cycloalkane structure.

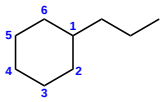


Solution

There are two different cycloalkanes in this molecule. Because it contains more carbons, the cyclopentane ring will be named as the parent chain. The smaller ring, cyclobutane, is named as a substituent on the parent chain. The name of this molecule is cyclobutylcyclopentane.

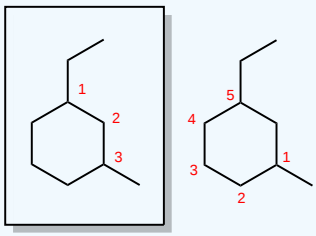
2. When there is only one substituent on the ring, the ring carbon attached to the substituent is automatically carbon #1. Indicating the number of the carbon with the substituent in the name is optional.

Example 1.3.1.3

	
1-chlorocyclobutane or cholorocyclobutane	1-propylcyclohexane or propylcyclohexane

3. If there are multiple substituents on the ring, number the carbons of the cycloalkane so that the carbons with substituents have the lowest possible number. A carbon with multiple substituents should have a lower number than a carbon with only one substituent or functional group. One way to make sure that the lowest number possible is assigned is to number the carbons so that when the numbers corresponding to the substituents are added, their sum is the lowest possible.
4. When naming the cycloalkane, the substituents must be placed in alphabetical order. Remember the prefixes di-, tri-, etc. , are not used for alphabetization.

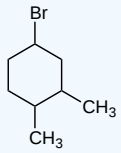
Example 1.3.1.4



In this example, the ethyl or the methyl subsistent could be attached to carbon one. The ethyl group attachment is assigned carbon 1 because ethyl comes before methyl alphabetically. After assigning carbon 1 the cyclohexane ring can be numbered going clockwise or counterclockwise. When looking at the numbers produced going clockwise produces lower first substituent numbers (1,3) than when numbered counterclockwise (1,5). So the correct name is 1-ethyl-3-methylcyclohexane.

Example 1.3.1.5

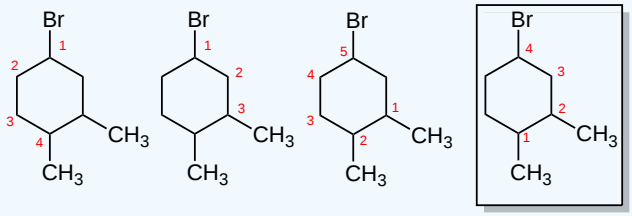
Name the following structure using IUPAC rules.



Solution

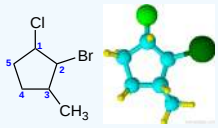
Remember when dealing with cycloalkanes with more than two substituents, finding the lowest possible 2nd substituent numbering takes precedence. Consider a numbering system with each substituent attachment point as being carbon one. Compare them and whichever produces the lowest first point of difference will be correct.

The first structure would have 1,4 for the relationship between the first two groups. The next structure would have 1,3. The final 2 structures both have 1,2 so those are preferable to the first two. Now we have to determine which is better between the final 2 structures. The 3rd substituent on structure 3 would be at the 5 position leading to 1,2,5 while in the final structure the 3rd methyl group is on carbon 4 leading to 1,2,4. This follows the rules of giving the lowest numbers at the first point of difference.



The correct name for the molecule is 4-Bromo-1,2-dimethylcyclohexane.

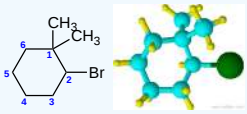
Example 1.3.1.6



2-bromo-1-chloro-3-methylcyclopentane

Notice that "b" of bromo alphabetically precedes the "m" of methyl. Also, notice that the chlorine attachment point is assigned carbon 1 because it comes first alphabetically and the overall sum of numbers would be the same if the methyl attachment carbon was assigned as 1 and the chlorine attachment as 3.

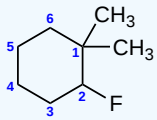
Example 1.3.1.7



(2-bromo-1,1-dimethylcyclohexane)

Although "di" alphabetically precedes "f", "di" is not used in determining the alphabetical order.

Example 1.3.1.8



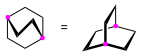
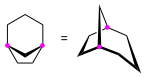
2-fluoro-1,1,-dimethylcyclohexane **NOT** 1,1-dimethyl-2-fluorocyclohexane also 2-fluoro-1,1,-dimethylcyclohexane **NOT** 1-fluoro-2,2-dimethylcyclohexane (as that would give a larger number to the first point of difference)

Although "di" alphabetically precedes "f", "di" is not used in determining the alphabetical order of the substituents. Notice that the attachment point of the two methyl groups is assigned carbon 1 despite the fact that fluorine comes first alphabetically. This is because this assignment allows for a lower overall numbering of substituents, so assigning alphabetical priority is not necessary.

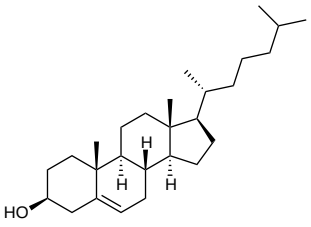
Polycyclic Compounds

Hydrocarbons having more than one ring are common, and are referred to as **bicyclic** (two rings), **tricyclic** (three rings) and in general, **polycyclic compounds**. The molecular formulas of such compounds have H/C ratios that decrease with the number of rings. In general, for a hydrocarbon composed of n carbon atoms associated with m rings the formula is: $\mathbf{C_nH_{2n+2-2m}}$. The structural relationship of rings in a polycyclic compound can vary. They may be separate and independent, or they may share one or two common atoms. Some examples of these possible arrangements are shown in the following table.

Table **1.3.1.2**: Examples of Isomeric $\mathbf{C_8H_{14}}$ Bicycloalkanes

Isolated Rings	Spiro Rings	Fused Rings	Bridged Rings
No common atoms	One common atom	One common bond	Two common atoms
			
			

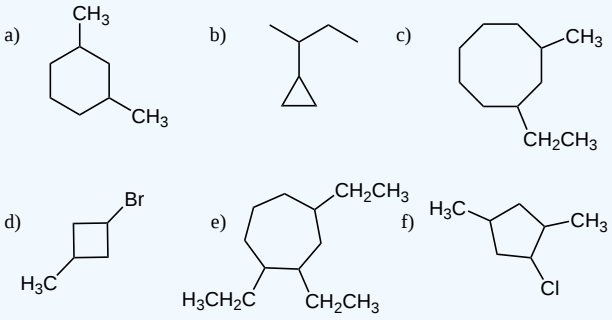
Polycyclic compounds, like cholesterol shown below, are biologically important and typically have common names accepted by IUPAC. However, the common names do not generally follow the basic IUPAC nomenclature rules, and will not be covered here.



Cholesterol (polycyclic)

Exercise 1.3.1.1

Give the IUPAC names for the following cycloalkane structures.



Answer

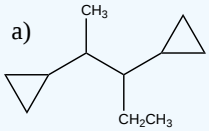
a. 1,3-Dimethylcyclohexane
b. 2-Cyclopropylbutane
c. 1-Ethyl-3-methylcyclooctane
d. 1-Bromo-3-methylcyclobutane
e. 1,2,4-Triethylcycloheptane
f. 1-Chloro-2,4-dimethylcyclopentane

Exercise 1.3.1.2

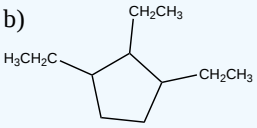
Draw the structures for the IUPAC names below.

a. 2,3-dicyclopropylpentane
b. 1,2,3-triethylcyclopentane
c. 3-cyclobutyl-2-methylhexane
d. 2-bromo-1-chloro-4-methylcyclohexane
e. 1-bromo-5-propylcyclododecane

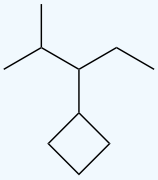
Answer

a) 

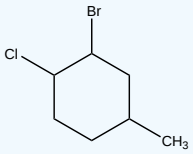
2,3-dicyclopropylpentane

b) 

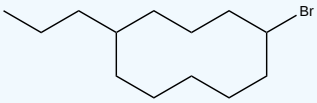
1,2,3-triethylcyclopentane

c) 

3-cyclobutyl-2-methylhexane

d) 

2-bromo-1-chloro-4-methylcyclohexane

e) 

1-bromo-5-propylcyclodecane

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1.3.2: Stability of Cycloalkanes - Ring Strain

Objectives

After completing this section, you should be able to:

- Describe the Baeyer strain theory.
- Describe how the measurement of heats of combustion provides information about the amount of strain present in a cycloalkane ring.
- Determine the relative stability of cyclic compounds, by assessing such factors as angle strain, torsional strain and steric strain.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- angle strain
- steric strain
- torsional strain
- ring strain
- heat of combustion

Heat of Combustion as a Measure of Bond Strength

The combustion of carbon compounds, especially hydrocarbons, has been the most important source of heat energy for human civilizations throughout recorded history. The practical importance of this reaction cannot be denied, but the massive and uncontrolled chemical changes that take place in combustion make it difficult to deduce mechanistic paths. Using the combustion of propane as an example, we see from the following equation that every covalent bond in the reactants has been broken and an entirely new set of covalent bonds have formed in the products. No other common reaction involves such a profound and pervasive change, and the mechanism of combustion is so complex that chemists are just beginning to explore and understand some of its elementary features.

$$\mathrm{CH_3CH_2CH_3 + 5\,O_2 \longrightarrow 3\,CO_2 + 4\,H_2O + heat}$$

Since all the covalent bonds in the reactant molecules are broken, the quantity of heat evolved in this reaction, and any other combustion reaction, is related to the strength of these bonds (and, of course, the strength of the bonds formed in the products). Precise heat of combustion measurements can provide useful information about the structure of molecules and their relative stability.

For example, heat of combustion is useful in determining the relative stability of isomers. Pentane has a heat of combustion of -782 kcal/mol, while that of its isomer, 2,2-dimethylpropane (neopentane), is –777 kcal/mol. These values indicate that 2,3-dimethylpentane is 5 kcal/mol more stable than pentane, since it has a lower heat of combustion.

Ring Strain

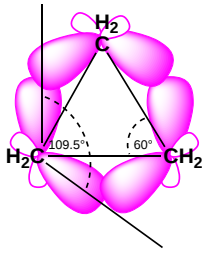
Table **1.3.2.1** lists the heat of combustion data for some simple cycloalkanes. These cycloalkanes do not have the same molecular formula, so the heat of combustion per each CH_2 unit present in each molecule is calculated (the fourth column) to provide a useful comparison. From the data, cyclopropane and cyclobutane have significantly higher heats of combustion per CH_2, while cyclohexane has the lowest heat of combustion. This indicates that cyclohexane is more stable than cyclopropane and cyclobutane, and in fact, that cyclohexane has a same relative stability as long chain alkanes that are not cyclic. This difference in stability is seen in nature where six membered rings are by far the most common. What causes the difference in stability or the strain in small cycloalkanes?

Table **1.3.2.1**: Heats of combustion of select hydrocarbons

Cycloalkane $(CH_2)_n$	CH_2 Units n	ΔH^{25^o} kcal/mol	ΔH^{25^o} per CH_2 Unit	Ring Strain kcal/mol
Cyclopropane	n = 3	468.7	156.2	27.6
Cyclobutane	n = 4	614.3	153.6	26.4
Cyclopentane	n = 5	741.5	148.3	6.5
Cyclohexane	n = 6	882.1	147.0	0.0
Cycloheptane	n = 7	1035.4	147.9	6.3
Cyclooctane	n = 8	1186.0	148.2	9.6
Cyclononane	n = 9	1335.0	148.3	11.7
Cyclodecane	n = 10	1481	148.1	11.0
$CH_3(CH_2)_mCH_3$	m = large	—	147.0	0.0

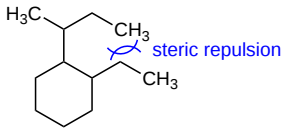
The Baeyer Theory on the Strain in Cycloalkane Rings

In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane are less stable than cyclohexane, because the the smaller rings are more "strained". There are many different types of strain that contribute to the overall ring strain in cycloalkanes, including angle strain, torsional strain, and steric strain. **Torsional strain** and **steric strain** were previously defined in the discussion of conformations of butane. **Angle Strain** occurs when the sp^3 hybridized carbons in cycloalkanes do not have the expected ideal bond angle of 109.5^o, causing an increase in the potential energy. An example of angle strain can be seen in the diagram of cyclopropane below in which the bond angle is 60° between the carbons. The compressed bond angles causes poor overlap of the hybrid orbitals forming the carbon-carbon sigma bonds which in turn creates destabilization.



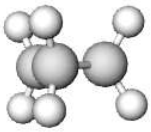
The C-C-C bond angles in cyclopropane (diagram above) (60°) and cyclobutane (90°) are much different than the ideal bond angle of 109.5^o. This bond angle causes cyclopropane and cyclobutane to be less stable than molecules such as cyclohexane and cyclopentane, which have a much lower ring strain because the bond angle between the carbons is much closer to 109.5^o. Changes in chemical reactivity as a consequence of angle strain are dramatic in the case of cyclopropane, and are also evident for cyclobutane.

In addition to angle strain, there is also steric (transannular) strain and torsional strain in many cycloalkanes. Transannular strain exists when there is steric repulsion between atoms.



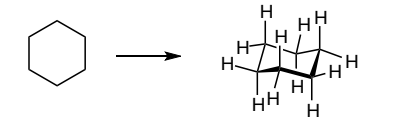
transannular strain

Because cycloalkane lack the ability to freely rotate, torsional (eclipsing) strain exists when a cycloalkane is unable to adopt a staggered conformation around a C-C bond. Torsional strain is especially prevalent in small cycloalkanes, such as cyclopropane, whose structures are nearly planar.



The Eclipsed C-H Bonds in Cyclopropane

Larger rings like cyclohexane, deal with torsional strain by forming conformers in which the rings are not planar. A conformer is a stereoisomer in which molecules of the same connectivity and formula exist as different isomers, in this case, to reduce ring strain. The ring strain is reduced in conformers due to the rotations around the sigma bonds, which decreases the angle and torsional strain in the ring. The non-planar structures of cyclohexane are very stable compared to cyclopropane and cyclobutane, and will be discussed in more detail in the next section.



The Types of Strain Which Contribute to Ring Strain in Cycloalkanes

- Angle Strain - The strain caused by the increase or reduction of bond angles
- Torsional Strain - The strain caused by eclipsing bonds on adjacent atoms
- Steric Strain - The strain caused by the repulsive interactions of atoms trying to occupy the same space

Exercise 1.3.2.1

trans-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane. Explain this observation.

Answer

The trans form does not have eclipsing methyl groups, therefore lowering the energy within the molecule. It does however have hydrogen-methyl eclipsing interactions which are not as high in energy as methyl-methyl interactions.

Exercise 1.3.2.2

Cyclobutane has more torsional stain than cyclopropane. Explain this observation.

Answer

Cyclobutane has 4 CH_2 groups while cyclopropane only has 3. More CH2 groups means cyclobutane has more eclipsing H-H interactions and therefore has more torsional strain.

Exercises

1. *Trans*-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane. Explain this observation.
2. The trans form does not have eclipsing methyl groups, therefore lowering the energy within the molecule. It does however have hydrogen-methyl interactions, but are not as high in energy than methyl-methyl interactions.

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1.4: Alkenes

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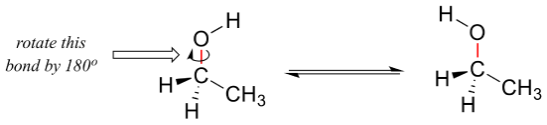
1.4.1: Bond Rotation

Learning Objective

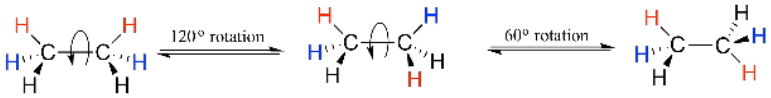
- distinguish between bonds that can rotate and those that cannot

Sigma Bonds can Rotate

We learned in section 2.1 that single bonds in organic molecules are free to rotate, due to the 'end-to-end' (sigma) nature of their orbital overlap. Consider the carbon-oxygen bond in ethanol, for example: with a 180° rotation about this bond, the shape of the molecule would look quite different:

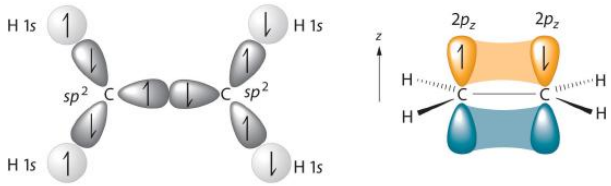


For ethane, rotation about the carbon-carbon sigma bond results in many different possible three-dimensional arrangements of the atoms.



Pi Bonds are rigid

Pi bonds are created from overlapping p orbitals. The lobes of the p orbitals prevent the atoms sharing pi bonds from rotating as shown in the diagram below.

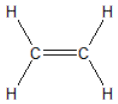


(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

Double and Triple Bonds cannot Rotate

The pi bonds in double and triple bonds prevent these bonds from rotating. This rigidity has an effect on the physical structure of compounds and can influence chemical reactivity. For now, we want to build the habit of looking at static drawings and diagrams of organic compounds and visualizing their dynamic nature.

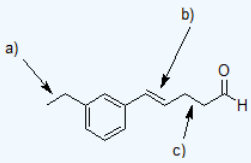
For ethene, there is no rotation about the carbon-carbon double bond because of the pi bond.



No rotation is possible between
the two carbon atoms sharing a double bond.

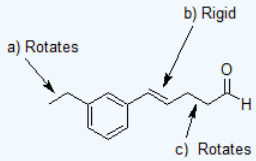
Exercise

1. Label the selected bonds in the compound below as "Rotates" or "Rigid."



Answer

1. Arrows for (a) and (c) are pointing to single bonds that can rotate. Arrow (b) is pointing to a double bond that is rigid because of the pi bond.



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1.4.2: Introduction to Alkenes

Objective

After completing this section, you should be able to give an example of a naturally occurring compound that contains at least one double bond.

Key Terms

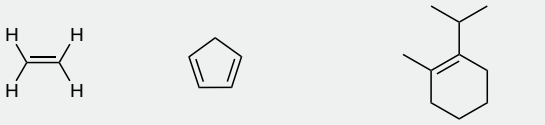
Make certain that you can define, and use in context, the key term below.

- olefin

Study Notes

Alkenes are a class of hydrocarbons (i.e., containing only carbon and hydrogen). They are unsaturated compounds with at least one carbon-to-carbon double bond. The double bond makes Alkenes more reactive than alkanes. Olefin is another term used to describe alkenes.

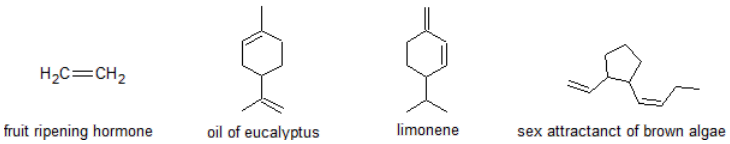
The graphic shows three alkenes. The more complex alkene is commonly known as 1-menthene, but its full proper IUPAC name is 1-methyl-2-(1-methylethyl)-cyclohexene.



ethene | 1,3-cyclopentadiene | 1-menthene (peppermint fragrance)

Alkenes

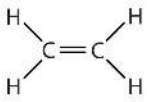
Alkenes are a class of hydrocarbons (i.e., containing only carbon and hydrogen). They are unsaturated compounds with at least one carbon-to-carbon double bond. The double bond makes alkenes more reactive than alkanes. Olefin is another term used to describe alkenes. The alkene group can also be called a vinyl group and the carbons sharing the double bond can be called vinyl carbons.



fruit ripening hormone | oil of eucalyptus | limonene | sex attractanct of brown algae

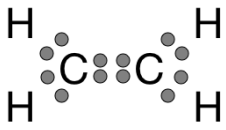
Structure of Ethene - the Simplest Alkene

Ethene is often written as CH_2=CH_2 which stands for:

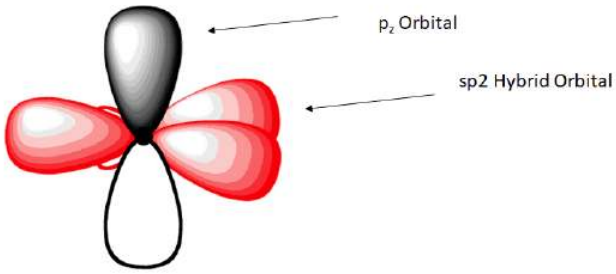


The double bond is shared by the two carbon atoms and does not involve the hydrogen atoms, although the condensed formula does not make this point obvious. Note that the molecular formula for ethene is C_2H_4, whereas that for ethane is C_2H_6.

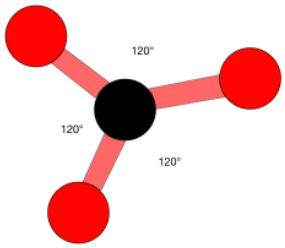
Ethene is not a very complicated molecule. It is made up of four $1s^1$ hydrogen atoms and two $2s^2$ $2p_x^1$ $2p_y^1$ carbon atoms. These carbon atoms already have four electrons, but they each want to get four more so that they have a full eight (octet) in the valence shell. Having eight valence electrons around carbon gives the atom the same electron configuration as neon, a noble gas. Carbon wants to have the same configuration as neon because when it has eight valence electrons carbon is at its most stable, lowest energy state.



This forms a total of three bonds to each carbon atom, giving them an sp^2 hybridization. Since the carbon atom is forming three sigma bonds instead of the four that it can, it only needs to hybridize three of its outer orbitals, instead of four. It does this by using the $2s$ electron and two of the $2p$ electrons, leaving the other unchanged. This new orbital is called an sp^2 hybrid because it is made from one s orbital and two p orbitals.



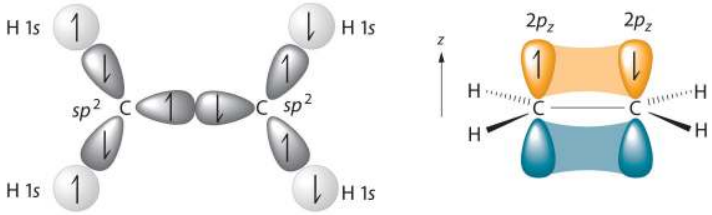
When atoms use sp^2 hybrids they have a trigonal planar structure. These structures are very similar to a 'peace' sign, there is a central atom with three atoms around it, all on one plane. Trigonal planar molecules have an ideal bond angle of 120° on each side.



The H-C-H bond angle is 117°, which is very close to the ideal 120° of a carbon with sp^2 hybridization. The other two angles (H-C=C) are both 121.5°.

Rigidity in Ethene

There is rigidity in the ethene molecule due to the double-bonded carbons. A double bond consists of one sigma bond formed by overlap of sp^2 hybrid orbitals and one pi bond formed by overlap of parallel 2 p orbitals. In ethene there is no free rotation about the carbon-carbon sigma bond because these two carbons also share a π bond. A π bond is only formed when there is adequate overlap between both top and bottom p-orbitals. Rotation of the p-orbitals causes them to be 90° from each other breaking the π bond because there would be no overlap. There is a much larger energy barrier to rotation than there is about a carbon-carbon sigma bond.



(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

(a) The σ-bonded framework is formed by the overlap of two sets of singly occupied carbon sp^2 hybrid orbitals and four singly occupied hydrogen 1s orbitals to form electron-pair bonds. This uses 10 of the 12 valence electrons to form a total of five σ bonds (four C–H bonds and one C–C bond).

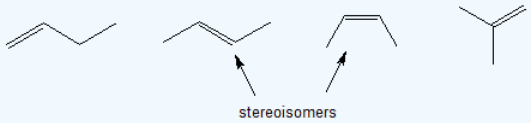
(b) One singly occupied unhybridized $2p_z$ orbital remains on each carbon atom to form a carbon–carbon π bond. (Note: by convention, in planar molecules the axis perpendicular to the molecular plane is the z-axis.)

? Exercise

1. Although there is only one alkene with the formula C_2H_4 (ethene) and only one with the formula C_3H_6 (propene), there are several alkenes with the formula C_4H_8. Draw all of the possible bond line structures for alkenes with the formula C_4H_8 including all possible structural and stereoisomers.

Answer

1. There are three possible structural isomers. 2-butene can exist as two different stereoisomers.



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1.4.3: Industrial Preparation and Use of Alkenes

Objectives

After completing this section, you should be able to

1. discuss the industrial importance of ethylene (ethene) and propylene (propene).
2. describe, briefly, the industrial process known as thermal cracking.

Study Notes

Among the most important and most abundant organic chemicals produced worldwide are the two simple alkenes, ethylene and propylene. They are used as the starting materials to synthesize numerous valuable compounds.

Produced from ethylene (ethene)

Chemical	Uses
ethanol	solvent; constituent of cleaning preparations; in synthesis of esters
acetaldehyde	slug killer, in the form of methaldehyde $(CH_3CHO)_4$
acetic acid	manufacture of vinyl acetate polymers, ethyl acetate solvent and cellulose acetate polymers
ethylene oxide	“cellosolves” (industrial solvents)
ethylene glycol	anti-freeze; production of DacronOR
ethylene dichloride	solvent; production of vinyl chloride
vinyl chloride	manufacture of poly (vinyl chloride)—PVC
vinyl acetate	manufacture of poly (vinyl acetate) used in paint emulsions, plywood adhesives and textiles
polyethylene	“plastic” bags; toys; packaging

Produced from propylene (propene)

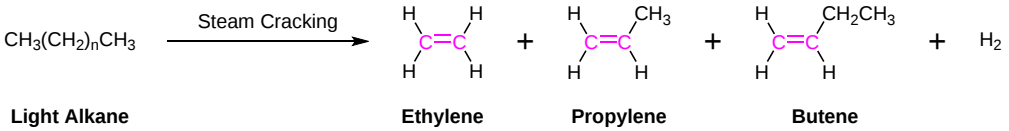
Chemical	Uses
isopropyl alcohol	rubbing alcohol; cosmetics; synthesis of acetone
propylene oxide	manufacture of polyurethanes; polyesters
cumene	industrial preparation of phenol and acetone
polypropylene	molded articles (e.g., kitchenware); fibres for indoor-outdoor carpeting

Industrial Preparation of Ethylene and Propylene

Ethene (CH_2CH_2) and propene (CH_3CHCH_2), are most often called by their common names—ethylene and propylene. Ethylene is a major commercial chemical. The US chemical industry produces about 25 billion kilograms of ethylene annually, more than any other synthetic organic chemical. More than half of this ethylene goes into the manufacture of polyethylene, one of the most familiar plastics. Propylene is also an important industrial chemical. It is converted to plastics, isopropyl alcohol, and a variety of

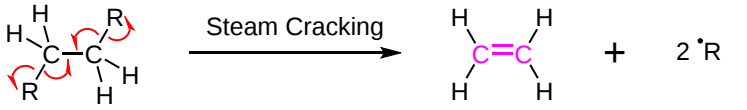
other products. Both ethylene and propylene are the feedstock for the industrial synthesis of a wide variety of small organic molecules.

Ethylene, propylene, and butylene ($CH_3CH_2CHCH_2$) are typically industrially synthesized through the steam cracking of light alkanes (C < 8) obtained from fractional distillation of crude oil. Cracking is the name given to a number of petroleum refining processes which break up large hydrocarbon molecules into smaller fragment. Steam cracking is achieved without a catalyst by using high temperatures (~900 ^oC) and produces a mixtures of products containing high proportions of hydrocarbons with double bonds. There is not any single unique reaction happening during steam cracking. The hydrocarbon molecules are broken up in a fairly random way but the process can be generically represented by the reaction below.



Light Alkane **Ethylene** **Propylene** **Butene**

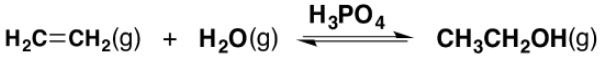
The mechanism of the steam cracking is complex and believed to involve the formation of free radicals. The high temperatures of steam cracking is enough to cause the homolytic cleavage of C-C and C-H bonds in the starting material. The cleavage of C-C bonds inherently creates smaller hydrocarbons as represented below.



Ethylene **Radical**

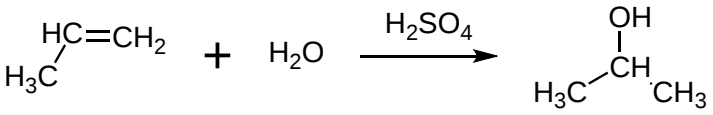
Industrial Preparations of Alcohols from Ethylene and Propylene

Ethanol is manufactured by reacting ethylene with steam. The catalyst used is solid silicon dioxide coated with phosphoric acid. The reaction is reversible.



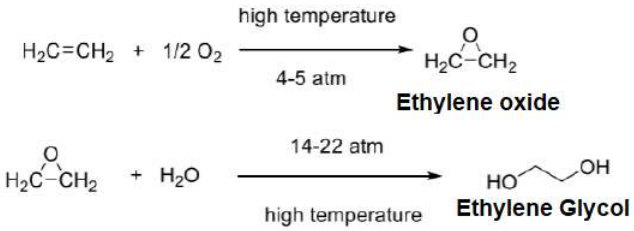
Only 5% of the ethylene is converted into ethanol at each pass through the reactor. By removing the ethanol from the equilibrium mixture and recycling the ethylene, it is possible to achieve an overall 95% conversion.

Isopropyl alcohol is synthesized on an industrial scale using a similar reaction with propylene.



Propylene **Isopropyl Alcohol**

Ethylene is also used in the industrial synthesis of ethylene glycol. Ethylene glycol is a major industrial compound with a wide range of applications. The traditional method to synthesize ethylene glycol is a two step process in which ethylene is directly oxidized to ethylene oxide. Next the three-membered ring of ethylene oxide is opened using water at high temperatures and pressures to form ethylene glycol.



Industrial Preparations of Plastics from Ethylene and Propylene

One of the primary uses of industrial synthesized ethylene is the production of the polymer **polyethylene (PE)**. Polyethylene is the most common plastic. As of 2017, over 100 million tons of polyethylene resins are produced annually, accounting for 34% of the total plastics market. Its primary use is in packaging (plastic bags, plastic films, geomembranes, containers including bottles, etc.). Many kinds of polyethylene are known, with most having the chemical formula $(C_2H_4)_n$.

It is the simplest polymer, consisting of random-length (but generally very long) chains made up of two-carbon units. During the polymerization process many ethylene molecules are linked together to form the carbon backbone of polyethylene. In the polyethylene structures are represented below. The squiggly lines at the ends of the long structure indicate that the same pattern extends indefinitely. The more compact notation on the right shows the minimal repeating unit enclosed in brackets; this means the same thing and is the preferred way of depicting polymer structures.

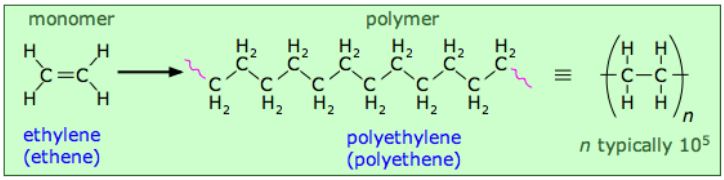


Figure **1.4.3.1** Polyethylene.

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1.4.4: Naming Alkenes

Objectives

After completing this section, you should be able to

- provide the correct IUPAC name for an acyclic or cyclic alkene, given its Kekulé, condensed or shorthand structure.
- draw the Kekulé, condensed or shorthand structure of an alkene (cyclic or acyclic), given its IUPAC name.
- give the IUPAC equivalent of the following trivial names: ethylene, propylene, isobutylene and isoprene.
- draw the structure of a vinyl (ethenyl) and allyl (2-propenyl) group, and use these names in alkene nomenclature.

Study Notes

This course uses IUPAC nomenclature; therefore, you need not usually memorize a large number of trivial names. However, you will encounter some trivial names so frequently in books and articles that they soon become familiar.

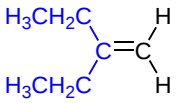
An alkene that can exhibit geometric isomerism has not been properly named unless its name specifies whether the double bond (or bonds) is (or are) cis or trans. The most effective way of giving this information is discussed, and more details of cis and trans follow in Section 7.4.

Alkenes contain carbon-carbon double bonds and are unsaturated hydrocarbons with the molecular formula is C_nH_{2n}; this is also the same molecular formula as cycloalkanes. The parent chain of an alkene is the longest chain containing both carbon atoms of the double bond. Alkenes are named by dropping the **-ane** ending of the parent and adding **-ene**. Also, the position of double bond in the parent chain of the alkene is indicated with a number.

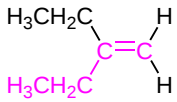
The Basic Rules for Naming Alkenes

For straight chain alkenes, it is the same basic rules as nomenclature of alkanes apply except the **-ane** suffix is changed to **-ene**.

1) Find the longest carbon chain that contains both carbons of the double bond.

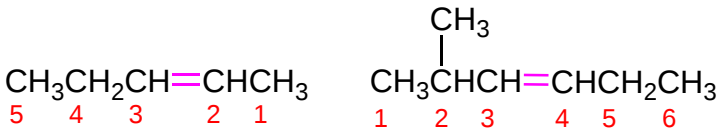


This compound is NOT named as an pentene



This compound is named as a butene because the double bond is contained in the four carbon chain

2) Start numbering from the end of the parent chain which gives the lowest possible number to the double bond. If the double bond is equidistant from both ends of the parent chain, number from the end which gives the substituents the lowest possible number. The double bond in cycloalkenes do not need to number because it is understood that they are in the one position.

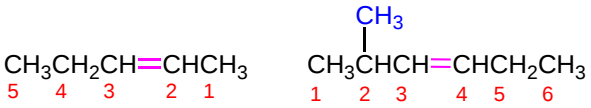


3) Place the location number of the double bond directly before the parent name. The location number indicates the position of the first carbon of the double bond. Add substituents and their position to the alkene as prefixes. Remember substituents are written in alphabetical order.

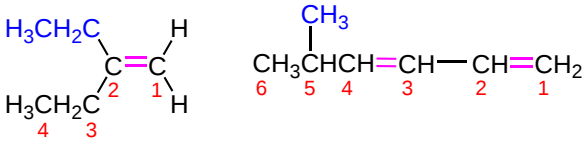
The presence of multiple double bonds is indicated by using the appropriate suffix such as **-diene**, **-triene**, ect. Each of the multiple bonds receives a location number. Also, only **-ne** is removed from the parent alkane chain name leaving an "a" in the name.

Overall, the name of an alkene should look like:

(Location number of substituent)-(Name of substituent)-(Location number of double bond)-(Name of parent chain) + ene



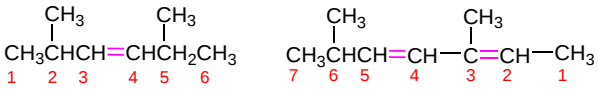
2-Pentene **2-Methyl-3-hexene**



3-Ethyl-1-butene **5-Methyl-1,3-hexadiene**

Newer IUPAC Nomenclature

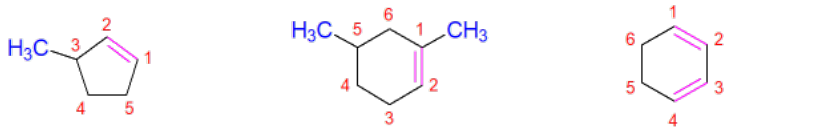
In 1993 IUPAC updated their naming recommendation to place the location number of the double bond before the -ene suffix of alkene names. The provides names such as hex-2-ene rather than 2-hexene. The newer system is slowly being accepted so it may occasionally be encountered.



Older Numbering System:	**2,5-Dimethyl-3-hexene**	**5-Methyl-1,3-hexadiene**
Newer Numbering System:	**2,5-Dimethylhex-3-ene**	**5-Methylhexa-1,3-diene**

Naming Cycloalkenes

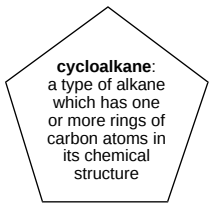
Because there are no chain ends in cycloalkenes, the double bond is assumed to numbered C1 and C2 and its location number is not required in the name. The direction of the numbering is determined by which will give the substituent closest to the double bond the lowest number. If multiple double bonds are present, it may be necessary to include their location numbers in the name. One of the double bonds will be number C1 and C2 and the numbering direction is determined by which gives the remaining double bonds the lowest possible number.



3-Methylcyclopent-1-ene **1,5-Dimethylcyclohexene** **1,3-Cyclohexadiene**
(New:Cyclohexa-1,3-diene)

Endocyclic vs. Exocyclic Alkenes

Endocyclic double bonds have both carbons in the ring and exocyclic double bonds have only one carbon as part of the ring.



Cyclopentene is an example of an endocyclic double bond.



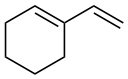
Methylenecylopentane is an example of an exocyclic double bond.



Name the following compounds...



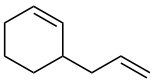
1-methylcyclobutene. The methyl group places the double bond. It is correct to also name this compound as 1-methylcyclobut-1-ene.



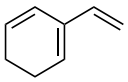
1-ethenylcyclohexene, the methyl group places the double bond. It is correct to also name this compound as 1-ethenylcyclohex-1-ene. A common name would be 1-vinylcyclohexene.

Try to draw structures for the following compounds...

- 3-allylcyclohex-1-ene

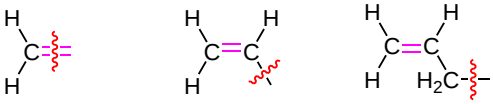


- 2-vinyl-1,3-cyclohexadiene



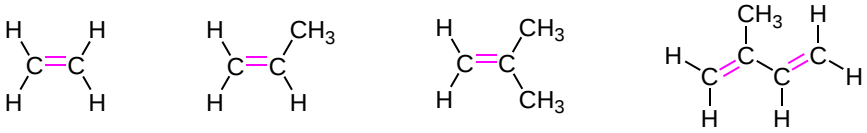
Common Names of Alkene Fragments

Some alkene containing fragments have common names which should be recognized. These common names can be used to simplify naming much the alkyl fragments discussed in **Section: 3.3**. Some of these fragments are the methylene group (H_2C=), the vinyl group (H_2C=CH-), and the allyl group (H_2C=CH-CH_2-).



Methylene Group **Vinyl Group** **Allyl Group**

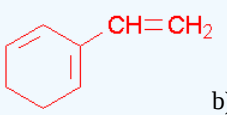
In addition, the common name some small alkene compounds are still accepted by IUPAC. It is important to be able to identify them.

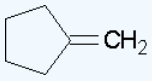


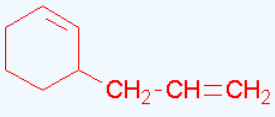
Common Name:	**Ethylene**	**Propylene**	**Isobutylene**	**Isoprene**
IUPAC Name:	**Ethene**	**Propene**	**2-Methylpropene**	**2-Methyl-1,3-butadiene**

Exercise 1.4.4.1

Name the following compounds using common fragment names.

a) 

b) 

C) 

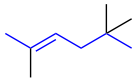
Answer

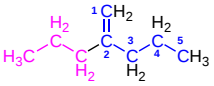
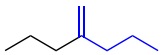
a) 2-Vinyl-cyclohexa-1,3-diene

b) Methylenecylopentane

c) 3-Allylcyclohex-1-ene

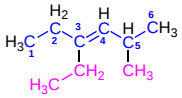
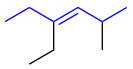
Examples

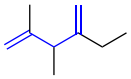
(1)  ≡  ≡ $(CH_3)_2C{=}CHCH_2C(CH_3)_3$
2,5,5-trimethyl-2-hexene

(2)  ≡  ≡ $(CH_3CH_2CH_2)_2C{=}CH_2$
2-propyl-1-pentene

Both these compounds have double bonds, making them alkenes. In example (1) the longest chain consists of six carbons, so the root name of this compound will be hexene. Three methyl substituents (colored red) are present. Numbering the six-carbon chain begins at the end nearest the double bond (the left end), so the methyl groups are located on carbons 2 & 5. The IUPAC name is therefore: 2,5,5-trimethyl-2-hexene.

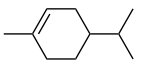
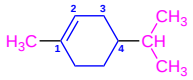
In example (2) the longest chain incorporating both carbon atoms of the double bond has a length of five. There is a seven-carbon chain, but it contains only one of the double bond carbon atoms. Consequently, the root name of this compound will be pentene. There is a propyl substituent on the inside double bond carbon atom (#2), so the IUPAC name is: 2-propyl-1-pentene.

(3)  ≡  ≡ $(CH_3CH_2)_2C{=}CHCH(CH_3)_2$
4-ethyl-2-methyl-3-hexene

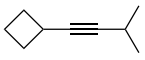
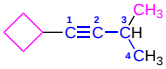
(4)  ≡  ≡ $CH_2{=}C(CH_3)CH(CH_3)C(C_2H_5){=}CH_2$
2-ethyl-3,4-dimethyl-1,4-pentadiene

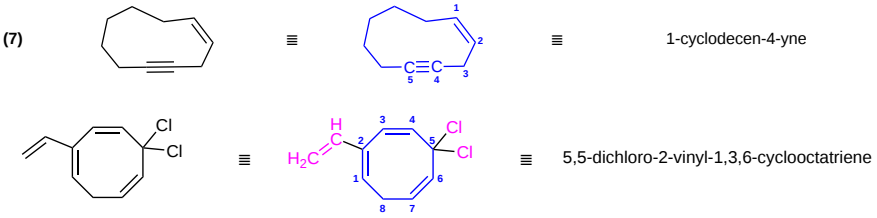
The double bond in example (3) is located in the center of a six-carbon chain. The double bond would therefore have a locator number of 3 regardless of the end chosen to begin numbering. The right hand end is selected because it gives the lowest first-substituent number (2 for the methyl as compared with 3 for the ethyl if numbering were started from the left). The IUPAC name is assigned as shown.

Example (4) is a diene (two double bonds). Both double bonds must be contained in the longest chain, which is therefore five- rather than six-carbons in length. The second and fourth carbons of this 1,4-pentadiene are both substituted, so the numbering begins at the end nearest the alphabetically first-cited substituent (the ethyl group).

(5)  ≡  ≡ 4-isopropyl-1-methylcyclohexene

4-isopropyl-1-methylcyclohex-1-ene

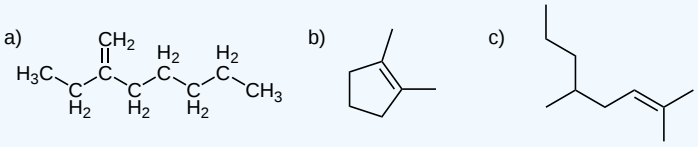
(6)  ≡  ≡ 1-cyclobutyl-3-methyl-1-butyne



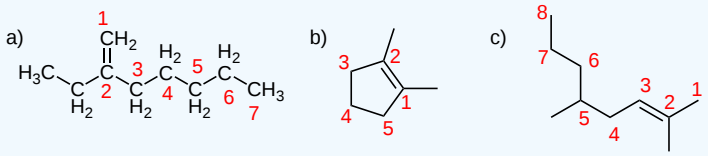
These examples include rings of carbon atoms as well as some carbon-carbon triple bonds. Example (6) is best named as an alkyne bearing a cyclobutyl substituent. Example (7) is simply a ten-membered ring containing both a double and a triple bond. The double bond is cited first in the IUPAC name, so numbering begins with those two carbons in the direction that gives the triple bond carbons the lowest locator numbers. Because of the linear geometry of a triple bond, a-ten membered ring is the smallest ring in which this functional group is easily accommodated. Example (8) is a cyclooctatriene (three double bonds in an eight-membered ring). The numbering must begin with one of the end carbons of the conjugated diene moiety (adjacent double bonds), because in this way the double bond carbon atoms are assigned the smallest possible locator numbers (1, 2, 3, 4, 6 & 7). Of the two ways in which this can be done, we choose the one that gives the vinyl substituent the lower number.

? Exercise 1.4.4.2

Name the following alkenes.



Answer



a) 2-ethylhept-1-ene or 2-ethyl-1-heptene

b) 1,2-dimethylcyclohept-1-ene

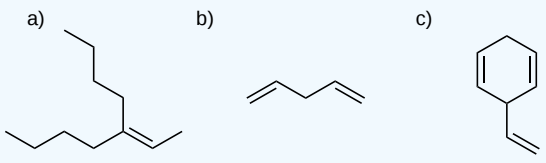
c) 2,5-dimethyloct-2-ene or 2,5-dimethyl-1-octene

? Exercise 1.4.4.3

Draw structures for the following compounds from the given names.

a. 3-butylhept-2-ene (3-butyl-2-heptene)
b. 1,4-pentadiene (penta-1,4-diene)
c. 3-vinyl-1,4-cyclohexadiene (cyclohexa-1,4-diene)

Answer



References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

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1.4.5: Polymerization of Alkenes

One of the most important technical reactions of alkenes is their conversion to higher-molecular-weight compounds or **polymers** (Table 10-4). A polymer is defined as a *long-chain molecule with recurring structural units*. Thus polymerization of propene gives a long-chain hydrocarbon with recurring $-\overset{\overset{CH_3}{|}}{CH}-CH_2-$ units:

$$n \times \underset{\text{propene (propylene)}}{CH_3CH{=}CH_2} \longrightarrow \underset{\text{polypropene (polypropylene)}}{\left[\begin{array}{l}CH_3\\|\\CH-CH_2\end{array}\right]_n} \qquad \Delta H^\circ = -n \times 20 \text{ kcal}$$

Table 10-4: *Alkene Monomers and Their Polymers*

Monomer	Formula	Type of addition polymerization	Polymer or Trade Name	Uses
ethene	$CH_2{=}CH_2$	radical (high pressure), coordination	polyethene	film, containers, piping
chloroethene (vinyl chloride)	$CH_2{=}CHCl$	radical	polyvinyl chloride (PVC)	film, insulation, piping, leatherette
fluoroethene	$CH_2{=}CHF$	radical	Tedlar	coatings
chlorotrifluoroethene	$CF_2{=}CFCl$	radical	Kel-F	gaskets, insulation
tetrafluoroethene	$CF_2{=}CF_2$	radical	Teflon	gaskets, valves, insulation, coatings
propene	$CH_3CH{=}CH_2$	coordination	polypropene, Herculon	fibers, molded articles
2-methylpropene	$(CH_3)_2C{=}CH_2$	cationic	Vistanex, Oppanol, butyl rubber	pressure-sensitive adhesives
styrene	$C_6H_5CH{=}CH_2$	radical	polystyrene	molded articles
propenenitrile (acrylonitrile)	$CH_2{=}CHCN$	radical	Orlon, Acrilan	acrylic fibers
methyl 2-methyl-propenoate (methyl methacrylate)	$CH_2{=}C(CH_3)CO_2CH_3$	radical anionic	Lucite, Plexiglas	coatings, molded articles

Most technically important polymerizations of alkenes occur by chain mechanisms and may be classed as anion, cation, or radical reactions, depending upon the character of the chain-carrying species. In each case, the key steps involve successive additions to molecules of the alkene, the differences being in the number of electrons that are supplied by the attacking agent for formation of the new carbon-carbon bond. For simplicity, these steps will be illustrated by using ethene, even though it does not polymerize very easily by any of them:

$$R{-}CH_2{-}\overset{\ominus}{C}H_2{:} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\overset{\ominus}{C}H_2{:}, \text{ etc.}$$

$$R{-}CH_2{-}\overset{\oplus}{C}H_2 + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}\overset{\oplus}{C}H_2, \text{ etc.}$$

$$R{-}CH_2{-}CH_2{\cdot} + CH_2{=}CH_2 \longrightarrow R{-}CH_2{-}CH_2{-}CH_2{-}CH_2{\cdot}, \text{ etc.}$$

1.4.5.1: Anionic Polymerization

Initiation of alkene polymerization by the anion-chain mechanism may be formulated as involving an attack by a nucleophilic reagent $\mathbf{Y^{\ominus}}$ on one end of the double bond and formation of a carbanion:

$$\overset{\ominus}{Y}{:} + CH_2{=}CH_2 \longrightarrow \underset{\text{carbanion}}{Y{:}CH_2{-}\overset{\ominus}{C}H_2{:}}$$

Attack by the carbanion on another alkene molecule would give a four-carbon carbanion, and subsequent additions to further alkene molecules would lead to a high-molecular-weight anion:

$$Y{:}CH{-}\overset{\ominus}{C}H_2{:} + CH_2{=}CH_2 \longrightarrow Y{:}CH_2{-}CH_2{-}CH_2{-}\overset{\ominus}{C}H_2{:}$$

$$\xrightarrow{n \times CH_2{=}CH_2} Y{:}CH_2{-}CH_2{-}(CH_2{-}CH_2)_n{-}CH_2{-}\overset{\ominus}{C}H_2{:}$$

The growing chain can be terminated by any reaction (such as the addition of a proton) that would destroy the carbanion on the end of the chain:

$$\mathrm{Y{:}CH_2{-}CH_2{-}(CH_2{-}CH_2)_n CH_2{-}\overset{\ominus}{C}H_2{:}} \xrightarrow{H^{\oplus}} \mathrm{Y{:}CH_2{-}CH_2{-}(CH_2{-}CH_2)_n CH_2{-}CH_2{-}H}$$

Anionic polymerization of alkenes is quite difficult to achieve because few anions (or nucleophiles) are able to add readily to alkene double bonds (see Section 10-6). Anionic polymerization occurs readily only with alkenes substituted with sufficiently powerful electron-attracting groups to expedite nucleophilic attack. By this reasoning, alkynes should polymerize more readily than alkenes under anionic conditions, but there appear to be no technically important alkyne polymerizations in operation by this or any other mechanism. Perhaps this is because the resultant polymer would be highly conjugated, and therefore highly reactive, and may not survive the experimental conditions:

$$n \times \underset{\text{ethyne}}{\mathrm{HC{\equiv}CH}} \longrightarrow \underset{\text{polyethyne (expected to be unstable)}}{\mathrm{YHC{=}CH{-}(CH{=}CH)_n CH{=}CH_2}}$$

1.4.5.2: Cationic Polymerization

Polymerization of an alkene by acidic reagents can be formulated by a mechanism similar to the addition of hydrogen halides to alkene linkages. First, a proton from a suitable acid adds to an alkene to yield a carbocation. Then, in the absence of any other reasonably strong nucleophilic reagent, another alkene molecule donates an electron pair and forms a longer-chain cation. Continuation of this process can lead to a high-molecular-weight cation. Termination can occur by loss of a proton. The following equations represent the overall reaction sequence:

$$\mathrm{H^{\oplus} + CH_2{=}CH_2 \rightleftharpoons CH_3{-}\overset{\oplus}{C}H_2 \xrightarrow{CH_2=CH_2} CH_3{-}CH_2{-}CH_2{-}\overset{\oplus}{C}H_2}$$

$$\xrightarrow{n \times CH_2=CH_2} \mathrm{CH_3{-}CH_2{-}(CH_2{-}CH_2)_n CH_2{-}\overset{\oplus}{C}H_2}$$

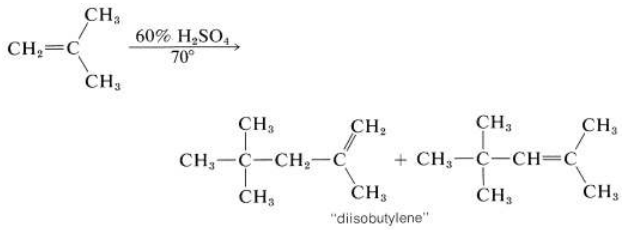
$$\xrightarrow{-H^{\oplus}} \mathrm{CH_3{-}CH_2{-}(CH_2{-}CH_2)_n CH{=}CH_2}$$

Ethene does not polymerize by the cationic mechanism because it does not have sufficiently electron-donating groups to permit easy formation of the intermediate growing-chain cation. 2-Methylpropene has electron-donating alkyl groups and polymerizes much more easily than ethene by this type of mechanism. The usual catalysts for cationic polymerization of 2-methylpropene are sulfuric acid, hydrogen fluoride, or a complex of boron trifluoride and water. Under nearly anhydrous conditions a very long chain polymer called polyisobutylene is formed.

$$n \times \underset{\substack{\text{2-methylpropene}\\ \text{(isobutylene)}}}{\mathrm{CH_2{=}C(CH_3)_2}} \xrightarrow{BF_3 \cdot H_2O} \underset{\substack{\text{poly-2-methylpropene}\\ \text{(polyisobutylene)}}}{\mathrm{CH_3{-}C(CH_3)_2{-}(CH_2{-}C(CH_3)_2)_{n-2}{-}CH_2{-}C(CH_3){=}CH_2}}$$

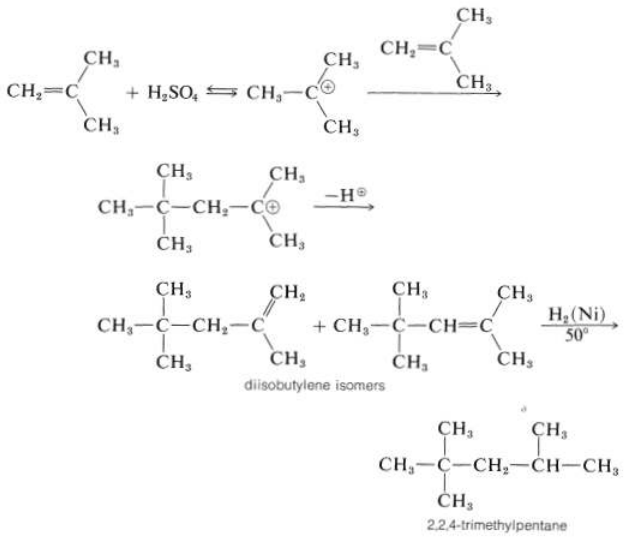
Polyisobutylene fractions of particular molecular weights are very tacky and are used as adhesives for pressure-sealing tapes.

In the presence of **60%** sulfuric acid, 2-methylpropene is *not* converted to a long-chain polymer, but to a mixture of eight-carbon alkenes. The mechanism is like that of the polymerization of 2-methylpropene under nearly anhydrous conditions, except that chain termination occurs after only one 2-methylpropene molecule has been added:



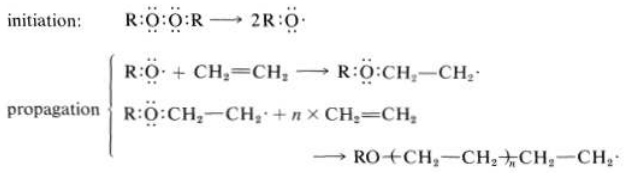
The short chain length is due to the *high water concentration*; the intermediate carbocation loses a proton to water *before* it can react with another alkene molecule.

The proton can be lost in two different ways, and a mixture of alkene isomers is obtained. The alkene mixture is known as "diisobutylene" and has a number of commercial uses. Hydrogenation yields 2,2,4-trimethylpentane (often erroneously called "isooctane"), which is used as the standard "100 antiknock rating" fuel for internal-combustion gasoline engines:

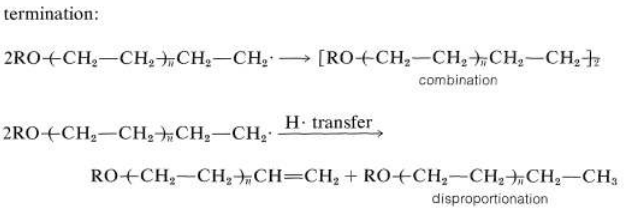


1.4.5.3: Radical Polymerization

Ethene can be polymerized with peroxide catalysts under high pressure (1000 atm or more, literally in a cannon barrel) at temperatures in excess of 100°. The initiation step involves formation of radicals, and chain propagation entails stepwise addition of radicals to ethene molecules.



Chain termination can occur by any reaction resulting in combination or disproportionation of free radicals.



The polyethene produced in this way has from 100 to 1000 ethene units in the hydrocarbon chain. The polymer possesses a number of desirable properties as a plastic and is used widely for electrical insulation, packaging films, piping, and a variety of molded

articles. Propene and 2-methylpropene do not polymerize satisfactorily by radical mechanisms.

1.4.5.4: Coordination Polymerization

A relatively low-pressure, low-temperature ethene polymerization has been achieved with an aluminum-molybdenum oxide catalyst, which requires occasional activation with hydrogen (Phillips Petroleum process). Ethene also polymerizes quite rapidly at atmospheric pressure and room temperature in an alkane solvent containing a suspension of the insoluble reaction product from triethylaluminum and titanium tetrachloride (Ziegler process). Both the Phillips and Ziegler processes produce very high-molecular-weight polyethene with exceptional physical properties. The unusual characteristics of these reactions indicate that no simple anion, cation, or radical mechanism can be involved. It is believed that the catalysts act by coordinating with the alkene molecules in somewhat the same way that hydrogenation catalysts combine with alkenes (Section 11-2A).

Polymerization of propene by the Ziegler process gives a very useful plastic material. It can be made into durable fibers or molded into a variety of shapes. Copolymers (polymers with more than one kind of monomer unit in the polymer chains) of ethene and propene made by the Ziegler process have highly desirable rubberlike properties and are potentially the cheapest useful elastomers (elastic polymers). A Nobel Prize was shared in 1963 by K. Ziegler and G. Natta for their work on alkene polymerization.

The properties and uses of polymers are discussed in greater detail in Chapters 13 and 29. The most important alkene monomers used in addition polymerizations are listed in Table 10-4 along with some names and uses of the corresponding polymers.

1.4.5.5: References

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1.5: Alkynes and Benzene

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1.5.1: Naming Alkynes

Objectives

After completing this section, you should be able to

- provide the correct IUPAC name of an alkyne, given its Kekulé, condensed or shorthand structure.
- provide the correct IUPAC name of a compound containing both double and triple bonds, given its Kekulé, condensed or shorthand structure.
- draw the structure of a compound containing one or more triple bonds, and possibly one or more double bonds, given its IUPAC name.
- name and draw the structure of simple alkynyl groups, and where appropriate, use these names as part of the IUPAC system of nomenclature.

Study Notes

Simple alkynes are named by the same rules that are used for alkenes (see Section 7.3), except that the ending is *-yne* instead of *-ene*. Alkynes cannot exhibit *E*,*Z* (cis-trans) isomerism; hence, in this sense, their nomenclature is simpler than that of alkenes.

Alkynes are organic molecules made of the functional group carbon-carbon triple bonds and are written in the empirical formula of $\mathbf{C_nH_{2n-2}}$. They are unsaturated hydrocarbons. Like alkenes have the suffix –ene, alkynes use the ending –yne; this suffix is used when there is only one alkyne in the molecule.

$$HC{\equiv}CH$$

Introduction

Here are the molecular formulas and names of the first ten carbon straight chain alkynes.

Name	Molecular Formula
Ethyne	C_2H_2
Propyne	C_3H_4
1-Butyne	C_4H_6
1-Pentyne	C_5H_8
1-Hexyne	C_6H_{10}
1-Heptyne	C_7H_{12}
1-Octyne	C_8H_{14}
1-Nonyne	C_9H_{16}
1-Decyne	$C_{10}H_{18}$

The more commonly used name for ethyne is acetylene, which used industrially.

Naming Alkynes

Like previously mentioned, the IUPAC rules are used for the naming of alkynes.

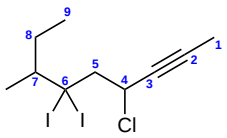
Rule 1

Find the longest carbon chain that includes both carbons of the triple bond.

Rule 2

Number the longest chain starting at the end closest to the triple bond. A 1-alkyne is referred to as a terminal alkyne and alkynes at any other position are called internal alkynes.

For example:

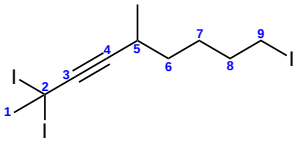


4-chloro-6,6-diiodo-7-methylnon-2-yne

Rule 3

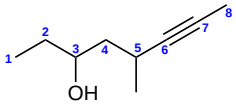
After numbering the longest chain with the lowest number assigned to the alkyne, label each of the substituents at its corresponding carbon. While writing out the name of the molecule, arrange the substituents in alphabetical order. If there are more than one of the same substituent use the prefixes di, tri, and tetra for two, three, and four substituents respectively. These prefixes are not taken into account in the alphabetical order.

For example:



2,2,9-triiodo-5-methylnon-3-yne

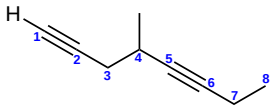
If there is an alcohol present in the molecule, number the longest chain starting at the end closest to it, and follow the same rules. However, the suffix would be –ynol, because the alcohol group takes priority over the triple bond.



5-methyl-6-octyn-3-ol

When there are two triple bonds in the molecule, find the longest carbon chain including both the triple bonds. Number the longest chain starting at the end closest to the triple bond that appears first. The suffix that would be used to name this molecule would be –diyne.

For example:

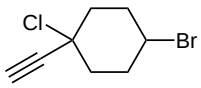


4-methyl-1,5-octadiyne

Rule 4

Substituents containing a triple bond are called alkynyl.

For example:



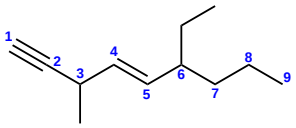
4-bromo-1-chloro-1-ethynylcyclohexane

Here is a table with a few of the alkynyl substituents:

Name	Molecule
Ethynyl	-C≡CH
2- Propynyl	$-CH_2C{\equiv}CH$
2-Butynyl	$-CH_3C{\equiv}CH_2CH_3$

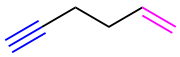
Rule 5

A molecule that contains both double and triple bonds is called an alkenyne. The chain can be numbered starting with the end closest to the functional group that appears first. For example:



(*E*)-6-ethyl-3-methyl-non-4-en-1-yne

If both functional groups are the exact same distance from the ending of the parent chain, the alkene takes precedence in the numbering.

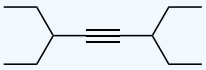


hex-1-en-5-yne

? Exercise 1.5.1.1

Name the following compounds:

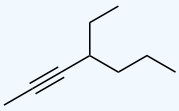
a)



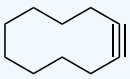
b)



c)



d)



Answer

a. 3,6-diethyl-4-octyne
b. 3-methylbutyne
c. 4-ethyl-2-heptyne
d. cyclodecyne

? Exercise 1.5.1.2

How many isomers are possible for C_5H_8? Draw them.

Answer

2 possible isomers

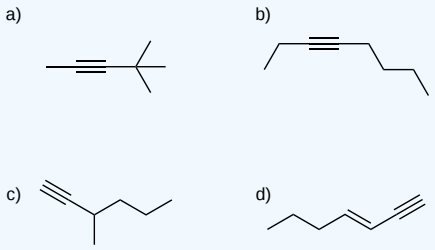


Exercise 1.5.1.3

Draw the following compounds:

a. 4,4-dimethyl-2-pentyne
b. 3-octyne
c. 3-methyl-1-hexyne
d. *trans* 3-hepten-1-yne

Answer



Exercise 1.5.1.4

Do alkynes show cis-trans isomerism? Explain.

Answer

No. A triply bonded carbon atom can form only one other bond and has linear electron geometry so there are no "sides". Allkenes have two groups attached to each inyl carbon with a trigonal planar electron geometry that creates the possibility of cis-trans isomerism.

Reference

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

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1.5.2: Introduction

Objectives

After completing this section, you should be able to

1. explain what is meant by the term “aromatic compound.”
2. identify the aromatic portions present in naturally occurring compounds, given the necessary structures.

Key Terms

Make certain that you can define, and use in context, the key term below.

- aromatic

Study Notes

At this point in the course, we shall use the term *aromatic* to describe those compounds which contain a benzene ring. A broader definition of aromaticity will be given in Section 15.3.

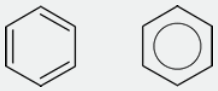


Figure 15.0.1: Two common ways of representing a benzene ring

The 100 Year Mystery of Benzene

It took humans over 100 years to determine and confirm the structure of benzene. Why did it take so long? Why was there such a curiosity? The 1:1 ratio of carbon to hydrogen in the empirical formula and low chemical reactivity of benzene were a paradox to chemists in the early 1800's.In 1825, Michael Faraday isolated an oily residue of gas lamps. Faraday called this liquid "bicarburet of hydrogen" and measured the boiling point to be 80°C. Additionally, Faraday determined the empirical formula to be CH. About nine years later, Eilhard Mitscherlich synthesized the same compound from benzoic acid and lime (CaO).

During the mid to late 1800's, several possible structures (shown below) were proposed for benzene.



It was not until the 1930's that Kekule's structure was confirmed by X-ray and electron diffraction. During the end of Kekule's career he revealed that the structure came to him in a vision after enjoying a glass or two of wine by the fire in his favorite chair. His inspiration for the structure of benzene was derived from an ouroboros in the flames.



Benzene, C_6H_6, is the simplest member of a large family of hydrocarbons, called aromatic hydrocarbons. These compounds contain ring structures and exhibit bonding that must be described using the resonance hybrid concept of valence bond theory or the delocalization concept of molecular orbital theory. (To review these concepts, refer to the earlier chapters on chemical bonding). The resonance structures for benzene, C_6H_6, are:

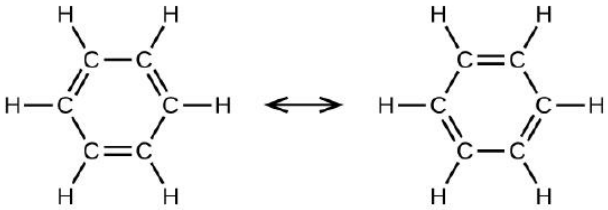


Figure 1.5.2.1.

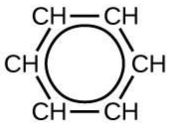
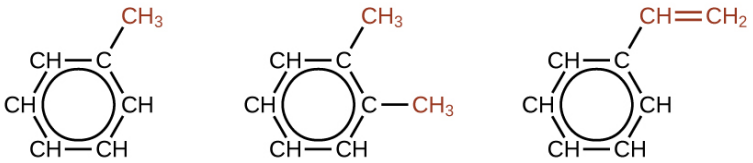


Figure 1.5.2.1: This condensed formula shows the unique bonding structure of benzene.

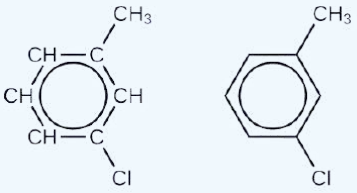
There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. The following are typical examples of substituted benzene derivatives:



Toluene and xylene are important solvents and raw materials in the chemical industry. Styrene is used to produce the polymer polystyrene.

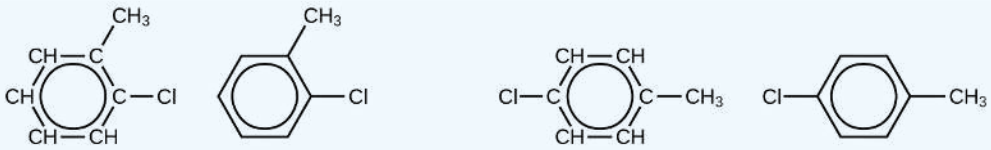
Structure of Aromatic Hydrocarbons

One possible isomer created by a substitution reaction that replaces a hydrogen atom attached to the aromatic ring of toluene with a chlorine atom is shown here. Draw two other possible isomers in which the chlorine atom replaces a different hydrogen atom attached to the aromatic ring:



Solution

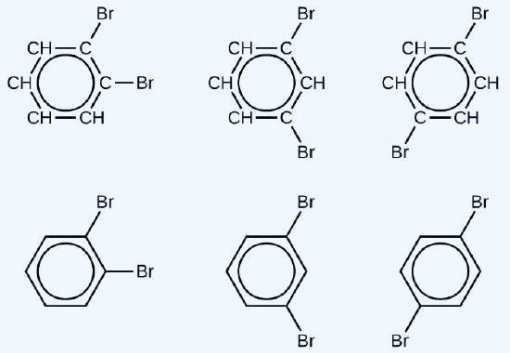
Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:



? Exercise 1.5.2.1

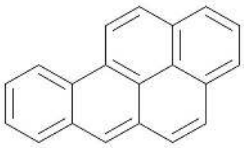
Draw three isomers of a six-membered aromatic ring compound substituted with two bromines.

Answer



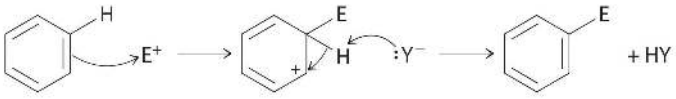
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive substituents can result in a net dipole moment that increases intermolecular attractive forces and raises the melting and boiling points. For example, 1,4-dichlorobenzene, a compound used as an alternative to naphthalene in the production of mothballs, has a melting point of 52.7°C, which is considerably greater than the melting point of benzene (5.5°C).

Certain aromatic hydrocarbons, such as benzene and benz[a]pyrene, are potent liver toxins and carcinogens. In 1775, a British physician, Percival Pott, described the high incidence of cancer of the scrotum among small boys used as chimney sweeps and attributed it to their exposure to soot. His conclusions were correct: benz[a]pyrene, a component of chimney soot, charcoal-grilled meats, and cigarette smoke, was the first chemical carcinogen to be identified.



Benz[a]pyrene

Although arenes are usually drawn with three C=C bonds, benzene is about 150 kJ/mol more stable than would be expected if it contained three double bonds. This increased stability is due to the delocalization of the π electron density over all the atoms of the ring. Compared with alkenes, arenes are poor nucleophiles. Consequently, they do not undergo addition reactions like alkenes; instead, they undergo a variety of electrophilic aromatic substitution reactions that involve the replacement of –H on the arene by a group –E, such as $–NO_2$, $–SO_3H$, a halogen, or an alkyl group, in a two-step process. The first step involves addition of the electrophile (E) to the π system of benzene, forming a carbocation. In the second step, a proton is lost from the adjacent carbon on the ring:



The carbocation formed in the first step is stabilized by resonance.

> *Arenes undergo substitution reactions rather than elimination because of increased stability arising from delocalization of their π electron density.*

Many substituted arenes have potent biological activity. Some examples include common drugs and antibiotics such as aspirin and ibuprofen, illicit drugs such as amphetamines and peyote, the amino acid phenylalanine, and hormones such as adrenaline.

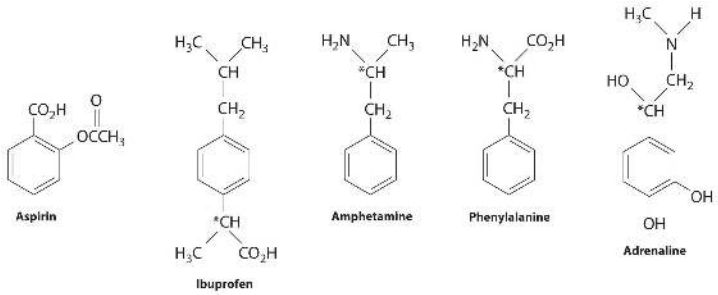


Figure 1.5.2.2: Biologically Active Substituted Arenes

Aspirin (antifever activity), ibuprofen (antifever and anti-inflammatory activity), and amphetamine (stimulant) have pharmacological effects. Phenylalanine is an amino acid. Adrenaline is a hormone that elicits the “fight or flight” response to stress. Chiral centers are indicated with an asterisk.

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1.5.3: Naming Aromatic Compounds

Objectives

After completing this section, you should be able to

1. draw the structure of each of the common aromatic compounds in Figure 16 (Common benzene derived compounds with various substituents), given their IUPAC-accepted trivial names.
2. write the IUPAC-accepted trivial name for each of the compounds in Figure 16, given the appropriate Kekulé, condensed or shorthand structure.
3. identify the ortho, meta and para positions in a monosubstituted benzene ring.
4. use the ortho/meta/para system to name simple disubstituted aromatic compounds.
5. draw the structure of a simple disubstituted aromatic compound, given its name according to the ortho/meta/para system.
6. provide the IUPAC name of a given aromatic compound containing any number of the following substituents: alkyl, alkenyl or alkynyl groups; halogens; nitro groups; carboxyl groups; amino groups; hydroxyl groups.
7. draw the structure of an aromatic compound containing any number of the substituents listed in Objective 6, above, given the IUPAC name.
8. provide the IUPAC name of a given aromatic compound in which the phenyl group is regarded as a substituent.
9. draw the Kekulé, condensed or shorthand structure of an aromatic compound in which the phenyl group is regarded as a substituent, given its IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- arene
- benzyl group
- phenyl group

Study Notes

You should already know the names and structures of several of the hydrocarbons shown in Figure 15.1. A compound containing a benzene ring which has one or more alkyl substituents is called an arene.

A phenyl group consists of a benzene ring with one of its hydrogens removed.



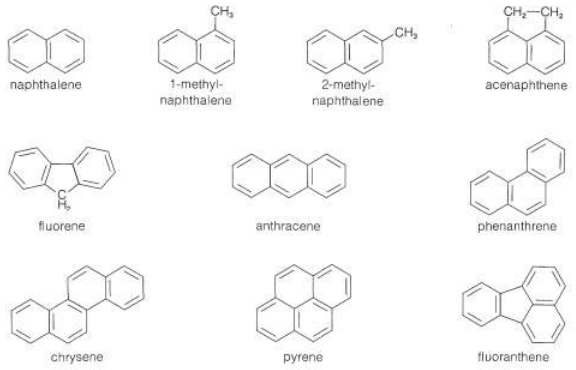
Figure **1.5.3.1**: Two ways of representing a phenyl group

You should memorize the structures and formulas shown in Figure 16. You will meet these compounds frequently throughout the remainder of this course.

Note that the ortho/meta/para system cannot be used when more than two substituents are present in the benzene ring. The “numbering system” can be used instead of the ortho/meta/para system in most cases when only two substituents are present.

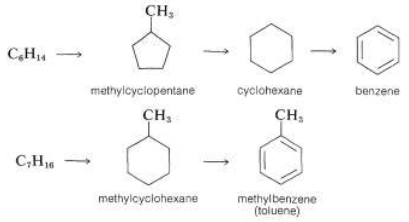
Sources of Aromatic Compounds

Initially aromatic compounds were isolated from coal tar. Coal tar, which is a distillate obtained when heating coal at 1000 ^{o}C in the absence of air, is a source of an amazing number of aromatic compounds. Many simple aromatic compounds, some of which includes nitrogen, oxygen, and sulfur, as well as hydrocarbons are obtained.



Some of the Aromatic Compounds Obtained from Coal Tar

Prior to World War II, coal tar was the only important source of aromatic hydrocarbons, but during the war the demand for benzene and toluene, a precursor to the explosive TNT, rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the toluene produced in the United States are derived from petroleum. Although petroleum does contain some aromatic compound, it primarily made up of alkanes of various chain lengths. Aromatic compounds are synthesized from petroleum the by a process referred to in the petroleum industry as catalytic re-forming or hydroforming. This involves heating a C6-C10 alkane fraction of petroleum with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C6-C7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, and methylbenzene (toluene) are produced primarily in this way.



Nomenclature of Mono-Substituted Benzenes

Unlike aliphatic organics, nomenclature of benzene-derived compounds can be confusing because a single aromatic compound can have multiple possible names (such as common and systematic names) be associated with its structure. Common names are often used in the nomenclature of aromatic compounds. IUPAC still allows for some of the more widely used common name to be used. A partial list of these common name is shown in Figure **1.5.3.2** and there are numerous others. These common names take the place of the benzene base name. Methylbenzene is commonly known with the base name toluene, hydroxyphenol is known as phenol etc. It is very important to be able to identify these structures as they will be utilized in the nomenclature of more complex compounds.

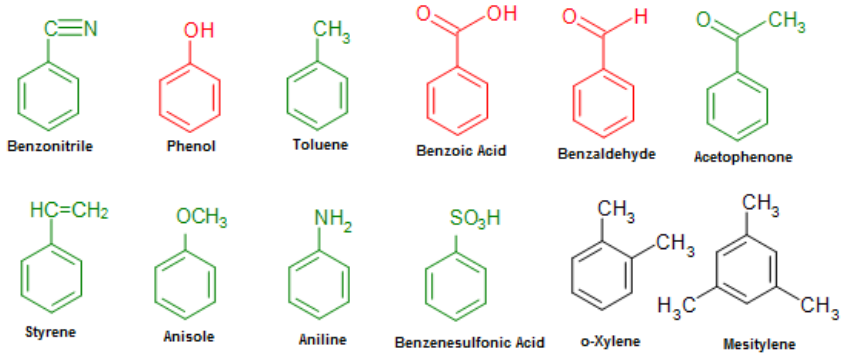
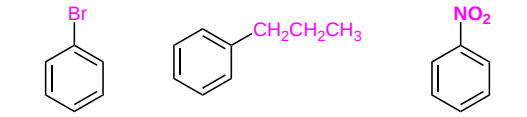


Figure **1.5.3.2**: Common Names for Mono-Substituted Benzenes

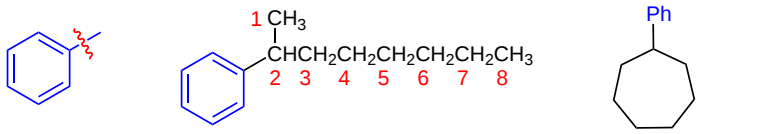
Mono-substituted benzene rings, with a substituent not on the list above, are named with benzene being the parent name. These compounds are named as such: *Name of the substituent + Benzene.*



Bromobenzene **Propyl**benzene **Nitro**benzene

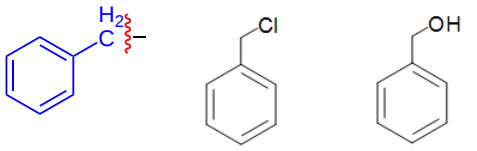
The use of Phenyl and Benzyl in Nomenclature

If the alkyl group attached to the benzene contains seven or more carbons the compounds is named as a phenyl substituted alkane. The name phenyl (C_6H_5-)is often abbreviated (Ph) and comes from the Greek word **pheno** which means "I bear light". This name commemorates the fact that benzene was first isolated by Michael Faraday in 1825 from the residue left in London street lamps which burned coal gas. If the alkyl substituent is smaller than the benzene ring (six or fewer carbons), the compound is named as an alkyl-substituted benzene following the rules listed above.



Phenyl group **2-Phenyl**octane **Phenyl**cycloheptane

The benzyl group (abbv. Bn), similar to the phenyl group and can be written as $C_6H_5CH_2$-R, $PhCH_2$-R, or Bn-R. Nomenclature of benzyl group based compounds are very similar to the phenyl group compounds. For example, a chlorine attached to a benzyl group would simply be called benzyl chloride, whereas an OH group attached to a benzyl group would simply be called benzyl alcohol.

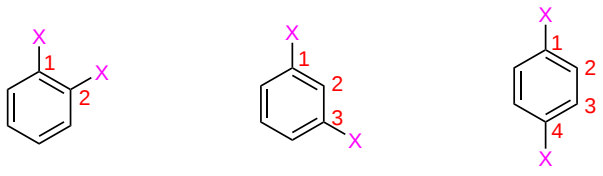


Benzyl group **Benzyl Chloride** **Benzyl Alcohol**

Nomenclature of Disubstituted Benzenes

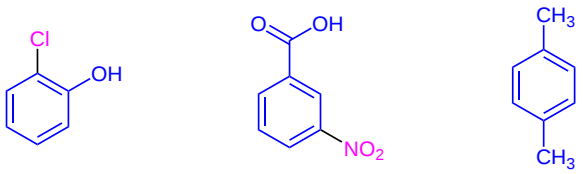
With disubstituted benzenes there are three distinct positional isomers which can occur and must be identified in the compounds name. Although numbering can be used to indicate the position of the two subsituents it is much more common for the compounds to be named using prefixes. These prefixes are italicized and are often abbreviated with a single letter. They are defined as the following:

- ***ortho*- *(o-):*** 1,2- (next to each other in a benzene ring)
- ***meta*- *(m):*** 1,3- (separated by one carbon in a benzene ring)
- ***para*- *(p):*** 1,4- (across from each other in a benzene ring)



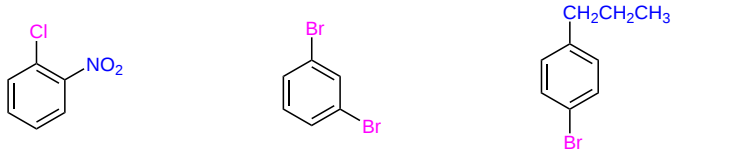
***ortho*-Disubstituted (1,2)** ***meta*-Disubstituted (1,3)** **para-Disubstituted (1,4)**

Figure **1.5.3.2**. If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*



ortho-Chlorophenol **meta-Nitrobenzoic acid** **para-Xylene**

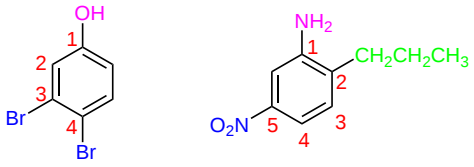
Figure **1.5.3.2** the compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



ortho-Chloronitrobenzene **meta-Dibromobenzene** **para-Bromopropylbenzene**

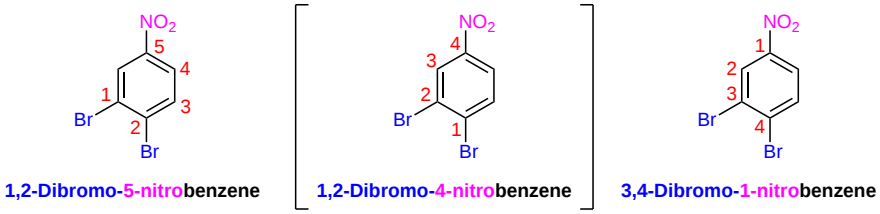
Nomenclature of Benzenes with Three or more Substituents

When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure 1.5.3.2.** If a substituent from **Figure 1.5.3.2** is present it is given the parent name in the nomenclature. Also, this substituent is given position one in the numbering system. The other substituents are numbered such that they get the lowest possible sum. In the compound's name the subsituents are given their position number and listed alphabetically. Remember that di-, tri, tetra- prefixes are still used to indicate multiple of the same substituent being present but are ignored for alphabetical listing.



3,4-Dibromophenol **5-Nitro-2-propylaniline**

Figure **1.5.3.2**, the benzene ring is name in the same fashion as cycloalkanes. The lowest possible number is given to the substituents present. This is best done by arbitrarily giving a substituent position one and then numbering the rest of the substituents. Then this process is repeated with the other substituents. Which ever iteration provides the lowest overall sum of numbers will be used in the compound's name. The substituents are assigned a location number, listed alphabetically and the suffix *-benzene* is added.



1,2-Dibromo-5-nitrobenzene **1,2-Dibromo-4-nitrobenzene** **3,4-Dibromo-1-nitrobenzene**

This numbering provides the lowest numbers to the substituents

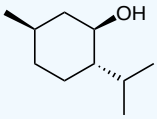
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Exercises

Exercise 1.5.3.1



(True/False) The compound above contains a benzene ring and thus is aromatic.

Answer

False, this compound does not contain a benzene ring in its structure.

Exercise 1.5.3.2

Benzene unusual stability is caused by how many conjugated pi bonds in its cyclic ring? ____

Answer

3

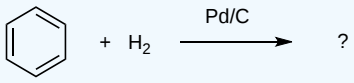
Exercise 1.5.3.3

Menthol, a topical analgesic used in many ointments for the relief of pain, releases a peppermint aroma upon exposure to the air. Based on this conclusion, can you imply that a benzene ring is present in its chemical structure? Why or why not?

Answer

No, a substance that is fragrant does not imply a benzene ring is in its structure. See camphor example (figure 1)

Exercise 1.5.3.4



Answer

No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

Exercise 1.5.3.5

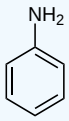
At normal conditions, benzene has ___ resonance structures.

Answer

2

Exercise 1.5.3.6

Which of the following name(s) is/are correct for the following compound?



a. nitrohydride benzene
b. phenylamine
c. phenylamide
d. aniline
e. nitrogenhydrogen benzene
f. All of the above is correct

Answer

b, d

Exercise 1.5.3.7

Convert 1,4-dimethylbenzene into its common name.

Answer

p-Xylene

Exercise 1.5.3.8

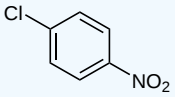
TNT's common name is: _____

Answer

2,4,6-trinitrotoluene

Exercise 1.5.3.9

Name the following compound using OMP nomenclature:



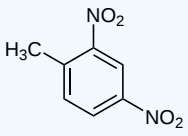
Answer

p-chloronitrobenzene

Exercise 1.5.3.10

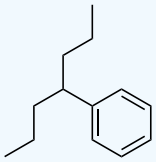
Draw the structure of 2,4-dinitrotoluene.

Answer



Exercise 1.5.3.11

Name the following compound:

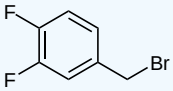


Answer

4-phenylheptane

Example 1.5.3.12

Which of the following is the correct name for the following compound?



a. 3,4-difluorobenzyl bromide
b. 1,2-difluorobenzyl bromide
c. 4,5-difluorobenzyl bromide
d. 1,2-difluoroethyl bromide
e. 5,6-difluoroethyl bromide
f. 4,5-difluoroethyl bromide

Solution

a

Exercise 1.5.3.13

(True/False) Benzyl chloride can be abbreviated Bz-Cl.

Answer

False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

Exercise 1.5.3.14

Benzoic Acid has what R group attached to its phenyl functional group?

Answer

COOH

Exercise 1.5.3.15

(True/False) A single aromatic compound can have multiple names indicating its structure.

Answer

True. TNT, for example, has the common name 2,4,6-trinitrotoluene and its systematic name is 2-methyl-1,3,5-trinitrobenzene.

Exercise 1.5.3.16

List the corresponding positions for the OMP system (o-, m-, p-).

Answer

Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

Exercise 1.5.3.17

A scientist has conducted an experiment on an unknown compound. He was able to determine that the unknown compound contains a cyclic ring in its structure as well as an alcohol (-OH) group attached to the ring. What is the unknown compound?

a. Cyclohexanol
b. Cyclicheptanol
c. Phenol
d. Methanol
e. Bleach
f. Cannot determine from the above information

Answer

The correct answer is f). We cannot determine what structure this is since the question does not tell us what kind of cyclic ring the -OH group is attached on. Just as cyclohexane can be cyclic, benzene and cycloheptane can also be cyclic.

Exercise 1.5.3.18

Which of the following statements is **false** for the compound, phenol?

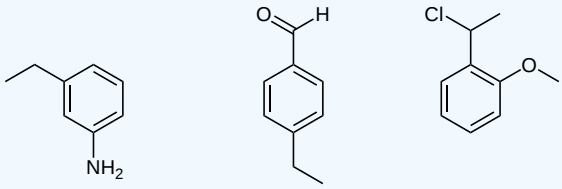
a. Phenol is a benzene derived compound.
b. Phenol can be made by attaching an -OH group to a phenyl group.
c. Phenol is highly toxic to the body even in small doses.
d. Phenol can be used as a catalyst in the hydrogenation of benzene into cyclohexane.
e. Phenol is used as an antiseptic in minute doses.
f. Phenol is amongst one of the three common names retained in the IUPAC nomenclature.

Answer

d

Exercise 1.5.3.19

State wither the following is para, meta, or ortho substituted.



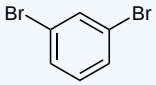
A B C

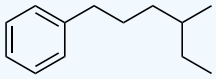
Answer

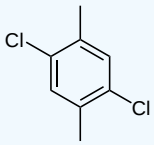
A – meta; B – para; C – ortho

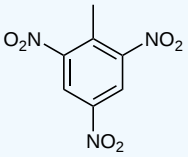
Exercise 1.5.3.20

Name the following compounds.

A) 

B) 

C) 

D) 

Answer

a. 1,3-Dibromobenzene

b. 1-phenyl-4-methylhexane

c. 1,4-Dichloro-2,5-dimethylbenzene

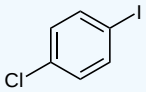
d. 2-methyl-1,3,5-trinitrobenzene. (Also known as trinitrotoluene, or TNT)

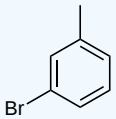
Exercise 1.5.3.21

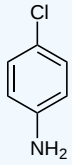
Draw the following structures

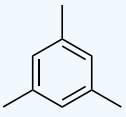
a. p-chloroiodobenzene
b. m-bromotoluene
c. p-chloroaniline
d. 1,3,5-trimethylbenzene

Answer

A) 

C) 

B) 

D) 

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1.5.4: Structure and Stability of Benzene

Objectives

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

Key Terms

Make certain that you can define, and use in context, the key term below.

- degenerate

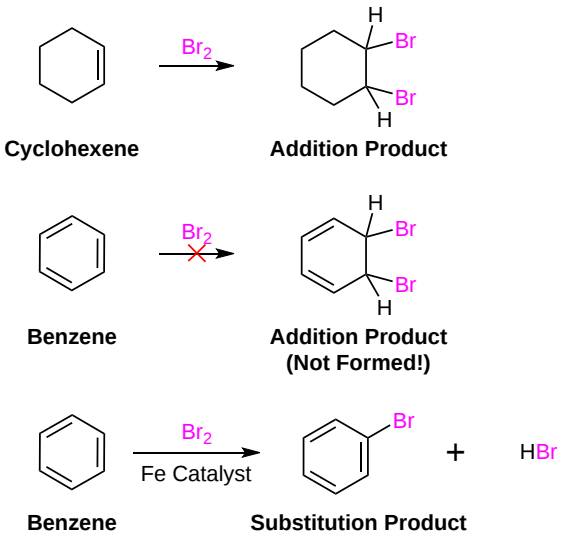
Study Notes

You may wish to review Sections 1.5 and 14.1 before you begin to study this section.

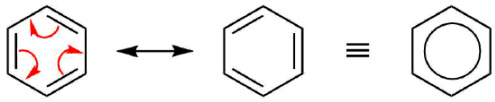
Note that the figure showing the molecular orbitals of benzene has two bonding (π_2 and π_3) and two anti-bonding (π^* and $\pi_5{}^*$) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

Structure of Benzene

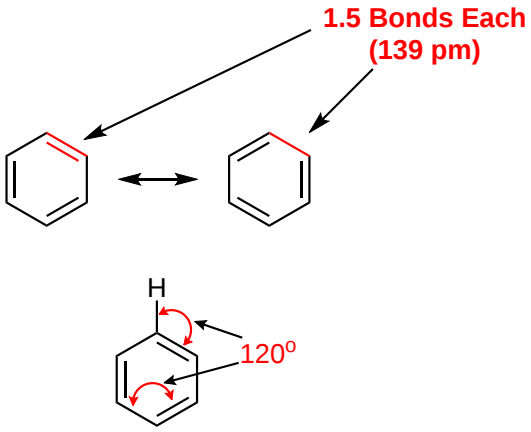
When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable to chemical modification.



The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of this system was attributed to special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.

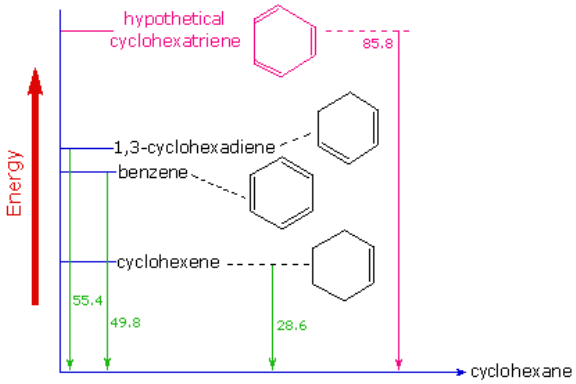


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120° and makes the overall molecule planar.



The High Stability of Benzene

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole.



These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an extraordinary 36 kcal/mole more stable than expected**. This sort of stability enhancement is called **aromaticity** and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

Atomic Orbitals of Benzene

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

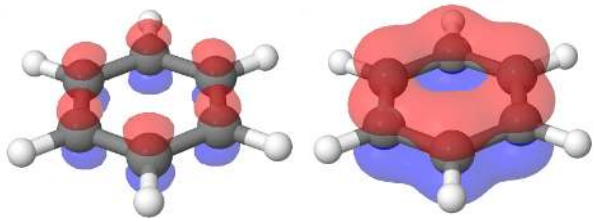


Figure **1.5.4.1**: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

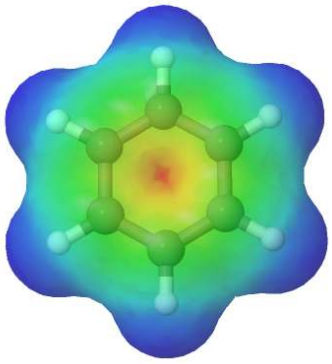
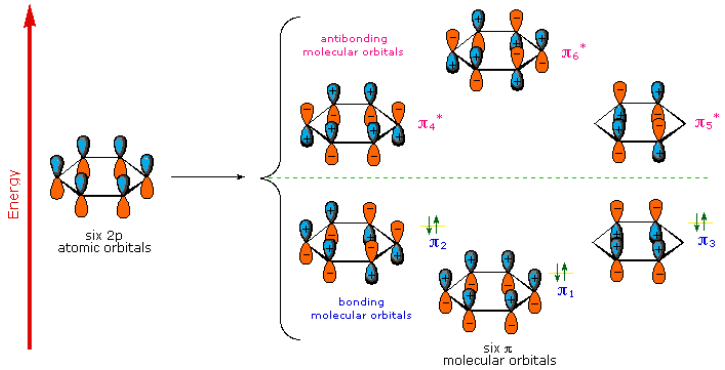


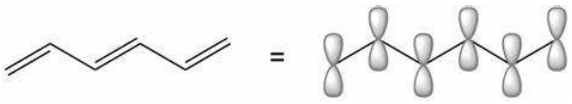
Figure **1.5.4.2**: An electrostatic potential map of benzene

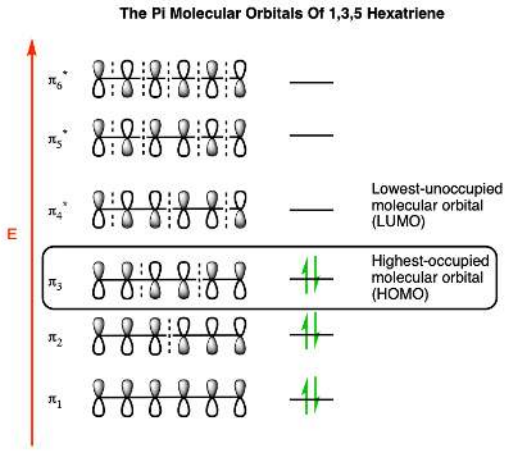
The Molecular Orbitals of Benzene

A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.





The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

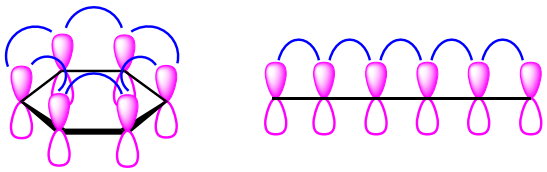
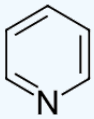


Figure **1.5.4.3**: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

Exercises

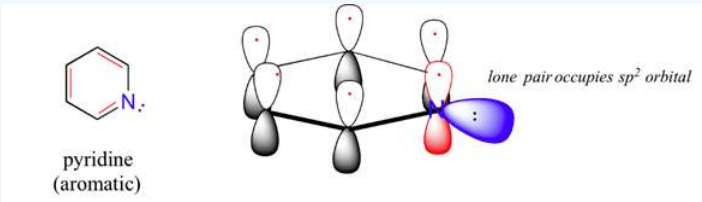
? Exercise 1.5.4.1

The molecule, pyridine, is planar with bond angles of 120°. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



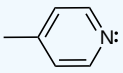
Answer

The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized p orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120° bond angles.

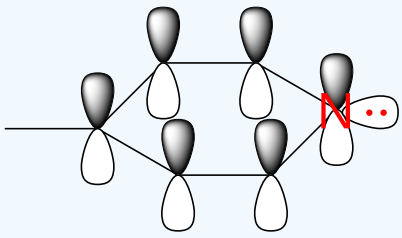


? Exercise 1.5.4.2

The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer



References

https://royalsocietypublishing.org/d...rspa.1964.0092 "A crystallographic study of solid benzene by neutron diffraction" G.E. Bacon, N. A. Curry, and S.A. Wilson, 1964

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- **2.3: Molecular orbital theory- conjugation and aromaticity** by Tim Soderberg is licensed CC BY-NC-SA 4.0. Original source: https://digitalcommons.morris.umn.edu/chem_facpubs/1/.

1.6: Halides

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1.6.1: Introduction to Organohalides

Objectives

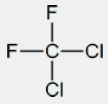
After completing this section, you should be able to

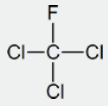
1. list the industrial uses of some important halogenated hydrocarbons including 1,1,1-trichloroethane, tetrafluoroethylene and dichlorodifluoromethane.
2. outline, briefly, how the chemistry of vinyl halides and aryl halides differs from that of the alkyl halides discussed.

Study Notes

There are several different types of halogen-substituted organic compounds, including aryl halides, acyl halides, vinyl halides and alkynyl halides. The primary focus of this chapter is on alkyl halides.

Freons™, also called fluorocarbons or chlorofluorocarbons, have been a source of concern to environmentalists since 1974, when Frank S. Rowland and Mario J. Molina suggested that these substances might be contributing to the destruction of Earth's ozone layer. The stratospheric ozone layer filters out much of the ultraviolet radiation from the sun's rays. It is believed that extensive depletion of this layer, and the consequent increase in the amount of ultraviolet radiation reaching Earth, could result in the destruction of certain crops, in climate modification, and in an increase in the incidence of skin cancer. In recent years, the manufacture and use of freons has declined sharply as the general public has become more aware of the problems that might be caused by these substances.

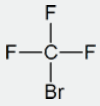


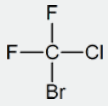


Note: "Freon" is a DuPont trademark.

Related to the freons are the halons—now used in some fire extinguishers, particularly in areas where foams or dry-chemical extinguishers cannot be used (e.g., in and around computers). If you examine such extinguishers, you will find that the halon is identified by a number; for example, halon 1301 or halon 1211. The first number represents the number of carbon atoms present, the second is the number of fluorines, the third is the number of chlorines and the fourth is the number of bromines.

Thus the halons given as examples above have the following structures:





You need not remember the names of the various freons and halons, but you should be prepared to name them by the IUPAC system according to the rules developed in the next section.

Many organic compounds are closely related to the alkanes. Alkanes react with halogens to produce halogenated hydrocarbons, the simplest of which have a single halogen atom substituted for a hydrogen atom of the alkane. Even more closely related are the cycloalkanes, compounds in which the carbon atoms are joined in a ring, or cyclic fashion.

The reactions of alkanes with halogens produce **halogenated hydrocarbons**, compounds in which one or more hydrogen atoms of a hydrocarbon have been replaced by halogen atoms:

CH_3CH_2Cl $CH_3CHBrCH_2Br$ CH_3CHICH_2Cl

The replacement of only one hydrogen atom gives an **alkyl halide (or haloalkane)**. A wide variety of interesting and often useful compounds have one or more halogen atoms per molecule. For example, methane (CH_4) can react with chlorine (Cl_2), replacing one, two, three, or all four hydrogen atoms with Cl atoms. Several halogenated products derived from methane and ethane (CH_3CH_3) are listed in Table 10.1, along with some of their uses.

Table 10.1: Some Halogenated Hydrocarbons

Formula	Common Name	IUPAC Name	Some Important Uses
Derived from CH_4			
CH_3Cl	methyl chloride	chloromethane	refrigerant; the manufacture of silicones, methyl cellulose, and synthetic rubber
CH_2Cl_2	methylene chloride	dichloromethane	laboratory and industrial solvent
$CHCl_3$	chloroform	trichloromethane	industrial solvent
CCl_4	carbon tetrachloride	tetrachloromethane	dry-cleaning solvent and fire extinguishers (but no longer recommended for use)
$CBrF_3$	halon-1301	bromotrifluoromethane	fire extinguisher systems
CCl_3F	chlorofluorocarbon-11 (CFC-11)	trichlorofluoromethane	foaming plastics
CCl_2F_2	chlorofluorocarbon-12 (CFC-12)	dichlorodifluoromethane	refrigerant
Derived from CH_3CH_3			
CH_3CH_2Cl	ethyl chloride	chloroethane	local anesthetic
$ClCH_2CH_2Cl$	ethylene dichloride	1,2-dichloroethane	solvent for rubber
CCl_3CH_3	methylchloroform	1,1,1-trichloroethane	solvent for cleaning computer chips and molds for shaping plastics

To Your Health: Halogenated Hydrocarbons

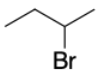
Once widely used in consumer products, many chlorinated hydrocarbons are suspected carcinogens (cancer-causing substances) and also are known to cause severe liver damage. An example is carbon tetrachloride (CCl_4), once used as a dry-cleaning solvent and in fire extinguishers but no longer recommended for either use. Even in small amounts, its vapor can cause serious illness if exposure is prolonged. Moreover, it reacts with water at high temperatures to form deadly phosgene ($COCl_2$) gas, which makes the use of CCl_4 in fire extinguishers particularly dangerous.

Ethyl chloride, in contrast, is used as an external local anesthetic. When sprayed on the skin, it evaporates quickly, cooling the area enough to make it insensitive to pain. It can also be used as an emergency general anesthetic.

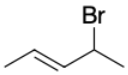
Bromine-containing compounds are widely used in fire extinguishers and as fire retardants on clothing and other materials. Because they too are toxic and have adverse effects on the environment, scientists are engaged in designing safer substitutes for them, as for many other halogenated compounds.

Reactivity of Halides

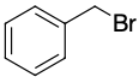
Alkyl halides have an sp^3 carbon atom with a halogen attached, this is also true for allylic halides and benzylic halides. These types of halides are all reactive toward most substitution and elimination reactions. Allyl and benzyl halides tend to form carbocations more easily due to resonance stabilization.



alkyl halide



allyl halide

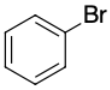


benzyl halide

However, halogens bonded to sp^2 carbon atoms are not typically reactive. Examples of this are vinyl and aryl halides.



vinyl halide



aryl halide

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1.6.2: Names and Properties of Alkyl Halides

Objectives

After completing this section, you should be able to

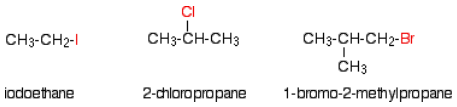
1. write the IUPAC name of a halogenated aliphatic hydrocarbon, given its Kekulé, condensed, or shorthand structure.
2. draw the Kekulé, condensed, or shorthand structure of a halogenated aliphatic hydrocarbon, given its IUPAC name.
3. write the IUPAC name and draw the Kekulé, condensed, or shorthand structure of a simple alkyl halide, given a systematic, non-IUPAC name (e.g., *sec*-butyl iodide).
4. arrange a given series of carbon-halogen bonds in order of increasing or decreasing length and strength.

Study Notes

This section contains little that is new. If you mastered the IUPAC nomenclature of alkanes, you should have little difficulty in naming alkyl halides. Notice that when a group such as CH_2Br must be regarded as a substituent, rather than as part of the main chain, we may use terms such as bromomethyl.

You will find it easier to understand the reactions of the alkyl halides if you keep the polarity of the C-X bond fixed permanently in your mind (see "The Polar C-X Bond" shown in the reading below).

Alkyl halides are also known as haloalkanes. This page explains what they are and discusses their physical properties. Alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). For example:

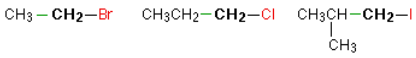


Halide Designations

Alkyl halides fall into different classes depending on how many alkyl groups are attached to the carbon which holds the halogen. There are some chemical differences between the various types. When there are **no** alkyl groups attached to the carbon holding the halogen, these are considered methyl halides (CH_3X).

Primary alkyl halides

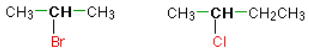
In a primary (1°) haloalkane, the carbon which carries the halogen atom is only attached to one other alkyl group. Some examples of primary alkyl halides include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the halogen. There is an exception to this: CH_3Br and the other methyl halides are often counted as primary alkyl halides even though there are **no** alkyl groups attached to the carbon with the halogen on it.

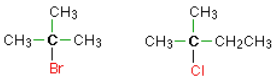
Secondary alkyl halides

In a secondary (2°) haloalkane, the carbon with the halogen attached is joined directly to two other alkyl groups, which may be the same or different. Examples:



Tertiary alkyl halides

In a tertiary (3°) haloalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



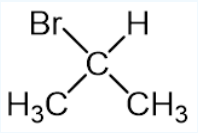
Example 1.6.2.1

Please indicate if the following haloalkanes are methyl, 1°, 2°, or 3°:

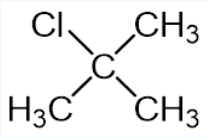
a) CH_3I

b) CH_3CH_2Br

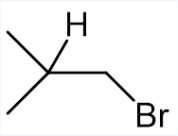
c)



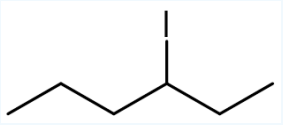
d)



e)



f)



Solution

a) methyl

b) 1°

c) 2°

d) 3°

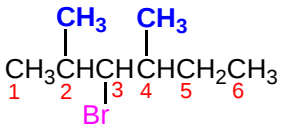
e) 1°

f) 2°

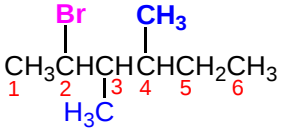
Nomenclature of Alkyl Halides

Alkyl halides are systematically named as alkanes (Section 3-4) where the halogen is a substituent on the parent alkane chain. To summarize the rules discussed in detail in **Section 3-4**, there are three basic steps to naming alkyl halides.

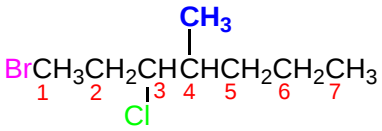
1. Find and name the longest carbon chain and name it as the parent chain. Remember is an alkene or alkyne is present, the parent chain must contain both carbons of the multiple bond.
2. Number the parent chain consecutively, starting at the end nearest a substituent group. Then assign each substituent a number. Remember the IUPAC system uses a prefix to indicate the halogen followed by the suffix -ide. The prefixes are *fluoro-* for fluorine, *chloro-* for chlorine, *bromo-* from bromine, and *iodo-* for iodine. The name of a halogen is preceded by a number indicating the substituent's location on the parent chain.



3-Bromo-2,4-Dimethylhexane

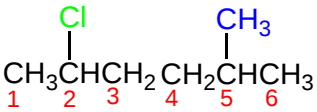


2-Bromo-3,4-Dimethylhexane



1-Bromo-3-Chloro-4-methylheptane

3. If there is an ambiguity in numbering the parent chain, begin on the end which is closer to the substituent which comes first alphabetically.



2-Chloro-5-methylhexane
(Not 5-Chloro-2-methylhexane)

Common Names of Alkyl Halides

Alkyl halides with simple alkyl groups are often called by common names. Those with a larger number of carbon atoms are usually given IUPAC names. The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the first syllable of the name of the halogen, with the ending *-ide*. The names of common alkyl groups are listed in Section 3.3.



IUPAC Name:	Bromomethane	2-Iodopropane	Chlorocyclohexane
Common Name:	Methyl bromide	Isopropy iodide	Cyclohexyl chloride

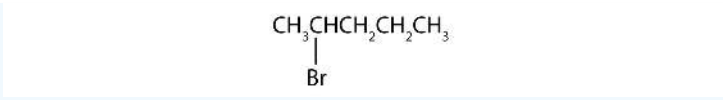
? Exercise 1.6.2.1

1) Give the common and IUPAC names for each compound.

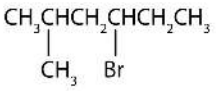
a. $CH_3CH_2CH_2Br$
b. $(CH_3)_2CHCl$
c. CH_3CH_2I
d. $CH_3CH_2CH_2CH_2F$

2) Give the IUPAC name for each compound.

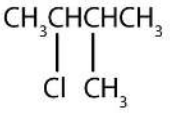
a)



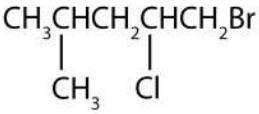
b)



c)



d)



Answer

1) a) The alkyl group ($CH_3CH_2CH_2$–) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.

b) The alkyl group [$(CH_3)_2CH$–] has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro*-) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.

c) The alkyl group (CH_3CH_2–) is a ethyl group, and the halogen is iodine (I). The common name is therefore ethyl iodide. For the IUPAC name, the prefix for iodine (iodo) is combined with the name for a two-carbon chain (ethane), preceded by a number identifying the carbon atom to which the I atom is attached, so the IUPAC name is 1-iodoethane.

d) The alkyl group ($CH_3CH_2CH_2CH_2$–) is a butyl group, and the halogen is fluorine (F). The common name is therefore butyl fluoride. For the IUPAC name, the prefix for fluorine (Fluoro) is combined with the name for a four-carbon chain (butane), preceded by a number identifying the carbon atom to which the F atom is attached, so the IUPAC name is 1-fluorobutane.

2) a) The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.

b) The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

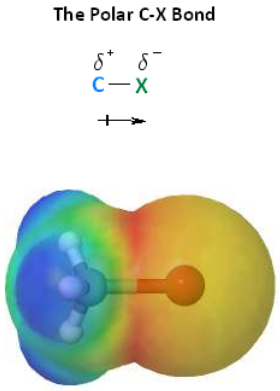
c) 2-Chloro-3-methylbutane

d) 1-Bromo-2-chloro-4-methylpentane.

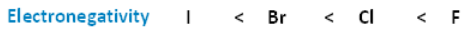
There is a fairly large distinction between the structural and physical properties of haloalkanes and the structural and physical properties of alkanes. As mentioned above, the structural differences are due to the replacement of one or more hydrogens with a halogen atom. The differences in physical properties are a result of factors such as electronegativity, bond length, bond strength, and molecular size.

Halogens and the Character of the Carbon-Halogen Bond

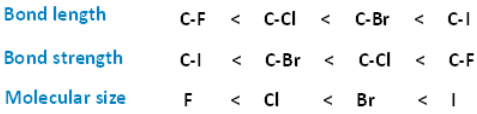
As discussed in Section 6.4, halogens are more electronegative than carbon. This results in a carbon-halogen bond that is polarized with the carbon atom bearing a partial positive charge and the halogen a partial negative charge. This polarity can be distinctly seen when viewing the electrostatic potential map of a methyl halide. Electron density is shown by a red/yellow color which is almost exclusively around the halogen atom. The methyl portion of the compound lacks electron density which is shown by a blue/green color.



The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.



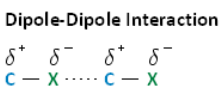
The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases, the bonds get longer, and the strength of those bonds decreases.



Haloalkanes Have Higher Boiling Points than Alkanes

When comparing alkanes and haloalkanes, we will see that haloalkanes have higher boiling points than alkanes containing the same number of carbons. London dispersion forces are the first of two types of forces that contribute to this physical property. You might recall from general chemistry that London dispersion forces increase with molecular surface area. In comparing haloalkanes with alkanes, haloalkanes exhibit an increase in surface area due to the substitution of a halogen for hydrogen. The increase in surface area leads to an increase in London dispersion forces, which then results in a higher boiling point.

Dipole-dipole interaction is the second type of force that contributes to a higher boiling point. As you may recall, this type of interaction is a coulombic attraction between the partial positive and partial negative charges that exist between carbon-halogen bonds on separate haloalkane molecules. Similar to London dispersion forces, dipole-dipole interactions establish a higher boiling point for haloalkanes in comparison to alkanes with the same number of carbons.



The table below illustrates how boiling points are affected by some of these properties. Notice that the boiling point increases when hydrogen is replaced by a halogen, a consequence of the increase in molecular size, as well as an increase in both London dispersion forces and dipole-dipole attractions. The boiling point also increases as a result of increasing the size of the halogen, as well as increasing the size of the carbon chain.

Boiling Points of Haloalkanes (°C)						
R	X =	H	F	Cl	Br	I
CH_3		-161.7	-78.4	-24.2	3.6	42.4
CH_3CH_2		-88.6	-37.7	12.3	38.4	72.3
$CH_3(CH_2)_2$		-42.1	-2.5	46.6	71.0	102.5
$CH_3(CH_2)_3$		-0.5	32.5	78.4	101.6	130.5
$CH_3(CH_2)_4$		36.1	62.8	107.8	129.6	157.0
$CH_3(CH_2)_7$		125.7	142.0	182.0	200.3	225.5

Solubility

Solubility in water

The alkyl halides are at best only slightly soluble in water. For a haloalkane to dissolve in water the attractions between the haloalkane molecules (van der Waals dispersion and dipole-dipole interactions) and hydrogen bonds between water molecules must be broken. Both of these cost energy. Energy is released when new intermolecular forces are generated between the haloalkane molecules and water molecules. These will only be dispersion forces and dipole-dipole interactions. These are not as strong as the original hydrogen bonds in the water, and so not as much energy is released as was used to separate the water molecules. The energetics of the changes are sufficiently "unprofitable" such that very little dissolves.

Solubility in organic solvents

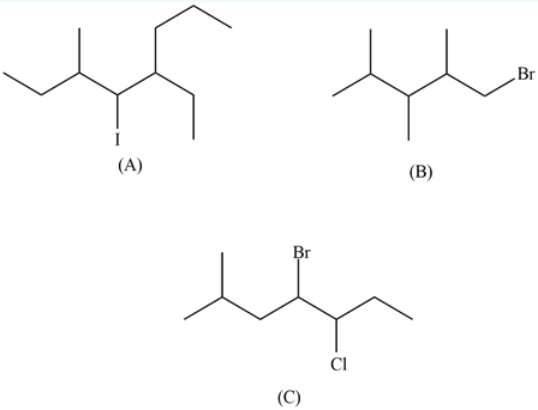
Alkyl halides tend to dissolve in organic solvents because the new intermolecular attractions have roughly the same strength as the ones being broken in the separate haloalkane and solvent.

Chemical Reactivity

The pattern in chemical reactiviy lies in the strength of the bond between the carbon atom and the halogen atom. Previously in this section, it was noted that the trend for bond strength increases from C-I to C-Br to C-Cl with C-F bonds being the strongest. To react with the alkyl halides, the carbon-halogen bond has got to be broken. Because that gets easier as you go from fluoride to chloride to bromide to iodide, the compounds get more reactive in that order. Iodoalkanes are the most reactive and fluoroalkanes are the least. In fact, fluoroalkanes are so unreactive that we will ignore them completely from now on in this section!

? Exercise 1.6.2.2

1) Give the names of the following organohalides:



2) Draw the structures of the following compounds:

a) 2-Chloro-3,3-dimethylpentane

b) 1,1-Dichloro-4-isopropylcyclohexane

c) 3-bromo-3-ethylhexane

Answer

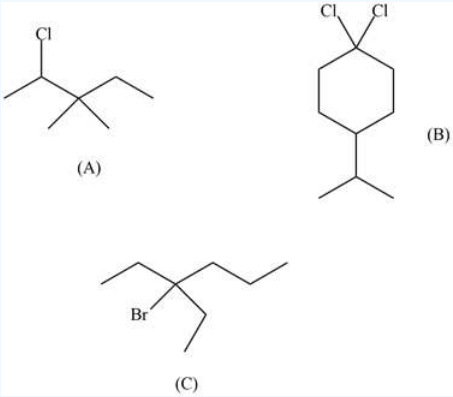
1)

a) 5-ethyl-4-iodo-3-methyloctane

b) 1-bromo-2,3,4-trimethylpentane

c) 4-bromo-5-chloro-2-methylheptane

2)



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1.7: Isomers

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1.7.1: Isomerism Introduction

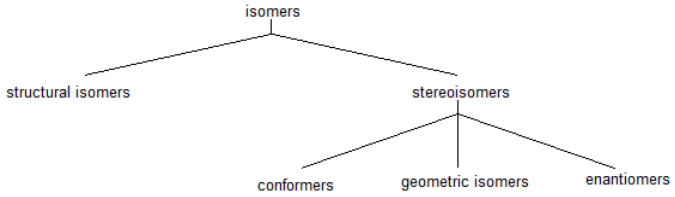
Learning Objective

- recognize the relationships between constitutional (structural) isomers, conformational isomers, and geometric isomers

Isomers

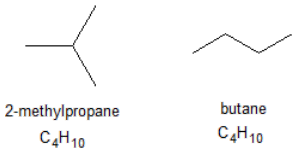
Isomers always have the same chemical formula. When the chemical formulae are different, then the compounds are completely different. Important information can be gained from the chemical formulas when comparing compounds.

Structural (constitutional) isomers have the same molecular formula but a different bonding arrangement among the atoms. Stereoisomers have identical molecular formulas and arrangements of atoms. They differ from each other only in the spatial orientation of groups in the molecule. For organic chemistry, there are several types of stereoisomers: enantiomers, diasteriomers, geometric isomers, and conformers. These stereoisomers will be introduced and explained throughout several chapters.



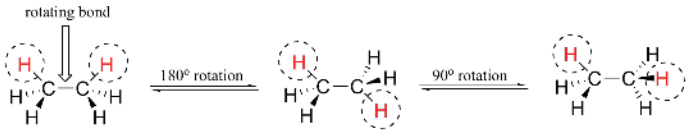
Structural (Constitutional) Isomers

Because carbon forms four bonds, there can be multiple ways to form molecules that follow the octet rule. Even with only four carbon atoms, there are two possible structures for the carbon backbone. The carbon atoms can be bonded to make a four carbon chain (butane) or there can be a one carbon branch from a three carbon chain (2-methylpropane). Butane and 2-methylpropane are structural isomers because they both have the chemical formula C_4H_{10}.



Identical vs Conformer

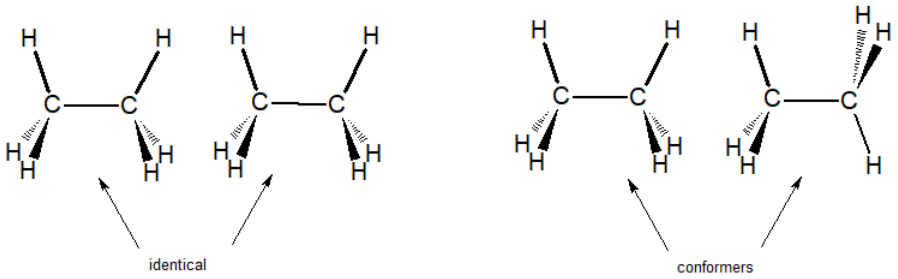
The rotation about single bonds creates dynamic molecules. When drawing and discussing molecules, it is important to be aware that our drawing are static while the molecule themselves are rotating. Although there are seven sigma bonds in the ethane molecule, rotation about the six carbon-hydrogen bonds does not result in any change in the shape of the molecule because the hydrogen atoms are essentially spherical. Rotation about the carbon-carbon bond, however, results in many different possible molecular conformations. Conformers are the simplest example of stereoisomerism.



Identical compounds are the same compound shown with ALL atoms in the same spatial orientation.

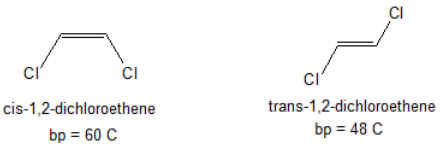
Conformers are the same compound shown with different rotations about single bonds.

In the example below, we can compare two identical structures for ethane with two conformers of ethane.

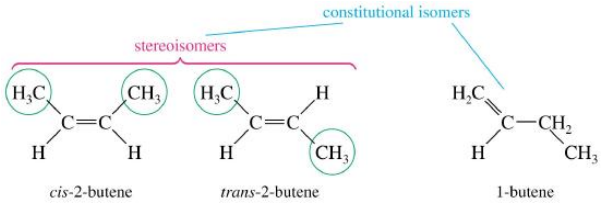


Geometric Isomers - an example of stereoisomerism

The rigidity of the pi bonds in double bonds can create geometric isomerism. Without rotation, there are two different orientations possible across the carbon-carbon double bond (C=C). The rigidity of the double bond creates a line of reference for spatial orientation. The prefixes cis and trans are used to distinguish between geometric isomers. The cis-stereoisomer has both non-hydrogen atoms on the same side of the double bond. Whereas, the trans-stereoisomer has the non-hydrogen atoms across the double bond. In the same way, we cross the ocean an a trans-Atlantic journey. This small difference may seem insignificant, but geometric isomers are different chemical compounds with different physical properties as shown in the example below.

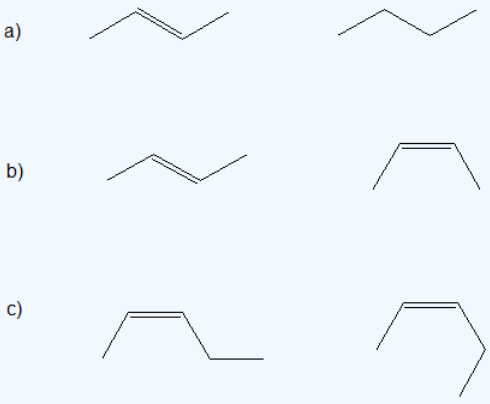


For now, it is important to distinguish between structural differences and spatial differences when comparing compounds. In the future, we will look more closely at isomerism.



Example

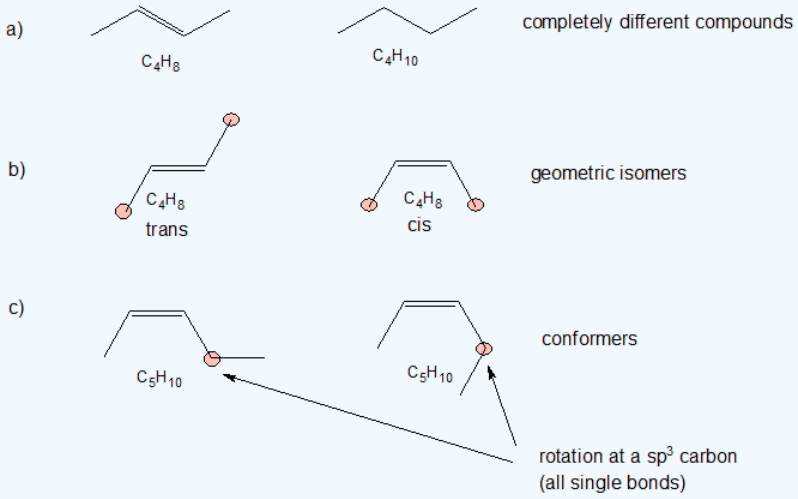
Let's look ate the bond-line structures below and determine the relationships between the following pairs of compounds: identical, conformers, structural isomers, geometric isomers, or completely different compounds.



The first important step (that is often skipped) is to determine the chemical formula of each compound. If the chemical formulas are different, then the compounds are completely different and there is NO isomeric relationship. If the chemical formulas are the same, then we identify the difference between to the compounds to determine their relatioship. If there are structural differences in the bonding patterns, then the compounds are constitutional (structural isomers). If the compounds have the same structural connections, but the spatial orientations are different, then the compounds are stereoisomers. For now,

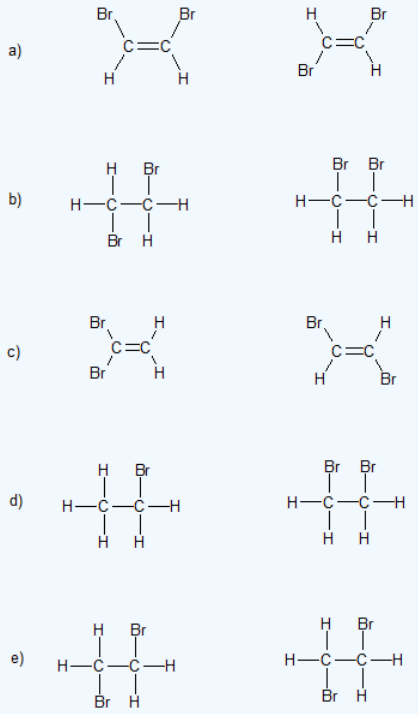
the possible stereoisomers are conformers showing the same compound with different carbon-carbon single bond rotations or geometric isomers of compounds with different orientations at the carbon-carbon double bonds.

Applying the logic above to our example, we determine the following.



Exercise

1. What is the relationship between the following pairs of compounds: identical, conformers, structural isomers, geometric isomers, or completely different compounds?



Answer

1.

a) geometric isomers

b) conformers

c) structural isomers

d) completely different compounds

e) identical

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1.8: Polarity and Lewis Structures

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1.8.1: Atomic Structure - Orbitals

Objectives

After completing this section, you should be able to

1. describe the physical significance of an orbital.
2. list the atomic orbitals from 1*s* to 3*d* in order of increasing energy.
3. sketch the shapes of *s* and *p* orbitals.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- nodal plane
- node
- orbital
- quantum mechanics
- wave function

Atomic Orbitals

An orbital is the quantum mechanical refinement of Bohr's orbit. In contrast to his concept of a simple circular orbit with a fixed radius, orbitals are mathematically derived regions of space with different *probabilities* of having an electron. One way of representing electron probability distributions is Ψ^2. Because Ψ^2 gives the probability of finding an electron in a given volume of space (such as a cubic picometer), a plot of Ψ^2 versus distance from the nucleus (r) is a plot of the **probability density**. For example, the 1*s* orbital is spherically symmetrical, so the probability of finding a 1*s* electron at any given point depends *only* on its distance from the nucleus. The probability density is greatest at $r = 0$ (at the nucleus) and decreases steadily with increasing distance. At very large values of *r*, the electron probability density is very small but *not* zero.

We can calculate the **radial probability** (the probability of finding a 1*s* electron at a distance *r* from the nucleus) by adding together the probabilities of an electron being at all points on a series of *x* spherical shells of radius r_1, r_2, r_3,…, r_{x-1}, r_x. In effect, we are dividing the atom into very thin concentric shells, much like the layers of an onion (part (a) in Figure 1.8.1.1), and calculating the probability of finding an electron on each spherical shell. Recall that the electron probability density is greatest at $r = 0$ (part (b) in Figure 1.8.1.1), so the density of dots is greatest for the smallest spherical shells in part (a) in Figure 1.8.1.1. In contrast, the surface area of each spherical shell is equal to $4\pi r^2$, which increases very rapidly with increasing *r* (part (c) in Figure 1.8.1.1). Because the surface area of the spherical shells increases more rapidly with increasing *r* than the electron probability density decreases, the plot of radial probability has a maximum at a particular distance (part (d) in Figure 1.8.1.1). Most important, when *r* is very small, the surface area of a spherical shell is so small that the *total* probability of finding an electron close to the nucleus is very low; at the nucleus, the electron probability vanishes (part (d) in Figure 1.8.1.1).

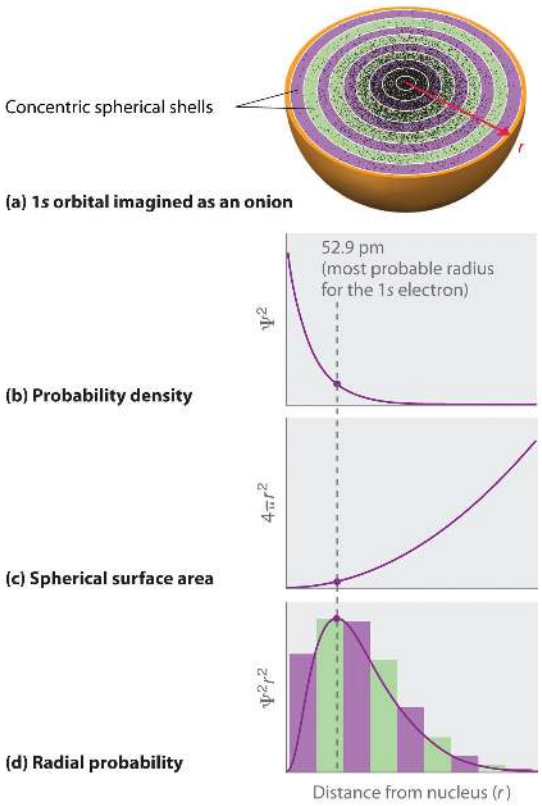


Figure **1.8.1.1**: Most Probable Radius for the Electron in the Ground State of the Hydrogen Atom. (a) Imagine dividing the atom's total volume into very thin concentric shells as shown in the onion drawing. (b) A plot of electron probability density Ψ^2 versus r shows that the electron probability density is greatest at $r = 0$ and falls off smoothly with increasing r. The density of the dots is therefore greatest in the innermost shells of the onion. (c) The surface area of each shell, given by $4\pi r^2$, increases rapidly with increasing r. (d) If we count the number of dots in each spherical shell, we obtain the total probability of finding the electron at a given value of r. Because the surface area of each shell increases more rapidly with increasing r than the electron probability density decreases, a plot of electron probability versus r (the *radial probability*) shows a peak. This peak corresponds to the most probable radius for the electron, 52.9 pm, which is exactly the radius predicted by Bohr's model of the hydrogen atom. (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

For the hydrogen atom, the peak in the radial probability plot occurs at $r = 0.529$ Å (52.9 pm), which is exactly the radius calculated by Bohr for the $n = 1$ orbit. Thus the *most probable radius* obtained from quantum mechanics is identical to the radius calculated by classical mechanics. In Bohr's model, however, the electron was assumed to be at this distance 100% of the time, whereas in the quantum mechanical Schrödinger model, it is at this distance only some of the time. The difference between the two models is attributable to the wavelike behavior of the electron and the Heisenberg uncertainty principle.

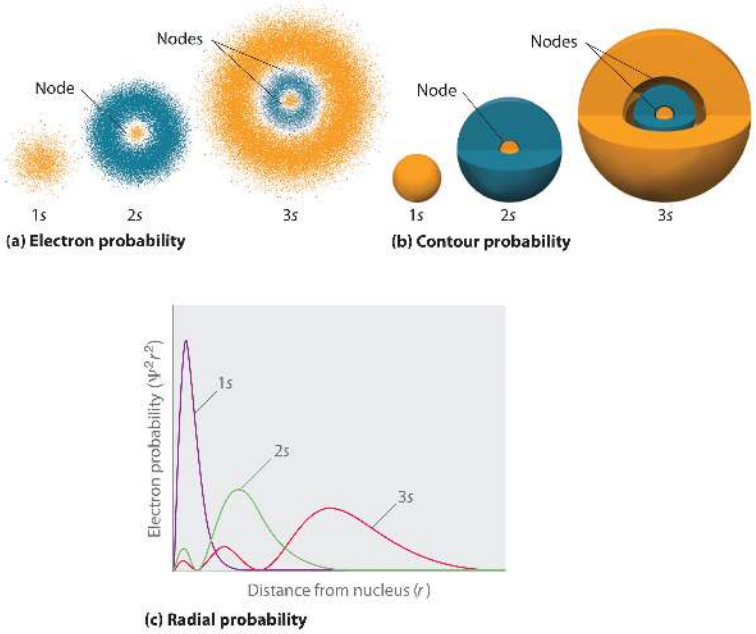


Figure **1.8.1.2**: Probability Densities for the 1*s*, 2*s*, and 3*s* Orbitals of the Hydrogen Atom. (a) The electron probability density in any plane that contains the nucleus is shown. Note the presence of circular regions, or nodes, where the probability density is zero. (b) Contour surfaces enclose 90% of the electron probability, which illustrates the different sizes of the 1*s*, 2*s*, and 3*s* orbitals. The cutaway drawings give partial views of the internal spherical nodes. The orange color corresponds to regions of space where the phase of the wave function is positive, and the blue color corresponds to regions of space where the phase of the wave function is negative. (c) In these plots of electron probability as a function of distance from the nucleus (*r*) in all directions (radial probability), the most probable radius increases as *n* increases, but the 2*s* and 3*s* orbitals have regions of significant electron probability at small values of *r*. (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

Figure **1.8.1.2** compares the electron probability densities for the hydrogen 1*s*, 2*s*, and 3*s* orbitals. Note that all three are spherically symmetrical. For the 2*s* and 3*s* orbitals, however (and for all other *s* orbitals as well), the electron probability density does not fall off smoothly with increasing *r*. Instead, a series of minima and maxima are observed in the radial probability plots (part (c) in Figure **1.8.1.2**). The minima correspond to spherical nodes (regions of zero electron probability), which alternate with spherical regions of nonzero electron probability.

s Orbitals

Three things happen to *s* orbitals as *n* increases (Figure **1.8.1.2**):

1. They become larger, extending farther from the nucleus.
2. They contain more nodes. This is similar to a standing wave that has regions of significant amplitude separated by nodes, points with zero amplitude.
3. For a given atom, the *s* orbitals also become higher in energy as *n* increases because of their increased distance from the nucleus.

Orbitals are generally drawn as three-dimensional surfaces that enclose 90% of the electron density, as was shown for the hydrogen 1*s*, 2*s*, and 3*s* orbitals in part (b) in Figure **1.8.1.2**. Although such drawings show the relative sizes of the orbitals, they do not normally show the spherical nodes in the 2*s* and 3*s* orbitals because the spherical nodes lie inside the 90% surface. Fortunately, the positions of the spherical nodes are not important for chemical bonding.

p Orbitals

Only *s* orbitals are spherically symmetrical. As the value of *l* increases, the number of orbitals in a given subshell increases, and the shapes of the orbitals become more complex. Because the 2*p* subshell has $l = 1$, with three values of m_l (−1, 0, and +1), there are three 2*p* orbitals.

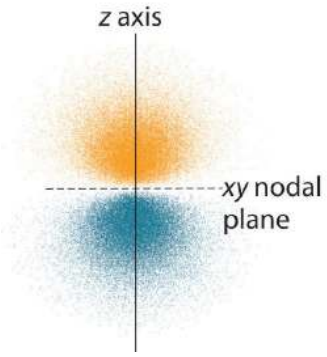


Figure **1.8.1.2**, the colors correspond to regions of space where the phase of the wave function is positive (orange) and negative (blue). (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

The electron probability distribution for one of the hydrogen 2*p* orbitals is shown in Figure **1.8.1.3**. Because this orbital has two lobes of electron density arranged along the *z* axis, with an electron density of zero in the *xy* plane (i.e., the *xy* plane is a nodal plane), it is a $2p_z$ orbital. As shown in Figure **1.8.1.4**, the other two 2*p* orbitals have identical shapes, but they lie along the *x* axis ($2p_x$) and *y* axis ($2p_y$), respectively. Note that each *p* orbital has just one nodal plane. In each case, the phase of the wave function for each of the 2*p* orbitals is positive for the lobe that points along the positive axis and negative for the lobe that points along the negative axis. It is important to emphasize that these signs correspond to the *phase* of the wave that describes the electron motion, *not* to positive or negative charges.

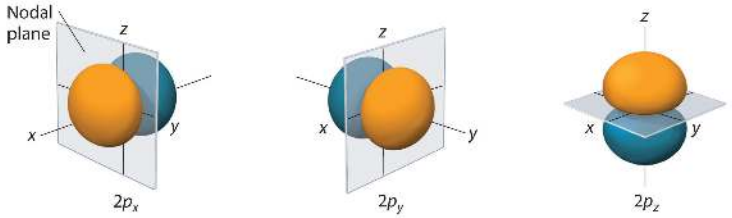


Figure **1.8.1.4** The Three Equivalent 2*p* Orbitals of the Hydrogen Atom. (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

The surfaces shown enclose 90% of the total electron probability for the $2p_x$, $2p_y$, and $2p_z$ orbitals. Each orbital is oriented along the axis indicated by the subscript and a nodal plane that is perpendicular to that axis bisects each 2*p* orbital. The phase of the wave function is positive (orange) in the region of space where *x*, *y*, or *z* is positive and negative (blue) where *x*, *y*, or *z* is negative.

Just as with the *s* orbitals, the size and complexity of the *p* orbitals for any atom increase as the principal quantum number *n* increases. The shapes of the 90% probability surfaces of the 3*p*, 4*p*, and higher-energy *p* orbitals are, however, essentially the same as those shown in Figure **1.8.1.4**.

The electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

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1.8.2: Atomic Structure - Electron Configurations

Objective

After completing this section, you should be able to write the ground-state electron configuration for each of the elements up to and including atomic number 36.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- ground-state electronic configuration
- Hund's rule
- Pauli exclusion principle
- aufbau principle

The electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

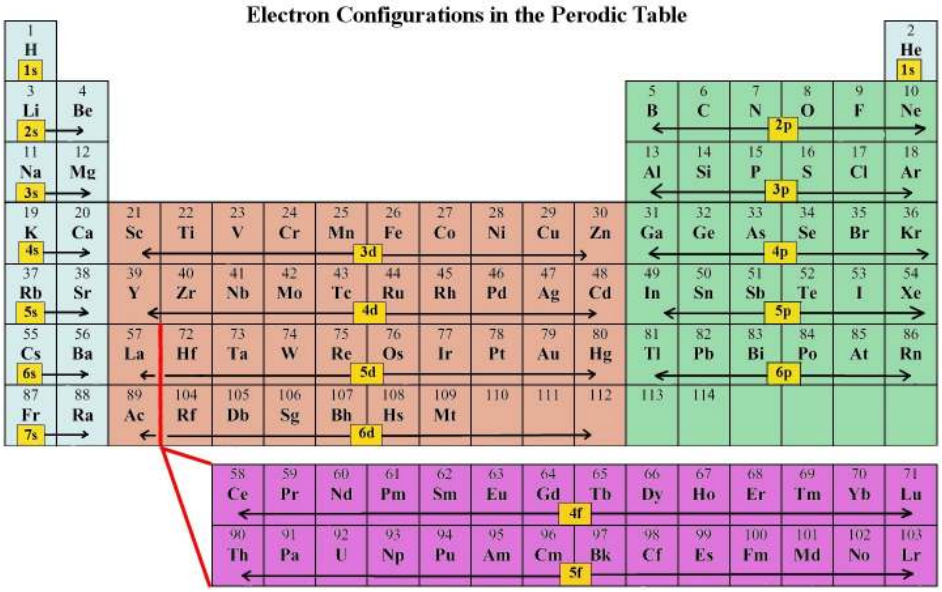


Figure 1.8.2.1: The Periodic Table. (CC BY-SA-NC; Sarah Faizi via LibreTexts)

Electron Configurations

The electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

Before assigning the electrons of an atom into orbitals, one must become familiar with the basic concepts of electron configurations. Every element on the periodic table consists of atoms, which are composed of protons, neutrons, and electrons. Electrons exhibit a negative charge and are found around the nucleus of the atom in electron orbitals, defined as the volume of space in which the electron can be found within 95% probability. The four different types of orbitals (s,p,d, and f) have different shapes, and one orbital can hold a maximum of two electrons. The p, d, and f orbitals have different sublevels, thus can hold more electrons.

As stated, the electron configuration of each element is unique to its position on the periodic table. The energy level is determined by the period and the number of electrons is given by the atomic number of the element. Orbitals on different energy levels are similar to each other, but they occupy different areas in space. The 1s orbital and 2s orbital both have the characteristics of an s orbital (radial nodes, spherical volume probabilities, can only hold two electrons, etc.) but, as they are found in different energy levels, they occupy different spaces around the nucleus. Each orbital can be represented by specific blocks on the periodic table. The s-block is the region of the alkali metals including helium (Groups 1 & 2), the d-block are the transition metals (Groups 3 to 12), the p-block are the main group elements from Groups 13 to 18, and the f-block are the lanthanides and actinides series.

Using the periodic table to determine the electron configurations of atoms is key, but also keep in mind that there are certain rules to follow when assigning electrons to different orbitals. The periodic table is an incredibly helpful tool in writing electron configurations. For more information on how electron configurations and the periodic table are linked, visit the Connecting Electrons to the Periodic Table module.

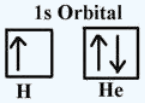
Rules for Assigning Electron Orbitals

Pauli Exclusion Principle

The Pauli exclusion principle states that no two electrons can have the same four quantum numbers. The first three (n, l, and m_l) may be the same, but the fourth quantum number must be different. A single orbital can hold a maximum of two electrons, which **must** have opposing spins; otherwise they would have the same four quantum numbers, which is forbidden. One electron is spin up (m_s = +1/2) and the other would spin down (m_s = -1/2). This tells us that each subshell has double the electrons per orbital. The s subshell has 1 orbital that can hold up to 2 electrons, the p subshell has 3 orbitals that can hold up to 6 electrons, the d subshell has 5 orbitals that hold up to 10 electrons, and the f subshell has 7 orbitals with 14 electrons.

Example 1: Hydrogen and Helium

The first three quantum numbers of an electron are n=1, l=0, m_l=0. Only two electrons can correspond to these, which would be either m_s = -1/2 or m_s = +1/2. As we already know from our studies of quantum numbers and electron orbitals, we can conclude that these four quantum numbers refer to the 1s subshell. If only one of the m_s values are given then we would have $1s^1$ (denoting hydrogen) if both are given we would have $1s^2$ (denoting helium). Visually, this is be represented as:



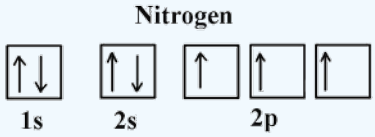
As shown, the 1s subshell can hold only two electrons and, when filled, the electrons have opposite spins.

Hund's Rule

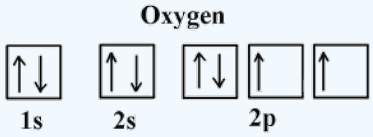
When assigning electrons in orbitals, each electron will first fill all the orbitals with similar energy (also referred to as degenerate) before pairing with another electron in a half-filled orbital. Atoms at ground states tend to have as many unpaired electrons as possible. When visualizing this processes, think about how electrons are exhibiting the same behavior as the same poles on a magnet would if they came into contact; as the negatively charged electrons fill orbitals they first try to get as far as possible from each other before having to pair up.

Example 2: Oxygen and Nitrogen

If we look at the correct electron configuration of the Nitrogen (Z = 7) atom, a very important element in the biology of plants: $1s^2\ 2s^2\ 2p^3$



We can clearly see that p orbitals are half-filled as there are three electrons and three p orbitals. This is because Hund's Rule states that the three electrons in the 2p subshell will fill all the empty orbitals first before filling orbitals with electrons in them. If we look at the element after nitrogen in the same period, oxygen (Z = 8) its electron configuration is: $1s^2\ 2s^2\ 2p^4$ (for an atom).



Oxygen has one more electron than nitrogen and as the orbitals are all half filled the electron must pair up.

Occupation of Orbitals

Electrons fill orbitals in a way to minimize the energy of the atom. Therefore, the electrons in an atom fill the principal energy levels in order of increasing energy (the electrons are getting farther from the nucleus). The relative energy of the orbitals is shown in Figure **1.8.2.2**

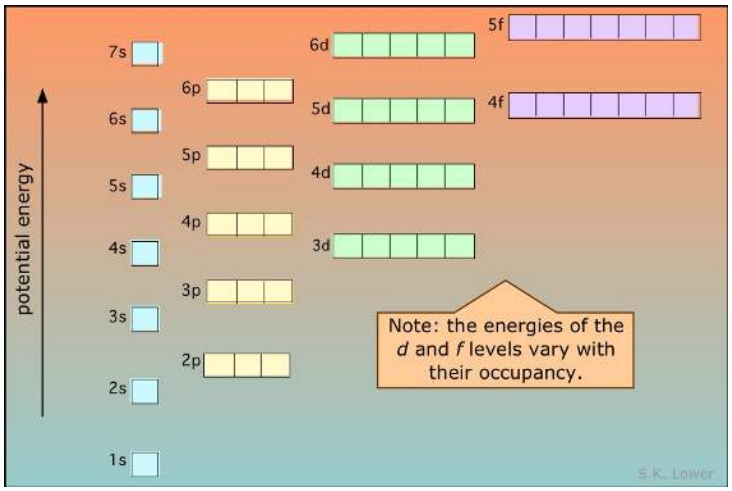


Figure **1.8.2.2**: The relative potential energy of atomic orbitals. (CC BY-NC; Stephen Lower)

The order of levels filled is then:

1s, 2s, 2p, 3s, 3p, 4s, 3d, 4p, 5s, 4d, 5p, 6s, 4f, 5d, 6p, 7s, 5f, 6d, and 7p

The general order in which orbitals are filled is depicted in Figure **1.8.2.3**. Subshells corresponding to each value of *n* are written from left to right on successive horizontal lines, where each row represents a row in the periodic table. The order in which the orbitals are filled is indicated by the diagonal lines running from the upper right to the lower left. Accordingly, the 4*s* orbital is filled prior to the 3*d* orbital because of shielding and penetration effects. Consequently, the electron configuration of potassium, which begins the fourth period, is $[Ar]4s^1$, and the configuration of calcium is $[Ar]4s^2$. Five 3*d* orbitals are filled by the next 10 elements, the transition metals, followed by three 4*p* orbitals. Notice that the last member of this row is the noble gas krypton (Z = 36), $[Ar]4s^23d^{10}4p^6$ = [Kr], which has filled 4*s*, 3*d*, and 4*p* orbitals. The fifth row of the periodic table is essentially the same as the fourth, except that the 5*s*, 4*d*, and 5*p* orbitals are filled sequentially.

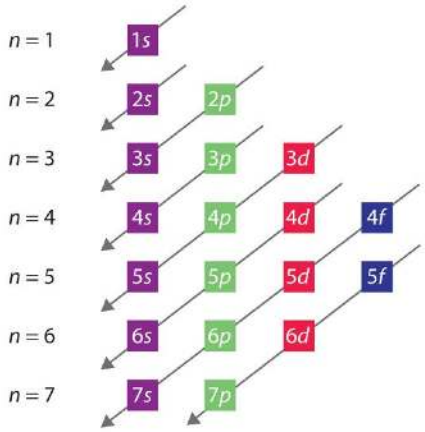


Figure **1.8.2.3**: Predicting the Order in Which Orbitals Are Filled in Multielectron Atoms. If you write the subshells for each value of the principal quantum number on successive lines, the observed order in which they are filled is indicated by a series of diagonal lines running from the upper right to the lower left.

The Aufbau Process

Aufbau comes from the German word "aufbauen" meaning "to build." When writing electron configurations, orbitals are built up from atom to atom. When writing the electron configuration for an atom, orbitals are filled in order of increasing atomic number. However, there are some exceptions to this rule.

✔ Example 3: 3rd row elements

Following the pattern across a period from B (Z=5) to Ne (Z=10), the number of electrons increases and the subshells are filled. This example focuses on the p subshell, which fills from boron to neon.

- B (Z=5) configuration: $1s^2\ 2s^2\ 2p^1$
- C (Z=6) configuration:$1s^2\ 2s^2\ 2p^2$
- N (Z=7) configuration:$1s^2\ 2s^2\ 2p^3$
- O (Z=8) configuration:$1s^2\ 2s^2\ 2p^4$
- F (Z=9) configuration:$1s^2\ 2s^2\ 2p^5$
- Ne (Z=10) configuration:$1s^2\ 2s^2\ 2p^6$

The Number of Valence Electrons

The number of valence electrons of an element can be determined by the periodic table group (vertical column) in which the element is categorized. With the exception of groups 3–12 (the transition metals), the units digit of the group number identifies how many valence electrons are associated with a neutral atom of an element listed under that particular column. For example in group 16, the units digit is 6 and elements in this group have 6 valence electrons.

Table **1.8.2.1**: Valence electrons derived from periodic table group

Periodic table group	Valence electrons
Group 1: alkali metals	1
Group 2: alkaline earth metals	2
Groups 3-12: transition metals	2* (The 4s shell is complete and cannot hold any more electrons)
Group 13: boron group	3
Group 14: carbon group	4
Group 15: pnictogens	5
Group 16: chalcogens	6
Group 17: halogens	7
Group 18: noble gases	8**

** The general method for counting valence electrons is generally not useful for transition metals. Instead the modified **d electron count method** is used.*

*** Except for helium, which has only two valence electrons.*

The electron configuration of an element is the arrangement of its electrons in its atomic orbitals. By knowing the electron configuration of an element, we can predict and explain a great deal of its chemistry.

Example 1.3.1

Draw an orbital diagram and use it to derive the electron configuration of phosphorus, $Z = 15$. What is its valence electron configuration?

Given: atomic number

Asked for: orbital diagram and valence electron configuration for phosphorus

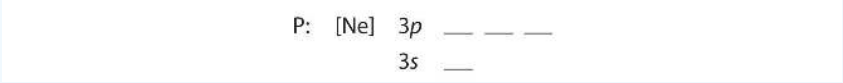
Strategy:

A. Locate the nearest noble gas preceding phosphorus in the periodic table. Then subtract its number of electrons from those in phosphorus to obtain the number of valence electrons in phosphorus.
B. Referring to Figure 1.3.1, draw an orbital diagram to represent those valence orbitals. Following Hund's rule, place the valence electrons in the available orbitals, beginning with the orbital that is lowest in energy. Write the electron configuration from your orbital diagram.
C. Ignore the inner orbitals (those that correspond to the electron configuration of the nearest noble gas) and write the valence electron configuration for phosphorus.

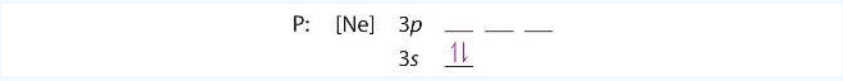
Solution:

A Because phosphorus is in the third row of the periodic table, we know that it has a [Ne] closed shell with 10 electrons. We begin by subtracting 10 electrons from the 15 in phosphorus.

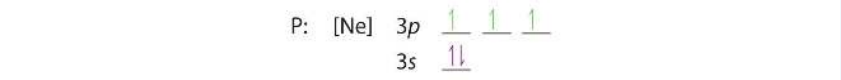
B The additional five electrons are placed in the next available orbitals, which Figure 1.2.5 tells us are the 3*s* and 3*p* orbitals:



Because the 3*s* orbital is lower in energy than the 3*p* orbitals, we fill it first:



Hund's rule tells us that the remaining three electrons will occupy the degenerate 3*p* orbitals separately but with their spins aligned:



The electron configuration is $[Ne]3s^23p^3$.

C We obtain the valence electron configuration by ignoring the inner orbitals, which for phosphorus means that we ignore the [Ne] closed shell. This gives a valence-electron configuration of $3s^23p^3$.

? Exercise 1.3.1

Draw an orbital diagram and use it to derive the electron configuration of chlorine, $Z = 17$. What is its valence electron configuration?

Answer

$[Ne]3s^23p^5$; $3s^23p^5$

The sixth row of the periodic table will be different from the preceding two because the 4*f* orbitals, which can hold 14 electrons, are filled between the 6*s* and the 5*d* orbitals. The elements that contain 4*f* orbitals in their valence shell are the lanthanides. When the 6*p* orbitals are finally filled, we have reached the next (and last known) noble gas, radon ($Z = 86$), $[Xe]6s^24f^{14}5d^{10}6p^6 = [Rn]$. In the last row, the 5*f* orbitals are filled between the 7*s* and the 6*d* orbitals, which gives the 14 actinide elements. Because the large number of protons makes their nuclei unstable, all the actinides are radioactive.

✔ Example 1.3.2

Write the electron configuration of mercury ($Z = 80$), showing all the inner orbitals.

Given: atomic number

Asked for: complete electron configuration

Strategy:

Using the orbital diagram in Figure **1.8.2.3** and the periodic table as a guide, fill the orbitals until all 80 electrons have been placed.

Solution:

By placing the electrons in orbitals following the order shown in Figure **1.8.2.3** and using the periodic table as a guide, we obtain

$1s^2$	row 1	2 electrons
$2s^22p^6$	row 2	8 electrons
$3s^23p^6$	row 3	8 electrons
$4s^23d^{10}4p^6$	row 4	18 electrons
$5s^24d^{10}5p^6$	row 5	18 electrons
	row 1–5	54 electrons

After filling the first five rows, we still have 80 − 54 = 26 more electrons to accommodate. According to Figure 1.3.1, we need to fill the 6*s* (2 electrons), 4*f* (14 electrons), and 5*d* (10 electrons) orbitals. The result is mercury's electron configuration:

$$1s^22s^22p^63s^23p^64s^23d^{10}4p^65s^24d^{10}5p^66s^24f^{14}5d^{10} = Hg = [Xe]6s^24f^{14}5d^{10}$$

with a filled 5*d* subshell, a $6s^2 4f^{14} 5d^{10}$ valence shell configuration, and a total of 80 electrons. (You should always check to be sure that the total number of electrons equals the atomic number.)

Summary

Based on the Pauli principle and a knowledge of orbital energies obtained using hydrogen-like orbitals, it is possible to construct the periodic table by filling up the available orbitals beginning with the lowest-energy orbitals (the **aufbau principle**), which gives rise to a particular arrangement of electrons for each element (its **electron configuration**). **Hund's rule** says that the lowest-energy arrangement of electrons is the one that places them in degenerate orbitals with their spins parallel. For chemical purposes, the most important electrons are those in the outermost principal shell, the **valence electrons**.

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1.8.3: Development of Chemical Bonding Theory

Objectives

After completing this section, you should be able to

1. draw Lewis Dot Symbols for main group elements and ions.
2. describe the three-dimensional nature of molecules.
3. sketch a tetrahedral molecule, CX_4, using the “wedge-and-broken-line” method of representation.
4. make a ball-and-stick model of a simple tetrahedral molecule such as methane, CH_4.
5. draw Lewis Dot Structures for 2 electron group molecules.
6. draw Lewis Dot Structures for 3 electron group molecules.
7. draw Lewis Dot Structures for 4 electron group molecules.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- bond strength
- covalent bond
- ionic bond
- Lewis structure
- lone-pair electron
- non-bonding electron

Study Notes

To draw Lewis structures successfully, you need to know the number of valence electrons present in each of the atoms involved. Memorize the number of valence electrons possessed by each of the elements commonly encountered in organic chemistry: C, H, O, N, S, P and the halogens.

When drawing any organic structure, you must remember that a neutral carbon atom will almost always have four bonds. Similarly, hydrogen always has one bond; neutral oxygen atoms have two bonds; and neutral nitrogen atoms have three bonds. By committing these simple rules to memory, you can avoid making unnecessary mistakes later in the course.

The “wedge-and-broken-line” type of representation, which helps to convey the three-dimensional nature of organic compounds, will be used throughout the course.

Bonding Overview

Why are some substances chemically bonded molecules and others are an association of ions? The answer to this question depends upon the electronic structures of the atoms and nature of the chemical forces within the compounds. Although there are no sharply defined boundaries, chemical bonds are typically classified into three main types: ionic bonds, covalent bonds, and metallic bonds. In this chapter, each type of bond and the general properties found in typical substances in which the bond type occurs will be discussed.

1. Ionic bonds results from ***electrostatic forces that exist between ions of opposite charge***. These bonds typically involve a metal with a nonmetal
2. Covalent bonds ***result from the sharing of electrons between two atoms***. The bonds typically involve one nonmetallic element with another
3. Metallic bonds are found in solid metals (copper, iron, aluminum) with each metal atom bonded to several neighboring metal atoms and the bonding electrons are free to move throughout the 3-dimensional structure.

Each bond classification is discussed in detail in subsequent sections of the chapter. Let's look at the preferred arrangements of electrons in atoms when they form chemical compounds.

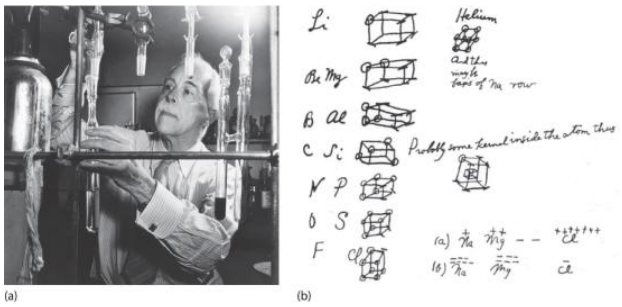


Figure 1.4.1: G. N. Lewis and the Octet Rule. (a) Lewis is working in the laboratory. (b) In Lewis's original sketch for the octet rule, he initially placed the electrons at the corners of a cube rather than placing them as we do now.

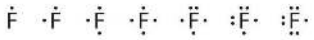
Lewis Symbols

At the beginning of the 20th century, the American chemist G. N. Lewis (1875–1946) devised a system of symbols—now called Lewis electron dot symbols, often shortened to *Lewis dot symbols*—that can be used for predicting the number of bonds formed by most elements in their compounds. Each Lewis dot symbol consists of the chemical symbol for an element surrounded by dots that represent its valence electrons.

Lewis Dot symbols:

- provide a convenient representation of valence electrons
- allows you to keep track of valence electrons during bond formation
- consists of the chemical symbol for the element plus a dot for each valence electron

To write an element's Lewis dot symbol, we place dots representing its valence electrons, one at a time, around the element's chemical symbol. Up to four dots are placed above, below, to the left, and to the right of the symbol (in any order, as long as elements with four or fewer valence electrons have no more than one dot in each position). The next dots, for elements with more than four valence electrons, are again distributed one at a time, each paired with one of the first four. Fluorine, for example, with the electron configuration $[He]2s^22p^5$, has seven valence electrons, so its Lewis dot symbol is constructed as follows:



Group	1	2	13	14	15	16	17	18
Electron Configuration	$[He]2s^1$	$[He]2s^2$	$[He]2s^22p^1$	$[He]2s^22p^2$	$[He]2s^22p^3$	$[He]2s^22p^4$	$[He]2s^22p^5$	$[He]2s^22p^6$
Lewis Dot Symbol	Li·	·Be·	·B·	·C·	·N·	:O·	:F·	:Ne:

Figure **1.8.3.2**: Lewis Dot Symbols for the Elements in Period 2

Lewis used the unpaired dots to predict the number of bonds that an element will form in a compound. Consider the symbol for nitrogen in Figure **1.8.3.2**. The Lewis dot symbol explains why nitrogen, with three unpaired valence electrons, tends to form compounds in which it shares the unpaired electrons to form three bonds. Boron, which also has three unpaired valence electrons in its Lewis dot symbol, also tends to form compounds with three bonds, whereas carbon, with four unpaired valence electrons in its Lewis dot symbol, tends to share all of its unpaired valence electrons by forming compounds in which it has four bonds. Lewis symbols are a tool to help draw structures. We will see why bonding in molecular compounds follow Lewis' theory in the next section.

Elements in the same group have the same number of valence electrons and similar Lewis symbols. For example, the electron configuration for atomic sulfur is $[Ne]3s^23p^4$, thus there are ***six*** valence electrons. Its Lewis symbol would therefore be similar to oxygen and look like:



The Octet Rule

Lewis's major contribution to bonding theory was to recognize that atoms tend to lose, gain, or share electrons to reach a total of eight valence electrons, called an *octet*. This so-called octet rule explains the stoichiometry of most compounds in the *s* and *p* blocks of the periodic table. We now know from quantum mechanics that the number eight corresponds to one *ns* and three *np* valence orbitals, which together can accommodate a total of eight electrons. Remarkably, though, Lewis's insight was made nearly a decade before Rutherford proposed the nuclear model of the atom. Common exceptions to the octet rule are helium, whose $1s^2$ electron configuration gives it a full $n = 1$ shell, and hydrogen, which tends to gain or share its one electron to achieve the electron configuration of helium.

Lewis's idea of an octet explains why noble gases rarely form compounds. They have the stable s^2p^6 configuration (full octet, no charge), so they have no reason to react and change their configuration. All other elements attempt to gain, lose, or share electrons to achieve a noble gas configuration. This explains why atom combine together to form compounds. By forming bond the makes the atoms more stable and lower in energy. Making bonds releases energy and represents a driving force for the formation of compounds.

Atoms often gain, lose, or share electrons to achieve the same number of electrons as the noble gas closest to them in the periodic table.

Lewis Structures

Lewis structures represent how Lewis symbols gain, lose, or share electrons to obtain an octet by forming compounds.

Lewis Structures of Ionic Compounds

Whenever there is a metal present in the structure of an organic compound, there is a high likelihood that at least one ionic bond is present. Ionic bonds are represented differently in Lewis structures than covalent bonds. Great care should be taken whenever drawing the Lewis structure of an organic compounds which contains and ionic bond. Ionic bonds typically are formed when a metal and a nonmetal are part of a compound. Some atoms achieve an octet by fully gaining or losing electrons to form ions. Ionic bonds form through the eletrostatic attraction of the created ions. The formula for table salt is NaCl. It is the result of Na^+ ions and Cl^- ions bonding together. If sodium metal and chlorine gas mix under the right conditions, they will form salt. The sodium loses an electron, and the chlorine gains that electron. In the process, a great amount of light and heat is released. The resulting salt is mostly unreactive — it is stable. It will not undergo any explosive reactions, unlike the sodium and chlorine that it is made of. Why? Referring to the octet rule, atoms attempt to get a noble gas electron configuration, which is eight valence electrons. Sodium ($1s^22s^22p^63s^1$) has one valence electron, so giving it up would result in the same electron configuration as neon ($1s^22s^22p^6$). Chlorine ($1s^22s^22p^63s^23p^7$)has seven valence electrons, so if it takes one it will have eight (an octet). Chlorine has the electron configuration of argon ($1s^22s^22p^63s^23p^8$) when it gains an electron.

The Lewis structure of an ionic compound show the movement of electrons. For NaCl, sodium is in group 1 and has one valence electron and chlorine is in group 17 and has seven valence electrons. Sodium loses its sole valence electron thereby becomes positively charged. Chlorine gains this electron, gaining a full octet, and a negative charge. After the gain/loss of an electron the new Lewis structures of Na^+ and Cl^- are written next to each other representing the ionic bond in NaCl.

Examples of Lewis Structures of Ionic Compounds

Metal		Nonmetal		Ionic Compound
Na·	+	:Cl·	→	$Na^+[:\ddot{Cl}:]^-$
sodium atom		chlorine atom		sodium chloride (sodium ion and chloride ion)
·Mg·	+	:O·	→	$Mg^{2+}[:\ddot{O}:]^{2-}$
magnesium atom		oxygen atom		magnesium oxide (magnesium ion and oxide ion)
·Ca·	+	2 :F·	→	$Ca^{2+}[:\ddot{F}:]^-_2$
calcium atom		fluorine atoms		calcium fluoride (calcium ion and two fluoride ions)

Covalent Bonds and the Lewis Structures of Molecular Compounds

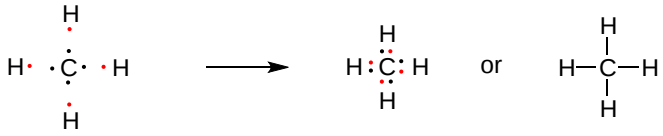
While alkali metals (such as sodium and potassium), alkaline earth metals (such as magnesium and calcium), and halogens (such as fluorine and chlorine) often form ions in order to achieve a full octet, the principle elements of organic chemistry - carbon, hydrogen, nitrogen, and oxygen - instead tend to fill their octet by *sharing* electrons with other atoms, forming covalent bonds. Consider the simplest case of hydrogen gas. An isolated hydrogen atom has only one electron, located in the 1*s* orbital. If two hydrogen atoms come close enough so that their respective 1*s* orbitals overlap, the two electrons can be shared between the two nuclei, and a covalently bonded H_2 molecule is formed. In the Lewis structure of H_2, each pair of electrons that is shared between two atoms is drawn as a single line, designating a single covalent bond.

H· ·H → H:H or H—H

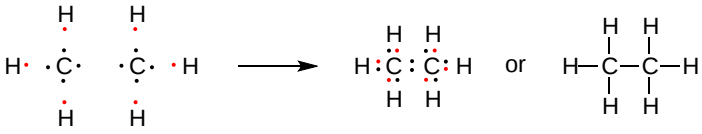
two hydrogen atoms — a hydrogen molecule (H_2)

Hydrogen represents a special case, because a hydrogen atom cannot fulfill the octet rule; it needs only two electrons to have a full shell. This is often called the ‘doublet rule’ for hydrogen.

One of the simplest organic molecules is methane with the molecular formula CH_4. Methane is the ‘natural gas’ burned in home furnaces and hot water heaters, as well as in electrical power generating plants. To illustrate the covalent bonding in methane using a Lewis structure, we first must recognize that, although a carbon atom has a total of six electrons it's Lewis symbol has four unpaired electrons. Following Lewis' theory the carbon atom wants to form four covalent bonds to fill its octet. In a methane molecule, the central carbon atom shares its four valence electrons with four hydrogen atoms, thus forming four bonds and fulfilling the octet rule (for the carbon) and the ‘doublet rule’ (for each of the hydrogens).



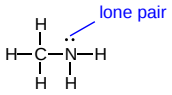
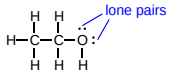
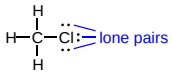
The next relatively simple organic molecule to consider is ethane, which has the molecular formula C_2H_6. If we draw each atom's Lewis symbol separately, we can see that the octet/doublet rule can be fulfilled for all of them by forming one carbon-carbon bond and six carbon-hydrogen bonds.



The same approach can be used for molecules in which there is no carbon atom. In a water molecule, the Lewis symbol of the oxygen atom has two unpaired electrons. These are paired with the single electron in the Lewis symbols of the hydrogens' two O-H covalent bonds. The remaining four non-bonding electrons on oxygen called ‘lone pairs’.

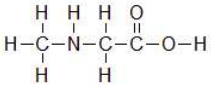


Since the lone pair electrons are often NOT shown in chemical structures, it is important to see mentally add the lone pairs. In the beginning, it can be helpful to physically add the lone pair electrons.

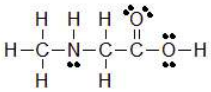
					
methylamine	ethanol	chloromethane			

Exercise

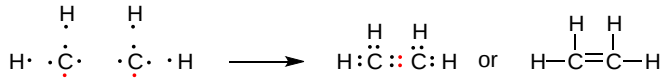
For the following structure, please fill in all of the missing lone pair electrons.



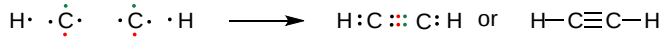
Answer



When two or more electrons are shared between atoms a multiple covalent bond is formed. The molecular formula for ethene (also known as ethylene, a compound found in fruits, such as apples, that signals them to ripen) is C_2H_4. Arranging Lewis symbols of the atoms, you can see that the octet/doublet rule can be fulfilled for all atoms only if the two carbons share *two* pairs of electrons between them. Ethene contains a carbon/carbon double bond.



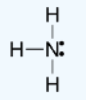
Following this pattern, the triple bond in ethyne molecular formula C_2H_2, (also known as acetylene, the fuel used in welding torches), is formed when the two carbon atoms share *three* pairs of electrons between them.



? Exercise 1.8.3.1

Draw the Lewis structure for ammonia, NH_3.

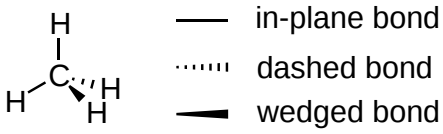
Answer



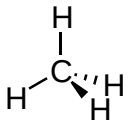
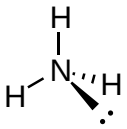
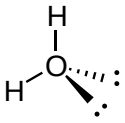
ammonia

Molecular Shape

A stick and wedge drawing of methane shows the tetrahedral angles...(The wedge is coming out of the paper and the dashed line is going behind the paper. The solid lines are in the plane of the paper.)



The following examples make use of this notation, and also illustrate the importance of including non-bonding valence shell electron pairs when viewing such configurations.

					
Methane	**Ammonia**	**Water**			

Bonding configurations are readily predicted by valence-shell electron-pair repulsion theory, commonly referred to as **VSEPR** in most introductory chemistry texts. This simple model is based on the fact that electrons repel each other, and that it is reasonable to expect that the bonds and non-bonding valence electron pairs associated with a given atom will prefer to be as far apart as possible. The bonding configurations of carbon are easy to remember, since there are only three categories.

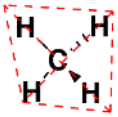
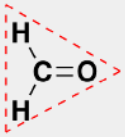
Configuration	Bonding Partners	Bond Angles	Example
Tetrahedral	4	109.5º	
Trigonal Planar	3	120º	
Linear	2	180º	

Figure 1.4.3

In the three examples shown above, the central atom (carbon) does not have any non-bonding valence electrons; consequently the configuration may be estimated from the number of bonding partners alone. However, for molecules of water and ammonia, the non-bonding electrons must be included in the calculation. In each case there are four regions of electron density associated with the valence shell so that a tetrahedral bond angle is expected. The measured bond angles of these compounds (H_2O 104.5º & NH_3 107.3º) show that they are closer to being tetrahedral than trigonal planar or linear. Of course, it is the configuration of atoms (not electrons) that defines the the shape of a molecule, and in this sense ammonia is said to be pyramidal (not tetrahedral). The compound boron trifluoride, BF_3, does not have non-bonding valence electrons and the configuration of its atoms is trigonal. Nice treatments of VSEPR theory have been provided by Oxford and Purdue. The best way to study the three-dimensional shapes of molecules is by using molecular models. Many kinds of model kits are available to students and professional chemists.

Two Electron Groups

Our first example is a molecule with two bonded atoms and no lone pairs of electrons, .

AX_2: BeH_2

1. The central atom, beryllium, contributes two valence electrons, and each hydrogen atom contributes one. The Lewis electron structure is



Figure 1.4.4: Lewis Structure for BeH_2

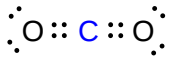
2. There are two electron groups around the central atom. We see from Figure 1.4.3 that the arrangement that minimizes repulsions places the groups 180° apart.

3. Both groups around the central atom are bonding pairs (BP). Thus BeH_2 is designated as AX_2.

4. From Figure 1.4.3 we see that with two bonding pairs, the molecular geometry that minimizes repulsions in BeH_2 is *linear*.

AX_2: CO_2

1. The central atom, carbon, contributes four valence electrons, and each oxygen atom contributes six. The Lewis electron structure is



2. The carbon atom forms two double bonds. Each double bond is a group, so there are two electron groups around the central atom. Like BeH_2, the arrangement that minimizes repulsions places the groups 180° apart.

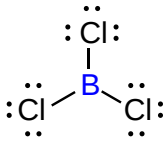
3. Once again, both groups around the central atom are bonding pairs (BP), so CO_2 is designated as AX_2.

4. VSEPR only recognizes groups around the *central* atom. Thus the lone pairs on the oxygen atoms do not influence the molecular geometry. With two bonding pairs on the central atom and no lone pairs, the molecular geometry of CO_2 is linear (Figure 1.4.3).

Three Electron Groups

AX_3: BCl_3

1. The central atom, boron, contributes three valence electrons, and each chlorine atom contributes seven valence electrons. The Lewis electron structure is



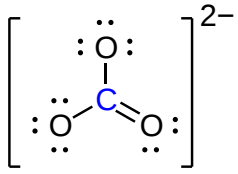
2. There are three electron groups around the central atom. To minimize repulsions, the groups are placed 120° apart (Figure 1.4.3).

3. All electron groups are bonding pairs (BP), so the structure is designated as AX_3.

4. From Figure 1.4.3 we see that with three bonding pairs around the central atom, the molecular geometry of BCl_3 is *trigonal planar*.

AX_3: CO_3^{2-}

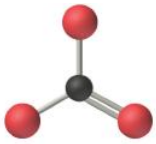
1. The central atom, carbon, has four valence electrons, and each oxygen atom has six valence electrons. As you learned previously, the Lewis electron structure of one of three resonance forms is represented as



2. The structure of CO_3^{2-} is a resonance hybrid. It has three identical bonds, each with a bond order of 4/3. We minimize repulsions by placing the three groups 120° apart (Figure 1.4.3).

3. All electron groups are bonding pairs (BP). With three bonding groups around the central atom, the structure is designated as AX_3.

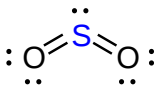
4. We see from Figure 1.4.3 that the molecular geometry of CO_3^{2-} is trigonal planar.



In our next example we encounter the effects of lone pairs and multiple bonds on molecular geometry for the first time.

- AX_2E: SO_2

  1. The central atom, sulfur, has 6 valence electrons, as does each oxygen atom. With 18 valence electrons, the Lewis electron structure is shown below.



  2. There are three electron groups around the central atom, two double bonds and one lone pair. We initially place the groups in a trigonal planar arrangement to minimize repulsions (Figure 1.4.3).

  3. There are two bonding pairs and one lone pair, so the structure is designated as AX_2E. This designation has a total of three electron pairs, two X and one E. Because a lone pair is not shared by two nuclei, it occupies more space near the central atom than a bonding pair (Figure 1.4.4). Thus bonding pairs and lone pairs repel each other electrostatically in the order BP–BP < LP–BP < LP–LP. In SO_2, we have one BP–BP interaction and two LP–BP interactions.

  4. The molecular geometry is described only by the positions of the nuclei, *not* by the positions of the lone pairs. Thus with two nuclei and one lone pair the shape is *bent*, or *V shaped*, which can be viewed as a trigonal planar arrangement with a missing vertex (Figures 1.4.2.1 and 1.4.3).

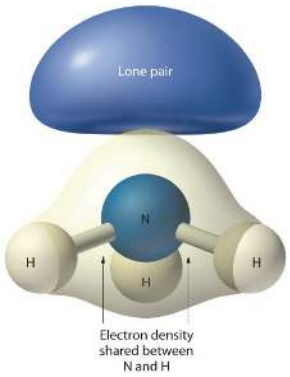
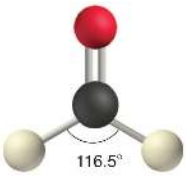


Figure 1.4.4: The Difference in the Space Occupied by a Lone Pair of Electrons and by a Bonding Pair

  As with SO_2, this composite model of electron distribution and negative electrostatic potential in ammonia shows that a lone pair of electrons occupies a larger region of space around the nitrogen atom than does a bonding pair of electrons that is shared with a hydrogen atom.

Like lone pairs of electrons, multiple bonds occupy more space around the central atom than a single bond, which can cause other bond angles to be somewhat smaller than expected. This is because a multiple bond has a higher electron density than a single bond, so its electrons occupy more space than those of a single bond. For example, in a molecule such as CH_2O (AX_3), whose structure is shown below, the double bond repels the single bonds more strongly than the single bonds repel each other. This causes a deviation from ideal geometry (an H–C–H bond angle of 116.5° rather than 120°).

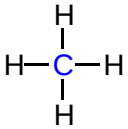


Four Electron Groups

One of the limitations of Lewis structures is that they depict molecules and ions in only two dimensions. With four electron groups, we must learn to show molecules and ions in three dimensions.

AX_4: CH_4

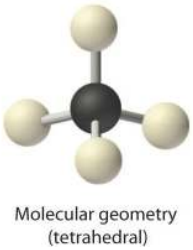
1. The central atom, carbon, contributes four valence electrons, and each hydrogen atom has one valence electron, so the full Lewis electron structure is



2. There are four electron groups around the central atom. As shown in Figure 1.4.2, repulsions are minimized by placing the groups in the corners of a tetrahedron with bond angles of 109.5°.

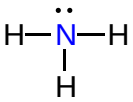
3. All electron groups are bonding pairs, so the structure is designated as AX_4.

4. With four bonding pairs, the molecular geometry of methane is *tetrahedral* (Figure 1.4.3).



AX_3E: NH_3

1. In ammonia, the central atom, nitrogen, has five valence electrons and each hydrogen donates one valence electron, producing the Lewis electron structure



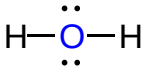
2. There are four electron groups around nitrogen, three bonding pairs and one lone pair. Repulsions are minimized by directing each hydrogen atom and the lone pair to the corners of a tetrahedron.

3. With three bonding pairs and one lone pair, the structure is designated as AX_3E. This designation has a total of four electron pairs, three X and one E. We expect the LP–BP interactions to cause the bonding pair angles to deviate significantly from the angles of a perfect tetrahedron.

4. There are three nuclei and one lone pair, so the molecular geometry is *trigonal pyramidal*. In essence, this is a tetrahedron with a vertex missing (Figure 1.4.3). However, the H–N–H bond angles are less than the ideal angle of 109.5° because of LP–BP repulsions.

AX_2E_2: H_2O

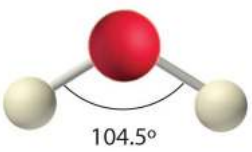
1. Oxygen has six valence electrons and each hydrogen has one valence electron, producing the Lewis electron structure



2. There are four groups around the central oxygen atom, two bonding pairs and two lone pairs. Repulsions are minimized by directing the bonding pairs and the lone pairs to the corners of a tetrahedron Figure 1.4.3.

3. With two bonding pairs and two lone pairs, the structure is designated as AX_2E_2 with a total of four electron pairs. Due to LP–LP, LP–BP, and BP–BP interactions, we expect a significant deviation from idealized tetrahedral angles.

4. With two hydrogen atoms and two lone pairs of electrons, the structure has significant lone pair interactions. There are two nuclei about the central atom, so the molecular shape is *bent*, or *V shaped*, with an H–O–H angle that is even less than the H–N–H angles in NH_3, as we would expect because of the presence of two lone pairs of electrons on the central atom rather than one.. This molecular shape is essentially a tetrahedron with two missing vertices.



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1.8.4: Describing Chemical Bonds - Valence Bond Theory

Objectives

After completing this section, you should be able to

1. explain how covalent bonds are formed as a result of the ability of atoms to share electrons.
2. describe the formation of covalent bonds in terms of the overlapping of atomic orbitals.

Key Terms

Make certain that you can define, and use in context, the key terms below.

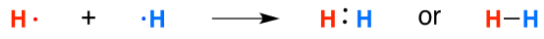
- bond strength
- covalent bond
- bond length
- sigma (σ) bond
- pi (π) bond
- valence bond theory

Valence Bond Theory

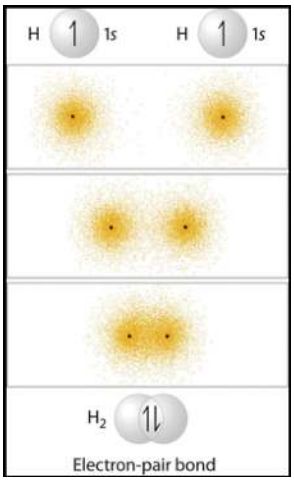
As we have been discussing how to use Lewis structures to depict the bonding in organic compounds, we have been very vague so far in our language about the actual nature of the chemical bonds themselves. We know that a covalent bond involves the 'sharing' of a pair of electrons between two atoms – but how does this happen, and how does it lead to the formation of a bond holding the two atoms together? Two main models have been developed to described how covalent bonds are formed: valence bond theory and molecularly orbital theory.

Valence bond theory is most often used to describe bonding in organic molecules. In this model, covalent bonds are considered to form from the overlap of two atomic orbitals on different atoms, each orbital containing a single electron. The electrons become paired in the orbital overlap bonding the atoms together.

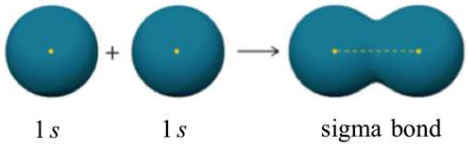
The simplest example valence bond theory can be demonstrated by the H_2 molecule. We can see from the periodic table that each hydrogen atom has a single valence electron. If 2 hydrogen atoms come together to form a bond, then each hydrogen atom effectively has a share in both electrons and thus each resembles the noble gas helium and is more stable. The 2 electrons shared in the orbital overlap are represented by a single dash between the atoms.



Valence bond theory describes a chemical bond as the overlap of atomic orbitals. In the case of the hydrogen molecule, the 1s orbital of one hydrogen atom overlaps with the 1s orbital of the second hydrogen atom to form a molecular orbital called a sigma bond which contains two electrons of opposite spin. The mutual attraction between this negatively charged electron pair and the two atoms' positively charged nuclei serves to physically link the two atoms through a force we define as a covalent bond. The strength of a covalent bond depends on the extent of overlap of the orbitals involved. Orbitals that overlap extensively form bonds that are stronger than those that have less overlap.



ne more characteristic of the covalent bond in H_2 is important to consider at this point. The two overlapping 1*s* orbitals can be visualized as two spherical balloons being pressed together. This means that the bond has **cylindrical symmetry**: if we were to take a cross-sectional plane of the bond at any point, it would form a circle. This type of bond is referred to as a **σ(sigma) bond**.



The energy of the system depends on how much the orbitals overlap. The energy diagram below illustrates how the sum of the energies of two hydrogen atoms (the colored curve) changes as they approach each other. When the atoms are far apart there is no overlap, and by convention we set the sum of the energies at zero. As the atoms move together, their orbitals begin to overlap. Each electron begins to feel the attraction of the nucleus in the other atom. In addition, the electrons begin to repel each other, as do the nuclei. While the atoms are still widely separated, the attractions are slightly stronger than the repulsions, and the energy of the system decreases. (A bond begins to form.) As the atoms move closer together, the overlap increases, so the attraction of the nuclei for the electrons continues to increase (as do the repulsions among electrons and between the nuclei). At some specific distance between the atoms, which varies depending on the atoms involved, the energy reaches its lowest (most stable) value. This optimum distance between the two bonded nuclei is called the the bond lengths between the two atoms. The bond is stable because at this point, the attractive and repulsive forces combine to create the lowest possible energy configuration.

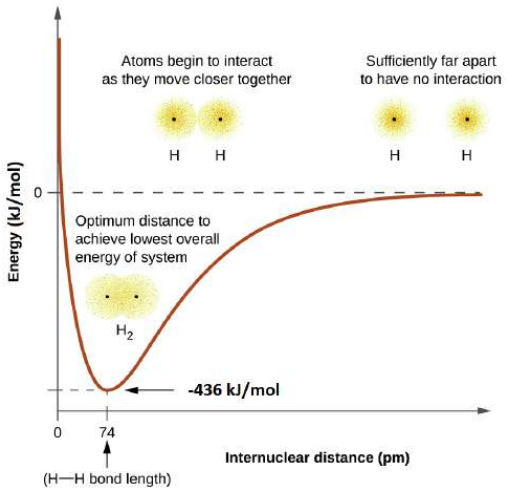


Figure **1.8.4.2**: A Plot of Potential Energy versus Internuclear Distance for the Interaction between Two Gaseous Hydrogen **Atoms**

This optimal internuclear distance is the **bond length**. For the H_2 molecule, the distance is 74 pm (picometers, 10^{-12} meters). Likewise, the difference in potential energy between the lowest energy state (at the optimal internuclear distance) and the state

where the two atoms are completely separated is called the **bond dissociation energy,** or, more simply**, bond strength**. For the hydrogen molecule, the H-H bond strength is equal to about 435 kJ/mol. This means it would take 435 kJ to break one mole of H-H bonds.

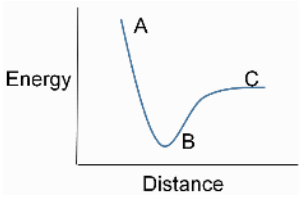
Every covalent bond in a given molecule has a characteristic length and strength. In general, the length of a typical carbon-carbon single bond in an organic molecule is about 150 pm, while carbon-carbon double bonds are about 130 pm, carbon-oxygen double bonds are about 120 pm, and carbon-hydrogen bonds are in the range of 100 to 110 pm. The strength of covalent bonds in organic molecules ranges from about 234 kJ/mol for a carbon-iodine bond (in thyroid hormone, for example), about 410 kJ/mole for a typical carbon-hydrogen bond, and up to over 800 kJ/mole for a carbon-carbon triple bond.

Table: Representative Bond Energies and Lengths

Bond	Length (pm)	Energy (kJ/mol)		Bond	Length (pm)	Energy (kJ/mol)
H-H	74	436		C-O	140.1	358
H-C	106.8	413		C=O	119.7	745
H-N	101.5	391		C≡O	113.7	1072
H-O	97.5	467		H-Cl	127.5	431
C-C	150.6	347		H-Br	141.4	366
C=C	133.5	614		H-I	160.9	298
C≡C	120.8	839		O-O	148	146
C-N	142.1	305		O=O	120.8	498
C=N	130.0	615		F-F	141.2	159
C≡N	116.1	891		Cl-Cl	198.8	243

Exercises

1) For the following energy diagram for energy vs. intermolecular distance is for a fluorine molecule (F_2). Please describe the importance for points A, B, & C on the graph.



Solutions

1)

A - Repulsive Forces are present, nuclei are too close to one another.

B - Optimal distance between the two orbitals to have a bond (the bond length)

C - Cannot form a bond, the orbitals are too far apart.

Exercises

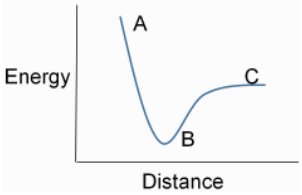
Questions

Q1.5.1

Draw an energy diagram for energy vs. intermolecular distance for a fluorine molecule (F_2) and describe the regions of the graph.

Solutions

S1.5.1



A - Repulsive Forces are present, p-orbitals are too close together

B - Optimal distance between the two p-orbitals to have a bond (the bond length)

C - Cannot form a bond, orbitals are too far away

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1.8.5: Polar Covalent Bonds - Electronegativity

Objectives

After completing this section, you should be able to

- describe how differences in electronegativity give rise to bond polarity.
- arrange a given series of the elements most often encountered in organic chemistry (C, H, O, N, S, P and the halogens) in order of increasing or decreasing electronegativity, without referring to a table of electronegativities.
- predict the partial positive and partial negative ends of a given bond formed between any two of the elements listed in Objective 2, above, without the use of a table of electronegativities or a periodic table.
- predict the partial positive and partial negative ends of a given bond formed between any two elements not listed in Objective 2, above, using a periodic table.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- electronegativity inductive effect
- polar covalent bond

Study Notes

Students often wonder why it is important to be able to tell whether a given bond is polar or not, and why they need to know which atoms carry a partial positive charge and which a partial negative charge. Consider the chloromethane (CH_3Cl) molecule. The carbon atom is shown as carrying a partial positive charge. Now, recall that opposite charges attract. Thus, it seems reasonable that the slightly positive carbon atom in chloromethane should be susceptible to attack by a negatively charged species, such as the hydroxide ion, OH^-. This theory is borne out in practice: hydroxide ions react with chloromethane by attacking the slightly positive carbon atom in the latter. It is often possible to rationalize chemical reactions in this manner, and you will find the knowledge of bond polarity indispensable when you start to write reaction mechanisms.

Note: Because of the small difference in electronegativity between carbon and hydrogen, the **C-H** bond is normally assumed to be nonpolar.

Electronegativity

Because the tendency of an element to gain or lose electrons is so important in determining its chemistry, various methods have been developed to quantitatively describe this tendency. The most important method uses a measurement called **electronegativity** (represented by the Greek letter *chi*, χ, pronounced “ky” as in “sky”), which is defined as the *relative* ability of an atom to attract electrons to itself *in a chemical compound*. Elements with high electronegativities tend to acquire electrons in chemical reactions and are found in the upper right corner of the periodic table. Elements with low electronegativities tend to lose electrons in chemical reactions and are found in the lower left corner of the periodic table.

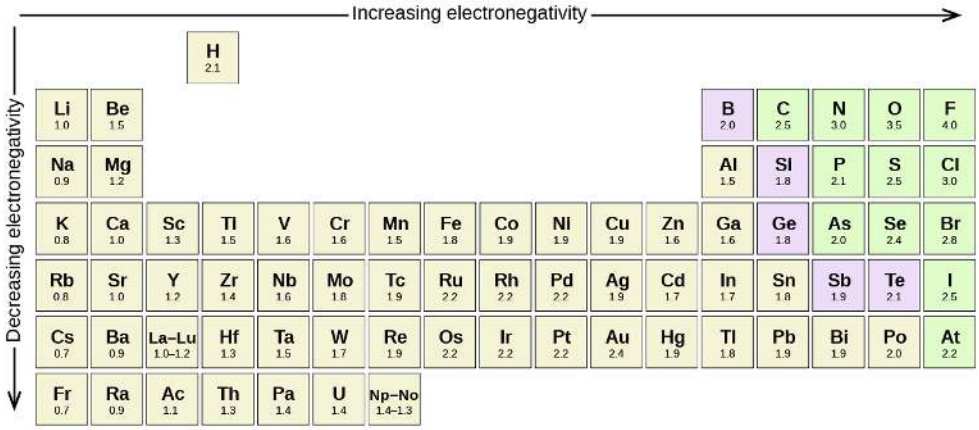


Figure **1.8.5.1**: Pauling scale electronegativities of elements

Electronegativity of an atom is not a simple, fixed property that can be directly measured in a single experiment. In fact, an atom's electronegativity should depend to some extent on its chemical environment because the properties of an atom are influenced by the neighboring atoms in a chemical compound. Nevertheless, when different methods for measuring the electronegativity of an atom are compared, they all tend to assign similar relative values to a given element. ***Figure* 1.8.5.1** shows the electronegativity values of the elements as proposed by one of the most famous chemists of the twentieth century: Linus Pauling. In this scale a value of 4.0 is arbitrarily given to the most electronegative element, fluorine, and the other electronegativities are scaled relative to this value. In general, electronegativity increases from left to right across a period in the periodic table and decreases down a group. Thus, the nonmetals, which lie in the upper right, tend to have the highest electronegativities, with fluorine the most electronegative element of all (EN = 4.0 as previously noted). It is important to notice that the elements most important to organic chemistry, carbon, nitrogen, and oxygen have some of the highest electronegativites in the periodic table (EN = 2.5, 3.0, 3.5 respectively). Metals, on the left, tend to be less electronegative elements, with cesium having the lowest (EN = 0.7). Note that noble gases are excluded from this figure because these atoms usually do not share electrons with others atoms since they have a full valence shell.

> Electronegativity is defined as the ability of an atom in a particular molecule to attract electrons to itself. The **larger** the electronegativity value, the **greater** the attraction.

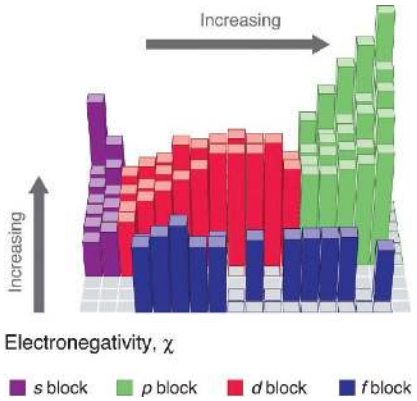


Figure **1.8.5.2**: Visual representation of electronegativities. (CC BY-SA-NC; Anonyumous via LibreTexts)

Electronegativity and Bond Type

The two idealized extremes of chemical bonding: (1) **ionic bonding**—in which one or more electrons are transferred completely from one atom to another, and the resulting ions are held together by purely electrostatic forces—and (2) **covalent bonding**, in which electrons are shared equally between two atoms. Most compounds, however, have **polar covalent bonds**, which means that electrons are shared unequally between the bonded atoms. Electronegativity determines how the shared electrons are distributed between the two atoms in a polar covalent bond. The more strongly an atom attracts the electrons in its bonds, the larger its electronegativity. Electrons in a polar covalent bond are shifted toward the more electronegative atom; thus, the more

electronegative atom is the one with the partial negative charge. The greater the difference in electronegativity, the more polarized the electron distribution and the larger the partial charges of the atoms. Recall that a lowercase Greek delta (δ) is used to indicate that a bonded atom possesses a partial positive charge, indicated by δ^+ , or a partial negative charge, indicated by δ^- , and a bond between two atoms that possess partial charges is a polar bond.

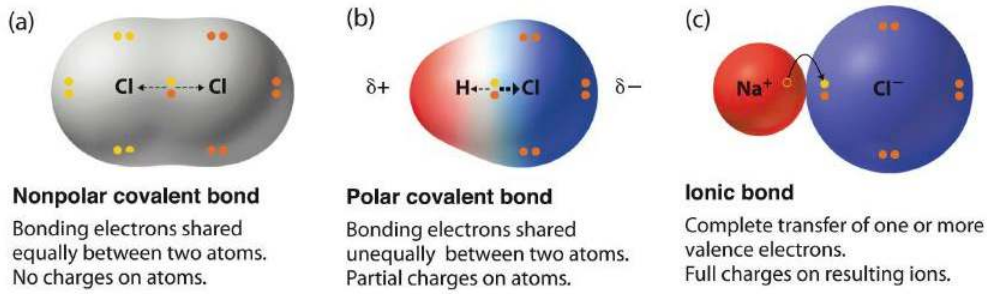
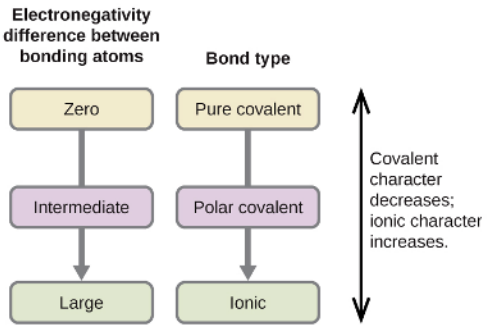


Figure **1.8.5.3**: The Electron Distribution in a Nonpolar Covalent Bond, a Polar Covalent Bond, and an Ionic Bond Using Lewis Electron Structures. Electron-rich (negatively charged) regions are shown in blue; electron-poor (positively charged) regions are shown in red. (CC BY-SA-NC; Anonymous via LibreTexts)

Whether a bond is **ionic**, **nonpolar covalent**, or **polar covalent** can be estimated by by calculating the absolute value of the difference in electronegativity (ΔEN) of two bonded atoms. When the difference is very small or zero, the bond is covalent and nonpolar. When it is large, the bond is polar covalent or ionic. The absolute values of the electronegativity differences between the atoms in the bonds H–H, H–Cl, and Na–Cl are 0 (nonpolar), 0.9 (polar covalent), and 2.1 (ionic), respectively. The degree to which electrons are shared between atoms varies from completely equal (pure covalent bonding) to not at all (ionic bonding). Figure 7.2.4 shows the relationship between electronegativity difference and bond type. This table is just a general guide, however, with many exceptions. The best guide to the covalent or ionic character of a bond is to consider the types of atoms involved and their relative positions in the periodic table. Bonds between two nonmetals are generally covalent; bonding between a metal and a nonmetal is often ionic.



Bond Type	Electronegativity Difference
pure covalent	< 0.4
polar covalent	between 0.4 and 1.8
ionic	> 1.8

Figure **1.8.5.4**: As the electronegativity difference increases between two atoms, the bond becomes more ionic. (CC BY 4.0; OpenStax)

Some compounds contain both covalent and ionic bonds. The atoms in polyatomic ions, such as OH^-, NO_3^-, and NH_4^+, are held together by polar covalent bonds. However, these polyatomic ions form ionic compounds by combining with ions of opposite charge. For example, potassium nitrate, KNO_3, contains the K^+ cation and the polyatomic NO_3^- anion. Thus, bonding in potassium nitrate is ionic, resulting from the electrostatic attraction between the ions K^+ and NO_3^-, as well as covalent between the nitrogen and oxygen atoms in NO_3^-.

✔ Example 1.8.5.1

Bond polarities play an important role in determining the structure of proteins. Using the electronegativity values in Table A2, arrange the following covalent bonds—all commonly found in amino acids—in order of increasing polarity. Then designate the positive and negative atoms using the symbols δ+ and δ–:

C–H, C–N, C–O, N–H, O–H, S–H

Solution

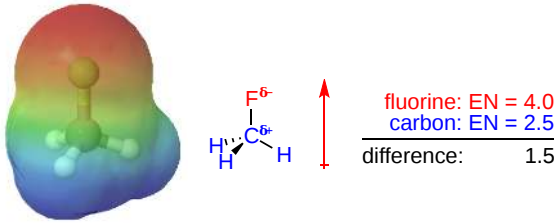
The polarity of these bonds increases as the absolute value of the electronegativity difference increases. The atom with the δ– designation is the more electronegative of the two. Table **1.8.5.1** shows these bonds in order of increasing polarity.

Table **1.8.5.1**: Bond Polarity and Electronegativity Difference

Bond	ΔEN	Polarity
C–H	0.4	$\overset{\delta-}{\mathrm{C}}-\overset{\delta+}{\mathrm{H}}$
S–H	0.4	$\overset{\delta-}{\mathrm{S}}-\overset{\delta+}{\mathrm{H}}$
C–N	0.5	$\overset{\delta+}{\mathrm{C}}-\overset{\delta-}{\mathrm{N}}$
N–H	0.9	$\overset{\delta-}{\mathrm{N}}-\overset{\delta+}{\mathrm{H}}$
C–O	1.0	$\overset{\delta+}{\mathrm{C}}-\overset{\delta-}{\mathrm{O}}$
O–H	1.4	$\overset{\delta-}{\mathrm{O}}-\overset{\delta+}{\mathrm{H}}$

Visualizing Bonding

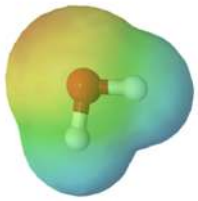
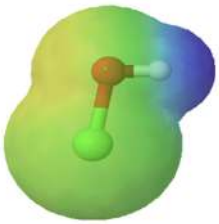
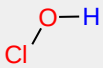
Calculated charge distributions in molecules can easily be visualized by using electrostatic potential maps. The color red is used to indicate electron-rich regions of a molecule while the color blue is used to indicated electron-poor regions. An easier method for visually representing electron displacement in a molecule uses a crossed arrow. By convention the arrow point in the direction of the electron-rich region of a molecule and away from the electron-poor. An example is shown in the molecule fluoromethane. The C-F bond is polarized drawing the bonding electrons toward the more electronegative fluorine giving it a partial negative charge. Consequently, the bonding electrons are drawn away from the less electronegative carbon giving it a partial positive charge. The the electron-rich fluorine is shown as red in the electrostatic potential map and while the electron-poor carbon is shown as blue. The crossed arrow points in the direction of the electron-rich fluorine.



Electrostatic Potential Map and Dipole Moment of Fluoromethane

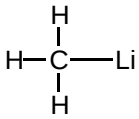
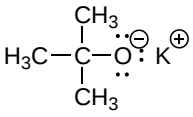
Chemists often use the term, **inductive effect**, to describe the shifting of electrons in a sigma by the electronegativity of atoms. Relatively electronegative atoms, such as fluorine, tend to inductively draw electrons towards themselves and away from nearby atoms. The inductive effect will be used to explain chemical reactivity in many situations in organic chemistry. An excellent example of the inductive effect is seen when comparing the O-H bond polarities of water (H_2O) and hypochlorous acid (ClOH). Replacing the less electronegative hydrogen (EN = 2.1) in water with the more electronegative chlorine (EN = 3.0) in hypochlorous

acid creates a greater bond polarity. The chlorine draws electrons away giving the hydrogen a greater partial positive charge. This is shown in the electrostatic potential map as an increase in the blue color around hydrogen.

	
	
water	hypochlorous acid

A "spectrum" of bonds

There is no clear-cut division between covalent and ionic bonds. In a pure non-polar covalent bond, the electrons are held on average exactly half way between the atoms. In a polar bond, the electrons have been dragged slightly towards one end. How far does this dragging have to go before the bond counts as ionic? There is no real answer to that. Sodium chloride is typically considered an ionic solid, but even here the sodium has not completely lost control of its electron. Because of the properties of sodium chloride, however, we tend to count it as if it were purely ionic. Lithium iodide, on the other hand, would be described as being "ionic with some covalent character". In this case, the pair of electrons has not moved entirely over to the iodine end of the bond. Lithium iodide, for example, dissolves in organic solvents like ethanol - not something which ionic substances normally do. Many bonds between metals and non-metal atoms, are considered ionic, however some of these bonds cannot be simply identified as one type of bond. Examples of this are the lithium - carbon bond in methyllithium which is usually considered as polar covalent (somewhat between covalent and ionic) and the potassium - oxygen bond in potassium *tert*-butoxide which is considered more ionic than covalent.

	
methyllithium	potassium *tert*-butoxide

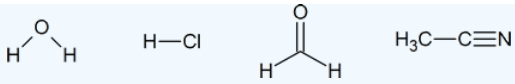
Summary

Covalent bonds form when electrons are shared between atoms and are attracted by the nuclei of both atoms. In pure covalent bonds, the electrons are shared equally. In polar covalent bonds, the electrons are shared unequally, as one atom exerts a stronger force of attraction on the electrons than the other. The ability of an atom to attract a pair of electrons in a chemical bond is called its electronegativity. The difference in electronegativity between two atoms determines how polar a bond will be. In a diatomic molecule with two identical atoms, there is no difference in electronegativity, so the bond is nonpolar or pure covalent. When the electronegativity difference is very large, as is the case between metals and nonmetals, the bonding is characterized as ionic.

- No electronegativity difference between two atoms leads to a non-polar covalent bond.
- A small electronegativity difference leads to a polar covalent bond.
- A large electronegativity difference leads to an ionic bond.

? Exercise 1.8.5.1

Identify the positive and negative ends of each of the bonds shown below.



Exercise 1.8.5.2

Which of the following elements is the more electronegative?

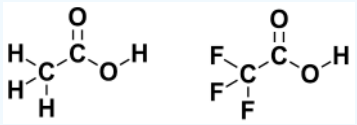
a. Br or C
b. C or H
c. Cl or I
d. C or Li

Answer

a. Br
b. C
c. Cl
d. C

Exercise 1.8.5.3

Which of the following molecules would you expect to have the more polarized O-H bond?

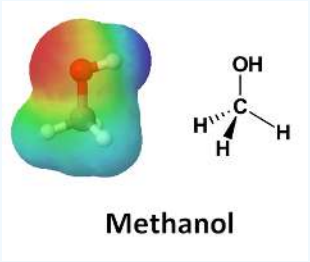


Answer

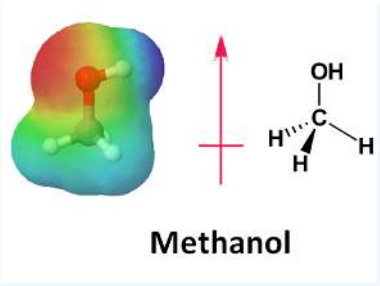
The molecule on the right would have the more polarized O-H bond. The presence of the highly electronegative fluorines would draw electrons away by the inductive effect.

Exercise 1.8.5.4

Predict the direction of polarizing C-O bond in methanol by looking at its electrostatic potential map.



Answer



Methanol

? Exercise 1.8.5.5

Rank the following from least polar to most polar using knowledge of electronegativity

CH_3CH_2-Li CH_3CH_2-K CH_3CH_2-F CH_3CH_2-OH

Answer

(least polar) OH < F < Li < K (most polar)

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1.9: Formal Charge and Resonance

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1.9.1: Lewis Structures and Formal Charges

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

Lewis Structures

Lewis structures, also known as Lewis-dot diagrams, show the bonding relationship between atoms of a molecule and the lone pairs of electrons in a molecule. While it can be helpful initially to write the individual shared electrons, this approach quickly becomes awkward.

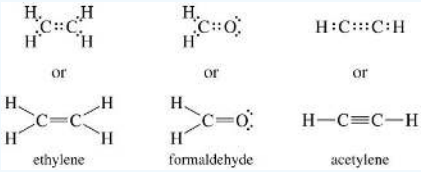
A single line is used to represent one pair of shared electrons. Line representations are only used for shared electrons. Lone pair (unshared) electrons are still shown as individual electrons. Double and triple bonds can also be communicated with lines as shown below.

2 shared electrons form a single bond shown as ':' or '–'

4 shared electrons form a double bond shown as '::' or '='

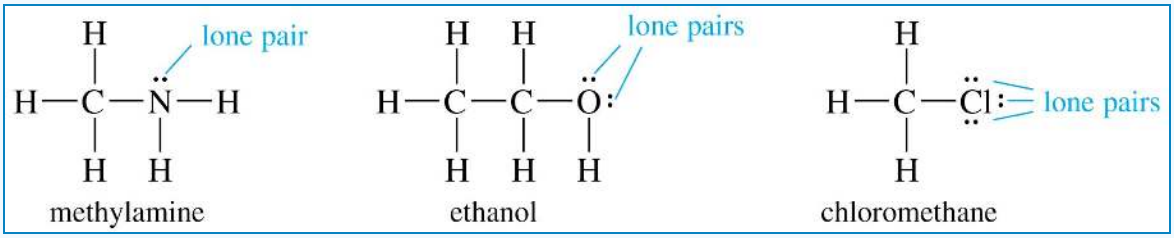
6 shared electrons form at triple bond shown as ':::' or HC≡CH

Unshared electrons are also called 'Lone Pairs' and are shown as ':'



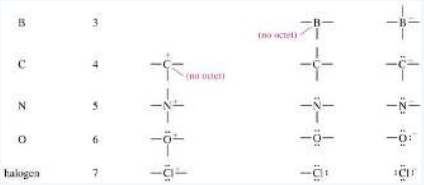
Drawing Lone Pairs

Since the lone pair electrons are often NOT shown in chemical structures, it is important to mentally add the lone pairs. In the beginning, it can be helpful to physically add the lone pair electrons.



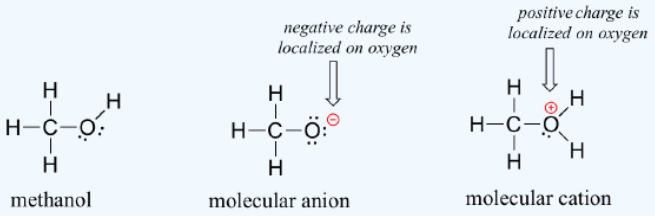
Bonding Patterns

For organic chemistry, the common bonding patterns of carbon, oxygen, and nitrogen have useful applications when evaluating chemical structures and reactivity.



Formal charges

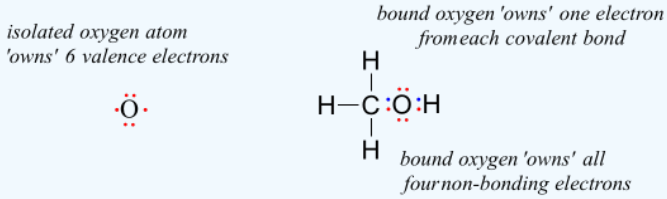
Organic molecules can also have positive or negative charges associated with them. During chemical reactions, it is common to have charge reactant, intermediates, and/or products. Recognizing and distinguishing between neutral and charged bonding patterns will be helpful in learning reaction mechanisms. Consider the Lewis structure of methanol, CH_3OH (methanol is the so-called 'wood alcohol' that unscrupulous bootleggers sometimes sold during the prohibition days in the 1920's, often causing the people who drank it to go blind). Methanol itself is a neutral molecule, but can lose a proton to become a molecular anion (CH_3O^-), or gain a proton to become a molecular cation ($CH_3OH_2^{+}$).



The molecular anion and cation have overall charges of -1 and +1, respectively. But we can be more specific than that - we can also state for each molecular ion that a **formal charge** is located specifically on the oxygen atom, rather than on the carbon or any of the hydrogen atoms.

Figuring out the formal charge on different atoms of a molecule is a straightforward process - it's simply a matter of adding up valence electrons.

A unbound oxygen atom has 6 valence electrons. When it is bound as part of a methanol molecule, however, an oxygen atom is surrounded by 8 valence electrons: 4 nonbonding electrons (two 'lone pairs') and 2 electrons in each of its two covalent bonds (one to carbon, one to hydrogen). In the formal charge convention, we say that the oxygen 'owns' all 4 nonbonding electrons. However, it only 'owns' one electron from each of the two covalent bonds, because covalent bonds involve the sharing of electrons between atoms. Therefore, the oxygen atom in methanol owns 2 + 2 + (½ x 4) = 6 valence electrons.



The formal charge on an atom is calculated as the number of valence electrons owned by the isolated atom minus the number of valence electrons owned by the bound atom in the molecule:

Determining formal charge on an atom

formal charge =

(number of valence electrons owned by the isolated atom)

- (number of valence electrons owned by the bound atom)

or . . .

formal charge =

(number of valence electrons owned by the isolated atom)

- (number of non-bonding electrons on the bound atom)

- (½ the number of bonding electrons on the bound atom)

Using this formula for the oxygen atom of methanol, we have:

formal charge on oxygen =

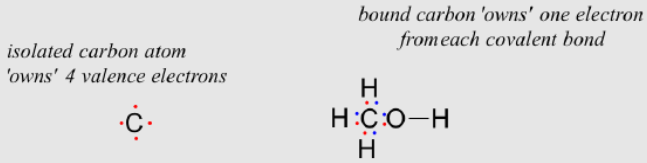
(6 valence electrons on isolated atom)

- (4 non-bonding electrons)

- (½ x 4 bonding electrons)

= 6 - 4 - 2 = **0**. Thus, oxygen in methanol has a formal charge of zero (in other words, it has *no formal charge*).

How about the carbon atom in methanol? An isolated carbon owns 4 valence electrons. The bound carbon in methanol owns (½ x 8) = 4 valence electrons:



formal charge on carbon =

(4 valence electron on isolated atom)

- (0 nonbonding electrons)

- (½ x 8 bonding electrons)

= 4 - 0 - 4 = **0**. So the formal charge on carbon is zero.

For each of the hydrogens in methanol, we also get a formal charge of zero:

formal charge on hydrogen =

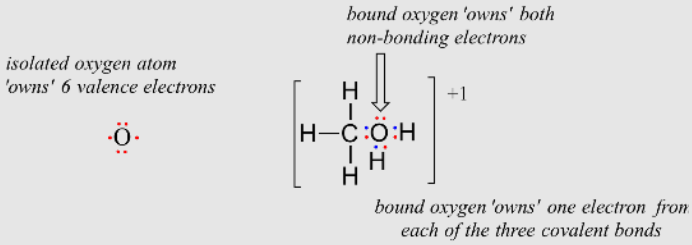
(1 valence electron on isolated atom)

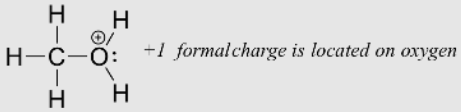
- (0 nonbonding electrons)

- (½ x 2 bonding electrons)

= 1 - 0 - 1 = **0**

Now, let's look at the cationic form of methanol, $CH_3OH_2^+$. The bonding picture has not changed for carbon or for any of the hydrogen atoms, so we will focus on the oxygen atom.





The oxygen owns 2 non-bonding electrons and 3 bonding elections, so the formal charge calculations becomes:

formal charge on oxygen =

(6 valence electrons in isolated atom)

- (2 non-bonding electrons)

- (½ x 6 bonding electrons)

= 6 - 2 - 3 = **1**. A formal charge of +1 is located on the oxygen atom.

For methoxide, the anionic form of methanol, the calculation for the oxygen atom is:

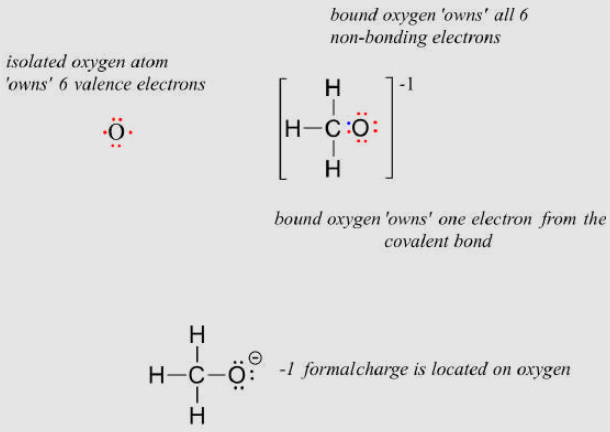
formal charge on oxygen =

(6 valence electrons in isolated atom)

- (6 non-bonding electrons)

- (½ x 2 bonding electrons)

= 6 - 6 - 1 = **-1**. A formal charge of -1 is located on the oxygen atom.

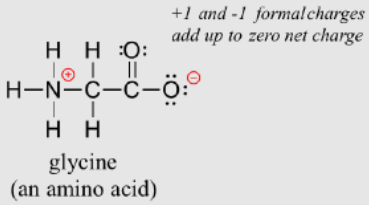


A very important rule to keep in mind is that *the sum of the formal charges on all atoms of a molecule must equal the net charge on the whole molecule.*

When drawing the structures of organic molecules, it is very important to show all non-zero formal charges, being clear about where the charges are located. *A structure that is missing non-zero formal charges is not correctly drawn, and will probably be marked as such on an exam!*

At this point, thinking back to what you learned in general chemistry, you are probably asking "What about dipoles? Doesn't an oxygen atom in an O-H bond 'own' more of the electron density than the hydrogen, because of its greater electronegativity?" This is absolutely correct, and we will be reviewing the concept of bond dipoles later on. For the purpose of calculating formal charges, however, bond dipoles don't matter - we always consider the two electrons in a bond to be shared equally, even if that is not an accurate reflection of chemical reality. Formal charges are just that - a formality, a method of electron book-keeping that is tied into the Lewis system for drawing the structures of organic compounds and ions. Later, we will see how the concept of formal charge can help us to visualize how organic molecules react.

Finally, don't be lured into thinking that just because the net charge on a structure is zero there are no atoms with formal charges: one atom could have a positive formal charge and another a negative formal charge, and the net charge would still be zero. **Zwitterions,** such as amino acids, have both positive and negative formal charges on different atoms:

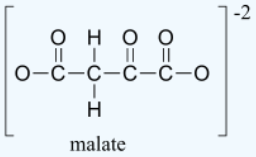


glycine
(an amino acid)

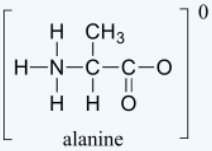
Even though the *net* charge on glycine is zero, it is still neccessary to show the location of the positive and negative formal charges.

Exercise 1.4

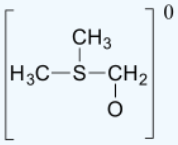
Fill in all missing lone pair electrons and formal charges in the structures below. Assume that all atoms have a complete valence shell of electrons. Net charges are shown outside the brackets.

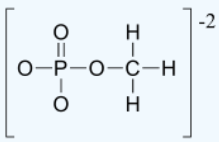
a) 

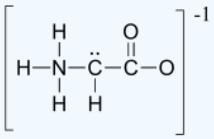
malate

b) 

alanine

c) 

d) 

e) 

Solutions to exercises

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1.9.2: Resonance

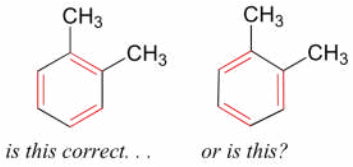
Learning Objective

- Draw resonance forms and predict the relative contribution of each resonance form to the overall structure of the compound or ion

Recognizing resonance

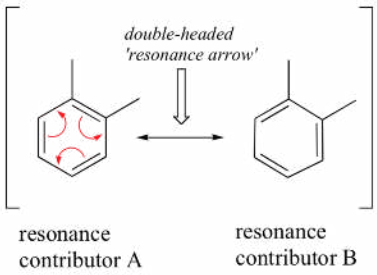
Resonance contributors involve the ‘imaginary movement’ of pi-bonded electrons or of lone-pair electrons that are adjacent to (i.e. conjugated to) pi bonds. You can never shift the location of electrons in sigma bonds – if you show a sigma bond forming or breaking, you are showing a chemical reaction taking place. Likewise, the positions of atoms in the molecule cannot change between two resonance contributors.

Because benzene will appear throughout this course, it is important to recognize the stability gained through the resonance delocalization of the six pi electrons throughout the six carbon atoms. Benzene also illustrates one way to recognize resonance - when it is possible to draw two or more equivalent Lewis strucutres. If we were to draw the structure of an aromatic molecule such as 1,2-dimethylbenzene, there are two ways that we could draw the double bonds:



Which way is correct? There are two simple answers to this question: 'both' and 'neither one'. Both ways of drawing the molecule are equally acceptable approximations of the bonding picture for the molecule, but neither one, by itself, is an accurate picture of the delocalized pi bonds. The two alternative drawings, however, *when considered together*, give a much more accurate picture than either one on its own. This is because they imply, together, that the carbon-carbon bonds are not double bonds, not single bonds, but about halfway in between.

When it is possible to draw more than one valid structure for a compound or ion, we have identified **resonance contributors**: two or more different Lewis structures depicting the same molecule or ion that, when considered together, do a better job of approximating delocalized pi-bonding than any single structure. By convention, resonance contributors are linked by a double-headed arrow, and are sometimes enclosed by brackets:

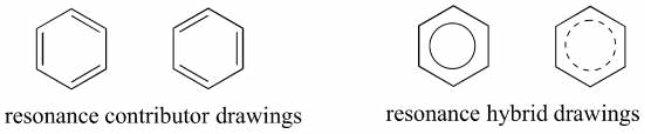


In order to make it easier to visualize the difference between two resonance contributors, small, curved arrows are often used. Each of these arrows depicts the ‘movement’ of two pi electrons. A few chapters from now when we begin to study organic reactions - a process in which electron density shifts and covalent bonds between atoms break and form - this ‘curved arrow notation’ will become extremely important in depicting electron movement. In the drawing of resonance contributors, however, this electron ‘movement’ occurs only in our minds, as we try to visualize delocalized pi bonds. Nevertheless, use of the curved arrow notation is an essential skill that you will need to develop in drawing resonance contributors.

The depiction of benzene using the two resonance contributors A and B in the figure above does *not* imply that the molecule at one moment looks like structure A, then at the next moment shifts to look like structure B. Rather, at all moments, the molecule is a combination, or **resonance hybrid** of both A and B.

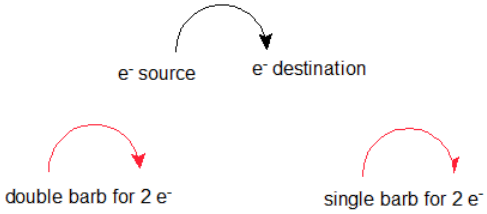
Caution! It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*. Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken place.

Usually, derivatives of benzene (and phenyl groups, when the benzene ring is incorporated into a larger organic structure) are depicted with only one resonance contributor, and it is assumed that the reader understands that resonance hybridization is implied. This is the convention that will be used for the most part in this book. In other books or articles, you may sometimes see benzene or a phenyl group drawn with a circle inside the hexagon, either solid or dashed, as a way of drawing a resonance hybrid.

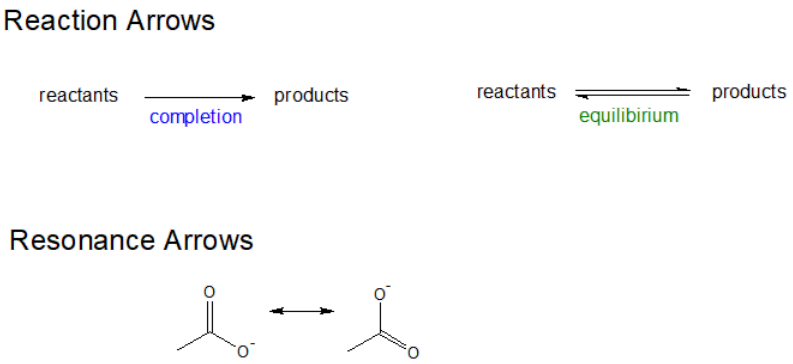


Curved arrows communicate electron flow (movement)

Curved arrows indicate electron flow. The base of the curved arrow is placed at the source of the electrons that are moving. The head of the arrow is placed at the destination of the electrons. A single barbed arrow represents one electron and a double barb represents two electrons. Electrons move from regions of relative high density to regions of low density or toward electronegative elements. It is important to use accuracy and precision when drawing curved arrows.



It is also important to consciously use the correct type of arrow. There are four primary types of arrows used by chemists to communicate one of the following: completion reaction, equilibrium reaction, electron movement, resonance forms. The three other types of arrows are shown below to build discernment between them.



Resonance Delocalizes Charge to Increase Stability

Resonance is most useful wen it delocalizes charge to stabilize reactive intermediates and products. Recognizing, drawing, and evaluating the relative stability of resonance contributors is essential to understanding organic reaction mechanisms.

Guidelines for drawing and working with resonance contributors

Learning to draw and interpret resonance structures, there are a few basic guidelines to help avoid drawing nonsensical structures. All of these guidellines make perfect sense as long as we remember that resonance contributors are merely a human-invented convention for depicting the delocalization of pi electrons in conjugated systems. When we see two different resonance contributors, we are not seeing a chemical reaction! We are seeing the exact same molecule or ion depicted in two different ways. All resonance contributors must be drawn as proper Lewis structures, with correct formal charges. Never show curved 'electron

movement' arrows that would lead to a situation where a second-row element (ie. carbon, nitrogen, or oxygen) has more than eight electrons: this would break the 'octet rule'. Sometimes, however, we will draw resonance contributors in which a carbon atom has only six electrons (ie. a carbocation). In general, all oxygen and nitrogen atoms should have a complete octet of valence electrons.

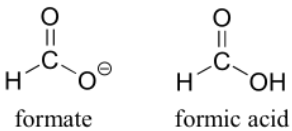
1. There is ONLY ONE STRUCTURE for each compound or ion. This structure takes its character from the sum of all the contributors, not all resonance structures contribute equally to the sum.
2. Atoms must maintain their same position.
3. Only e- move !
4. All resonance contributors for a molecule or ion must have the same net charge.
5. Recognize which electrons can participate in resonance
    a) unshared e^- pairs or radicals
    b) pi bond electrons
6. Recognize electron receptors
    a) atoms with a positive (+) charge
    b) electronegative atoms that can tolerate a negative charge
    c) atoms which possess delocalizable electrons - see #4 above
7. Common electron flow patterns
    a) move pi e^- toward positive (+) charge or other pi bonds
    b) move non-bonding e^- pairs toward pi bonds
    c) move single non-bonding e^- toward pi bonds

Evaluating Resonance Contributors

1. Identical structures are equally important.
2. Structures will a greater number of bonds are more important.
3. Structures with charge separation are less important.
4. Pay attention to electronegativities.
5. Neutral atoms need to have complete octets.

Resonance Contributors for the Carboxylate Group

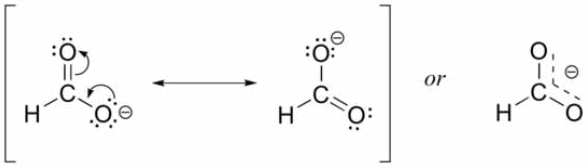
The convention of drawing two or more resonance contributors to approximate a single structure may seem a bit clumsy to you at this point, but as you gain experience you will see that the practice is actually very useful when discussing the manner in which many functional groups react. Let’s next consider the carboxylate ion (the conjugate base of a carboxylic acid). As our example, we will use formate, the simplest possible carboxylate-containing molecule. The conjugate acid of formate is formic acid, which causes the painful sting you felt if you have ever been bitten by an ant.



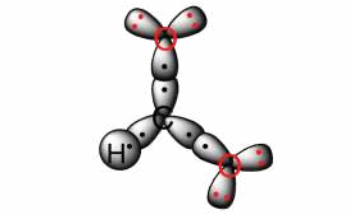
formate formic acid

Usually, you will see carboxylate groups drawn with one carbon-oxygen double bond and one carbon-oxygen single bond, with a negative formal charge located on the single-bonded oxygen. In actuality, however, the two carbon-oxygen bonds are the same length, and although there is indeed an overall negative formal charge on the group, it is shared equally between the two oxygens. Therefore, the carboxylate can be more accurately depicted by a *pair* of resonance contributors. Alternatively, a single structure can

be used, with a dashed line depicting the resonance-delocalized pi bond and the negative charge located in between the two oxygens.

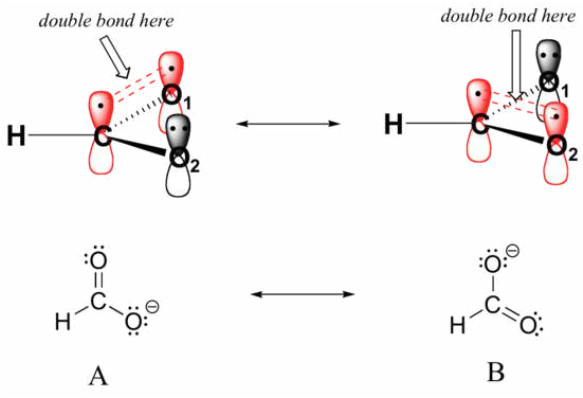


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as well. Both carbon-oxygen sigma bonds, then, are formed from the overlap of carbon sp^2 orbitals and oxygen sp^2 orbitals.



the σ-bonding framework of formate

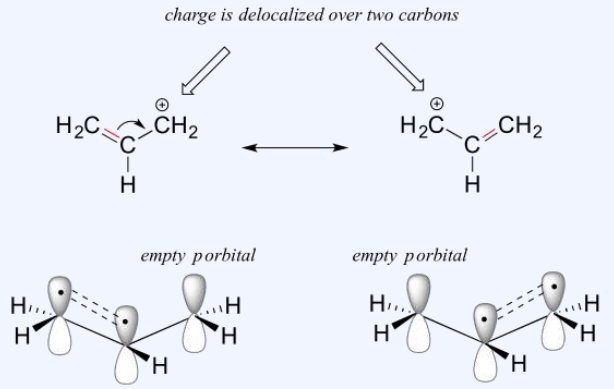
In addition, the carbon and both oxygens each have an unhybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.



Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in its $2p_z$ orbital. Overall, the situation is one of *three parallel, overlapping $2p_z$ orbitals sharing four delocalized pi electrons*. Because there is one more electron than there are $2p_z$ orbitals, the system has an overall charge of –1. This is the kind of 3D picture that resonance contributors are used to approximate, and once you get some practice you should be able to quickly visualize overlapping $2p_z$ orbitals and delocalized pi electrons whenever you see resonance structures being used. In this text, carboxylate groups will usually be drawn showing only one resonance contributor for the sake of simplicity, but you should always keep in mind that the two C-O bonds are equal, and that the negative charge is delocalized to both oxygens.

Exercise 2.13: There is a third resonance contributor for formate (which we will soon learn is considered a 'minor' contributor). Draw this resonance contributor.

Here's another example, this time with a carbocation. Recall from section 2.1 that carbocations are sp^2-hybridized, with an empty *2p* orbital oriented perpendicular to the plane formed by three sigma bonds. If a carbocation is adjacent to a double bond, then three *2p* orbitals can overlap and share the two pi electrons - another kind of conjugated pi system in which the positive charge is shared over two carbons.

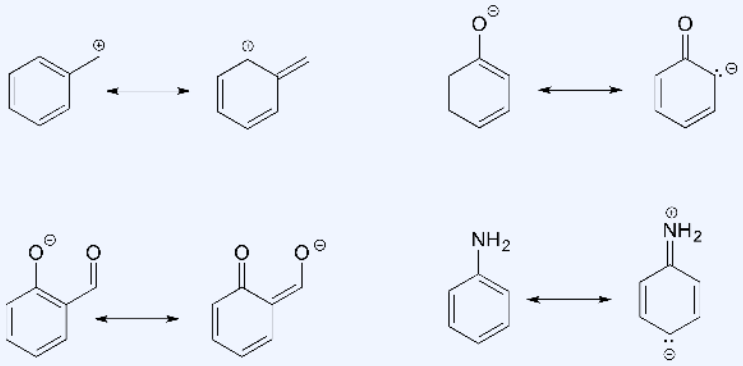


three *p* orbitals sharing two ≠ electrons

Exercise 2.14: Draw the resonance contributors that correspond to the curved, two-electron movement arrows in the resonance expressions below.



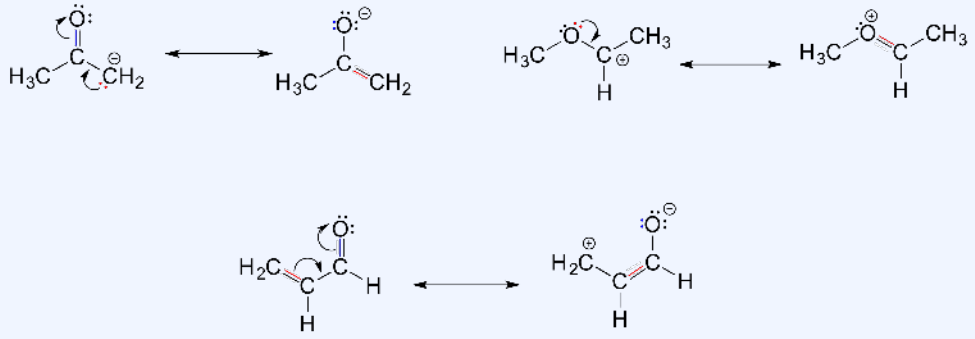
Exercise 2.15: In each resonance expression, draw curved two-electron movement arrows on the left-side contributor that shows how we get to the right-side contributor. Be sure to include formal charges.



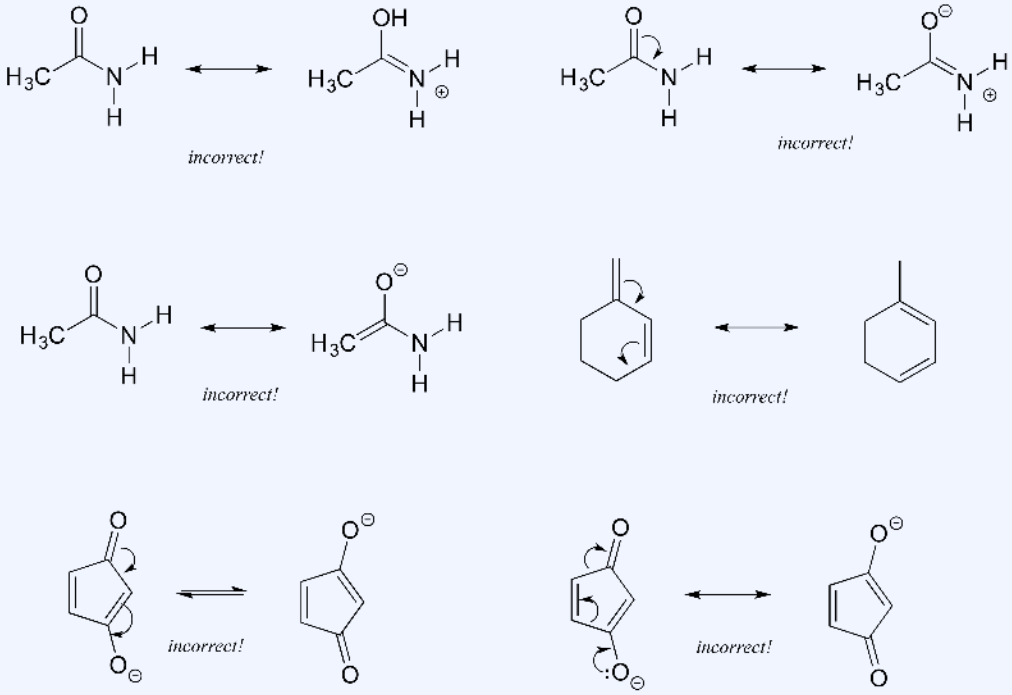
Solutions to exercises

Guided Resonance Practice

Below are a few more examples of 'legal' resonance expressions. Confirm for yourself that the octet rule is not exceeded for any atoms, and that formal charges are correct.



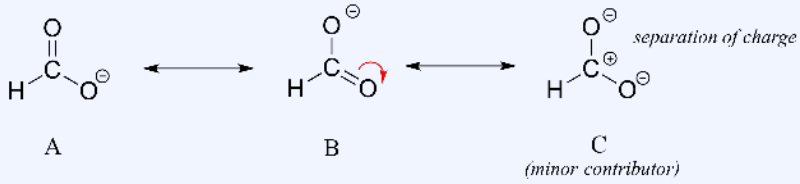
Exercise 2.16: Each of the 'illegal' resonance expressions below contains one or more mistakes. Explain what is incorrect in each.



Solutions to exercises

Major vs minor resonance contributors

Different resonance contributors do not always make the same contribution to the overall structure of the hybrid - rather, in many cases one contributor comes closer to depicting the actual bonding picture than another. In the case of carboxylates, contributors A and B below are equivalent in terms of their relative contribution to the hybrid structure. However, there is also a third resonance contributor 'C, in which the carbon bears a positive formal charge and both oxygens are single-bonded and bear negative charges.



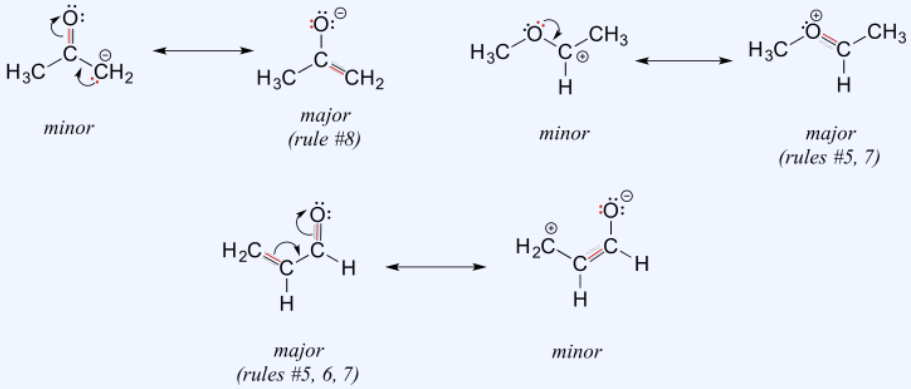
Structure C makes a less important contribution to the overall bonding picture of the group relative to A and B. How do we know that structure C is the 'minor' contributor? There are four basic rules which you need to learn in order

to evaluate the relative importance of different resonance contributors. We will number them 5-8 so that they may be added to in the 'rules for resonance' list earlier on this page.

Rules for determining major and minor resonance contributors:

5. The carbon in contributor C does not have an octet – in general, resonance contributors in which a carbon does not fulfill the octet rule are relatively less important.
6. In structure C, a separation of charge has been introduced that is not present in A or B. In general, resonance contributors in which there is a greater separation of charge are relatively less important.
7. In structure C, there are only three bonds, compared to four in A and B. In general, a resonance structure with a lower number of total bonds is relatively less important.
8. The resonance contributor in which a negative formal charge is located on a more electronegative atom, usually oxygen or nitrogen, is more stable than one in which the negative charge is located on a less electronegative atom such as carbon. An example is in the upper left expression in the next figure.

Below are some additional examples of major and minor resonance contributors:

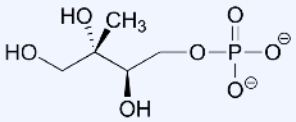


Why do we worry about a resonance contributor if it is the minor one? We will see later that very often a minor contributor can still be extremely important to our understanding of how a molecule reacts.

Exercise 2.17:

a. Draw a minor resonance structure for acetone (IUPAC name 2-propanone). Explain why it is a minor contributor.
b. Are acetone and 2-propanol resonance contributors of each other? Explain.

Exercise 2.18: Draw four additional resonance contributors for the molecule below. Label each one as major or minor (the structure below is of a major contributor).



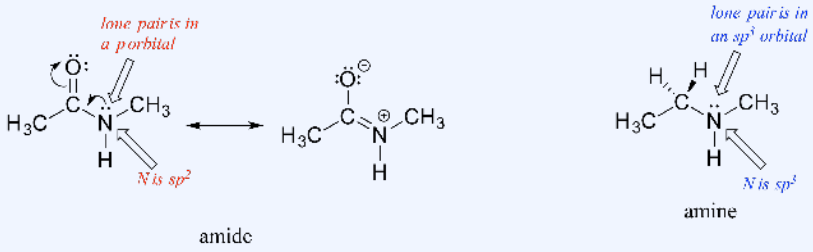
Exercise 2.19: Draw three resonance contributors of methyl acetate (IUPAC name methyl methanoate), and order them according to their relative importance to the bonding picture of the molecule. Explain your reasoning.

Solutions to exercises

Resonance and peptide bonds

What is the hybridization state of the nitrogen atom in an amide? At first glance, it would seem logical to say that it is sp^3-hybridized, because, like the nitrogen in an amine, the Lewis structure shows three single bonds and a lone pair. The picture looks quite different, though, if we consider another resonance contributor in which

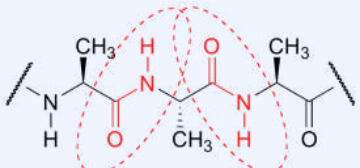
the nitrogen has a double bond to the carbonyl carbon: in this case, we would have to say that applicable hybridization is sp^2, and the bonding geometry trigonal planar rather than tetrahedral.



amide amine

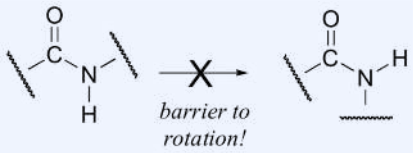
In fact, the latter picture is more accurate: the lone pair of electrons on an amide nitrogen are not localized in an sp^3 orbital, rather, they are delocalized as part of a conjugated pi system, and the bonding geometry around the nitrogen is trigonal planar as expected for sp^2 hybridization. This is a good illustration of an important point: conjugation and the corresponding delocalization of electron density is stabilizing, thus if conjugation can occur, it probably will.

One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.



peptide bonds in a polypeptide

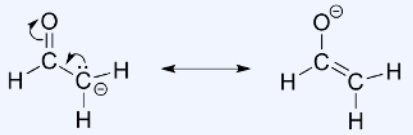
Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, *the C-N bond in a peptide linkage has a significant barrier to rotation*, indicating that to some degree, C-N pi overlap is present - in other words, there is some double bond character, and the nitrogen is sp^2 hybridized with trigonal planar geometry.



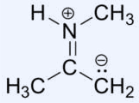
The barrier to rotation in peptide bonds is an integral part of protein structure, introducing more rigidity to the protein's backbone. If there were no barrier to rotation in a peptide bond, proteins would be much more 'floppy' and three dimensional folding would be very different.

Exercise 2.20: Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in methyl amide. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping *2p* orbitals are sharing how many pi-bonded electrons?

Exercise 2.21: Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in the 'enolate' anion shown below. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping 2*p* orbitals are sharing how many pi-bonded electrons?

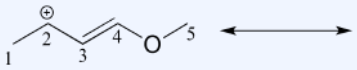


Exercise 2.22: Below is a minor resonance contributor of a species known as an 'enamine', which we will study more in chapter 12. Draw the major resonance contributor for the enamine, and explain why your contributor is the major one (refer to resonance rules #5-8 from this section).

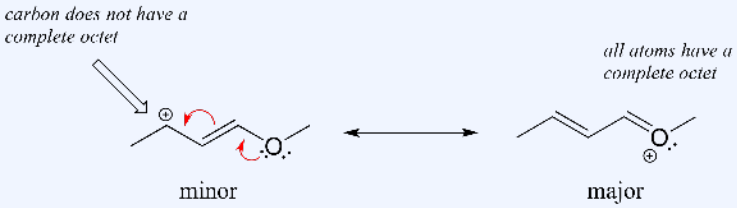


Solutions to exercises

Solved example: Draw the major resonance contributor of the structure below. Include in your figure the appropriate curved arrows showing how you got from the given structure to your structure. Explain why your contributor is the major one. In what kind of orbitals are the two lone pairs on the oxygen?

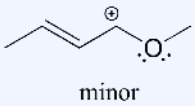


Solution: In the structure above, the carbon with the positive formal charge does not have a complete octet of valence electrons. Using the curved arrow convention, a lone pair on the oxygen can be moved to the adjacent bond to the left, and the electrons in the double bond shifted over to the left (see the rules for drawing resonance contributors to convince yourself that these are 'legal' moves).



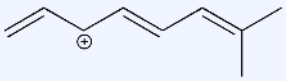
The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #5 and #7 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, and C_4, plus one on oxygen) sharing four pi electrons. One lone pair on the oxygen is in an unhybridized *2p* orbital and is part of the conjugated pi system, and the other is located in an sp^2 orbital.

Also note that one additional contributor can be drawn, but it is also minor because it has a carbon with an incomplete octet:



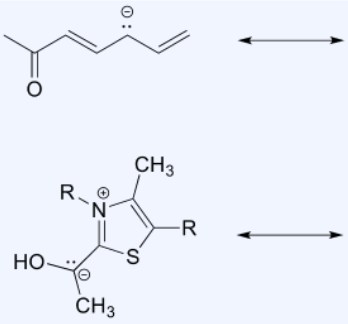
Exercise 2.23:

a) Draw three additional resonance contributors for the carbocation below. Include in your figure the appropriate curved arrows showing how one contributor is converted to the next.



b) Fill in the blanks: the conjugated pi system in this carbocation is composed of _____ *2p* orbitals sharing _____ delocalized pi electrons.

Exercise 2.24: Draw the major resonance contributor for each of the anions below.

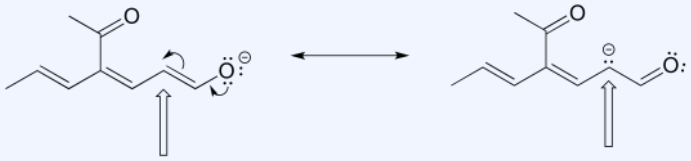


c) Fill in the blanks: the conjugated pi system in part (a) is composed of _____ *2p* orbitals containing _____ delocalized pi electrons.

Exercise 2.25: The figure below shows how the negative formal charge on the oxygen can be delocalized to the carbon indicated by an arrow. More resonance contributors can be drawn in which negative charge is delocalized to three other atoms on the molecule.

a) Circle these atoms.

b) Draw the two most important resonance contributors for the molecule.



Solutions to exercises

A word of advice

Becoming adept at drawing resonance contributors, using the curved arrow notation to show how one contributor can be converted to another, and understanding the concepts of conjugation and resonance delocalization are some of the most challenging but also most important jobs that you will have as a beginning student of organic chemistry. If you work hard now to gain a firm grasp of these ideas, you will have come a long way toward understanding much of what follows in your organic chemistry course. Conversely, if you fail to come to grips with these concepts now, a lot of what you see later in the course will seem like a bunch of mysterious and incomprehensible lines, dots, and arrows, and you will be in for a rough ride, to say the least. More so than many other topics in organic chemistry, *understanding bonding, conjugation, and resonance is something that most students really need to work on 'in person' with an instructor or tutor, preferably using a molecular modeling kit*. Keep working problems, keep asking questions, and keep at it until it all makes sense!

Kahn Academy video tutorials

Drawing resonance structures

More on resonance

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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1.10: Common Bonding Patterns for Organic Chemistry

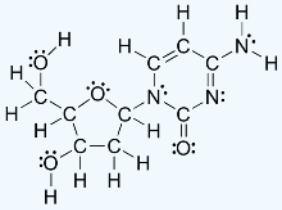
Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

Common bonding patterns in organic structures

The Lewis structure below (of one of the four nucleoside building blocks that make up DNA) can appear complex and confusing at first glance. Fortunately, common bonding patterns occur that can allow for simplifications when drawing structures. The rules for the simplifies structures rely on the neutral bonding patterns for carbon, orygen, nitrogen, phosphorus, and sulfur primarily. Since organic compounds have a hydrocarbon backbone, the atoms that are NOT carbon and hydrogen are called heteroatoms. 2'-deoxycytidine contains seven heteroatoms: four oxygen atoms land three nitrogen atoms. Heteroatoms are a primary source of chemical reactivity for organic chemistry.



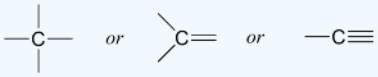
2'-deoxycytidine

Heteroatoms: atoms in an organic compound that are NOT carbon or hydrogen,

typically oxygen, nitrogen, phosphorus, and sulfur

The ability to quickly and efficiently draw large structures and determine formal charges is not terribly hard to come by - all it takes is a few shortcuts and some practice at recognizing common bonding patterns.

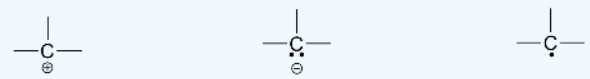
Let’s start with carbon, the most important element for organic chemists. Carbon is said to be tetravalent, meaning that it tends to form four bonds. If you look at the simple structures of methane, methanol, ethane, ethene, and ethyne in the figures from the previous section, you should quickly recognize that in each molecule, the carbon atom has four bonds, and a formal charge of zero.



carbon usually has 4 bonds

This is a pattern that holds throughout most of the organic molecules we will see, but there are also exceptions.

<style type="text/css"></style> In carbon dioxide, the carbon atom has double bonds to oxygen on both sides (O=C=O). Later on in this chapter and throughout this book we will see examples of organic ions called ‘carbocations’ and carbanions’, in which a carbon atom bears a positive or negative formal charge, respectively. If a carbon has only three bonds and an unfilled valence shell (in other words, if it does not fulfill the octet rule), it will have a positive formal charge.



3 bonds, no lone pair: carbocation

3 bonds + lone pair: carbanion

3 bonds + unpaired electron: carbon radical

If, on the other hand, it has three bonds plus a lone pair of electrons, it will have a formal charge of -1. Another possibility is a carbon with three bonds and a single, unpaired (free radical) electron: in this case, the carbon has a formal charge of zero. (One

last possibility is a highly reactive species called a ‘carbene’, in which a carbon has two bonds and one lone pair of electrons, giving it a formal charge of zero. You may encounter carbenes in more advanced chemistry courses, but they will not be discussed any further in this book).

You should certainly use the methods you have learned to check that these formal charges are correct for the examples given above. More importantly, you will need, before you progress much further in your study of organic chemistry, to simply recognize these patterns (and the patterns described below for other atoms) and be able to identify carbons that bear positive and negative formal charges by a quick inspection.

The pattern for hydrogens is easy: hydrogen atoms have only one bond, and no formal charge. The exceptions to this rule are the proton, H^+, and the hydride ion, H^-, which is a proton plus two electrons. Because we are concentrating in this book on organic chemistry as applied to living things, however, we will not be seeing ‘naked’ protons and hydrides as such, because they are too reactive to be present in that form in aqueous solution. Nonetheless, the *idea* of a proton will be very important when we discuss acid-base chemistry, and the *idea* of a hydride ion will become very important much later in the book when we discuss organic oxidation and reduction reactions. As a rule, though, all hydrogen atoms in organic molecules have one bond, and no formal charge.

Let us next turn to oxygen atoms. Typically, you will see an oxygen bonding in three ways, all of which fulfill the octet rule.



neutral oxygen: 2 bonds + 2 lone pairs

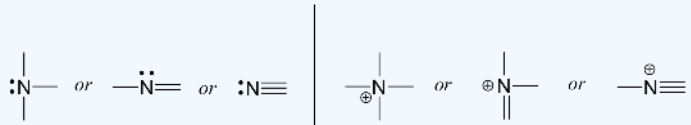
negative formal charge: 1 bond + 3 lone pairs

positive formal charge: 3 bonds + 1 lone pair

If it has two bonds and two lone pairs, as in water, it will have a formal charge of zero. If it has one bond and three lone pairs, as in hydroxide ion, it will have a formal charge of-1. If it has three bonds and one lone pair, as in hydronium ion, it will have a formal charge of +1.

When we get to our discussion of free radical chemistry in chapter 17, we will see other possibilities, such as where an oxygen atom has one bond, one lone pair, and one unpaired (free radical) electron, giving it a formal charge of zero. For now, however, concentrate on the three main non-radical examples, as these will account for virtually everything we see until chapter 17.

Nitrogen has two major bonding patterns, both of which fulfill the octet rule:

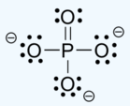


neutral nitrogen: 3 bonds, 1 lone pair

positive nitrogen: 4 bonds

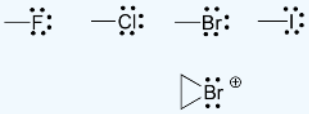
If a nitrogen has three bonds and a lone pair, it has a formal charge of zero. If it has four bonds (and no lone pair), it has a formal charge of +1. In a fairly uncommon bonding pattern, negatively charged nitrogen has two bonds and two lone pairs.

Two third row elements are commonly found in biological organic molecules: sulfur and phosphorus. Although both of these elements have other bonding patterns that are relevant in laboratory chemistry, in a biological context sulfur almost always follows the same bonding/formal charge pattern as oxygen, while phosphorus is present in the form of phosphate ion (PO_4^{3-}), where it has five bonds (almost always to oxygen), no lone pairs, and a formal charge of zero. Remember that atoms of elements in the third row and below in the periodic table have 'expanded valence shells' with *d* orbitals available for bonding, and the the octet rule does not apply.



phosphate

Finally, the halogens (fluorine, chlorine, bromine, and iodine) are very important in laboratory and medicinal organic chemistry, but less common in naturally occurring organic molecules. Halogens in organic compounds usually are seen with one bond, three lone pairs, and a formal charge of zero. Sometimes, especially in the case of bromine, we will encounter reactive species in which the halogen has two bonds (usually in a three-membered ring), two lone pairs, and a formal charge of +1.



These rules, if learned and internalized so that you don't even need to think about them, will allow you to draw large organic structures, complete with formal charges, quite quickly.

Once you have gotten the hang of drawing Lewis structures, it is not always necessary to draw lone pairs on heteroatoms, as you can assume that the proper number of electrons are present around each atom to match the indicated formal charge (or lack thereof). Occasionally, though, lone pairs are drawn if doing so helps to make an explanation more clear.

Exercise 1: Draw one structure that corresponds to each of the following molecular formulas, using the common bonding patters covered above. Be sure to include all lone pairs and formal charges where applicable, and assume that all atoms have a full valence shell of electrons. More than one correct answer is possible for each, so you will want to check your answers with your instructor or tutor.

a) $C_5H_{10}O$ b) C_5H_8O c) $C_6H_8NO^+$ d) $C_4H_3O_2^-$

Solutions to exercises

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CHAPTER OVERVIEW

2: Tools of Organic Chemistry

2.1: Intermolecular Forces (IMFs) - Review
2.1.1: Intermolecular Forces and Relative Boiling Points (bp)
2.1.2: Intermolecular Forces and Solubilities
2.1.3: Chromatography
2.1.4: Thin Layer Chromatography (TLC)
2.1.4A: Overview of TLC
2.1.4B: Uses of TLC
2.1.4C: The Retention Factor
2.1.4D: Separation Theory
2.1.4E: Step-by-Step Procedures for Thin Layer Chromatography
2.1.4F: Visualizing TLC Plates
2.1.5: Gas Chromatography (GC)
2.1.5A: Overview of GC
2.1.5B: Uses of Gas Chromatography
2.1.5C: Separation Theory
2.1.5D: Quantitating with GC
2.1.5E: GC Parameters
2.1.5F: Sample Preparation for Gas Chromatography
2.2: Column Chromatography
2.2.1: Macroscale Columns
2.2.2: Microscale (Pipette) Columns
2.2.3: 5.5 Polarimetry
2.2.4: Crystallization
2.2.4.1: Overview of Crystallization
2.2.4.2: Uses of Crystallization
2.2.4.2A: Reagent Purification
2.2.4.2B: Purification of Product Mixtures
2.2.4.3: Choice of Solvent
2.2.4.3A: Ideal Temperature Profile
2.2.4.3B: General Procedures for Removing Impurities
2.2.4.3C: Determining Which Solvent to Use
2.2.4.3D: Using Solubility Data
2.2.4.3E: Experimentally Testing Solvents
2.2.4.3F: Mixed Solvents
2.2.4.4: Crystallization Theory
2.2.4.4A: Purification
2.2.4.4B: Cooling Slowly
2.2.4.4C: Using the Minimum Amount of Hot Solvent
2.2.4.4D: The Unavoidable Loss of Recovery
2.2.4.4E: Quantitating Crystallization

2.2.4.4F: Second Crop Crystallization
2.2.4.5: Procedural Generalities
2.2.4.5A: General Procedure
2.2.4.5B: Heat Source and Bump Prevention
2.2.4.5C: Charcoal
2.2.4.5D: Cooling Slowly
2.2.4.5E: Initiating Crystallization
2.2.4.6: Step-by-Step Procedures
2.2.4.6A: Single Solvent Crystallization
2.2.4.6B: Crystallization Summary
2.2.4.6C: Using Solvents Other Than Water
2.2.4.6D: Mixed Solvent Crystallization
2.2.4.6E: Mixed Solvent Summary
2.2.4.6F: Troubleshooting

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2.1: Intermolecular Forces (IMFs) - Review

learning objective

- determine the dominant intermolecular forces (IMFs) of organic compounds

The properties of liquids are intermediate between those of gases and solids, but are more similar to solids. In contrast to *intra*molecular forces, such as the covalent bonds that hold atoms together in molecules and polyatomic ions, *inter*molecular forces hold molecules together in a liquid or solid. Intermolecular forces are generally much weaker than covalent bonds. For example, it requires 927 kJ to overcome the intramolecular forces and break both O–H bonds in 1 mol of water, but it takes only about 41 kJ to overcome the intermolecular attractions and convert 1 mol of liquid water to water vapor at 100°C. (Despite this seemingly low value, the intermolecular forces in liquid water are among the strongest such forces known!) Given the large difference in the strengths of intra- and intermolecular forces, changes between the solid, liquid, and gaseous states almost invariably occur for molecular substances *without breaking covalent bonds*.

> *The properties of liquids are intermediate between those of gases and solids but are more similar to solids.*

Intermolecular forces determine bulk properties such as the melting points of solids and the boiling points of liquids. Liquids boil when the molecules have enough thermal energy to overcome the intermolecular attractive forces that hold them together, thereby forming bubbles of vapor within the liquid. Similarly, solids melt when the molecules acquire enough thermal energy to overcome the intermolecular forces that lock them into place in the solid.

Intermolecular forces are electrostatic in nature; that is, they arise from the interaction between positively and negatively charged species. Like covalent and ionic bonds, intermolecular interactions are the sum of both attractive and repulsive components. Because electrostatic interactions fall off rapidly with increasing distance between molecules, intermolecular interactions are most important for solids and liquids, where the molecules are close together. These interactions become important for gases only at very high pressures, where they are responsible for the observed deviations from the ideal gas law at high pressures. (For more information on the behavior of real gases and deviations from the ideal gas law,.)

In this section, we explicitly consider three kinds of intermolecular interactions: There are two additional types of electrostatic interaction that you are already familiar with: the ion–ion interactions that are responsible for ionic bonding and the ion–dipole interactions that occur when ionic substances dissolve in a polar substance such as water. The first two are often described collectively as van der Waals forces.

Dipole–Dipole Interactions

Polar covalent bonds behave as if the bonded atoms have localized fractional charges that are equal but opposite (i.e., the two bonded atoms generate a *dipole*). If the structure of a molecule is such that the individual bond dipoles do not cancel one another, then the molecule has a net dipole moment. Molecules with net dipole moments tend to align themselves so that the positive end of one dipole is near the negative end of another and vice versa, as shown in Figure **2.1.1*a***.

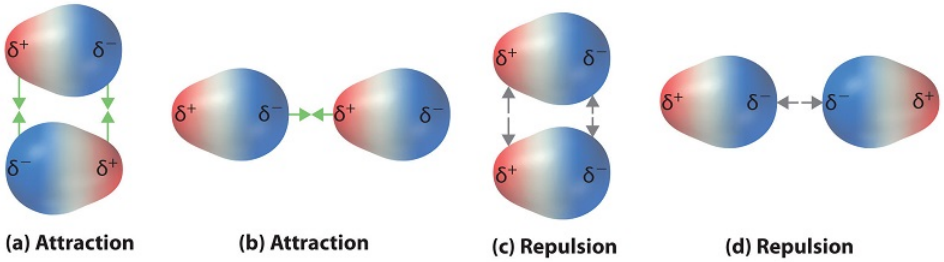


Figure **2.1.1**: Attractive and Repulsive Dipole–Dipole Interactions. (a and b) Molecular orientations in which the positive end of one dipole (δ^+) is near the negative end of another (δ^-) (and vice versa) produce attractive interactions. (c and d) Molecular orientations that juxtapose the positive or negative ends of the dipoles on adjacent molecules produce repulsive interactions.

These arrangements are more stable than arrangements in which two positive or two negative ends are adjacent (Figure **2.1.1***c*). Hence dipole–dipole interactions, such as those in Figure **2.1.1***b*, are *attractive intermolecular interactions*, whereas those in Figure **2.1.1***d* are *repulsive intermolecular interactions*. Because molecules in a liquid move freely and continuously, molecules always experience both attractive and repulsive dipole–dipole interactions simultaneously, as shown in Figure **2.1.2**. On average, however, the attractive interactions dominate.

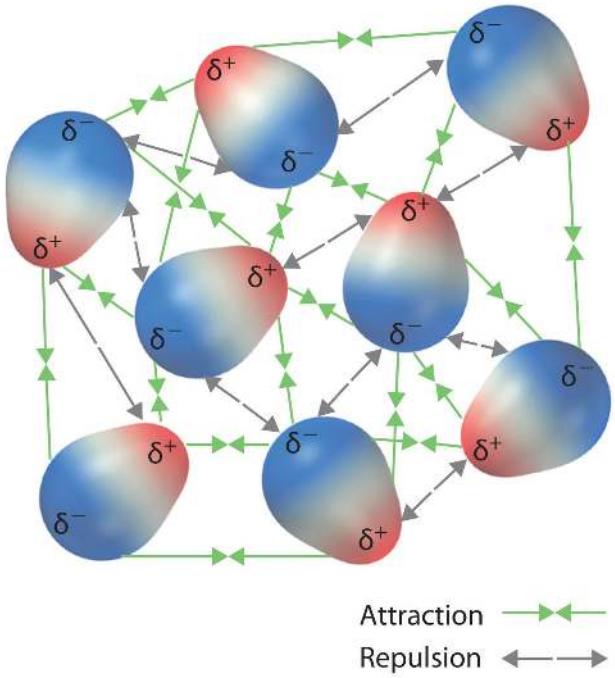


Figure **2.1.2**: Both Attractive and Repulsive Dipole–Dipole Interactions Occur in a Liquid Sample with Many Molecules

Because each end of a dipole possesses only a fraction of the charge of an electron, dipole–dipole interactions are substantially weaker than the interactions between two ions, each of which has a charge of at least ±1, or between a dipole and an ion, in which one of the species has at least a full positive or negative charge. In addition, the attractive interaction between dipoles falls off much more rapidly with increasing distance than do the ion–ion interactions. Recall that the attractive energy between two ions is proportional to $1/r$, where r is the distance between the ions. Doubling the distance ($r \rightarrow 2r$) decreases the attractive energy by one-half. In contrast, the energy of the interaction of two dipoles is proportional to $1/r^3$, so doubling the distance between the dipoles decreases the strength of the interaction by 2^3, or 8-fold. Thus a substance such as **HCl**, which is partially held together by dipole–dipole interactions, is a gas at room temperature and 1 atm pressure, whereas **NaCl**, which is held together by interionic interactions, is a high-melting-point solid. Within a series of compounds of similar molar mass, the strength of the intermolecular interactions increases as the dipole moment of the molecules increases, as shown in Table **2.1.1**.

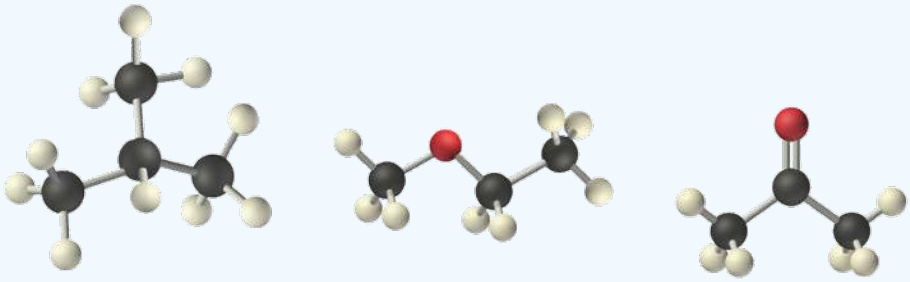
Table **2.1.1**: Relationships between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

Compound	Molar Mass (g/mol)	Dipole Moment (D)	Boiling Point (K)
C_3H_6 (cyclopropane)	42	0	240
CH_3OCH_3 (dimethyl ether)	46	1.30	248
CH_3CN (acetonitrile)	41	3.9	355

> *The attractive energy between two ions is proportional to 1/r, whereas the attractive energy between two dipoles is proportional to 1/r6.*

Example

Arrange ethyl methyl ether ($CH_3OCH_2CH_3$), 2-methylpropane [isobutane, $(CH_3)_2CHCH_3$], and acetone (CH_3COCH_3) in order of increasing boiling points. Their structures are as follows:



2-Methylpropane Ethyl methyl ether Acetone

Given: compounds

Asked for: order of increasing boiling points

Strategy:

Compare the molar masses and the polarities of the compounds. Compounds with higher molar masses and that are polar will have the highest boiling points.

Solution:

The three compounds have essentially the same molar mass (58–60 g/mol), so we must look at differences in polarity to predict the strength of the intermolecular dipole–dipole interactions and thus the boiling points of the compounds.

The first compound, 2-methylpropane, contains only C–H bonds, which are not very polar because C and H have similar electronegativities. It should therefore have a very small (but nonzero) dipole moment and a very low boiling point.

Ethyl methyl ether has a structure similar to H_2O; it contains two polar C–O single bonds oriented at about a 109° angle to each other, in addition to relatively nonpolar C–H bonds. As a result, the C–O bond dipoles partially reinforce one another and generate a significant dipole moment that should give a moderately high boiling point.

Acetone contains a polar C=O double bond oriented at about 120° to two methyl groups with nonpolar C–H bonds. The C–O bond dipole therefore corresponds to the molecular dipole, which should result in both a rather large dipole moment and a high boiling point.

Thus we predict the following order of boiling points:

2-methylpropane < ethyl methyl ether < acetone.

This result is in good agreement with the actual data: 2-methylpropane, boiling point = −11.7°C, and the dipole moment (μ) = 0.13 D; methyl ethyl ether, boiling point = 7.4°C and μ = 1.17 D; acetone, boiling point = 56.1°C and μ = 2.88 D.

Exercise

Arrange carbon tetrafluoride (CF_4), ethyl methyl sulfide ($CH_3SC_2H_5$), dimethyl sulfoxide [$(CH_3)_2S{=}O$], and 2-methylbutane [isopentane, $(CH_3)_2CHCH_2CH_3$] in order of decreasing boiling points.

Answer

dimethyl sulfoxide (boiling point = 189.9°C) > ethyl methyl sulfide (boiling point = 67°C) > 2-methylbutane (boiling point = 27.8°C) > carbon tetrafluoride (boiling point = −128°C)

London Dispersion Forces

Thus far we have considered only interactions between polar molecules, but other factors must be considered to explain why many nonpolar molecules, such as bromine, benzene, and hexane, are liquids at room temperature, and others, such as iodine and naphthalene, are solids. Even the noble gases can be liquefied or solidified at low temperatures, high pressures, or both (Table **2.1.2**).

What kind of attractive forces can exist between nonpolar molecules or atoms? This question was answered by Fritz London (1900–1954), a German physicist who later worked in the United States. In 1930, London proposed that temporary fluctuations in the electron distributions within atoms and nonpolar molecules could result in the formation of short-lived instantaneous dipole moments, which produce attractive forces called London dispersion forces between otherwise nonpolar substances.

Table **2.1.2**: Normal Melting and Boiling Points of Some Elements and Nonpolar Compounds

Substance	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)
Ar	40	−189.4	−185.9
Xe	131	−111.8	−108.1
N_2	28	−210	−195.8
O_2	32	−218.8	−183.0
F_2	38	−219.7	−188.1
I_2	254	113.7	184.4
CH_4	16	−182.5	−161.5

Consider a pair of adjacent He atoms, for example. On average, the two electrons in each He atom are uniformly distributed around the nucleus. Because the electrons are in constant motion, however, their distribution in one atom is likely to be asymmetrical at any given instant, resulting in an instantaneous dipole moment. As shown in part (a) in Figure **2.1.3**, the instantaneous dipole moment on one atom can interact with the electrons in an adjacent atom, pulling them toward the positive end of the instantaneous dipole or repelling them from the negative end. The net effect is that the first atom causes the temporary formation of a dipole, called an induced dipole, in the second. Interactions between these temporary dipoles cause atoms to be attracted to one another. These attractive interactions are weak and fall off rapidly with increasing distance. London was able to show with quantum mechanics that the attractive energy between molecules due to temporary dipole–induced dipole interactions falls off as $1/r^6$. Doubling the distance therefore decreases the attractive energy by 2^6, or 64-fold.

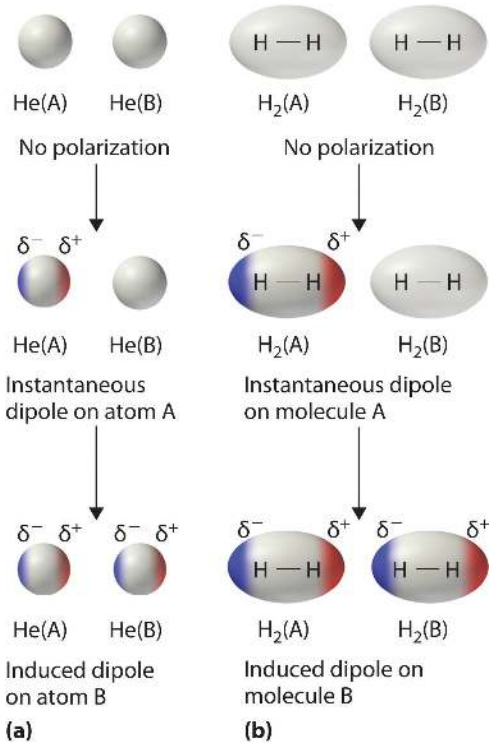


Figure **2.1.3**: Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.

Instantaneous dipole–induced dipole interactions between nonpolar molecules can produce intermolecular attractions just as they produce interatomic attractions in monatomic substances like Xe. This effect, illustrated for two H_2 molecules in part (b) in Figure **2.1.3**, tends to become more pronounced as atomic and molecular masses increase (Table **2.1.2**). For example, Xe boils at −108.1°C, whereas He boils at −269°C. The reason for this trend is that the strength of London dispersion forces is related to the ease with which the electron distribution in a given atom can be perturbed. In small atoms such as He, the two 1*s* electrons are held close to the nucleus in a very small volume, and electron–electron repulsions are strong enough to prevent significant asymmetry in their distribution. In larger atoms such as Xe, however, the outer electrons are much less strongly attracted to the nucleus because of filled intervening shells. As a result, it is relatively easy to temporarily deform the electron distribution to generate an instantaneous or induced dipole. The ease of deformation of the electron distribution in an atom or molecule is called its polarizability. Because the electron distribution is more easily perturbed in large, heavy species than in small, light species, we say that heavier substances tend to be much more *polarizable* than lighter ones.

> *For similar substances, London dispersion forces get stronger with increasing molecular size.*

The polarizability of a substance also determines how it interacts with ions and species that possess permanent dipoles. Thus London dispersion forces are responsible for the general trend toward higher boiling points with increased molecular mass and greater surface area in a homologous series of compounds, such as the alkanes (part (a) in Figure **2.1.4**). The strengths of London dispersion forces also depend significantly on molecular shape because shape determines how much of one molecule can interact with its neighboring molecules at any given time. For example, part (b) in Figure **2.1.4** shows 2,2-dimethylpropane (neopentane) and *n*-pentane, both of which have the empirical formula C_5H_{12}. Neopentane is almost spherical, with a small surface area for intermolecular interactions, whereas *n*-pentane has an extended conformation that enables it to come into close contact with other *n*-pentane molecules. As a result, the boiling point of neopentane (9.5°C) is more than 25°C lower than the boiling point of *n*-pentane (36.1°C).

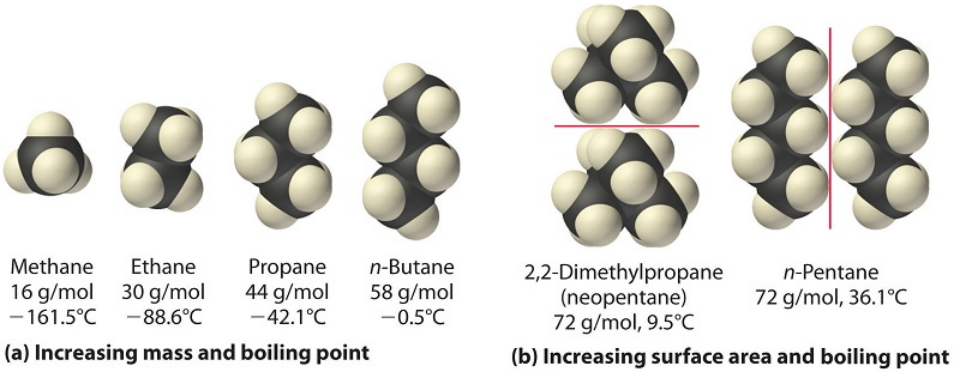


Figure **2.1.4**: Mass and Surface Area Affect the Strength of London Dispersion Forces. (a) In this series of four simple alkanes, larger molecules have stronger London forces between them than smaller molecules and consequently higher boiling points. (b) Linear *n*-pentane molecules have a larger surface area and stronger intermolecular forces than spherical neopentane molecules. As a result, neopentane is a gas at room temperature, whereas *n*-pentane is a volatile liquid.

All molecules, whether polar or nonpolar, are attracted to one another by London dispersion forces in addition to any other attractive forces that may be present. In general, however, dipole–dipole interactions in small polar molecules are significantly stronger than London dispersion forces, so the former predominate.

Example

Arrange *n*-butane, propane, 2-methylpropane [isobutene, $(CH_3)_2CHCH_3$], and *n*-pentane in order of increasing boiling points.

Given: compounds

Asked for: order of increasing boiling points

Strategy:

Determine the intermolecular forces in the compounds and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

The four compounds are alkanes and nonpolar, so London dispersion forces are the only important intermolecular forces. These forces are generally stronger with increasing molecular mass, so propane should have the lowest boiling point and *n*-pentane should have the highest, with the two butane isomers falling in between. Of the two butane isomers, 2-methylpropane is more compact, and *n*-butane has the more extended shape. Consequently, we expect intermolecular interactions for *n*-butane to be stronger due to its larger surface area, resulting in a higher boiling point. The overall order is thus as follows, with actual boiling points in parentheses: propane (−42.1°C) < 2-methylpropane (−11.7°C) < *n*-butane (−0.5°C) < *n*-pentane (36.1°C).

Exercise

Arrange GeH_4, $SiCl_4$, SiH_4, CH_4, and $GeCl_4$ in order of decreasing boiling points.

Answer

$GeCl_4$ (87°C) > $SiCl_4$ (57.6°C) > GeH_4 (−88.5°C) > SiH_4 (−111.8°C) > CH_4 (−161°C)

Hydrogen Bonds

Molecules with hydrogen atoms bonded to electronegative atoms such as O, N, and F (and to a much lesser extent Cl and S) tend to exhibit unusually strong intermolecular interactions. These result in much higher boiling points than are observed for substances in which London dispersion forces dominate, as illustrated for the covalent hydrides of elements of groups 14–17 in Figure **2.1.5**. Methane and its heavier congeners in group 14 form a series whose boiling points increase smoothly with increasing molar mass. This is the expected trend in nonpolar molecules, for which London dispersion forces are the exclusive intermolecular forces. In contrast, the hydrides of the lightest members of groups 15–17 have boiling points that are more than 100°C greater than predicted

on the basis of their molar masses. The effect is most dramatic for water: if we extend the straight line connecting the points for H_2Te and H_2Se to the line for period 2, we obtain an estimated boiling point of −130°C for water! Imagine the implications for life on Earth if water boiled at −130°C rather than 100°C.

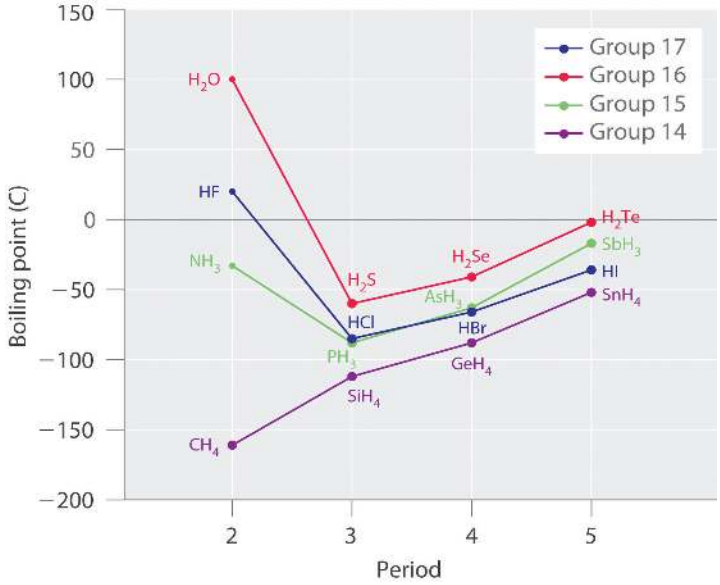


Figure **2.1.5**: The Effects of Hydrogen Bonding on Boiling Points. These plots of the boiling points of the covalent hydrides of the elements of groups 14–17 show that the boiling points of the lightest members of each series for which hydrogen bonding is possible (HF, NH_3, and H_2O) are anomalously high for compounds with such low molecular masses.

Why do strong intermolecular forces produce such anomalously high boiling points and other unusual properties, such as high enthalpies of vaporization and high melting points? The answer lies in the highly polar nature of the bonds between hydrogen and very electronegative elements such as O, N, and F. The large difference in electronegativity results in a large partial positive charge on hydrogen and a correspondingly large partial negative charge on the O, N, or F atom. Consequently, H–O, H–N, and H–F bonds have very large bond dipoles that can interact strongly with one another. Because a hydrogen atom is so small, these dipoles can also approach one another more closely than most other dipoles. The combination of large bond dipoles and short dipole–dipole distances results in very strong dipole–dipole interactions called hydrogen bonds, as shown for ice in Figure **2.1.6**. A hydrogen bond is usually indicated by a dotted line between the hydrogen atom attached to O, N, or F (the *hydrogen bond donor*) and the atom that has the lone pair of electrons (the *hydrogen bond acceptor*). Because each water molecule contains two hydrogen atoms and two lone pairs, a tetrahedral arrangement maximizes the number of hydrogen bonds that can be formed. In the structure of ice, each oxygen atom is surrounded by a distorted tetrahedron of hydrogen atoms that form bridges to the oxygen atoms of adjacent water molecules. The bridging hydrogen atoms are *not* equidistant from the two oxygen atoms they connect, however. Instead, each hydrogen atom is 101 pm from one oxygen and 174 pm from the other. In contrast, each oxygen atom is bonded to two H atoms at the shorter distance and two at the longer distance, corresponding to two O–H covalent bonds and two O···H hydrogen bonds from adjacent water molecules, respectively. The resulting open, cagelike structure of ice means that the solid is actually slightly less dense than the liquid, which explains why ice floats on water rather than sinks.

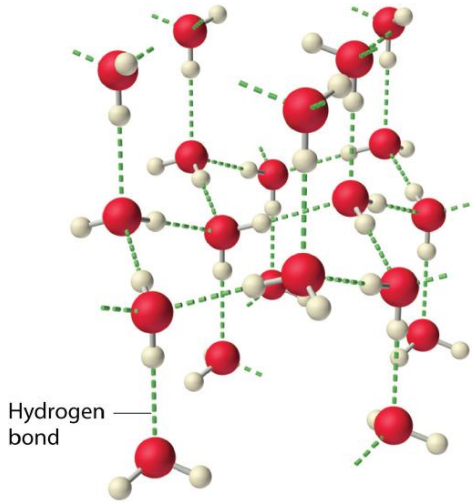


Figure **2.1.6**: The Hydrogen-Bonded Structure of Ice.

Each water molecule accepts two hydrogen bonds from two other water molecules and donates two hydrogen atoms to form hydrogen bonds with two more water molecules, producing an open, cagelike structure. The structure of liquid water is very similar, but in the liquid, the hydrogen bonds are continually broken and formed because of rapid molecular motion.

> *Hydrogen bond formation requires both a hydrogen bond donor and a hydrogen bond acceptor.*

Because ice is less dense than liquid water, rivers, lakes, and oceans freeze from the top down. In fact, the ice forms a protective surface layer that insulates the rest of the water, allowing fish and other organisms to survive in the lower levels of a frozen lake or sea. If ice were denser than the liquid, the ice formed at the surface in cold weather would sink as fast as it formed. Bodies of water would freeze from the bottom up, which would be lethal for most aquatic creatures. The expansion of water when freezing also explains why automobile or boat engines must be protected by “antifreeze” and why unprotected pipes in houses break if they are allowed to freeze.

Example

Considering CH_3OH, C_2H_6, Xe, and $(CH_3)_3N$, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Given: compounds

Asked for: formation of hydrogen bonds and structure

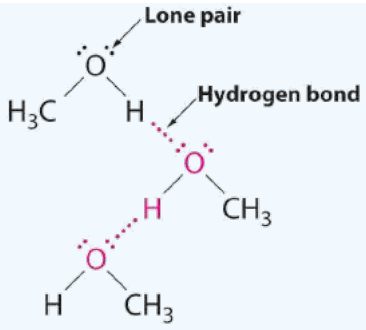
Strategy:

A. Identify the compounds with a hydrogen atom attached to O, N, or F. These are likely to be able to act as hydrogen bond donors.
B. Of the compounds that can act as hydrogen bond donors, identify those that also contain lone pairs of electrons, which allow them to be hydrogen bond acceptors. If a substance is both a hydrogen donor and a hydrogen bond acceptor, draw a structure showing the hydrogen bonding.

Solution:

A Of the species listed, xenon (Xe), ethane (C_2H_6), and trimethylamine [$(CH_3)_3N$] do not contain a hydrogen atom attached to O, N, or F; hence they cannot act as hydrogen bond donors.

B The one compound that can act as a hydrogen bond donor, methanol (CH_3OH), contains both a hydrogen atom attached to O (making it a hydrogen bond donor) and two lone pairs of electrons on O (making it a hydrogen bond acceptor); methanol can thus form hydrogen bonds by acting as either a hydrogen bond donor or a hydrogen bond acceptor. The hydrogen-bonded structure of methanol is as follows:



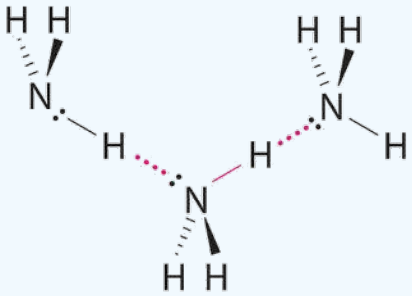
Hydrogen bonding in methanol

Exercise

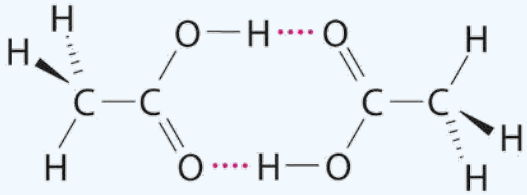
Considering CH_3CO_2H, $(CH_3)_3N$, NH_3, and CH_3F, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Answer

CH_3CO_2H and NH_3;



Hydrogen bonding in ammonia



Hydrogen bonding in acetic acid

Although hydrogen bonds are significantly weaker than covalent bonds, with typical dissociation energies of only 15–25 kJ/mol, they have a significant influence on the physical properties of a compound. Compounds such as HF can form only two hydrogen bonds at a time as can, on average, pure liquid NH_3. Consequently, even though their molecular masses are similar to that of water, their boiling points are significantly lower than the boiling point of water, which forms *four* hydrogen bonds at a time.

Example: Buckyballs

Arrange C_{60} (buckminsterfullerene, which has a cage structure), NaCl, He, Ar, and N_2O in order of increasing boiling points.

Given: compounds

Asked for: order of increasing boiling points

Strategy:

Identify the intermolecular forces in each compound and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

Electrostatic interactions are strongest for an ionic compound, so we expect NaCl to have the highest boiling point. To predict the relative boiling points of the other compounds, we must consider their polarity (for dipole–dipole interactions), their ability to form hydrogen bonds, and their molar mass (for London dispersion forces). Helium is nonpolar and by far the lightest, so it should have the lowest boiling point. Argon and N_2O have very similar molar masses (40 and 44 g/mol, respectively), but N_2O is polar while Ar is not. Consequently, N_2O should have a higher boiling point. A C_{60} molecule is nonpolar, but its molar mass

is 720 g/mol, much greater than that of Ar or N_2O. Because the boiling points of nonpolar substances increase rapidly with molecular mass, C_{60} should boil at a higher temperature than the other nonionic substances. The predicted order is thus as follows, with actual boiling points in parentheses:

$$\text{He } (-269°C) < \text{Ar } (-185.7°C) < N_2O\ (-88.5°C) < C_{60}\ (>280°C) < \text{NaCl } (1465°C).$$

Exercise

Arrange 2,4-dimethylheptane, Ne, CS_2, Cl_2, and KBr in order of decreasing boiling points.

Answer

KBr (1435°C) > 2,4-dimethylheptane (132.9°C) > CS_2 (46.6°C) > Cl_2 (−34.6°C) > Ne (−246°C)

Example

Identify the most significant intermolecular force in each substance.

a. C_3H_8
b. CH_3OH
c. H_2S

Solution

a. Although C–H bonds are polar, they are only minimally polar. The most significant intermolecular force for this substance would be dispersion forces.

b. This molecule has an H atom bonded to an O atom, so it will experience hydrogen bonding.

c. Although this molecule does not experience hydrogen bonding, the Lewis electron dot diagram and VSEPR indicate that it is bent, so it has a permanent dipole. The most significant force in this substance is dipole-dipole interaction.

Exercise

Identify the most significant intermolecular force in each substance.

a. HF
b. HCl

Answer a

hydrogen bonding

Answer b

dipole-dipole interactions

More complex examples of hydrogen bonding

The hydration of negative ions

When an ionic substance dissolves in water, water molecules cluster around the separated ions. This process is called hydration. Water frequently attaches to positive ions by co-ordinate (dative covalent) bonds. It bonds to negative ions using hydrogen bonds.

> *If you are interested in the bonding in hydrated positive ions, you could follow this link to co-ordinate (dative covalent) bonding.*

The diagram shows the potential hydrogen bonds formed to a chloride ion, Cl-. Although the lone pairs in the chloride ion are at the 3-level and would not normally be active enough to form hydrogen bonds, in this case they are made more attractive by the full negative charge on the chlorine.

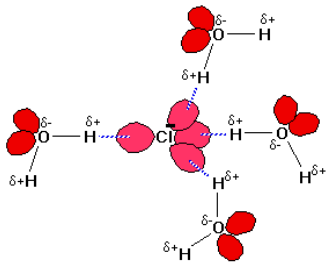


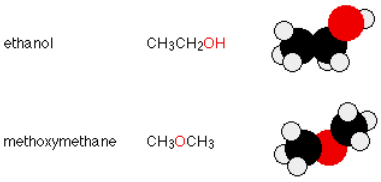
Figure 5: Hydrogen bonding between chloride ions and water.

However complicated the negative ion, there will always be lone pairs that the hydrogen atoms from the water molecules can hydrogen bond to.

Hydrogen bonding in alcohols

An alcohol is an organic molecule containing an -OH group. Any molecule which has a hydrogen atom attached directly to an oxygen or a nitrogen is capable of hydrogen bonding. Such molecules will always have higher boiling points than similarly sized molecules which don't have an -O-H or an -N-H group. The hydrogen bonding makes the molecules "stickier", and more heat is necessary to separate them.

Ethanol, CH_3CH_2OH, and methoxymethane, CH_3OCH_3, are structural isomers with the same molecular formula, C_2H_6O.

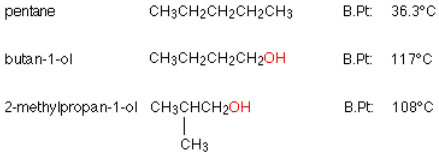


They have the same number of electrons, and a similar length to the molecule. The van der Waals attractions (both dispersion forces and dipole-dipole attractions) in each will be much the same. However, ethanol has a hydrogen atom attached directly to an oxygen - and that oxygen still has exactly the same two lone pairs as in a water molecule. Hydrogen bonding can occur between ethanol molecules, although not as effectively as in water. The hydrogen bonding is limited by the fact that there is only one hydrogen in each ethanol molecule with sufficient $\delta+$ charge.

In methoxymethane, lone pairs on the oxygen are still there, but the hydrogens are not sufficiently $\delta+$ for hydrogen bonds to form. Except in some rather unusual cases, the hydrogen atom has to be attached directly to the very electronegative element for hydrogen bonding to occur. The boiling points of ethanol and methoxymethane show the dramatic effect that the hydrogen bonding has on the stickiness of the ethanol molecules:

ethanol (with hydrogen bonding)	78.5°C
methoxymethane (without hydrogen bonding)	-24.8°C

The hydrogen bonding in the ethanol has lifted its boiling point about 100°C. It is important to realize that hydrogen bonding exists in addition to van der Waals attractions. For example, all the following molecules contain the same number of electrons, and the first two are much the same length. The higher boiling point of the butan-1-ol is due to the additional hydrogen bonding.



Comparing the two alcohols (containing -OH groups), both boiling points are high because of the additional hydrogen bonding due to the hydrogen attached directly to the oxygen - but they are not the same. The boiling point of the 2-methylpropan-1-ol isn't as

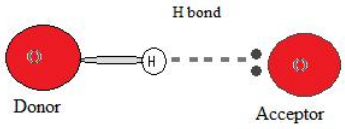
high as the butan-1-ol because the branching in the molecule makes the van der Waals attractions less effective than in the longer butan-1-ol.

Hydrogen bonding in organic molecules containing nitrogen

Hydrogen bonding also occurs in organic molecules containing N-H groups - in the same sort of way that it occurs in ammonia. Examples range from simple molecules like CH_3NH_2 (methylamine) to large molecules like proteins and DNA. The two strands of the famous double helix in DNA are held together by hydrogen bonds between hydrogen atoms attached to nitrogen on one strand, and lone pairs on another nitrogen or an oxygen on the other one.

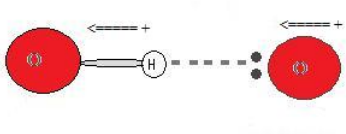
Donors and Acceptors

In order for a hydrogen bond to occur there must be both a hydrogen donor and an acceptor present. The donor in a hydrogen bond is the atom to which the hydrogen atom participating in the hydrogen bond is covalently bonded, and is usually a strongly electronegative atom such as N,O, or F. The hydrogen acceptor is the neighboring electronegative ion or molecule, and must posses a lone electron pair in order to form a hydrogen bond.



Why does a hydrogen bond occur?

Since the hydrogen donor is strongly electronegative, it pulls the covalently bonded electron pair closer to its nucleus, and away from the hydrogen atom. The hydrogen atom is then left with a partial positive charge, creating a dipole-dipole attraction between the hydrogen atom bonded to the donor, and the lone electron pair on the accepton. This results in a hydrogen bond.(see Interactions Between Molecules With Permanent Dipoles)

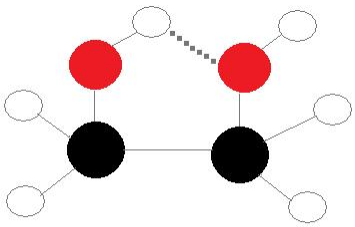


Types of hydrogen bonds

Hydrogen bonds can occur within one single molecule, between two like molecules, or between two unlike molecules.

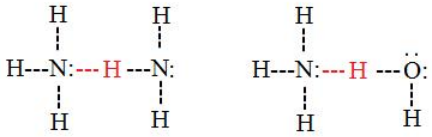
Intramolecular hydrogen bonds

Intramolecular hydrogen bonds are those which occur within one single molecule. This occurs when two functional groups of a molecule can form hydrogen bonds with each other. In order for this to happen, both a hydrogen donor an acceptor must be present within one molecule, and they must be within close proximity of each other in the molecule. For example, intramolecular hydrogen bonding occurs in ethylene glycol ($C_2H_4(OH)_2$) between its two hydroxyl groups due to the molecular geometry.


Intramolecular h-bonding in Ethylene Glycol molecule

Intermolecular hydrogen bonds

Intermolecular hydrogen bonds occur *between* separate molecules in a substance. They can occur between any number of like or unlike molecules as long as hydrogen donors and acceptors are present an in positions in which they can interact.For example, intermolecular hydrogen bonds can occur between NH_3 molecules alone, between H_2O molecules alone, or between NH_3 and H_2O molecules.



Properties and effects of hydrogen bonds

On Boiling Point

When we consider the boiling points of molecules, we usually expect molecules with larger molar masses to have higher normal boiling points than molecules with smaller molar masses. This, without taking hydrogen bonds into account, is due to greater dispersion forces (see Interactions Between Nonpolar Molecules). Larger molecules have more space for electron distribution and thus more possibilities for an instantaneous dipole moment. However, when we consider the table below, we see that this is not always the case.

Compound	Molar Mass	Normal Boiling Point
H_2O	18 g/mol	373 K
HF	20 g/mol	292.5 K
NH_3	17 g/mol	239.8 K
H_2S	34 g/mol	212.9 K
HCl	36.4 g/mol	197.9 K
PH_3	34 g/mol	185.2 K

We see that H_2O, HF, and NH_3 each have higher boiling points than the same compound formed between hydrogen and the next element moving down its respective group, indicating that the former have greater intermolecular forces. This is because H_2O, HF, and NH_3 all exhibit hydrogen bonding, whereas the others do not. Furthermore, H_2O has a smaller molar mass than HF but partakes in more hydrogen bonds per molecule, so its boiling point is consequently higher.

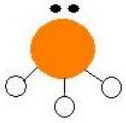
On Viscosity

The same effect that is seen on boiling point as a result of hydrogen bonding can also be observed in the viscosity of certain substances. Those substances which are capable of forming hydrogen bonds tend to have a higher viscosity than those that do not. Substances which have the possibility for multiple hydrogen bonds exhibit even higher viscosities.

Factors preventing Hydrogen bonding

Electronegativity

Hydrogen bonding cannot occur without significant electronegativity differences between hydrogen and the atom it is bonded to. Thus, we see molecules such as PH3, which no not partake in hydrogen bonding. PH3 exhibits a trigonal pyramidal molecular geometry like that of ammmonia, but unlike NH3 it cannot hydrogen bond. This is due to the similarity in the electronegativities of phosphorous and hydrogen. Both atoms have an electronegativity of 2.1, and thus, no dipole moment occurs. This prevents the hydrogen bonding from acquiring the partial positive charge needed to hydrogen bond with the lone electron pair in another molecule. (see Polarizability)



Atom Size

The size of donors and acceptors can also effect the ability to hydrogen bond. This can account for the relatively low ability of Cl to form hydrogen bonds. When the radii of two atoms differ greatly or are large, their nuclei cannot achieve close proximity when they interact, resulting in a weak interaction.

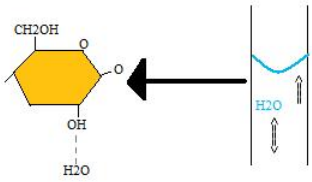


Hydrogen Bonding in Nature

Hydrogen bonding plays a crucial role in many biological processes and can account for many natural phenomena such as the Unusual properties of Water. In addition to being present in water, hydrogen bonding is also important in the water transport system of plants, secondary and tertiary protein structure, and DNA base pairing.

Plants

The cohesion-adhesion theory of transport in vascular plants uses hydrogen bonding to explain many key components of water movement through the plant's xylem and other vessels. Within a vessel, water molecules hydrogen bond not only to each other, but also to the cellulose chain which comprises the wall of plant cells. This creates a sort of capillary tube which allows for capillary action to occur since the vessel is relatively small. This mechanism allows plants to pull water up into their roots. Furthermore,hydrogen bonding can create a long chain of water molecules which can overcome the force of gravity and travel up to the high altitudes of leaves.



Proteins

Hydrogen bonding is present abundantly in the secondary structure of proteins, and also sparingly in tertiary conformation. The secondary structure of a protein involves interactions (mainly hydrogen bonds) between neighboring polypeptide backbones which contain Nitrogen-Hydrogen bonded pairs and oxygen atoms. Since both N and O are strongly electronegative, the hydrogen atoms bonded to nitrogen in one polypeptide backbone can hydrogen bond to the oxygen atoms in another chain and visa-versa. Though they are relatively weak,these bonds offer great stability to secondary protein structure because they repeat a great number of times.

In tertiary protein structure,interactions are primarily between functional R groups of a polypeptide chain; one such interaction is called a hydrophobic interaction. These interactions occur because of hydrogen bonding between water molecules around the hydrophobe and further reinforce conformation.

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2. Petrucci, et al. General Chemistry: Principles & Modern Applications. 9th ed. Upper Saddle River, New Jersey: Pearson/Prentice Hall, 2007.

Contributors

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2.1: Intermolecular Forces (IMFs) - Review is shared under a not declared license and was authored, remixed, and/or curated by LibreTexts.

2.1.1: Intermolecular Forces and Relative Boiling Points (bp)

Learning Objective

- predict the relative boil points of organic compounds

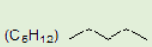
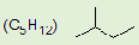
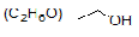
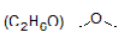
Intermolecular forces (IMFs) can be used to predict relative boiling points. The stronger the IMFs, the lower the vapor pressure of the substance and the higher the boiling point. Therefore, we can compare the relative strengths of the IMFs of the compounds to predict their relative boiling points.

H-bonding > dipole-dipole > London dispersion (van der Waals)

When comparing compounds with the same IMFs, we use size and shape as tie breakers since the London dispersion forces increase as the surface area increases. Since all compounds exhibit some level of London dispersion forces and compounds capable of H-bonding also exhibit dipole-dipole, we will use the phrase "dominant IMF" to communicate the IMF most responsible for the physical properties of the compound.

In the table below, we see examples of these relationships. When comparing the structural isomers of pentane (pentane, isopentane, and neopentane), they all have the same molecular formula C_5H_{12}. However, as the carbon chain is shortened to create the carbon branches found in isopentane and neopentane the overall surface area of the molecules decreases. The visual image of MO theory can be helpful in seeing each compound as a cloud of electrons in an all encompassing MO system. Branching creates more spherical shapes noting that the sphere allows the maximum volume with the least surface area. The structural isomers with the chemical formula C_2H_6O have different dominant IMFs. The H-bonding of ethanol results in a liquid for cocktails at room temperature, while the weaker dipole-dipole of the dimethylether results in a gas a room temperature. In the last example, we see the three IMFs compared directly to illustrate the relative strength IMFs to boiling points.

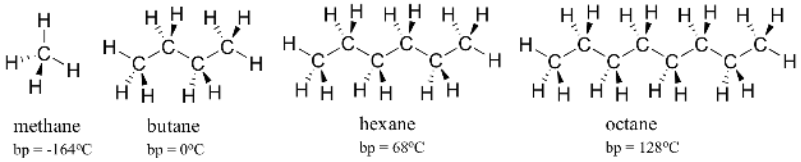
IMFs and Boiling Points

Compounds	bp	"dominant IMF"	
(C_6H_{12}) 	36°C	London dispersion	↑ branching ↓ surface area ↓ the London force ↓ the boiling points
(C_5H_{12}) 	28°C	London dispersion	
(C_5H_{12}) 	10°C	London dispersion	
(C_2H_6O) 	78°C	H-bonding	H-bond > dip-dip
(C_2H_6O) 	-25°C	dipole-dipole	
(methane) CH_4	-161°C	London dispersion	H-bond > dip-dip > London
(chloromethane) CH_3Cl	-24°C	dipole-dipole	
(methanol) CH_3OH	80°C	H-bonding	

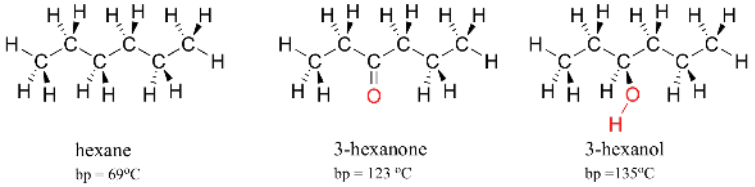
Boiling points and melting points

The observable melting and boiling points of different organic molecules provides an additional illustration of the effects of noncovalent interactions. The overarching principle involved is simple: the stronger the noncovalent interactions between molecules, the more energy that is required, in the form of heat, to break them apart. Higher melting and boiling points signify stronger noncovalent intermolecular forces.

Consider the boiling points of increasingly larger hydrocarbons. More carbons means a greater surface area possible for hydrophobic interaction, and thus higher boiling points.



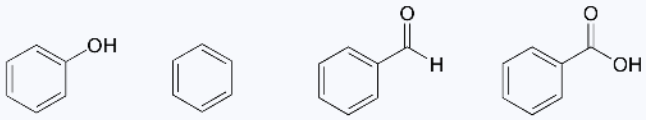
As you would expect, the strength of intermolecular hydrogen bonding and dipole-dipole interactions is reflected in higher boiling points. Just look at the trend for hexane (nonpolar London dispersion interactions only), 3-hexanone (dipole-dipole interactions), and 3-hexanol (hydrogen bonding).



Of particular interest to biologists (and pretty much anything else that is alive in the universe) is the effect of hydrogen bonding in water. Because it is able to form tight networks of intermolecular hydrogen bonds, water remains in the liquid phase at temperatures up to 100 ^{O}C, (slightly lower at high altitude). The world would obviously be a very different place if water boiled at 30 ^{O}C.

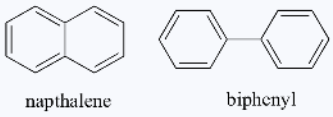
Exercise

1. Based on their structures, rank phenol, benzene, benzaldehyde, and benzoic acid in terms of lowest to highest boiling point.

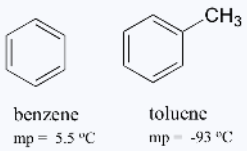


Solution

By thinking about noncovalent intermolecular interactions, we can also predict relative melting points. All of the same principles apply: stronger intermolecular interactions result in a higher melting point. Ionic compounds, as expected, usually have very high melting points due to the strength of ion-ion interactions (there are some ionic compounds, however, that are liquids at room temperature). The presence of polar and especially hydrogen-bonding groups on organic compounds generally leads to higher melting points. Molecular shape, and the ability of a molecule to pack tightly into a crystal lattice, has a very large effect on melting points. The flat shape of aromatic compounds such as napthalene and biphenyl allows them to stack together efficiently, and thus aromatics tend to have higher melting points compared to alkanes or alkenes with similar molecular weights.



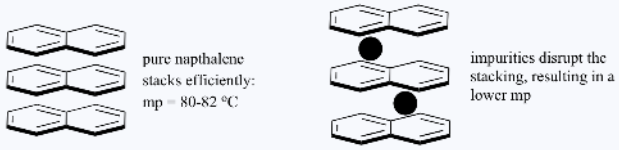
Comparing the melting points of benzene and toluene, you can see that the extra methyl group on toluene disrupts the molecule's ability to stack, thus decreasing the cumulative strength of intermolecular London dispersion forces.



Note also that the *boiling* point for toluene is 111 ^{o}C, well *above* the boiling point of benzene (80 ^{o}C). The key factor for the boiling point trend in this case is size (toluene has one more carbon), whereas for the melting point trend, shape plays a much

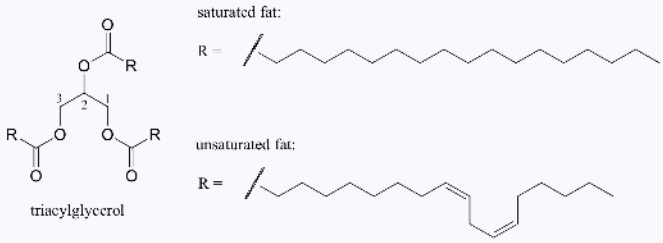
more important role. This makes sense when you consider that melting involves 'unpacking' the molecules from their ordered array, whereas boiling involves simply separating them from their already loose (liquid) association with each other.

If you are taking an organic lab course, you may have already learned that impurities in a crystalline substance will cause the observed melting point to be lower compared to a pure sample of the same substance. This is because impurities disrupt the ordered packing arrangement of the crystal, and make the cumulative intermolecular interactions weaker.



The melting behavior of lipid structures

An interesting biological example of the relationship between molecular structure and melting point is provided by the observable physical difference between animal fats like butter or lard, which are solid at room temperature, and vegetable oils, which are liquid. Both solid fats and liquid oils are based on a 'triacylglycerol' structure, where three hydrophobic hydrocarbon chains of varying length are attached to a glycerol backbone through an ester functional group (compare this structure to that of the membrane lipids discussed in section 2.4B).



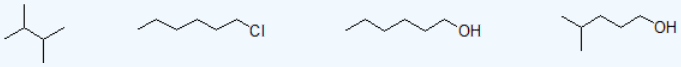
Interactive 3D image of a saturated triacylglycerol (BioTopics)

Saturated vs mono-unsaturated fatty acid (BioTopics)

In vegetable oils, the hydrophobic chains are **unsaturated**, meaning that they contain one or more double bonds. Solid animal fat, in contrast, contains **saturated** hydrocarbon chains, with no double bonds. The double bonds in vegetable oils cause those hydrocarbon chains to be more rigid, and 'bent' at an angle (remember that rotation is restricted around double bonds), with the result that they don't pack together as closely, and thus can be broken apart (*ie*. melted) more readily. Shown in the figure above is a polyunsaturated fatty acid chain (two double bonds), and you can click on the link to see interactive images of a saturated fatty acid compared to a monounsaturated fatty acid (one double bond).

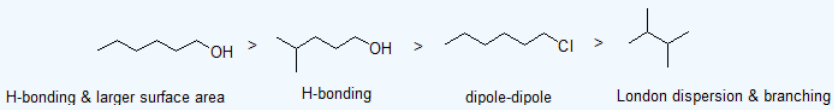
Exercise

2. Arrange the following compounds in order of decreasing boiling point.



Answer

2.



Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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2.1.2: Intermolecular Forces and Solubilities

Learning Objective

- predict whether a mixture of compounds will a form homogeneous or heterogeneous solution

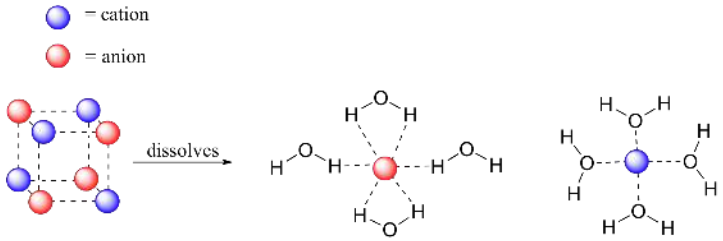
The type of intermolecular forces (IMFs) exhibited by compounds can be used to predict whether two different compounds can be mixed to form a homogeneous solution (soluble or miscible). Because organic chemistry can perform reactions in non-aqueous solutions using organic solvents. It is important to consider the solvent as a reaction parameter and the solubility of each reagent. With this said, solvent effects are secondary to the sterics and electrostatics of the reactants. Make sure that you do not drown in the solvent.

Solubility

Virtually all of the organic chemistry that you will see in this course takes place in the solution phase. In the organic laboratory, reactions are often run in nonpolar or slightly polar solvents such as toluene (methylbenzene), hexane, dichloromethane, or diethylether. In recent years, much effort has been made to adapt reaction conditions to allow for the use of 'greener' (in other words, more environmentally friendly) solvents such as water or ethanol, which are polar and capable of hydrogen bonding. In organic reactions that occur in the cytosolic region of a cell, the solvent is of course water. It is critical for any organic chemist to understand the factors which are involved in the solubility of different molecules in different solvents.

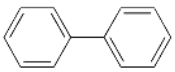
You probably remember the rule you learned in general chemistry regarding solubility: 'like dissolves like' (and even before you took any chemistry at all, you probably observed at some point in your life that oil does not mix with water). Let's revisit this old rule, and put our knowledge of covalent and noncovalent bonding to work.

Imagine that you have a flask filled with water, and a selection of substances that you will test to see how well they dissolve in the water. The first substance is table salt, or sodium chloride. As you would almost certainly predict, especially if you've ever inadvertently taken a mouthful of water while swimming in the ocean, this ionic compound dissolves readily in water. Why? Because water, as a very polar molecule, is able to form many ion-dipole interactions with both the sodium cation and the chloride anion, the energy from which is more than enough to make up for energy required to break up the ion-ion interactions in the salt crystal and some water-water hydrogen bonds.



The end result, then, is that in place of sodium chloride crystals, we have individual sodium cations and chloride anions surrounded by water molecules – the salt is now *in solution*. Charged species as a rule dissolve readily in water: in other words, they are very **hydrophilic** (water-loving).

Now, we'll try a compound called biphenyl, which, like sodium chloride, is a colorless crystalline substance (the two compounds are readily distinguishable by sight, however – the crystals look quite different).

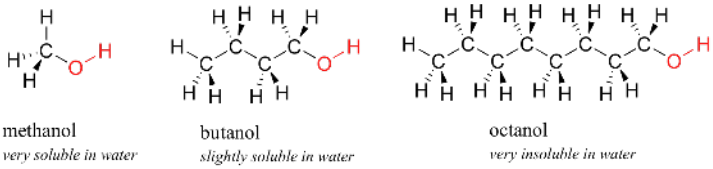


biphenyl

Biphenyl does not dissolve at all in water. Why is this? Because it is a very non-polar molecule, with only carbon-carbon and carbon-hydrogen bonds. It is able to bond to itself very well through nonpolar (London dispersion) interactions, but it is not able to form significant attractive interactions with the very polar solvent molecules. Thus, the energetic cost of breaking up the biphenyl-

to-biphenyl interactions in the solid is high, and very little is gained in terms of new biphenyl-water interactions. Water is a terrible solvent for nonpolar hydrocarbon molecules: they are very **hydrophobic** ('water-fearing').

Next, you try a series of increasingly large alcohol compounds, starting with methanol (1 carbon) and ending with octanol (8 carbons).



methanol
very soluble in water

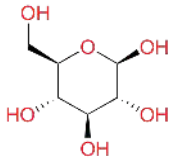
butanol
slightly soluble in water

octanol
very insoluble in water

You find that the smaller alcohols - methanol, ethanol, and propanol - dissolve easily in water. This is because the water is able to form hydrogen bonds with the hydroxyl group in these molecules, and the combined energy of formation of these water-alcohol hydrogen bonds is more than enough to make up for the energy that is lost when the alcohol-alcohol hydrogen bonds are broken up. When you try butanol, however, you begin to notice that, as you add more and more to the water, it starts to form its own layer on top of the water.

The longer-chain alcohols - pentanol, hexanol, heptanol, and octanol - are increasingly non-soluble. What is happening here? Clearly, the same favorable water-alcohol hydrogen bonds are still possible with these larger alcohols. The difference, of course, is that the larger alcohols have larger nonpolar, hydrophobic regions in addition to their hydrophilic hydroxyl group. At about four or five carbons, the hydrophobic effect begins to overcome the hydrophilic effect, and water solubility is lost.

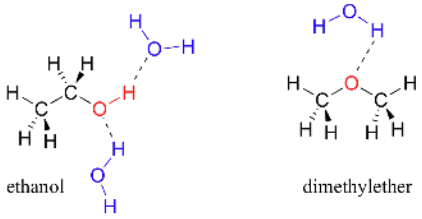
Now, try dissolving glucose in the water – even though it has six carbons just like hexanol, it also has five hydrogen-bonding, hydrophilic hydroxyl groups in addition to a sixth oxygen that is capable of being a hydrogen bond acceptor.



glucose

We have tipped the scales to the hydrophilic side, and we find that glucose is quite soluble in water.

We saw that ethanol was very water-soluble (if it were not, drinking beer or vodka would be rather inconvenient!) How about dimethyl ether, which is a constitutional isomer of ethanol but with an ether rather than an alcohol functional group? We find that diethyl ether is much less soluble in water. Is it capable of forming hydrogen bonds with water? Yes, in fact, it is –the ether oxygen can act as a hydrogen-bond acceptor. The difference between the ether group and the alcohol group, however, is that the alcohol group is both a hydrogen bond donor *and* acceptor.

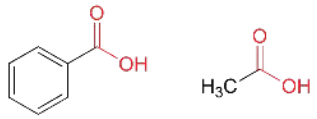


ethanol

dimethylether

The result is that the alcohol is able to form more energetically favorable interactions with the solvent compared to the ether, and the alcohol is therefore more soluble.

Here is another easy experiment that can be done (with proper supervision) in an organic laboratory. Try dissolving benzoic acid crystals in room temperature water – you'll find that it is not soluble. As we will learn when we study acid-base chemistry in a later chapter, carboxylic acids such as benzoic acid are relatively weak acids, and thus exist mostly in the acidic (protonated) form when added to pure water.

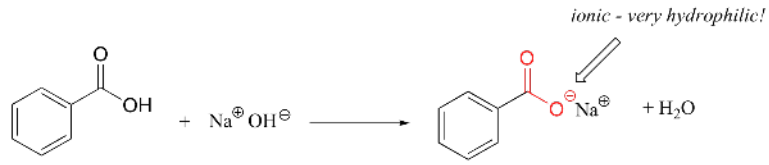


benzoic acid
insoluble in water

acetic acid
soluble in water

Acetic acid, however, is quite soluble. This is easy to explain using the small alcohol vs large alcohol argument: the hydrogen-bonding, hydrophilic effect of the carboxylic acid group is powerful enough to overcome the hydrophobic effect of a single methyl group on acetic acid, but not the larger hydrophobic effect of the 6-carbon benzene group on benzoic acid.

Now, try slowly adding some aqueous sodium hydroxide to the flask containing undissolved benzoic acid. As the solvent becomes more and more basic, the benzoic acid begins to dissolve, until it is completely in solution.



benzoic acid
insoluble in water

sodium benzoate
soluble in water

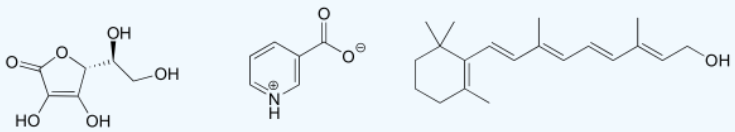
What is happening here is that the benzoic acid is being converted to its conjugate base, benzoate. The *neutral* carboxylic acid group was not hydrophilic enough to make up for the hydrophobic benzene ring, but the carboxylate group, with its *full negative charge*, is much more hydrophilic. Now, the balance is tipped in favor of water solubility, as the powerfully hydrophilic anion part of the molecule drags the hydrophobic part, kicking and screaming, (if a benzene ring can kick and scream) into solution. If you want to precipitate the benzoic acid back out of solution, you can simply add enough hydrochloric acid to neutralize the solution and reprotonate the carboxylate.

If you are taking a lab component of your organic chemistry course, you will probably do at least one experiment in which you will use this phenomenon to separate an organic acid like benzoic acid from a hydrocarbon compound like biphenyl.

Similar arguments can be made to rationalize the solubility of different organic compounds in nonpolar or slightly polar solvents. In general, the greater the content of charged and polar groups in a molecule, the less soluble it tends to be in solvents such as hexane. The ionic and very hydrophilic sodium chloride, for example, is not at all soluble in hexane solvent, while the hydrophobic biphenyl is very soluble in hexane.

Exercise

1. Vitamins can be classified as water-soluble or fat-soluble (consider fat to be a very non-polar, hydrophobic 'solvent'. Decide on a classification for each of the vitamins shown below.



Vitamin C
(ascorbic acid)

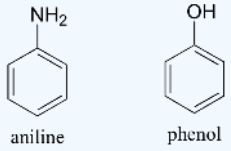
Vitamin B_3
(niacin)

Vitamin A
(retinol)

Solutions

Exercise

2. Both aniline and phenol are insoluble in pure water. Predict the solubility of these two compounds in 10% aqueous hydrochloric acid, and explain your reasoning. Hint – in this context, aniline is basic, phenol is not!

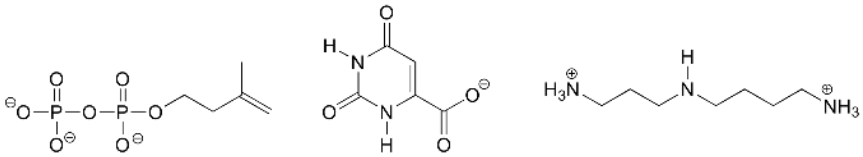


aniline phenol

Solutions

Illustrations of solubility concepts: metabolic intermediates, lipid bilayer membranes, soaps and detergents

Because water is the biological solvent, most biological organic molecules, in order to maintain water-solubility, contain one or more charged functional groups. These are most often phosphate, ammonium or carboxylate, all of which are charged when dissolved in an aqueous solution buffered to pH 7.



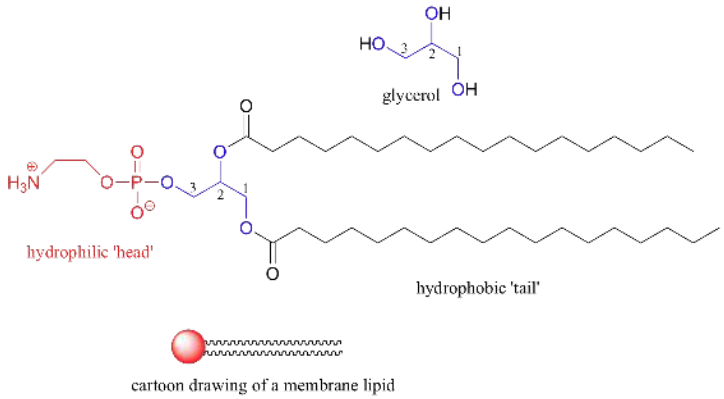
ispentenyl diphosphate
an early precuror to cholesterol

orotate
a precursor to the RNA base uridine

spermidine
binds tightly to DNA in rapidly dividing cells

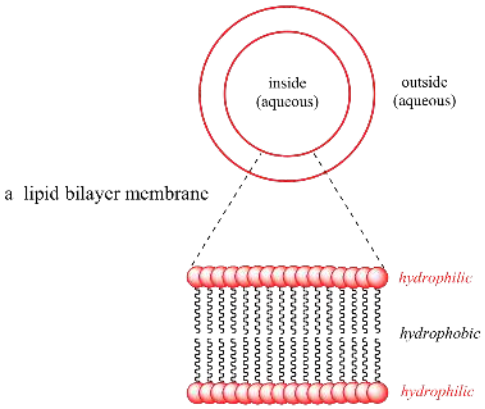
Sugars often lack charged groups, but as we discussed in our ‘thought experiment’ with glucose, they are quite water-soluble due to the presence of multiple hydroxyl groups.

Some biomolecules, in contrast, contain distinctly nonpolar, hydrophobic components. The ‘lipid bilayer’ membranes of cells and subcellular organelles serve to enclose volumes of water and myriad biomolecules in solution. The lipid (fat) molecules that make up membranes are **amphipathic**: they have a charged, hydrophilic ‘head’ and a hydrophobic hydrocarbon ‘tail’.



interactive 3D image of a membrane phospholipid *(BioTopics)*

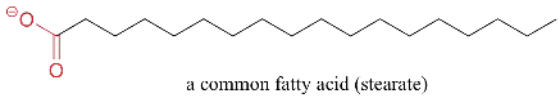
Notice that the entire molecule is built on a ‘backbone’ of glycerol, a simple 3-carbon molecule with three alcohol groups. In a biological membrane structure, lipid molecules are arranged in a spherical bilayer: hydrophobic tails point inward and bind together by London dispersion forces, while the hydrophilic head groups form the inner and outer surfaces in contact with water.



Interactive 3D Image of a lipid bilayer *(BioTopics)*

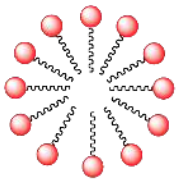
Because the interior of the bilayer is extremely hydrophobic, biomolecules (which as we know are generally charged species) are not able to diffuse through the membrane– they are simply not soluble in the hydrophobic interior. The transport of molecules across the membrane of a cell or organelle can therefore be accomplished in a controlled and specific manner by special transmembrane transport proteins, a fascinating topic that you will learn more about if you take a class in biochemistry.

A similar principle is the basis for the action of soaps and detergents. Soaps are composed of fatty acids, which are long (typically 18-carbon), hydrophobic hydrocarbon chains with a (charged) carboxylate group on one end,



a common fatty acid (stearate)

Fatty acids are derived from animal and vegetable fats and oils. In aqueous solution, the fatty acid molecules in soaps will spontaneously form **micelles**, a spherical structure that allows the hydrophobic tails to avoid contact with water and simultaneously form favorable London dispersion contacts.

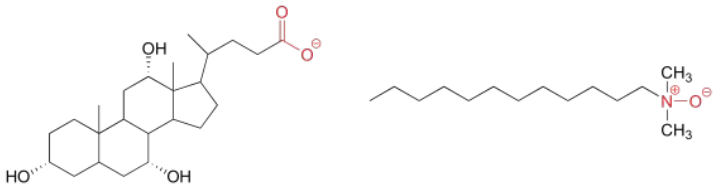


micelle

Interactive 3D images of a fatty acid soap molecule and a soap micelle (Edutopics)

Because the outside of the micelle is charged and hydrophilic, the structure as a whole is soluble in water. Micelles will form spontaneously around small particles of oil that normally would not dissolve in water (like that greasy spot on your shirt from the pepperoni slice that fell off your pizza), and will carry the particle away with it into solution. We will learn more about the chemistry of soap-making in a later chapter (section 12.4B).

Synthetic detergents are non-natural amphipathic molecules that work by the same principle as that described for soaps.



synthetic detergents

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2.1.3: Chromatography

Another useful set of techniques for separating mixtures is called **chromatography**. Perhaps the simplest of these techniques to describe is paper chromatography, an example of which is shown in the video below.



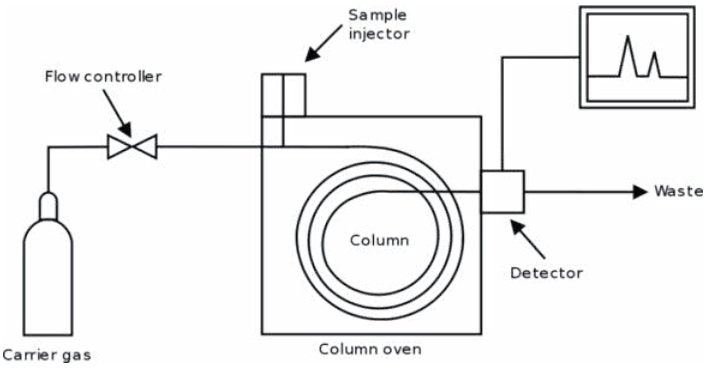
Video: Simple paper chromatography. A simple demonstration on paper chromatography using marker ink and water

Three substances are applied to a strip of chromatography-grade paper (the **stationary phase** of this experiment). As the liquid level rises and meets the spots, the sample partially dissolves in the liquid (the **mobile phase** because it is moving) and travels up the plate within the solution. Different substances will travel different distances along the plate. The distance that a substance will travel depends on how strongly it adheres to the stationary phase (a process called **adsorption**) versus how much time it spends dissolved in the mobile phase.

The more a substance adsorbs, the less it dissolves and the less it moves along the plate. The pink and blue spots at the end of the video are examples of substances highly adsorbed to the stationary phase. The less a substance adsorbs, the more it dissolves and the farther it travels, such as the yellow on the far left. The process is continued until a good separation is created. In this manner, a mixture of substances may be separated such as the middle sample, which was originally green but separated into blue and yellow. Notice that while it was not initially obvious that the middle spot contained both substances, this fact is clear after performing paper chromatography.

All forms of chromatography work on the same general principle as paper chromatography. There is always a stationary phase which does not move and a mobile phase which does. The various components in the mixture being chromatographed separate from each other because they are more strongly held by one phase or the other. Those which have the greatest affinity for the mobile phase move along the fastest.

The most important form of chromatography is **gas chromatography** or vapor-phase chromatography. A long column is packed with a finely divided solid whose surface has been coated with an inert liquid. This liquid forms the stationary phase. The mobile phase is provided by an inert **carrier gas**, such as He or N_2, which passes continuously through the column (seen below), among the solid particles. A liquid sample can be injected into the gas stream at the **sample injector** and vaporized just before it enters the tube. As this sample is carried through the **column** by the slow stream of gas, those components which are most soluble in the inert liquid are held up, while the less-soluble components move on more rapidly. The components thus emerge one by one from the end of the tube, into the detector. In this way it is possible to separate and analyze mixtures of liquids which it would be impossible to deal with by distillation or any other technique.



The development of chromatography is one of the major revolutions in technique in the history of chemistry, comparable to that which followed the development of an accurate balance. Separations which were previously considered impossible are now easily achieved, sometimes with quite simple apparatus. This technique is particular essential to the science of biochemistry, in which complex mixtures are almost always encountered. In the field of environmental chemistry, chromatography has helped us separate and detect very low concentrations of contaminants like DDT or PCB (polychlorinated biphenyls). The major drawback to chromatography is that it does not lend itself to large-scale operation. As a result it remains largely a laboratory, rather than an industrial, technique for separating mixtures.

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SECTION OVERVIEW

2.1.4: Thin Layer Chromatography (TLC)

Many students enter organic chemistry having already done a form of chromatography in their academic career, either in grade school or in general chemistry. Most likely, this will have been **paper chromatography** (Figure 2.4), as the materials are cheap but still effective. Paper chromatography can be used to separate the dyes in pens, markers, and food coloring.



Figure 2.4: Paper chromatography.

When components separate in paper chromatography it is because the components of the mixtures have different attractions to the stationary phase (the cellulose in the paper) and the mobile phase (the solvent wicking up the paper), and spend different amounts of time in each. Thin layer chromatography (TLC) is an extension of paper chromatography and uses a different stationary phase.

2.1.4A: Overview of TLC

2.1.4B: Uses of TLC

2.1.4C: The Retention Factor

2.1.4D: Separation Theory

2.1.4E: Step-by-Step Procedures for Thin Layer Chromatography

2.1.4F: Visualizing TLC Plates

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2.1.4A: Overview of TLC

Two commonly used stationary phases in chromatography are silica ($SiO_2 \cdot xH_2O$) and alumina ($Al_2O_3 \cdot xH_2O$). Both of these materials are fine white powders that, unlike paper, do not stand up by themselves, so they are deposited in a thin layer on some sort of backing (either glass, aluminum, or plastic). Using these thin layers of stationary phase for separations is called "**thin layer chromatography**" (TLC), and is procedurally performed much the same way as paper chromatography (Figure 2.5).

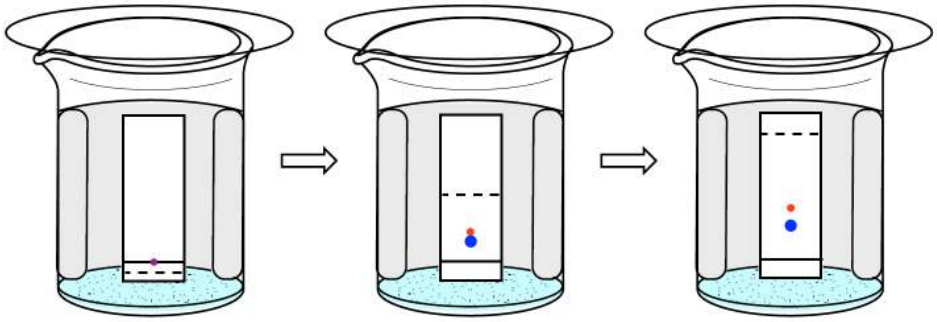


Figure 2.5: TLC sequence to separate the components of a purple sample.

It is very common for organic compounds to appear colorless on the white adsorbent background, which poses the challenge of *seeing* the separation that occurs in a TLC. TLC plates often have to be "visualized," meaning something has to be done to the plate in order to temporarily see the compounds. Common methods of visualization are to use UV light (Figures 2.6 a+b) or a chemical stain (Figure 2.6c).

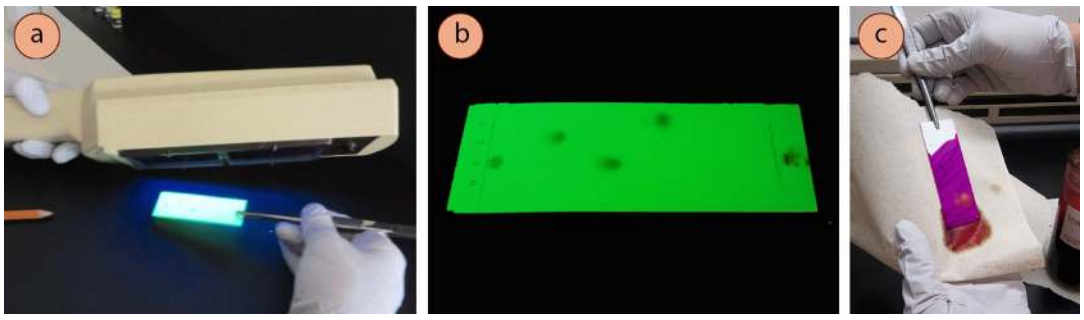


Figure 2.6: a) Visualization of a TLC plate using UV light, b) Compounds appear dark against a fluorescent green background, c) Use of a chemical stain to visualize a plate.

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2.1.4B: Uses of TLC

TLC is a common technique in the organic chemistry laboratory because it can give quick and useful information about the purity of a sample and whether or not a reaction in progress is complete. When low polarity solvents are used, a TLC plate can be complete in less than 5 minutes.

Assessing Purity

One of the uses of TLC is to assess the purity of a sample. In Figure 2.7 are TLC plates of acetophenone and cinnamaldehyde: samples that were diluted from their reagent bottle, run, and visualized with UV light. Acetophenone appeared as only one spot on the TLC plate, indicating the reagent is likely pure. Conversely, cinnamaldehyde is unquestionably impure as its TLC showed two large spots, and had a few fainter spots as well. Aldehydes are prone to air oxidation, and it is common for aldehydes to be found in their reagent bottles alongside with their corresponding carboxylic acids. TLC is one method that can be used to determine how much an aldehyde has degraded.

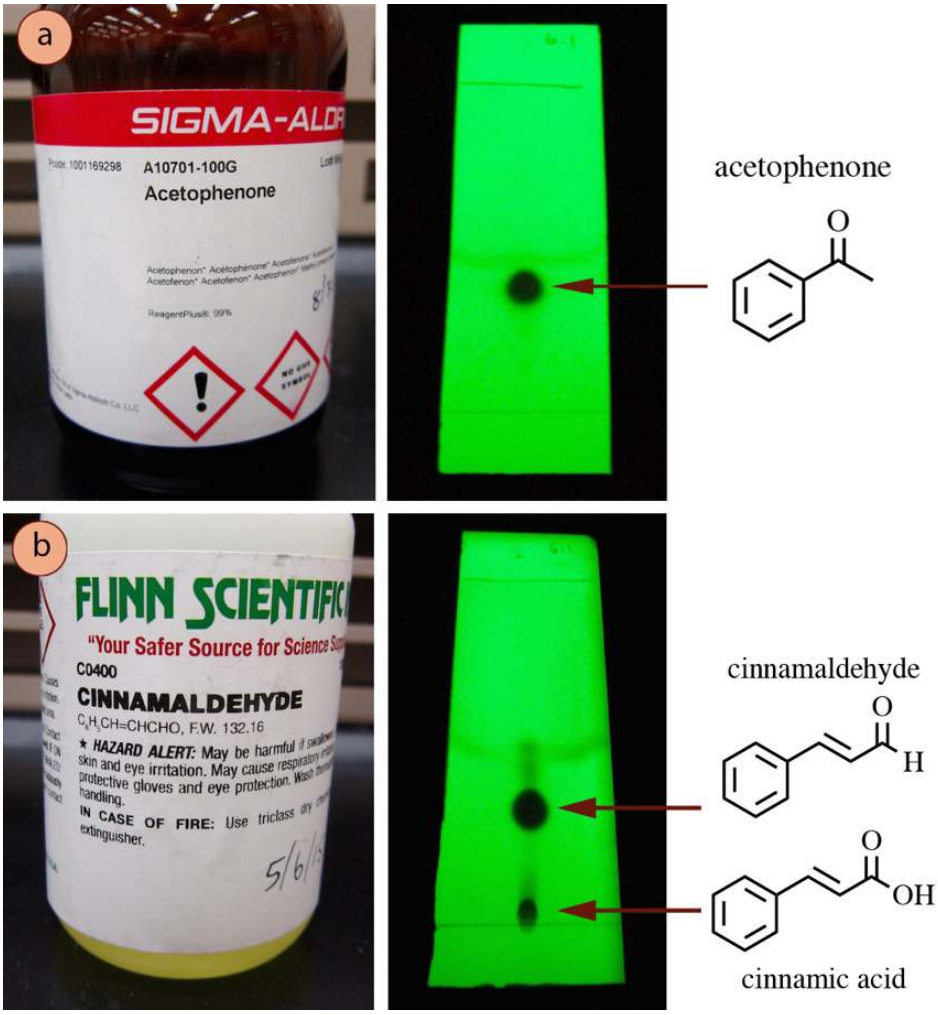


Figure 2.7: Eluted TLC plates visualized with UV light of: a) Acetophenone, b) Cinnamaldehyde.

Assessing Reaction Progress

Use of a Co-Spot

TLC can be used to analyze a chemical reaction, for example to determine if the reactants have been consumed and a new product has formed. A pure sample of the reactant can be spotted in one lane of a TLC, and the product mixture in another lane. Often the central lane is used for reference, where both reactant and product mixture are spotted over top of one another, in what is called the "**co-spot**."

For example, the reaction shown in Figure 2.8a is analyzed by TLC in Figure 2.8b. In the first lane of Figure 2.8b (labeled F) is spotted a pure sample of the reactant ferrocene. In the last lane (labeled AF) is spotted the product mixture, which is assumed to be acetylferrocene. In the central lane (labeled co) is spotted both pure ferrocene and the product mixture. The right-most "AF" lane shows that the reaction appears to be a success: the higher spot of ferrocene is absent (meaning it has been consumed), and a new product spot is present. More tests would have to be done to confirm that the lower spot is the expected product of acetylferrocene, but the TLC results look promising.

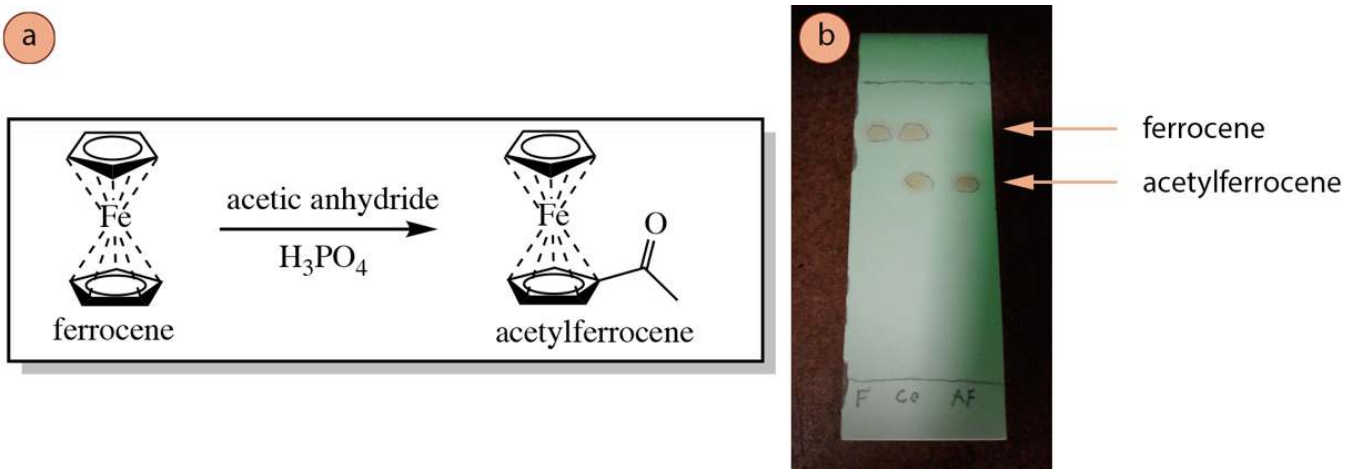


Figure 2.8: a) Reaction scheme of the acetylation of ferrocene, b) TLC plate (visualized with UV light) with 3 lanes: F for pure ferrocene, Co for the co-spot, and AF for the acetylferrocene product.

The co-spot is used for reference, and can be useful in interpreting certain situations. For example, at times the solvent may run with a slight diagonal, causing identical components to elute to slightly different heights. The co-spot can be useful in tracking these variations. It can also be helpful in identifying spots as different if they have similar R_f values (a feature difficult to be certain of in Figure 2.9a). Two compounds with slightly different R_f values eluted over top of one another in the co-spot lane may produce a spot with an elongated shape (Figure 2.9b), making it more obvious they are different compounds. Furthermore, a cospot can be helpful in deciphering a TLC plate if the reaction solvent persists in the product mixture lane (for example if the solvent has a relatively high boiling point like DMF or DMSO), such that the residual solvent has an effect on the component's R_f values.

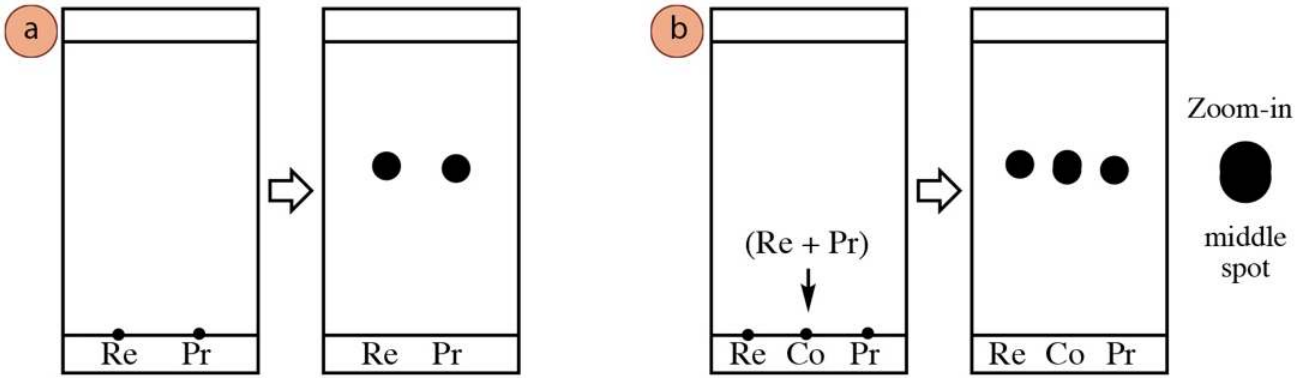


Figure 2.9: a) Two compounds with similar R_f values (Re stands for reactant and Pr stands for the product), b) How the co-spot lane may appear if the reactant and product lanes contain different compounds.

Monitoring a Reaction by TLC

TLC can be used to monitor the progress of a reaction. This method is often used in research, and one such journal article reporting its usage is shown in Figure 2.10.

Method B for Olefin Synthesis: Ethyl 4-methyl-5-(prop-1-en-2-yl)thiazole-2-carboxylate (3{*3*}). Methyltriphenylphosphonium bromide (12.4 g, 33.6 mmol) was dissolved in dry THF (90 mL) and cooled to 0 °C. Potassium *tert*-butoxide (42.0 mL of a 1.0 M solution in THF, 42.0 mmol) was added dropwise, and the reaction mixture was warmed to room temperature with stirring for 15 min and then heated to reflux for 2 h. TLC indicated the disappearance of starting material after 2 h. The suspension was cooled to 0 °C and added via syringe to a solution of **2**{*3*} (5.72 g, 26.9 mmol) in THF (90 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h, at which time TLC showed the reaction was complete. The mixture was then concentrated by rotary evaporation, and water (100 mL) and EtOAc (100 mL) were added. The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification by flash chromatography (EtOAc/hexane 1:9) afforded **3**{*3*} (4.10 g, 70%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.27 (s, 1H,), 4.45 (q, J = 7.2 Hz, 2H), 2.55 (s, 3H), 2.14 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 153.5, 150.7, 140.9, 135.1, 118.6, 62.5, 25.1, 17.4, 14.4; $C_{10}H_{13}NO_2$, ESI-MS m/z 212 $(M + H)^+$. Purity was determined to be 100% by HPLC analysis.

Figure 2.10: From: K. A. Milinkevich, M. J. Kurth, J. Comb. Chem. 2008, 10, 521-525.

To use TLC in this manner, three lanes are spotted on a TLC plate: one for the limiting reactant, one for the co-spot, and one for the reaction mixture. The goal is to note the disappearance of the limiting reactant in the reaction mixture lane and the appearance of a new product spot. When the limiting reactant has completely disappeared, the chemist deduces that the reaction is complete, and can then be "worked up".

To demonstrate how TLC can be used to monitor a reaction, the transesterification reaction in Figure 2.11 was studied over time (Figure 2.12). In the first lane of each TLC plate (marked "BA") was spotted a dilute sample of the reactant benzyl acetate, while in the third lane of each was spotted the reaction mixture (marked "Pr") at different times. In the central lane (marked "Co" for the co-spot), both benzyl acetate and the reaction mixture were delivered over top of one another.

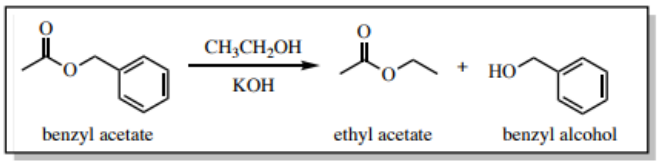


Figure 2.11: Reaction scheme of transesterification reaction.

Figure 2.12 shows the progress of the reaction over time. In Figure 2.12a, with the third lane representing the reaction mixture after one minute of mixing, a faint spot near the middle of the plate corresponds to unreacted benzyl acetate. A new spot appears below it, representing the benzyl alcohol product. Over time (Figure 2.12b-e), the top benzyl acetate spot disappears in the reaction mixture lane, and the lower benzyl alcohol spot intensifies. It is apparent from the TLC plates that the reaction was nearing completion at 10 minutes, and was complete at 20 minutes. The TLC demonstrates that the reaction mixture could be worked up after 20 minutes of mixing.

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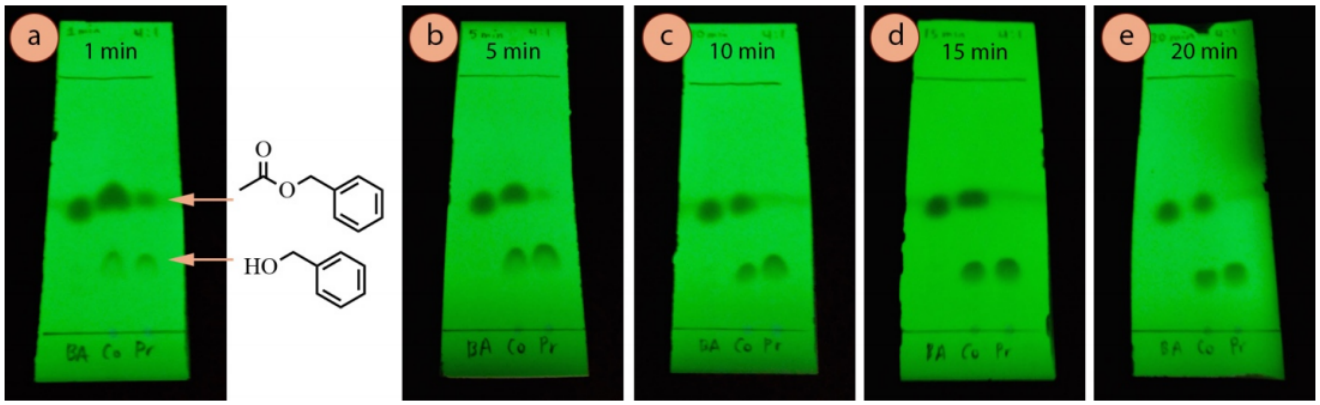


Figure 2.12: Monitoring of the transesterification reaction of benzyl acetate with TLC at 5-minute increments (using 4:1 hexanes:ethyl acetate and visualized with UV light): a) After 1 minute, b) 5 minutes, c) 10 minutes, d) 15 minutes, e) 20 minutes.

Obtaining an Aliquot of a Reaction in Progress

To monitor a reaction's progress by TLC, an "**aliquot**" (or tiny sample) of the reaction mixture is necessary.

If the reaction is run at room temperature or with only mild heating, and the concentration of reactants is conducive to TLC, a capillary spotter can be directly inserted into the flask where the reaction is taking place (Figure 2.13a). A long spotter is ideal if one is available. The aliquot can then be directly spotted on the TLC plate.

If the sample is expected to be UV active, it is a good idea to view the TLC plate under UV light before eluting the plate. If the sample spot is not visible before elution it will not be visible afterwards, as compounds diffuse during elution.

If the sample is expected to be UV active, and only a faint hint of material is seen on the baseline, the material can be deposited multiple times before elution (Figure 2.13b): deliver a small spot of sample on the baseline, and let it *fully dry* before delivering another spot over top of the first. If the spots are not allowed to dry in between applications, the spot will be too large. Check the plate under UV light again, and if necessary spot more times.

It is important to fully allow a spot to dry on the TLC plate before placement in the TLC chamber. In Figure 2.13c the spot for the reaction mixture (labeled Pr) was not fully dry before elution, and the ethanol solvent likely affected the appearance of the lower R_f spot. In Figure 2.13d the sample was allowed to fully dry before elution, and the lower R_f spot was more distinct. Furthermore, residual ethanol was likely the reason why the compound spotted in the reagent lane (labeled "BA") had a different R_f than it did in the central co-spot lane ("Co").

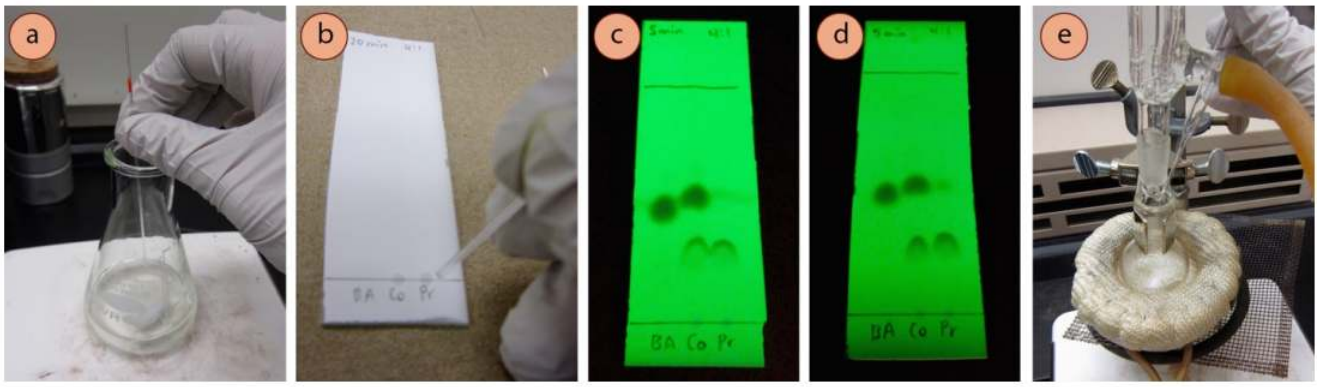


Figure 2.13: a) Obtaining an "aliquot" from a reaction mixture, b) Spotting the reaction mixture multiple times in the same lane, c) The appearance of the reaction mixture when it was not fully dried before elution, d) When the sample was fully dried before elution, e) Obtaining an aliquot for a refluxing solution.

To obtain an aliquot of a refluxing solution, briefly remove the condenser and insert a spotter into the reaction mixture (Figure 2.13e). Immediately re-connect the condenser and adjust the clamps while holding the aliquot. Alternatively, lift the flask from the

heat source to temporarily cease the reflux before inserting the spotter. The sample may be able to be spotted directly on the TLC plate, but if too concentrated it can be first diluted by running an appropriate solvent (e.g. acetone) through the pipette and into a small vial.

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2.1.4C: The Retention Factor

A convenient way for chemists to report the results of a TLC plate in lab notebooks is through a "**retention factor**",[2] or R_f **value**, which quantitates a compound's movement (Equation 2.1.4C.1).

$$R_f = \frac{\text{distance traveled by the compound}}{\text{distance traveled by the solvent front}} \tag{2.1.4C.1}$$

To measure how far a compound traveled, the distance is measured from the compound's original location (the baseline marked with pencil) to the compound's location after elution (the approximate middle of the spot, Figure 2.14a). Due to the approximate nature of this measurement, ruler values should be recorded only to the nearest millimeter. To measure how far the solvent traveled, the distance is measured from the baseline to the solvent front.

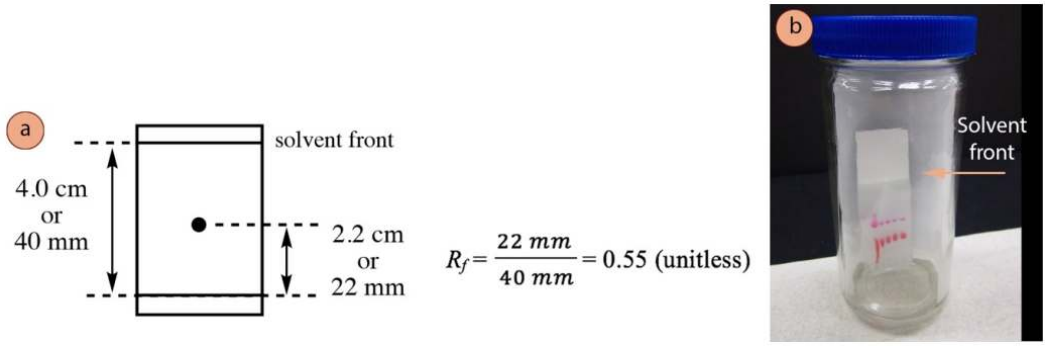


Figure 2.14: a) Sample R_f calculation, b) Appearance of the solvent front on an eluting TLC plate.

The solvent front (Figure 2.14b) is essential to this R_f calculation. When removing a TLC plate from its chamber, the solvent front needs to be marked *immediately* with pencil, as the solvent will often evaporate rapidly.

The R_f value is a ratio, and it represents the relative distance the spot traveled compared to the distance it could have traveled if it moved with the solvent front. An R_f of 0.55 means the spot moved 55% as far as the solvent front, or a little more than halfway.

Since an R_f is essentially a percentage, it is not particularly important to let a TLC run to any particular height on the TLC plate. In Figure 2.15, a sample of acetophenone was eluted to different heights, and the R_f was calculated in each case to be similar, although not *identical*. Slight variations in R_f arise from error associated with ruler measurements, but also different quantities of adsorbed water on the TLC plates that alter the properties of the adsorbent. R_f values should always be regarded as approximate.

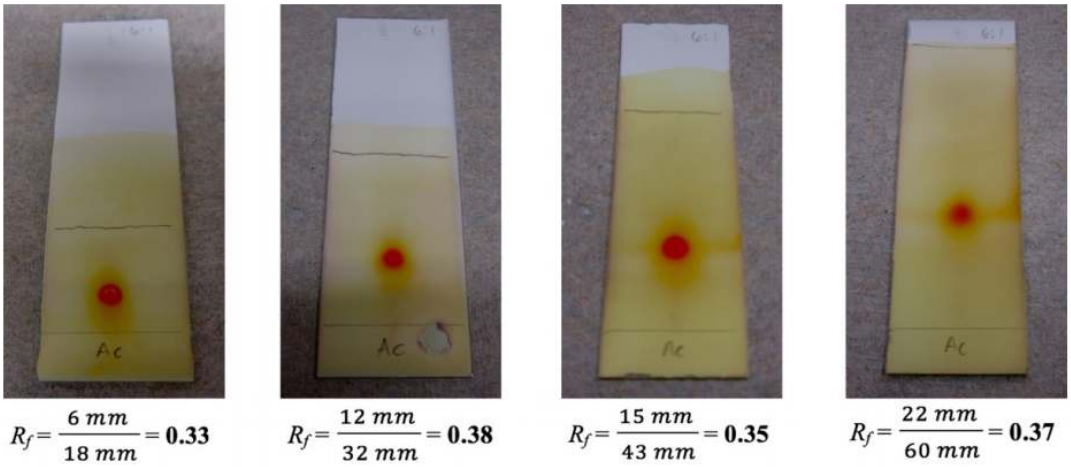


Figure 2.15: Acetophenone run to different heights on the TLC plate, using 6:1 hexanes:ethyl acetate and visualized with anisaldehyde stain.

Although in theory a TLC can be run to any height, it's customary to let the solvent run approximately 0.5 cm from the top of the plate to minimize error in the R_f calculations, and to achieve the best separation of mixtures. A TLC plate should not be allowed to

run completely to the top of the plate as it may affect the results. However, if using a saturated, sealed TLC chamber, the R_f can still be calculated.

[2]Sometimes the R_f is called the retardation factor, as it is a measurement of how the movement of the spots is slowed, or retarded.

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2.1.4D: Separation Theory

General Theory

TLC is an excellent analytical tool for separating mixtures in a sample. In this section are discussed the details of the separation, and expand upon the general discussion of Section 2.1.B.

In all forms of chromatography, samples equilibrate between stationary and mobile phases. In almost all applications of TLC, the stationary phase is a silica or alumina adsorbent and the mobile phase is an organic solvent or solvent mixture (the "**eluent**") that rises up the plate (equation 3).

$$\mathbf{X}_{(\text{silica/alumina})} \rightleftharpoons \mathbf{X}_{(\text{solvent})} \tag{2.1.4D.1}$$

Silica gel (shown in Figure 2.16) is composed of a network of silicon-oxygen bonds, with $\mathbf{O{-}H}$ bonds on its surface, as well as a layer of water molecules. Silica gel ($\mathbf{SiO_2 \cdot \mathit{x}H_2O}$) is used in this discussion, but is structurally analogous to alumina ($\mathbf{Al_2O_3 \cdot \mathit{x}H_2O}$). This very polar stationary phase is paired with a relatively nonpolar mobile phase (an organic solvent or solution), in what is referred to as "normal phase" TLC. Although this is the most common form of TLC (and what will be focused on in this section), "reverse phase" TLC (with a nonpolar stationary phase and a polar mobile phase) is sometimes used.

Figure 2.16 shows how acetophenone would cling to the surface of silica gel through intermolecular forces (IMF's). In this case, acetophenone can hydrogen bond (the IMF indicated in Figure 2.16a) to the silica surface through its oxygen atom. As eluent flows over the sample (Figure 2.16b), an equilibrium is established between the sample being adsorbed on the stationary phase and dissolved in the mobile phase. When in the mobile phase, the compound moves up the plate with the flow of liquid (Figure 2.16c) to later readsorb on the stationary phase further up the plate. The resulting R_f of the compound is dependent on the amount of time spent in the stationary and mobile phases.

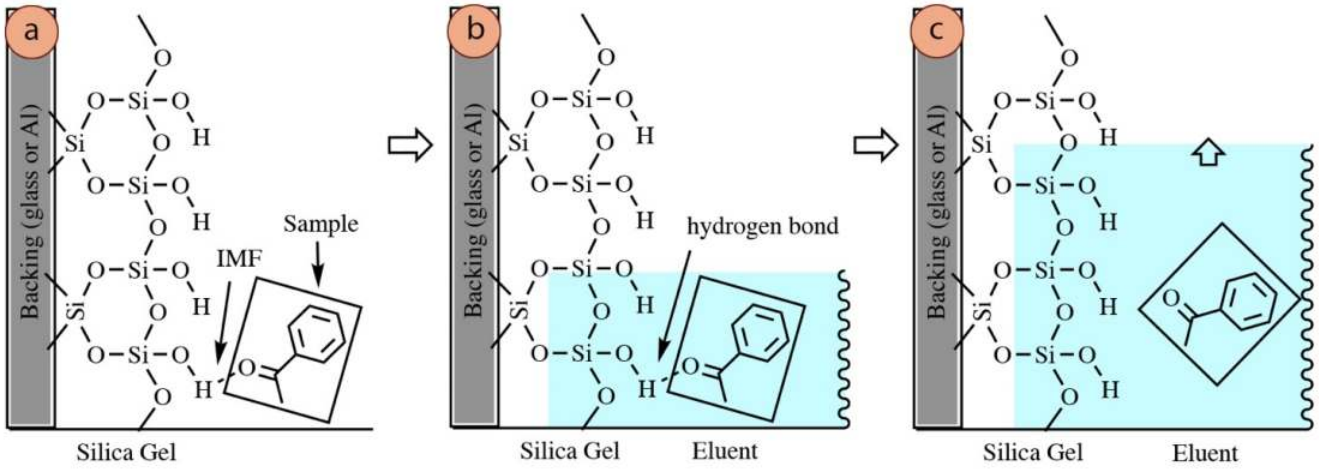


Figure 2.16: Structural diagrams of compounds bound to a silica coated TLC plate (side view). In reality the silica layer is much thicker than shown ($\mathbf{0.25\ mm}$ of powder), and the surface is more porous and uneven than implied. a) Acetophenone spotted on the baseline of the TLC plate, b) Eluent crawling up the TLC plate, c) Acetophenone in the mobile phase after breaking its IMF's with the silica surface.

The equilibrium distribution between the two phases depends on several factors:

1. It depends on the strength of intermolecular forces between the sample and the **stationary phase**.

   A compound that forms strong IMF's with the silica or alumina will often favor the stationary phase, and will spend much of the elution time adhered to the plate. This means it will spend less time in the mobile phase (which is the only means for it to travel up the plate), causing it to end up low on the TLC plate, and have a low R_f.

   Compounds that have oxygen or nitrogen atoms should be able to hydrogen bond with the stationary phase (have strong IMF's with the stationary phase), and thus will have lower R_f values than compounds of similar size that can only interact through London dispersion forces (LDF's).

2. It depends on the strength of interaction between the sample and the **mobile phase**.

   As the mobile phase is always less polar than the stationary phase in normal phase TLC, polar compounds will tend to have a lesser affinity for the mobile phase than nonpolar compounds (based on the "like dissolves like" principle). Therefore, polar compounds tend to spend less of the elution time mobile than a nonpolar compound, so will travel "slower" up the plate, and have a low R_f.

The degree of attraction by a compound to the stationary and mobile phases lead to the same conclusion:

- The stronger IMF's possible with the stationary phase (often the more polar functional groups on a compound), the more time the compound will be stationary $\rightarrow$ lower R_f.
- The more polar functional groups present on a compound, the less it tends to be attracted to the less polar eluent, and the less time the compound will be mobile $\rightarrow$ lower R_f.

Thus, a compound with a lower R_f tends to have more polar functional groups than a compound with a higher R_f (summarized in Figure 2.17).

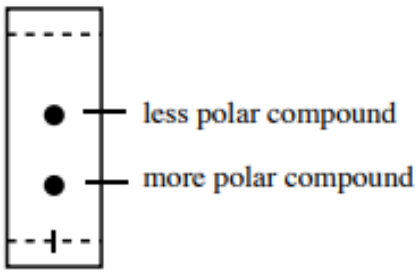


Figure 2.17: Relation of polarity to R_f.

Structural Considerations

To demonstrate the effect of structural features on R_f, an eluted TLC plate of benzyl alcohol, benzaldehyde, and ethylbenzene is shown in Figure 2.18. The relative order of R_f reflects the polarity trend in the series.

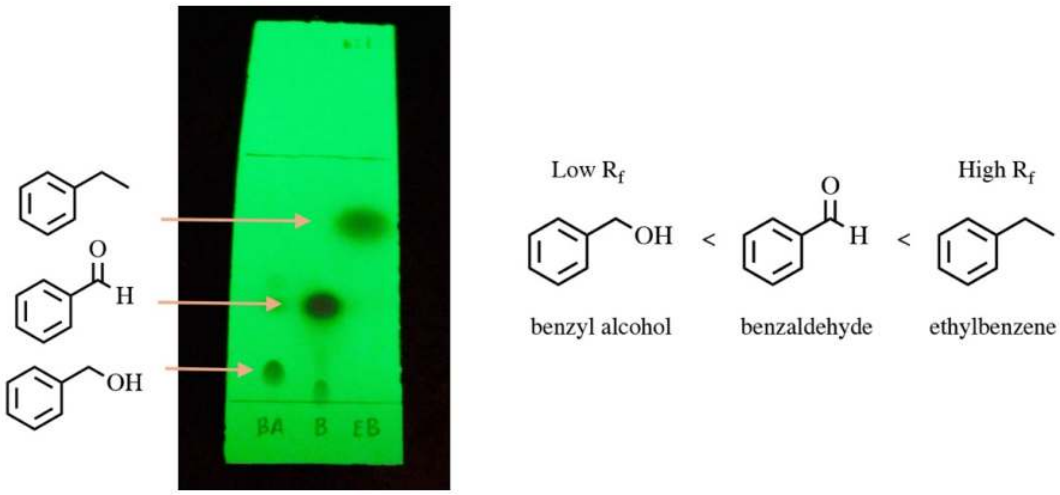


Figure 2.18: TLC of benzyl alcohol (lane 1), benzaldehyde (lane 2), and ethylbenzene (lane 3). The plate was eluted using 6:1 hexanes:ethyl acetate and visualized with UV light.

Benzyl alcohol and benzaldehyde have polar functional groups so thus had lower R_f values than ethylbenzene, which is completely nonpolar. Both compounds are able to hydrogen bond to the polar stationary phase (Figure 2.19a+b), so are more strongly attracted to the stationary phase than ethylbenzene, which interacts only through weak London dispersion forces (Figure 2.19c). As the least "polar" of the series, ethylbenzene is also the best dissolved by the weakly polar eluent. For these reasons, ethylbenzene spent the least time in the stationary phase and the most time in the mobile phase, which is why it traveled the furthest up the plate and had the highest R_f of the series.

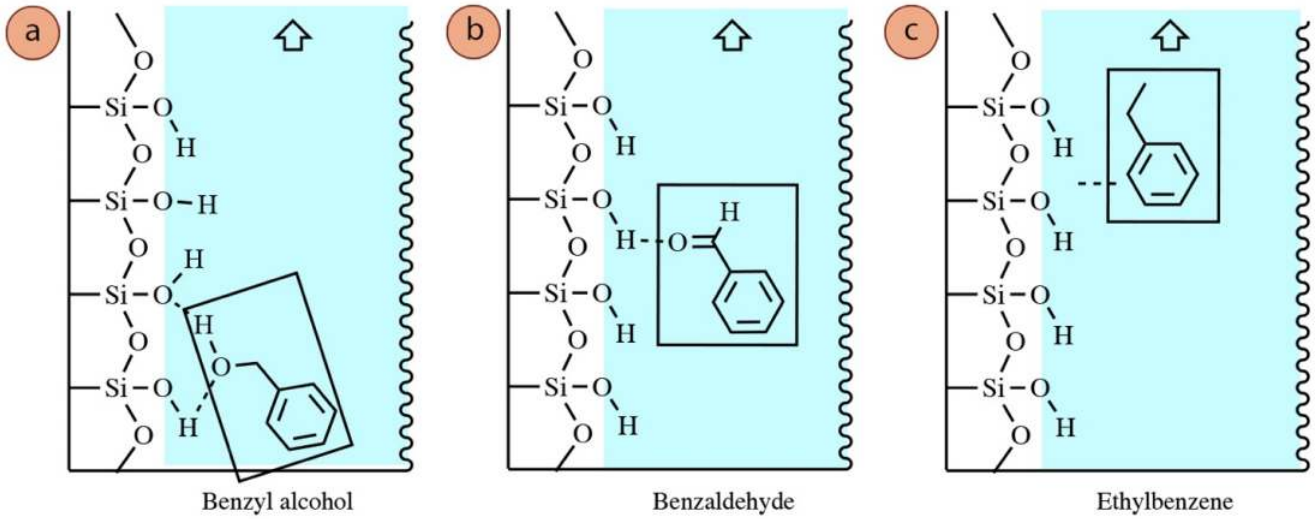


Figure 2.19: Intermolecular forces between silica gel and: a) benzyl alcohol, b) benzaldehyde, c) ethylbenzene.

Both benzaldehyde and benzyl alcohol are capable of hydrogen bonding with the stationary phase, but benzyl alcohol had the lower R_f because it can form *more* hydrogen bonds (through both the oxygen and hydrogen atoms of the **OH** group, Figure 2.19a). This caused benzyl alcohol to be more strongly adhered to the silica/alumina than benzaldehyde, causing it to spend more time in the stationary phase.

To demonstrate a different structural effect on R_f, an eluted TLC plate of acetophenone and benzophenone is shown in Figure 2.20. Both compounds are similar in that they can hydrogen bond to the stationary phase through their oxygen atom. However, the larger size of benzophenone causes it to have a slightly higher R_f than acetophenone.

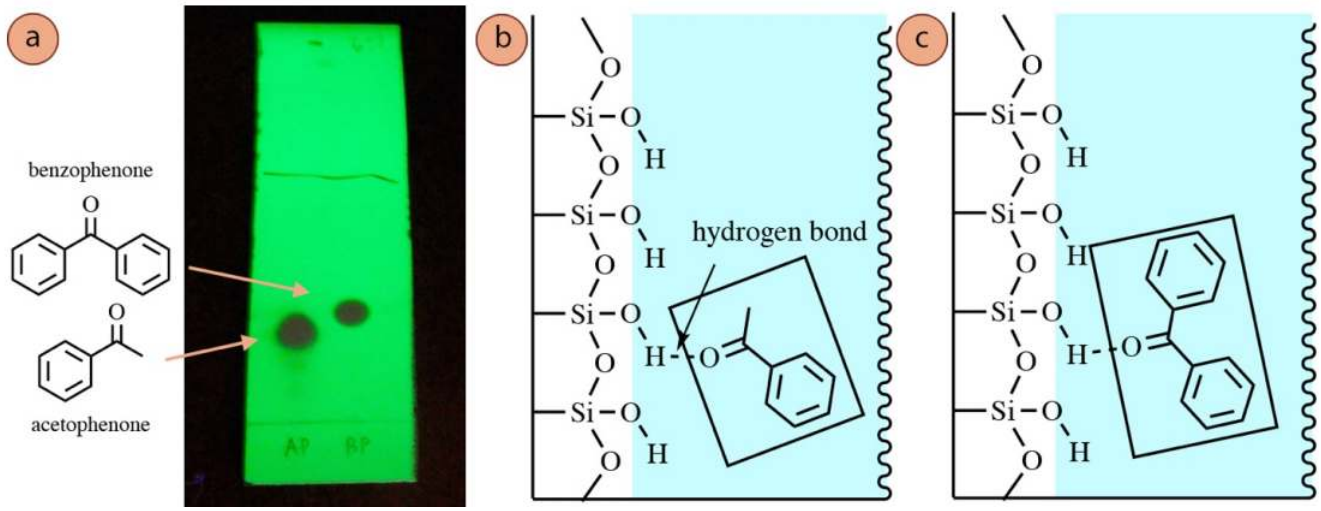


Figure 2.20: a) TLC plate of acetophenone (lane 1) and benzophenone (lane 2), using 6:1 hexanes:ethyl acetate and UV light visualization. Interaction with the stationary phase and: b) Acetophenone, c) Benzophenone.

This result can be explained in multiple ways:

- The oxygen atom in benzophenone is more crowded by the aromatic rings than the oxygen atom of acetophenone, which may impede its ability to strongly hydrogen bond with the silica gel. This can lead to a smaller amount of time adsorbed by the stationary phase.
- The additional nonpolar bulk of benzophenone makes it dissolve better in the weakly polar eluent, causing it to spend more time in the mobile phase.

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Mobile Phase Polarity

The ability of chromatography to separate components in a mixture depends on equilibration of a compound between the stationary and mobile phases. Since the mobile phase is an important factor, it is possible to change the R_f of a compound by changing the polarity of the mobile phase.

When a mobile phase is made more polar than originally, all compounds travel further and have a higher R_f.

This general trend is demonstrated in Figure 2.21b+c, where the TLC of three UV-active compounds (lanes 2-4) was run using two different mixed solvents. The first plate was run using a 6:1 hexane:ethyl acetate mixture, which means the solvent was created by using 6 volumes of hexane for every 1 volume of ethyl acetate. This mixed solvent is mostly nonpolar due to the high percentage of hexane, but is more polar than straight hexane, due to the presence of some ethyl acetate (which has polar bonds, Figure 2.21a). The second plate was run using a 3:2 hexane:ethyl acetate mixture, which is more polar than the 6:1 mixture because there is a higher percentage of ethyl acetate present.

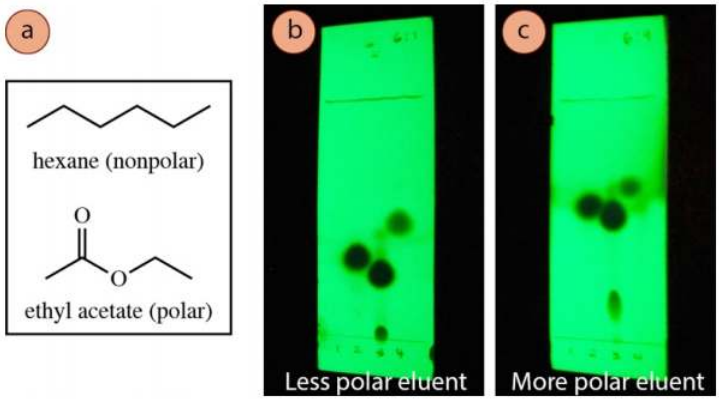


Figure 2.21: a) Structures of hexane and ethyl acetate, b) Three compounds visualized by UV light and run with 6:1 hexanes:ethyl acetate mixtures, c) Same three compounds with a 3:2 ratio (more polar).

Table 2.2: Summary of Rf values for Figure 2.21

Lane	R_f in 6:1 (less polar eluent)	R_f in 3:2 (more polar eluent)
2	0.33	0.54
3 (bottom spot)	0.02	0.17
3 (top spot)	0.28	0.52
4	0.49	0.65

Note that in Figure 2.21c all spots maintained their relative order but traveled to a greater height on the plate and increased their R_f values (Table 2.2) in the more polar eluent.

An increase in solvent polarity increases R_f values for two reasons:

1. Moderately polar compounds have a greater attraction to the mobile phase.

   When equilibrating between a polar stationary phase and nonpolar eluent, a polar compound tends to favor the polar stationary phase and have a low R_f. If the eluent is made to be moderately polar, polar compounds are then more attracted to the mobile phase, causing the equilibrium to change such that the compound spends more time in the mobile phase, resulting in a higher R_f.
2. The polar solvent may occupy binding sites on the silica or alumina surface, such that they displace the sample from the stationary phase.

   If a polar solvent is able to hydrogen bond and therefore strongly associated with the stationary phase, it may "lock up" binding

sites, and force less polar compounds to spend more time in the mobile phase. The result is an increased R_f for polar and nonpolar compounds alike.

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2.1.4E: Step-by-Step Procedures for Thin Layer Chromatography

General TLC Procedure

The TLC pictured in this section shows elution of a TLC plate containing several samples of red food dye at different aqueous dilutions (0 = undiluted, 3 = 1 drop dye + 3 drops water, etc.).



Figure 2.22: a) Red food dye spotted at different dilutions, b) Elution, c) Developed TLC plate.

Dissolve the Samples

1. Dissolve all the samples you want to run (solids and liquids) in small vials using a volatile solvent in which they are soluble (e.g. acetone, diethyl ether, or dichloromethane). Ideally the vials will have a lid to minimize vapors and preserve the samples if tipped over (Figure 2.23a).

   The optimal concentration for TLC is typically determined empirically, but a good place to start is to use 50-100 times as much solvent as sample (i.e. 1 drop sample for $\sim 1\ \text{mL}$ solvent). If you have already prepared an NMR sample ($\sim 5\ \text{mg}/0.75\ \text{mL}$ for high field NMR), you can use that sample directly.

   Label the vials. Also prepare a vial of clean acetone (or other solvent, e.g. CH_2Cl_2) to be used to rinse the spotters in a later step. (A rinse vial of water is pictured in Figure 2.23a, as the dye solutions are water soluble.)

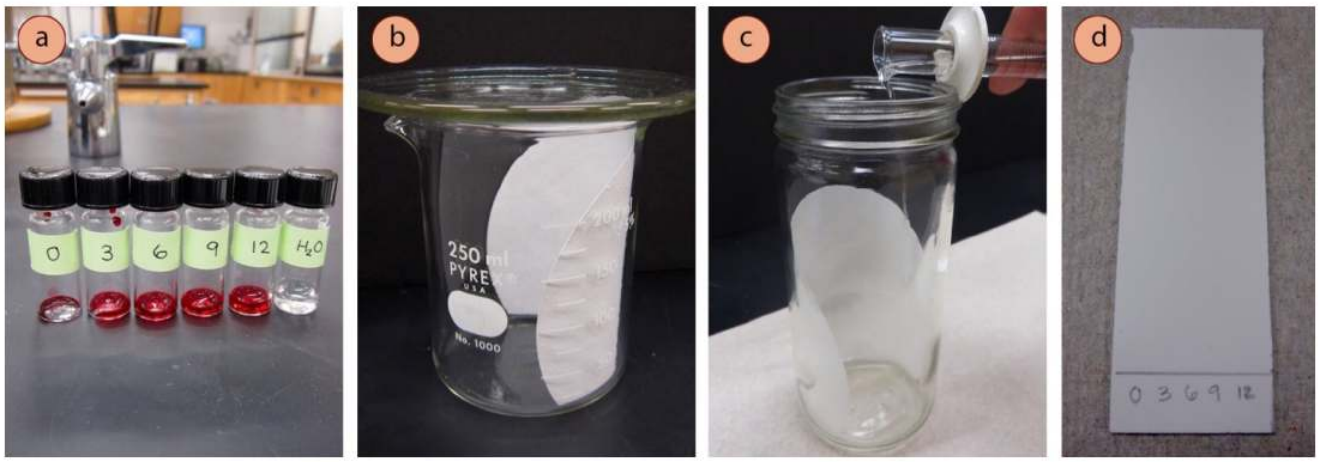


Figure 2.23: a) Prepared samples, b) TLC chamber made with a beaker and watch glass, c) Adding eluent to a TLC chamber, d) Prepared plate.

Prepare the TLC Chamber and Plate

2. Obtain a TLC chamber with lid. An inexpensive chamber can be made using a beaker and watch glass (Figure 2.23b). Cut a piece of filter paper (or two) so that when placed in the chamber, the filter paper fits inside the chamber and is flat on the bottom but not obscuring your view of the inside (Figure 2.23c).

The filter paper keeps the chamber saturated with vapors so when the eluent rises on the plate it doesn't easily evaporate, but continues to climb and undergo the chromatography. If the eluent evaporated, movement would stop, but could also change the local composition of a mixed eluent and affect the results.

3. Add a portion of a prepared solvent for chromatography (Figure 2.23c, 5-10 mL for this type of TLC chamber). Close the lid (or place the watch glass) and tilt the chamber to wet the filter paper.
4. Obtain a TLC plate, touching the plate only on the back or edges, but not on the white surface. Use a rule to lightly draw a straight line with a pencil[3] roughly 1 cm from the bottom. Do not gouge the silica or alumina.

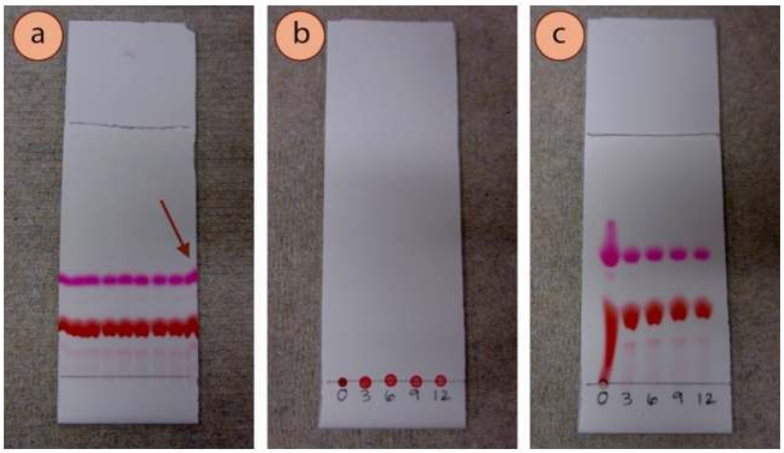


Figure 2.24: *a) Red food dye sample spotted many times, with arrow indicating the creep of sample on the edges, b) Diluted red food dye samples at different dilutions - before elution, c) after elution.*

5. Label the areas with pencil where you plan to place the samples (Figure 2.23d). A one-inch wide TLC plate can comfortably accommodate three samples (have three lanes), and if the spot size is kept small it can fit at maximum five spots. If more than five spots are necessary on one plate, TLC plates can be purchased in sheets and cut wider than one inch.

   The lanes should not be placed too close to the edge (keep at least 5 mm away from each edge), as it is not unusual for solvent to travel slightly "fast" at the edge where capillary action of the solvent is greater (Figure 2.24).

   The lanes should also not be placed too close to one another, or the spots may overlap after elution. A spot is always larger after elution compared to its original size (Figure 2.24b+c) because diffusion occurs in all directions (contact with a liquid spreads the material in both the horizontal and vertical directions). Broadening also occurs as solutes in the mobile phase move at different rates as the flow of eluent is weaker near the adsorbent surface. This can even sometimes cause compounds to get stuck in adsorbent pores where the flow of eluent is especially weak.[4]. Spot broadening means that samples deposited right next to each other on the baseline of a TLC plate will probably bleed together during elution.

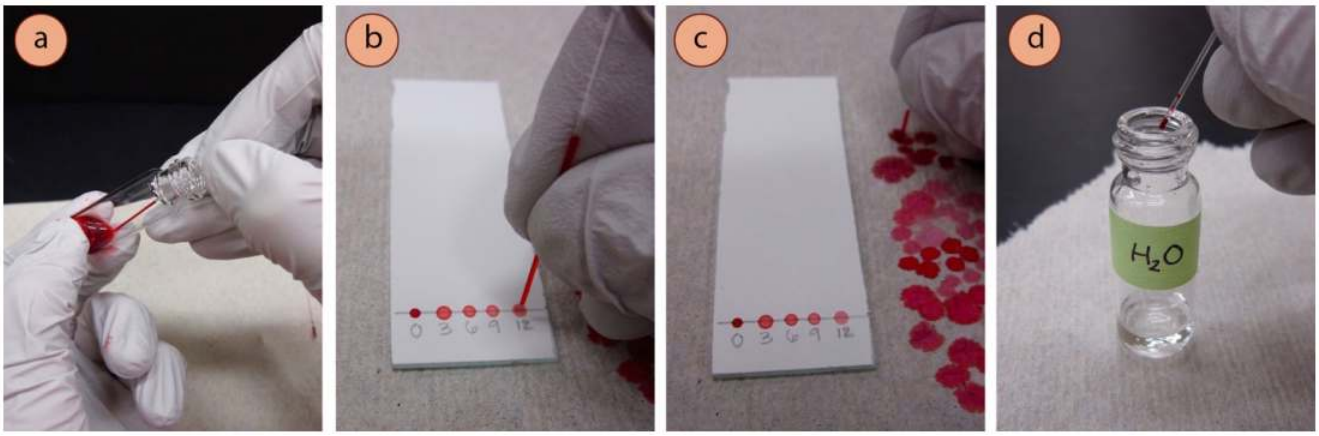


Figure 2.25: a) Tipping the vial to withdraw liquid into the spotter, b) Spotting samples onto a TLC plate, c) Excess sample drained on a paper towel, d) Rinsing the spotter with solvent (water in this case).

Spot the TLC plate with sample

6. Obtain a capillary spotter (a very thin hollow piece of glass open at both ends). In some institutions, you may need to make your own spotter by stretching a softened pipette. Place your spotter into the diluted sample you want to analyze to withdraw liquid into the spotter through capillary action. If the liquid level is low in your vial and your spotter short, you may have to tip the vial to withdraw liquid (Figure 2.25a).
7. Keeping the spotter mostly vertical, make a practice "spot" on a paper towel or scrap piece of silica or alumina to familiarize yourself with how the liquid delivers from the spotter. The spots should be very small, around **2 mm** in diameter. Deliver a very small spot of material on the pencil line of the appropriate lane (Figure 2.25b) using a quick "up and down" motion with your hand. Don't gouge the silica or alumina with the spotter.
8. Still keeping the spotter vertical, immediately touch the spotter to a paper towel to expunge all of the liquid remaining in the spotter (Figure 2.25c). If the spotter is set down without immediate draining the liquid, air may get into the spotter making it impossible to dispense and use again.
9. Rinse the spotter with acetone (or another volatile solvent with which your compounds are soluble, Figure 2.25d). Place the empty spotter in your rinse vial to withdraw liquid and drain the solvent onto a paper towel. Rinse once or twice before reusing the spotter for other samples.

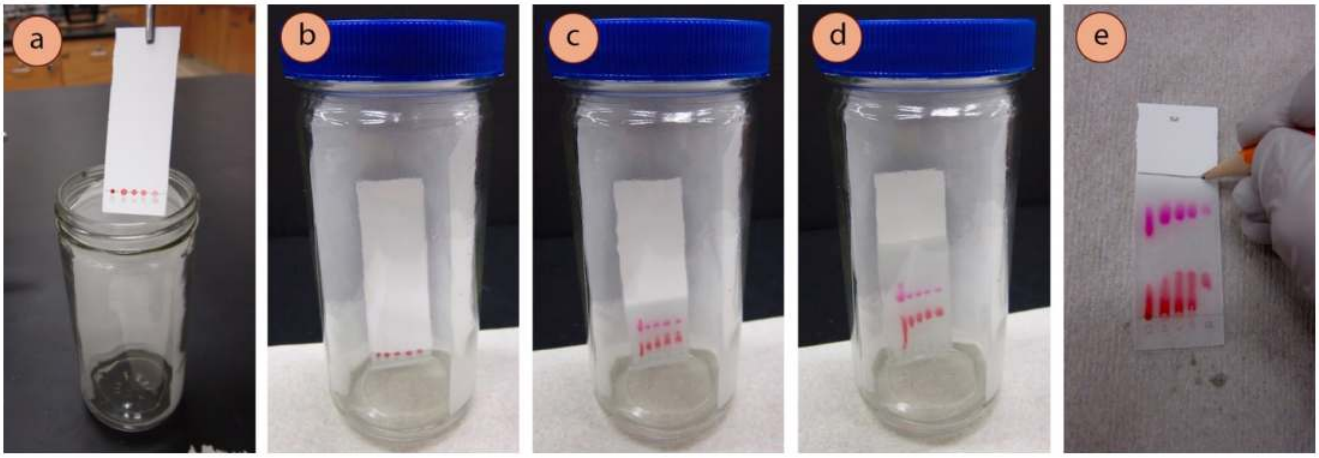


Figure 2.26: a) Using forceps to place the TLC plate into the chamber, b-d) Elution, e) Marking the solvent line with a pencil.

Place the TLC plate in the chamber to "elute"

10. Use forceps to delicately place the TLC plate into the chamber (Figure 2.26a). Don't allow the liquid to splash onto the plate.

The liquid level must be below the pencil line where the samples are spotted or the compounds will dissolve in the pool of

eluent instead of traveling up the plate. Cap the chamber delicately while keeping it vertical, and don't touch it again until the TLC is complete.

11. Allow the TLC to develop (Figure 2.26b-d). As liquid moves up the TLC plate it will appear transparent and wet. A dark background will allow the solvent front to be more easily seen. If the eluent is very polar (e.g. contains large amounts of ethanol or water), elution will take a relatively long time (can be 30-40 minutes). If the eluent is very nonpolar (e.g. contains large amounts of hexane or petroleum ether), elution will be relatively quick (can be 2-5 minutes for a $10\ \text{cm}$ tall plate).
12. Depending on the goals of the TLC experiment, the chromatography can be stopped when the solvent level is anywhere between halfway to roughly $0.5\ \text{cm}$ from the top of the plate. It is best to let the TLC run to around $0.5\ \text{cm}$ from the top of the plate to get the best separation of spots and to minimize error in R_f calculations.

Remove the TLC plate from the chamber

13. Open the TLC chamber, and remove the TLC plate with forceps. *Immediately* mark the solvent line with a pencil (Figure 2.26e) to enable an R_f calculation, as the solvent often readily evaporates. Alternatively, the silica can be lightly gouged with the forceps to mark the solvent front.
14. If the compounds on the TLC plate are colored, the process is complete. If the compounds are colorless, they need to next be visualized.

Thin Layer Chromatography Summary

			
Place a small portion of solvent (5-$10\ \text{mL}$ for this chamber) into a TLC chamber with lid, along with a cut piece of filter paper.	Dissolve liquid or solid samples (1 drop per $\sim 1\ \text{mL}$ solvent) using a low boiling solvent (e.g. acetone or dichloromethane).	Draw a pencil line on a TLC plate $\sim 1\ \text{cm}$ from the bottom with a ruler, and mark the lanes. Don't put lanes too close to the edge or to each other. Spot a dilute sample on the pencil line of the correct lane, making very small spots ($2\ \text{mm}$ in diameter). Rinse the spotter with a solvent (e.g. acetone) if going to use it for another sample.	Place the sample in the TLC chamber with forceps, cap it, and leave it alone. Remove the plate when the solvent line is $\sim 0.5\ \text{cm}$ from the top. Immediately mark the solvent line with a pencil. Visualize if necessary.

Table 2.3: *Procedural summary for TLC.*

TLC Troubleshooting

The spots are streaky or "blobby"

The components of a sample can appear as long streaks or "blobby" spots on a TLC plate if the samples are run at too high a concentration.

For example, Figure 2.27b shows an eluted TLC plate containing five red food dye samples of different concentrations (lane 0 contains the dye in the concentration found at the grocery store; lane 3 contains 1 drop of dye diluted with 3 drops of water, etc.). After elution, the red and pink components from the undiluted dye (lane 0) streaked severely, as the TLC plate was "overloaded". When this happens proper equilibration between stationary and mobile phases does not occur. With further dilution (lane 12), the streaking disappeared and the spot shapes sharpened.

If streaking is seen on a TLC plate, the sample should be diluted and run again.

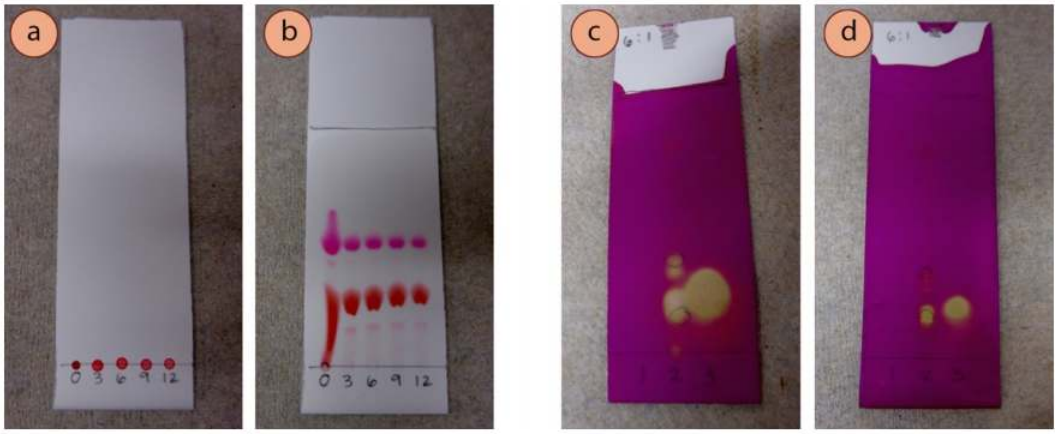


Figure 2.27: a) Before elution of red food dye samples at different aqueous dilutions, b) After elution, c) Alkene and alkyne samples too concentrated (visualized with $KMnO_4$ stain, d) Alkene and alkyne samples at proper dilution.

Figure 2.27c also demonstrates how dilution can improve the shape of a spot after elution. In this TLC, alkene and alkyne samples were spotted at somewhat high concentrations, while an improved dilution was used in Figure 2.27d. Note how the R_f appears to change in the two TLC plates. The more accurate R_f is of the diluted sample. Running TLC on concentrated samples gives inaccurate R_f values and may hide multiple spots.

The spots ran unevenly

At times the solvent front may run unevenly on a TLC plate. This may occur if the plate was placed in the chamber at a slight tilt, if eluent splashed onto the plate during placement in the chamber, or if the chamber was jostled during elution. In cases where the front is dramatically different from one position to the other, the front should be measured for each *lane* of the plate (if calculating an R_f) instead of only once.

Making Capillary TLC Spotters

Although capillary spotters for TLC can be purchased, some chemists prefer to create their own by stretching Pasteur pipettes (Figure 2.28). To make a spotter, hold a pipette by the edges while wearing thick gloves and position the middle of the pipette into the flame of a large Meker burner (Figure 2.28a). Warm the pipette until the glass becomes quite pliable (borosilicate glass softens at $820^{\circ}C$,[5] so this will take some time). Only rotate, but do not stretch the pipette at all while the pipette is in the flame. Then remove the pipette from the flame and immediately and rapidly pull the pipette to an arm's length. The thin sections can be broken into 6-12 inch segments and used for TLC.

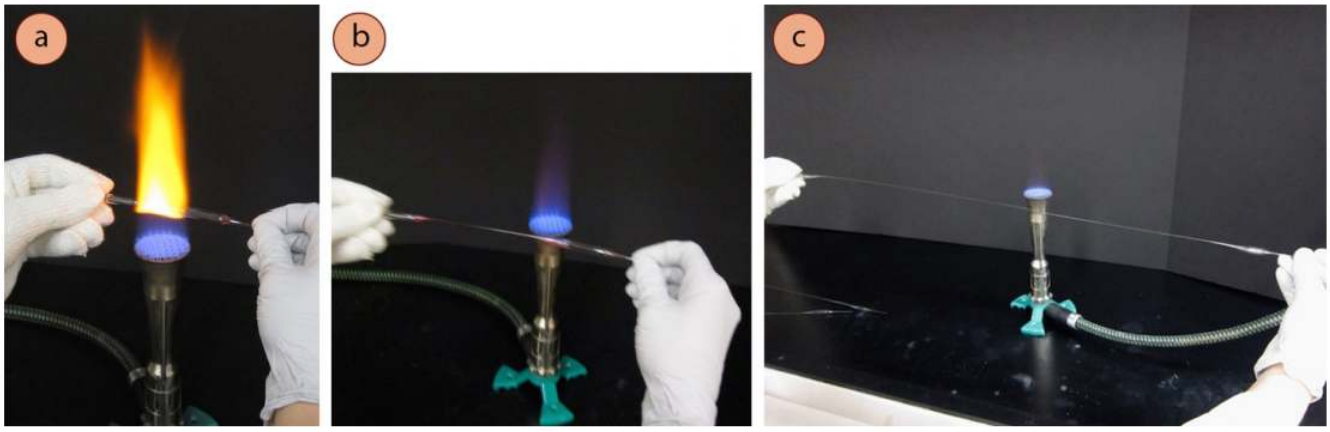


Figure 2.28: a) Warming a pipette in a Meker burner, b+c) Stretching the pipette.

Notebook Record of TLC's

Some chemists scan, photograph, or electronically record their developed TLC plates, but it is much more common to copy a likeness of a TLC plate by hand into a laboratory notebook. It is important to copy a TLC plate "to scale", meaning the dimensions should be the same in the notebook as they are in actuality.

To accomplish this, the TLC plate can be placed atop a notebook page and a rendering created beside it (Figure 2.29c). The back of the TLC plate should previously be wiped clean or else staining reagents may degrade the paper. It is important to copy the TLC plate as accurately as possible, drawing the spots exactly as they appear, even if they are streaky or blobby. All spots seen in a lane should be recorded, even if they are faint. Good record keeping means to record all observations, even if the importance is unknown; a faint, unexpected spot may become relevant at a later time.

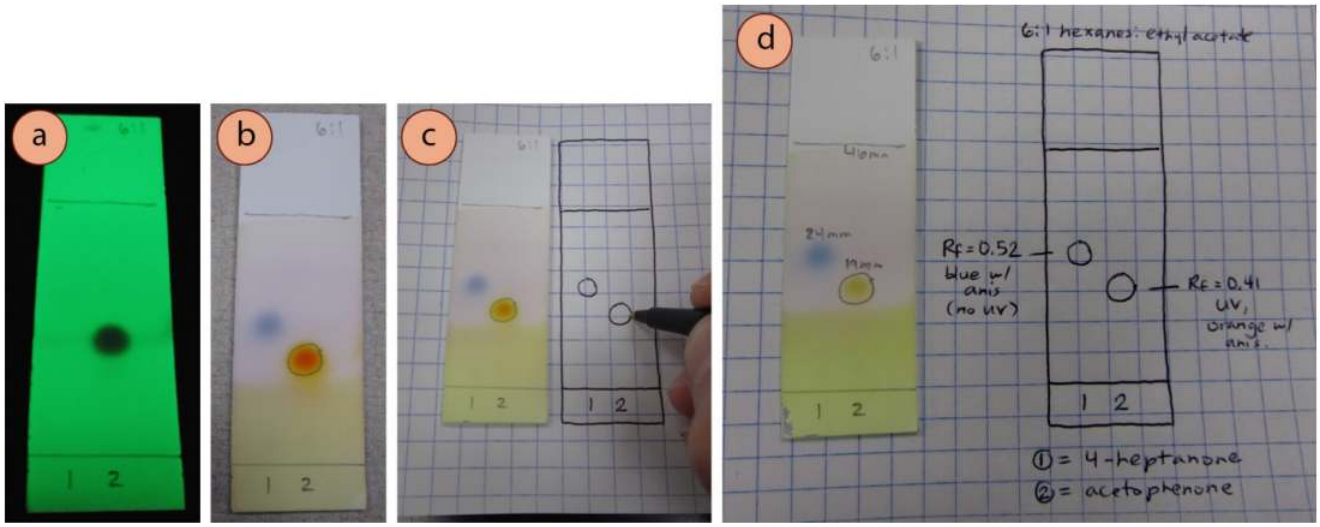


Figure 2.29: Record of a TLC plate into a lab notebook: a) Plate under UV light, b) Plate stained with p-anisaldehyde, as it appeared directly after heating, c) Copying the TLC into the notebook, d) Final record in the notebook.

Several other notations should be made along with the sketch of the TLC plate (Figure 2.29d). The solvent system and identity of what was spotted in each lane must be recorded. For each spot, an R_f should be calculated (some chemists like to write the measurements on the TLC plate; see the plate in Figure 2.29d) along with notation of UV activity and stain color. If a spot changes appearance over time, as the orange spot in Figure 2.29b faded to light green over time (Figure 2.29d), the initial appearance should be recorded.

https://chem.libretexts.org/@go/page/406389



Figure 2.30: Organic chemistry students making entries in their notebooks.

[3]The graphite in pencil will not travel with the eluent, but pen ink would.

[4]J. Sherman and B. Fried, *Handbook of Thin Layer Chromatography*, **1991**.

[5]G. L. Weissler, *Vacuum Physics and Technology*, 2nd edition, **1979**, p. 315.

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2.1.4F: Visualizing TLC Plates

Organic compounds most commonly appear colorless on the white background of a TLC plate, which means that after running a TLC, chemists often cannot simply *see* where compounds are located. The compounds have to be "visualized" after elution, which means to temporarily convert them into something visible.

Visualization methods can be either **non-destructive** (compound is unchanged after the process) or **destructive** (compound is converted into something new after the process. Viewing a TLC plate under ultraviolet light is non-destructive, while using a chemical stain is destructive.

Visualization Summary

Below is a summary of various visualization techniques, and the functional groups that generally react with each. A more detailed discussion of each technique is provided later in this section.

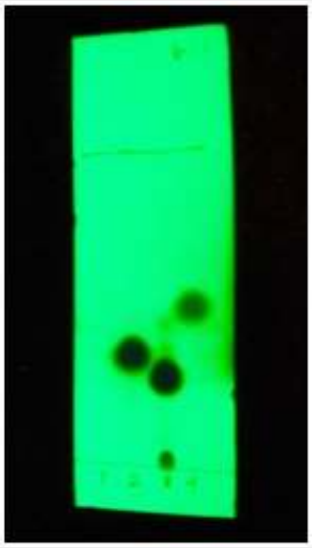
UV Light: For aromatics + conjugated systems	**Iodine:** Visualizes ~half the time. Strongly reacts with aromatics	***p*-Anisaldehyde:** For many aldehydes, ketones, and alcohols	**Vanillin:** For many aldehydes, ketones, and alcohols
			
Permanganate: For alkenes, alkynes, or oxidizable groups (aldehydes, alcohols)	**Phosphomolybdic Acid (PMA):** For alcohols, phenols, alkenes, and many carbonyl compounds	**Iron(III) Chloride:** For phenols	**Bromocresol Green:** For acidic compounds
			

Table 2.4: *Summary table for TLC visualization methods.*

Ultraviolet Absorption

The most common non-destructive visualization method for TLC plates is ultraviolet (UV) light. A UV lamp can be used to shine either short-waved ($254\ \text{nm}$) or long-waved ($365\ \text{nm}$) ultraviolet light on a TLC plate with the touch of a button. Most commercially

bought TLC plates contain a fluorescent material (e.g. zinc sulfide) in the silica or alumina, so the background of the plate will appear green when viewing with short-waved UV light. If a compound absorbs 254 nm UV light, it will appear dark, as the compound prevents the fluorescent material from receiving the UV light.

This method is so quick and easy that it is often the first visualization method tried. It is most useful for visualizing aromatic compounds and highly conjugated systems, as these strongly absorb UV. Most other functional groups do not absorb UV light at the wavelengths used and will not appear dark under the UV lamp even though they are still there. It doesn't hurt to try UV after performing TLC with all compounds just in case. Since the compounds remain unchanged after viewing with UV light, a further visualization technique can be used afterwards on the same plate.



Figure 2.31: a) Tilting a UV lamp to visualize a TLC plate, b) Box to protect eyes from UV damage, c) Appearance under UV.

Procedure for UV visualization of TLC plate:

1. Use a UV lamp to look at your developed TLC plate by pressing the short-waved button. Depending on what is available at your institution, you might tilt the UV lamp at an angle in a darkened area of the room (Figure 2.31a), or you might look at the plate inside a box designed to protect eyes from UV damage (Figure 2.31b).

   Safety note: Care should be taken to never look directly at the UV source, and to minimize exposure to eyes.
2. The plate background will appear green under short-waved UV light, and UV-active compounds will appear dark (Figure 2.31c). Use a pencil to lightly circle spots, as they will disappear when the UV light is removed.
3. Some compounds themselves fluoresce (Figure 2.32), appearing a variety of colors when exposed to either short- or long-waved UV light (bright purple or blue is the most common). Record these types of observations in your notebook if you see them, as they are rare, and are therefore an excellent identification tool. They are most common with highly conjugated compounds.

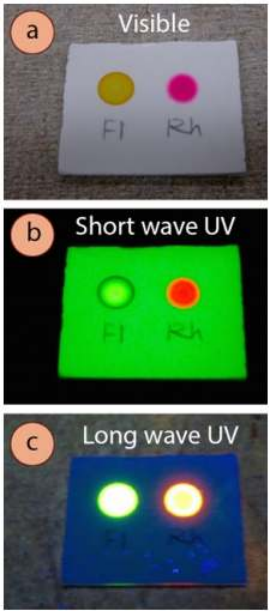


Figure 2.32: Fluorescein and rhodamine B solutions viewed with: a) Visible light, b) Short-wave UV, c) Long-wave UV.

4. The TLC plate can be further visualized with some other method if desired (iodine or a chemical stain).

Iodine

A commonly used semi-destructive visualization method is to expose a developed TLC plate to iodine (I_2) vapor. An "iodine chamber" can be created by adding a few iodine crystals to a TLC chamber, or by adding a few iodine crystals to a chamber containing a portion of powdered silica or alumina (Figure 2.33a). When a developed TLC plate is placed in the chamber and capped, the iodine sublimes and reacts with the compounds on the plate, forming yellow-brown spots (Figure 2.33d). The coloration occurs because iodine forms colored complexes with many organic compounds. This stain will work with approximately half the compounds you may encounter.

This method is considered "semi-destructive" because complexation is reversible, and the iodine will eventually evaporate from the TLC plate, leaving the original compound behind. When the coloration fades, it is theoretically possible to use another visualization technique on the TLC plate, although it's possible the compound may have also evaporated by that time.

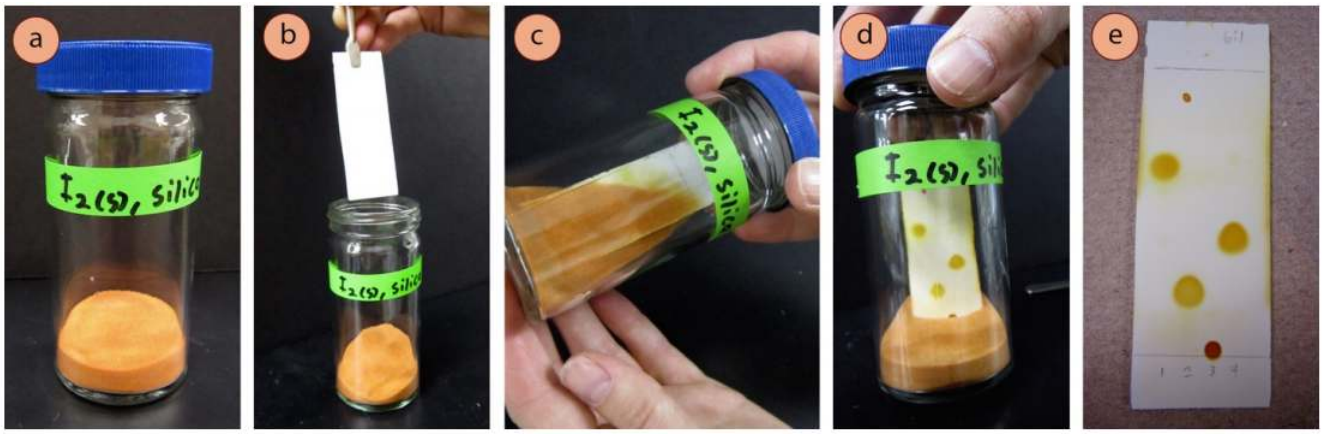


Figure 2.33: a) An iodine chamber using silica gel, b-d) Inserting a plate into the chamber and jostling, e) Developed TLC plate with iodine.

Procedure for visualization of TLC plate with iodine:

1. If not already prepared, make an "iodine chamber" (Figure 2.33a): in a fume hood, place a few centimeters of powdered silica or alumina in a screw-capped TLC chamber and add a few crystals of solid iodine (**safety note:** silica and alumina are lung irritants, and iodine vapor is considered an irritant and toxic). A beaker and watch glass will not work in this context as the iodine vapors will escape. Let the silica or alumina and iodine sit together for a while with periodic swirling, and eventually the powder will become orange from adsorbing the iodine vapor.
2. In a fume hood, place the developed TLC plate in the iodine chamber with forceps (Figure 2.33b) and close the lid. Gently shake the chamber to bury the TLC plate in the iodine-stained silica or alumina (Figure 2.33c) until the spots become colored (Figure 2.33d). Many spots will appear yellow-brown almost immediately, and may darken with extended time. For many compounds, it takes less than 10 seconds to develop a plate, but some compounds require 10 minutes or longer. (Note: alcohols, carboxylic acids, and alkyl halides often do not stain.)
3. Promptly record appropriate observations of the TLC in your notebook, or circle the spots with a pencil, as the colors will soon fade as the iodine evaporates from the plate. Further visualization may be attempted after the color fades.

Chemical Stains

There are a variety of destructive visualization methods that can turn colorless compounds on a TLC plate into colored spots. A plate is either sprayed with or dipped in a reagent that undergoes a chemical reaction with a compound on the TLC plate to convert it into a colored compound, enabling the spot to be seen with the naked eye. Since a chemical reaction is occurring in the process, it is common to gently heat a plate after exposure to the reagent to speed up the reaction, although this may be unnecessary with some stains. Not every compound can be visualized with every reagent if they do not react together, and stains are often designed to work with only certain functional groups. The specific stain should be chosen based on the presumed structure of the compounds you want to visualize.

General Staining Procedure

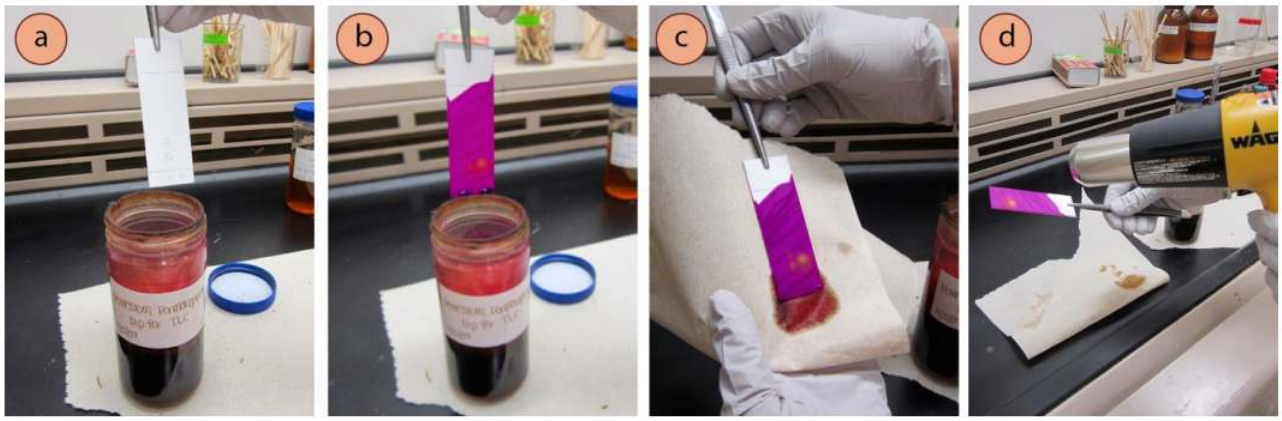


Figure 2.34: Staining sequence using permanganate stain: a) Inserting plate into the dip, b) Letting it drip, c) Wiping the back, d) Heating the plate with a heat gun.

1. While wearing gloves and holding the TLC plate with forceps in a fume hood, quickly dip the plate into and out of the chemical dip jar so that the stain covers the area where the solvent traveled on the plate (Figure 2.34b).
2. Let excess liquid drip off the plate for a few seconds, then wipe the back of the plate with a paper towel (Figure 2.34c).
3. Gently heat the plate to develop the spots. Preferably use a heat gun (Figure 2.34d), but a hotplate can also be used (Figure 2.35, charring is common).
    a. If using a heat gun, hold the TLC plate with forceps and wave the heat gun back and forth onto the front of the plate. The "high" setting can be used at first, with the setting turned to "low" if the plate begins to char. **Safety note:** Heat guns are not simple hair dryers, and can get **quite hot**. Be careful to not touch the nozzle, and remember that it remains hot for a long time after heating has ceased. The hot nozzles can even mar benchtops, so be cautious when setting the gun down.
    b. If using a hot plate, place the TLC plate on the warm surface (set between low and medium-low, and covered in foil to prevent dip residue from staining the ceramic surface). Periodically move the plate around to distribute the heat.

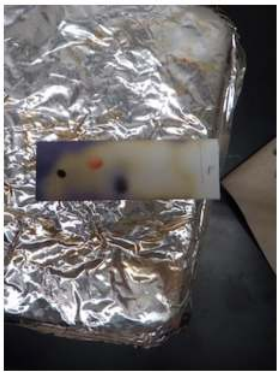


Figure 2.35: Using a hotplate to develop spots.

4. A TLC plate cannot be further visualized after using a stain.

p-Anisaldehyde/Vanillin Stains

Generalities

The *p*-anisaldehyde and vanillin stains are general purpose, and work for many strong and weak nucleophiles (alcohols, amines), and for many aldehydes and ketones. They do not work on alkenes, aromatics, esters, or carboxylic acids. The TLC plates need to be mildly heated, and will develop a light pink to dark pink background.

A TLC of four samples visualized with three different techniques is shown in Figure 2.36. The plate is visualized with UV light (Figure 2.36b), *p*-anisaldehyde stain (Figure 2.36c), and vanillin stain (Figure 2.36d). 4-heptanone (lane #1) and acetophenone (lane #2) showed similar colorations using the two stains. Ethyl benzoate (lane #4) was unreactive to both. Cinnamaldehyde (lane

#3) was reactive to *p*-anisaldehyde but not vanillin, while its impurity (cinnamic acid, on the baseline of lane #3) showed the opposite behavior.

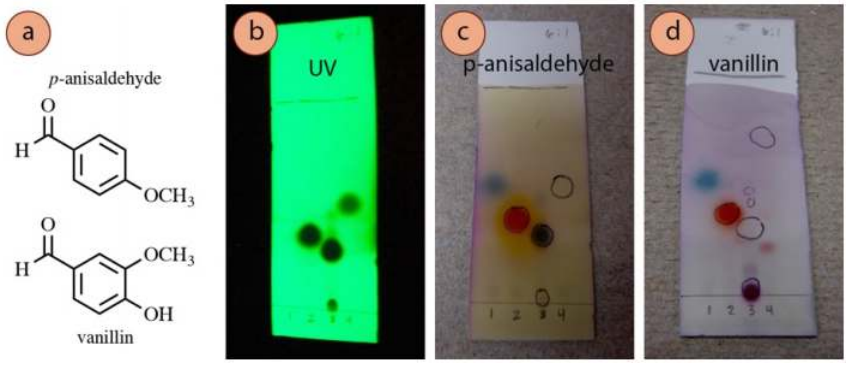


Figure 2.36: a) Structures of p-anisaldehyde and vanillin. 4-Heptanone (lane 1), acetophenone (lane 2), cinnamaldehyde (lane 3), and ethyl benzoate (lane 4) visualized with: b) UV light, c) p-*Anisaldehyde stain, d) Vanillin stain.*

Recipe (*p*-Anisaldehyde): **135 mL** absolute ethanol, **5 mL** concentrated H_2SO_4, **1.5 mL** glacial acetic acid, and **3.7 mL** *p*-anisaldehyde. This stain is susceptible to degradation by light, so store wrapped in aluminum foil (Figure 2.37e), ideally in the refrigerator when not in use. Compared to other stains, this stain has a somewhat short shelf life (approximately half a year). The stain will at first be colorless (Figure 2.37a), but over time will turn to a light then dark pink (Figure 2.37b-d). The stain is less potent when it darkens, but is often still usable. **Safety note:** wear gloves while using this highly acidic stain.

Recipe (Vanillin): **250 mL** ethanol, **15 g** vanillin, and **2.5 mL** concentrated H_2SO_4. This stain is light sensitive and should be stored wrapped in aluminum foil in the refrigerator. It is originally light yellow, but darkens over time (Figure 2.37f+g). It should be discarded if it acquires a blue color. **Safety note:** wear gloves while using this highly acidic stain.

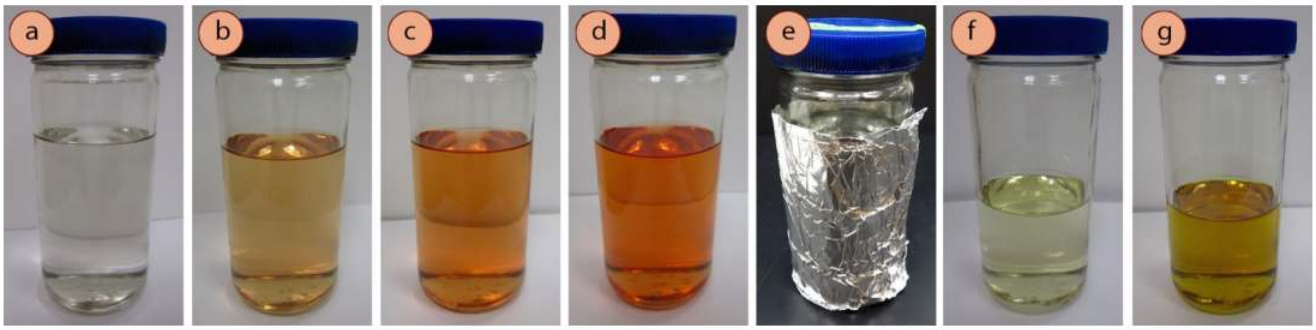


Figure 2.37: a) p-Anisaldehyde stain, within 1 week of preparation, b) After 10 weeks (covered with foil and in the refrigerator), c) After 20 weeks, d) After 30 weeks, e) Stain covered in foil for storage, f) Vanillin stain, as it appeared immediately after preparation, g) After 9 weeks.

Reaction Pathways

The *p*-anisaldehyde and vanillin stains react in a similar manner, and commonly undergo Aldol and acetalization reactions to produce highly conjugated (and thus colored) compounds on TLC plates.

Aldol Reactions

Under the acidic conditions of the stain, some aldehydes or ketones can undergo a keto-enol tautomerism, and the enol can undergo acid-catalyzed nucleophilic addition to *p*-anisaldehyde or vanillin through an aldol mechanism. Dehydration of the aldol product (encouraged by heating the TLC plate), results in a highly-conjugated compound (Figure 2.38d), which is why spots become colored.

For example, a TLC plate containing acetophenone and benzophenone (as seen with UV, Figure 2.38a), are stained with *p*-anisaldehyde and vanillin stains. Acetophenone produced a colored spot with these stains (Figures 2.38b+c) while benzophenone did not. The main difference is that benzophenone cannot form an enol, or be a nucleophile to *p*-anisaldehyde, so the stain is unreactive.

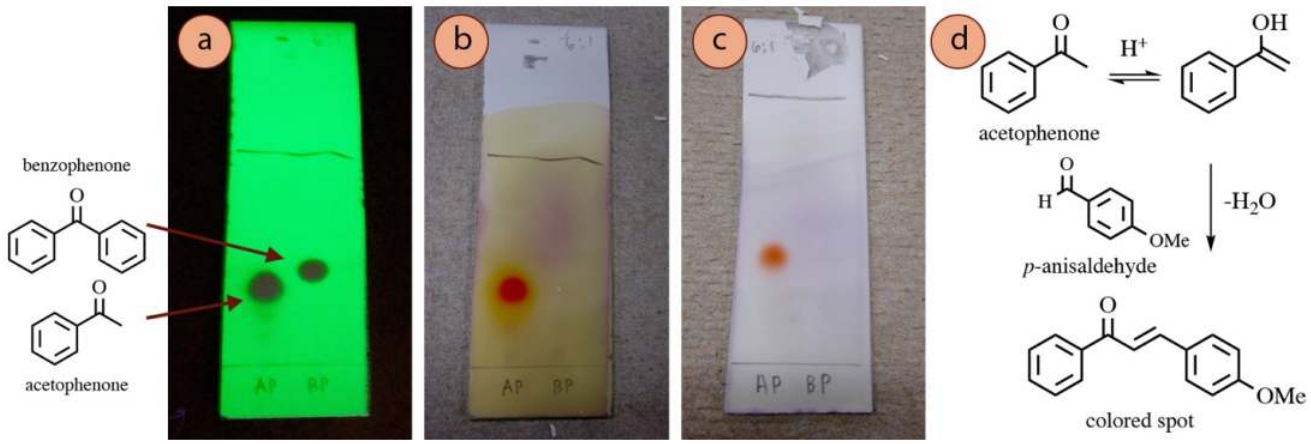


Figure 2.38: TLC's of acetophenone (lane 1) and benzophenone (lane 2), using 6:1 hexanes:ethyl acetate and visualized with: a) UV light, b) p-Anisaldehyde stain, c) Vanillin stain, d) A proposed reaction of acetophenone with p-*anisaldehyde stain.*

Acetalization Reactions

Some alcohols react with *p*-anisaldehyde and vanillin stains through acetalization reactions. A proposed reaction of *p*-cresol with *p*-anisaldehyde is shown in Figure 2.39b to produce a highly-conjugated cation, a possible structure of the pink spot on the TLC plate in lane #2 of Figure 2.39a. This cationic structure may look unusual, but is a feasible structure in the highly acidic conditions of the stain.

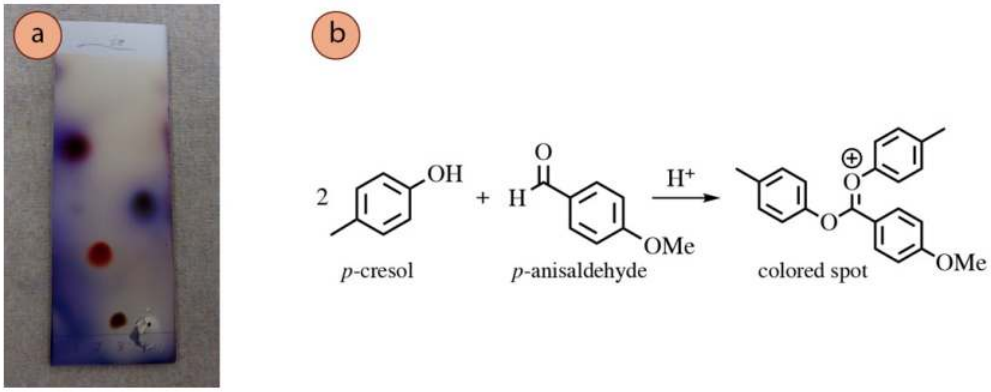


Figure 2.39: a) TLC of various phenols visualized with p-anisaldehyde stain, b) Proposed reaction of p-*cresol (lane 2) with the stain.*

Permanganate Stain

The permanganate ion (MnO_4^-) is a deep purple color, and when it reacts with compounds on a TLC plate (and is consumed), the plate is left with a yellow color (Figure 2.40a). The stain easily visualizes alkenes and alkynes by undergoing addition reactions (Figure 2.40d), and the color change is often immediate with these functional groups.

Permanganate is also capable of oxidizing many functional groups (e.g. aldehydes, lane 1 in Figure 2.40c), and so is considered by some to be a universal stain. Heat may be required to visualize some functional groups, and often improves the contrast between spots and the background. Heating may be done (if needed) until the background color just begins to yellow, but a brown background means the plate was overheated.

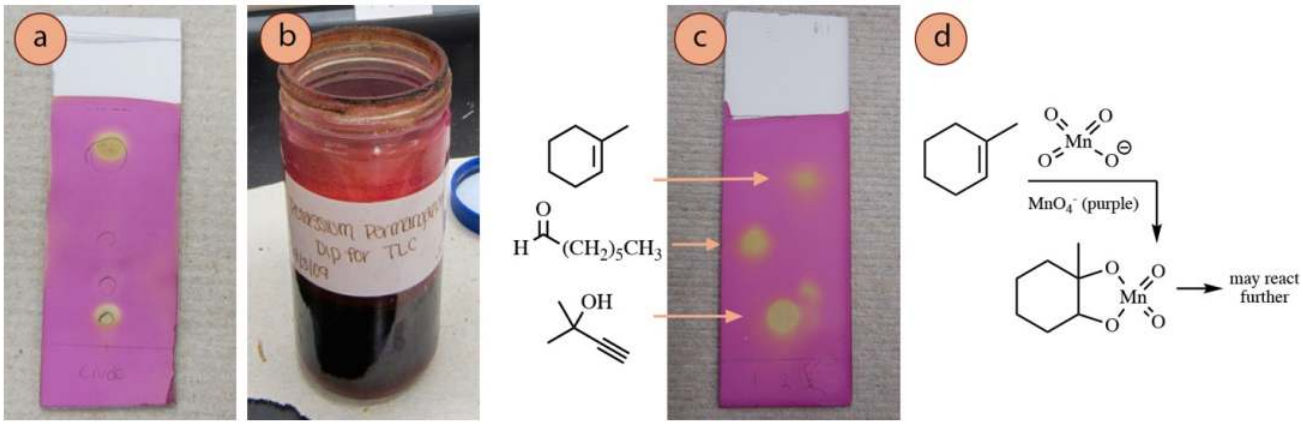


Figure 2.40: a) Crude product of a Grignard reaction stained with $KMnO_4$, b) $KMnO_4$ Reagent jar, c) TLC plate stained with $KMnO_4$ (lane 1: heptaldehyde, lane 2: 2-methyl-3-butyn-2-ol, lane 3: 1-methylcyclohexene), d) Partial mechanism for reaction of alkenes with $KMnO_4$.

Recipe: $1.5\ g\ KMnO_4$, $10\ g\ K_2CO_3$, $1.25\ mL\ 10\%\ NaOH\ (aq)$, and $200\ mL$ water. **Safety note:** wear gloves while using this stain, as permanganate is corrosive and will stain skin brown.

Phosphomolybdic Acid Stain

The phosphomolybdic acid stain (PMA) is considered by some a universal stain, able to visualize a wide variety of compounds (alcohols, alkenes, alkyl iodides, and many carbonyl compounds). The yellow-green PMA reagent (Mo^{6+}) oxidizes the compound on the plate while itself being reduced to molybdenum blue (Mo^{5+} or Mo^{4+}). Vigorous heating is required to develop the spots, but the plate is overheated when the background begins to darken. There is typically no color differentiation between spots, as most compounds visualize as green or blue spots (Figure 2.41c).

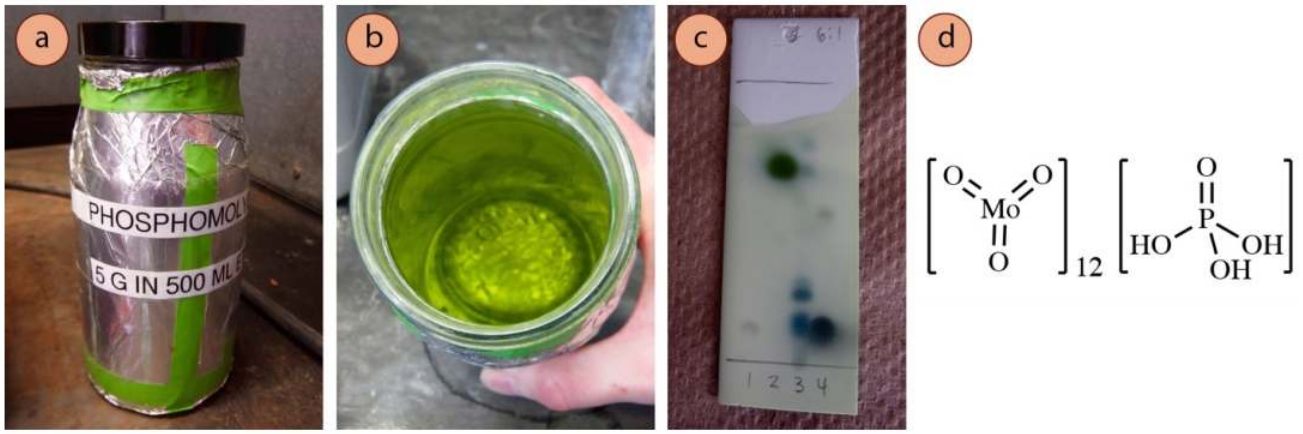


Figure 2.41: a+b) Phosphomolybdic acid reagent jar, c) TLC plate stained with the reagent (#1: benzoic acid, #2: 2,6-di-t-butylphenol, *#3: 1-methylcyclohexene - not seen, but impurities stain, #4: benzyl alcohol), d) Formula of phosphomolybdic acid.*

Recipe: $5\ g$ phosphomolybdic acid in $500\ mL$ ethanol. The stain is light sensitive and so should be stored in a jar under aluminum foil. The reagent is expensive, but the stain has a very long shelf life (5+ years).

Iron(III) Chloride Stain

The ferric chloride ($FeCl_3$) stain is highly specific, and is used mainly to visualize phenols ($ArOH$). Some carbonyl compounds with high enol content may also be visualized. Fe^{3+} forms colored complexes with phenols (often faint blue), in the general sense of what is shown in Figure 2.42c. The actual structure of these complexes is debated[6]. The coloration fades rather quickly with this stain, so observations should be recorded immediately.

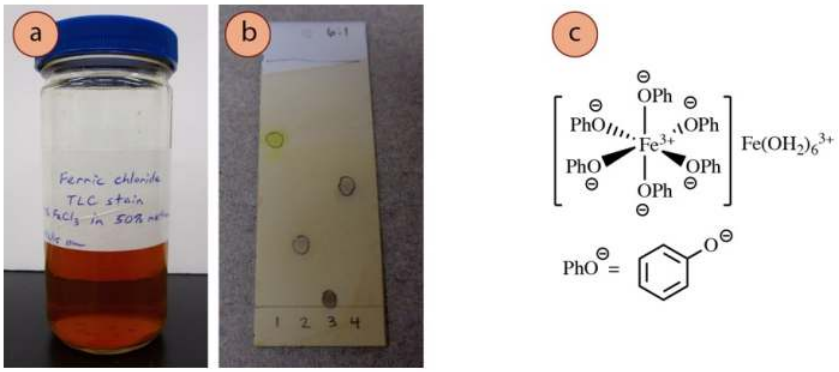


Figure 2.42: a) $FeCl_3$ reagent jar, b) TLC plate with various phenols stained with $FeCl_3$, c) Generic phenol-Fe^{3+} colored complex.

Recipe: 1% $FeCl_3$ in water and CH_3OH (50% each). This stain has a high shelf life (5+ years).

Bromocresol Green Stain

The bromocresol green stain is specific for acidic compounds, and should be able to visualize compounds that produce a solution lower than pH 5. Experience has shown that carboxylic acids work moderately well (first lane in Figure 2.43d) but phenols are only barely visible (indicated with an arrow in Figure 2.43d). In theory, the plate does not need to be heated after exposure to this stain, but in practice it often improves the contrast between the spots and the background.

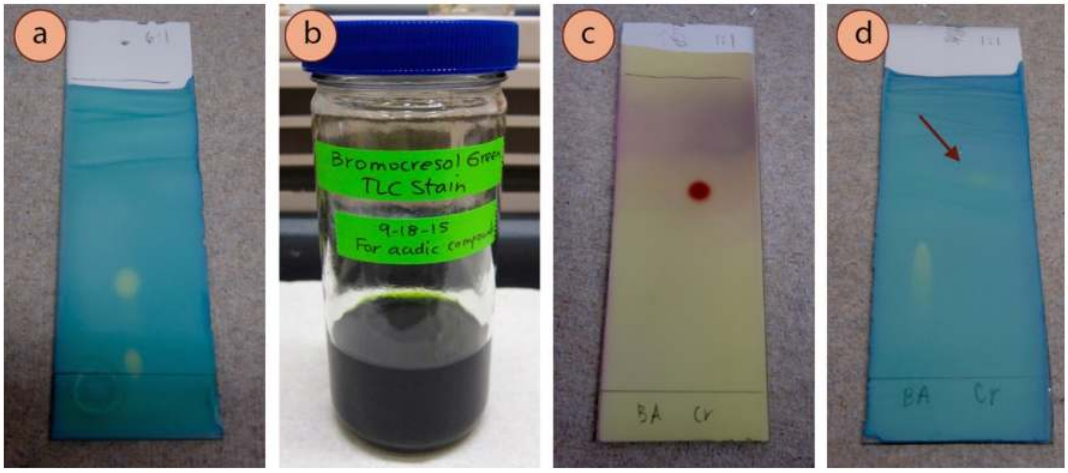


Figure 2.43: a) A plate stained with bromocresol green, b) Bromocresol green stain jar, c) Benzoic acid (lane 1) and p-cresol (lane 2) stained with p-anisaldehyde *to show position of* p-*cresol, d) Same plate stained with bromocresol green* (p-*cresol is very faint and is indicated with an arrow).*

Recipe: 100 mL absolute ethanol, 0.04 g bromocresol green, and 0.10 M NaOH (aq) drop wise until solution turns from yellow to blue (green works as well, as in Figure 2.43b).

This stain uses an acid-base indicator, which works in a similar manner to phenolphthalein. Bromocresol green is yellow below pH 3.8 and blue above pH 5.4 (Figure 2.44a). When an acidic compound is spotted on the plate, the acid lowers the pH and causes the indicator to shift to the lower pH yellow form (Figure 2.44b).

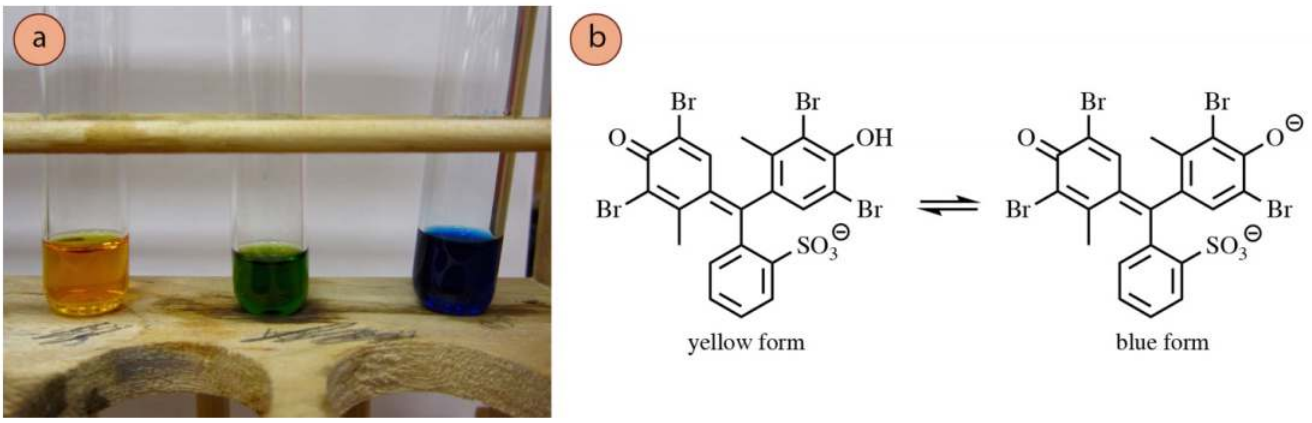


Figure 2.44: a) The colors of the bromocresol green stain (left = very acidic, middle = color of reagent jar, right = higher pH), b) The chemical structures of the yellow and blue forms of bromocresol green.

Visualization Troubleshooting

The Compound Didn't Show Up

Even when a compound has certainly been applied on the baseline of a TLC plate, it is possible that the compound is not seen on the plate after elution. There are several possible reasons for this:

1. The compound may be too dilute.

A simple solution to a dilution problem is to add more compound to the original sample and run the TLC again using a new plate. If the compound is expected to be UV active (i.e. if it contains an aromatic ring), it is a good idea to view the TLC plate under UV light *before* eluting the plate (Figure 2.45a). If the sample spot is not visible before elution it will not be visible afterwards, as compounds diffuse during elution.

If the sample is determined to be only *slightly* too dilute, the material can be deposited multiple times before elution (Figure 2.45b). To do this, deliver a small spot of sample on the baseline, and let it *fully dry* (it helps to blow on it) before delivering another spot over top of the first. If the spots are not allowed to dry in between applications, the spot will be too large. If the compound is expected to be UV active, check the plate under UV light, and if necessary spot more times before elution.

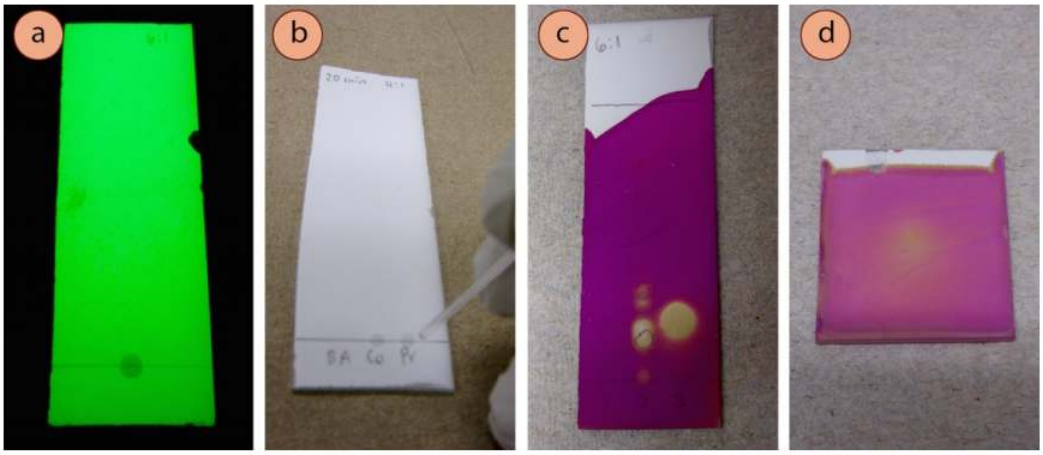


Figure 2.45: a) Using a UV lamp to see if enough sample was spotted before elution, b) Multiple spotting, c) TLC visualized with $KMnO_4$ (2-pentene was in lane 1 and was not seen), d) Undiluted 2-pentene spotted on a scrap TLC plate and visualized with $KMnO_4$.

2. The compound may have evaporated.

A TLC plate should be visualized immediately after elution, so if a moderate amount of time was left between running the TLC and visualizing it, evaporation may be the cause of the problem. A solution to this problem is to run the TLC again and visualize it immediately.

If the compound has a low boiling point, it probably evaporated during elution. For example, 2-pentene (boiling point 36°C) was spotted in lane #1 of Figure 1.45c. It did not stain with permanganate after elution even though the compound is reactive to the stain (an undiluted, uneluted sample of 2-pentene did stain somewhat on a scrap TLC plate, Figure 2.45d). Compounds with boiling points lower than approximately 120°C are difficult to analyze through TLC.

3. The compound may be unreactive to the visualization technique.

Visualization techniques are often tailored toward certain functional groups. For example, ultraviolet light is generally good at visualizing aromatic compounds but poor at other functional groups. If UV, iodine, or a stain fails to visualize a compound, it could mean the compound is simply not reactive to the technique, and another method should be tried.

For example, Figure 2.46 shows for different compounds visualized with UV (Figure 2.46a), *p*-anisaldehyde stain (Figure 2.46b) and iodine (Figure 2.46c). The compound in lane #1 of all the plates (4-heptanone) was only visible with anisaldehyde stain (blue spot), and not with UV or I_2. The compound in lane #4 of all the plates (ethyl benzoate) was unreactive to anisaldehyde stain, but could be visualized with UV and I_2. The impurity present on the baseline of lane #3 (the impurity cinnamic acid) was strongly UV active, but could hardly be seen with the other stains.

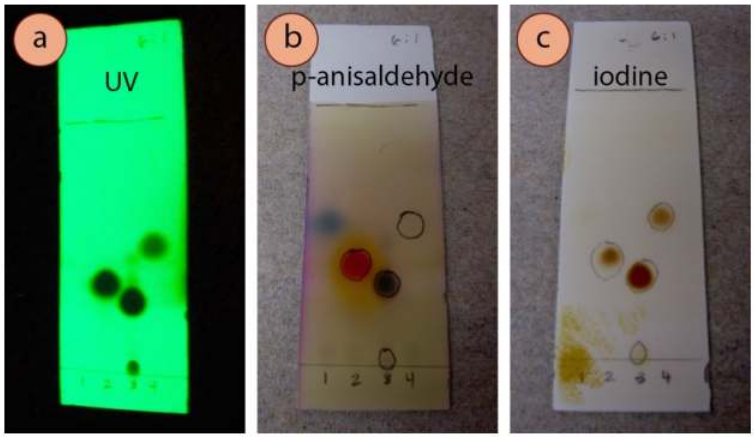


Figure 2.46: Four compounds eluted with 6:1 hexanes:ethyl acetate and visualized with 3 methods: a) UV, b) p-anisaldehyde, c) iodine[7]. The compounds were: #1: 4-heptanone, #2: acetophenone, #3: cinnamaldehyde, and #4: ethyl benzoate.

The Pencil Marking from UV is Different Than the Stain

Ultraviolet light is often the first visualization technique attempted on an eluted TLC plate because it is nondestructive and rather simple to carry out. If a dark spot is seen with a UV lamp, it is customary to circle the spot with pencil (as in Figure 2.46b), as the spot will be invisible when the lamp is removed. Another visualization technique is often carried out after viewing the plate under UV, and it is not uncommon that the subsequent stain extends to a smaller or larger region than the pencil marking.

For example, the compound in lane 2 of Figure 2.46 (acetophenone) can be easily seen with ultraviolet light (Figure 2.46a), but on the plate visualized with iodine (Figure 2.46c), the pencil markings encapsulate a larger region than is seen darkened by the iodine. This is because acetophenone is very strongly UV active, but only mildly complexes with iodine. It is not uncommon for one technique to visualize a compound *more effectively* than another technique.

It is therefore important to be cautious in using TLC to interpret the *quantity* of material present in a sample, for example when assessing the quantity of an impurity (such as in lane #3 of Figure 2.46, which contains cinnamaldehyde and its impurity cinnamic acid). It is *likely* that a large spot is present in a greater quantity than a small spot, but it could also be that the large spot is more *responsive* to the visualization technique.

A Stain's Color Faded or Changed With Time

It is very common for the coloration produced by a stain to fade with time, as the compounds eventually evaporate from the plate or other slower reactions take place. For this reason, it may be a good idea to circle the spots with pencil immediately after a plate is visualized, although as spots are generally circled after viewing with UV, additional markings may cause confusion as to which compounds are UV-active. Another alternative is to place clear tape across the plate to prevent the spots from evaporating.

It is possible that the coloration produced by a stain will change with extended heating, or with time. For example, the plate in Figure 2.47 was visualized with *p*-anisaldehyde stain, and Figure 2.47a shows how the plate appeared immediately after heating. Figure 2.47b shows how the same plate appeared after sitting at room temperature for 30 minutes. The compound in lane #2 (acetophenone) had the most dramatic change in color during that time, changing from a bright orange to a green color. Observations recorded into a lab notebook should be of the original color of a spot.

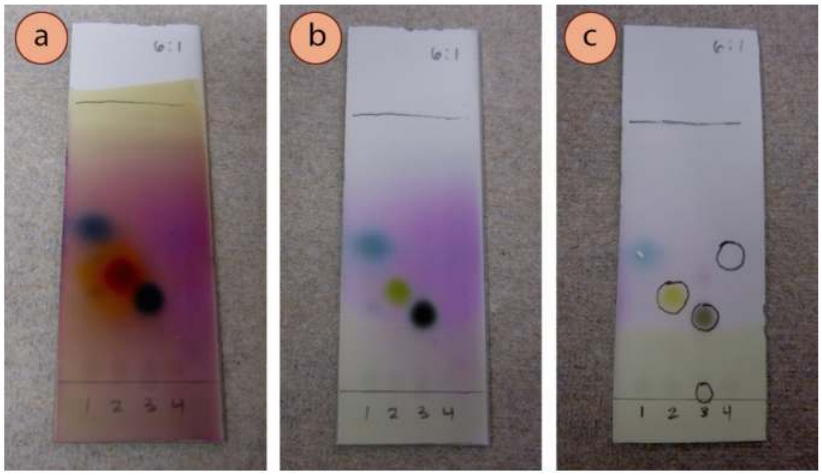


Figure 2.47: The same four compounds used in Figure 2.46, all visualized with p-anisaldehyde: a) The plate as it looked immediately after heating, b) After 30 minutes, c) Another trial of this same system after time.

The Staining Doesn't Make Sense

Certain visualization methods work best for certain functional groups, so a positive result with a stain can give clues about the identity of an unknown spot. However, sometimes a compound stains when it isn't "supposed to", and this can be confusing.

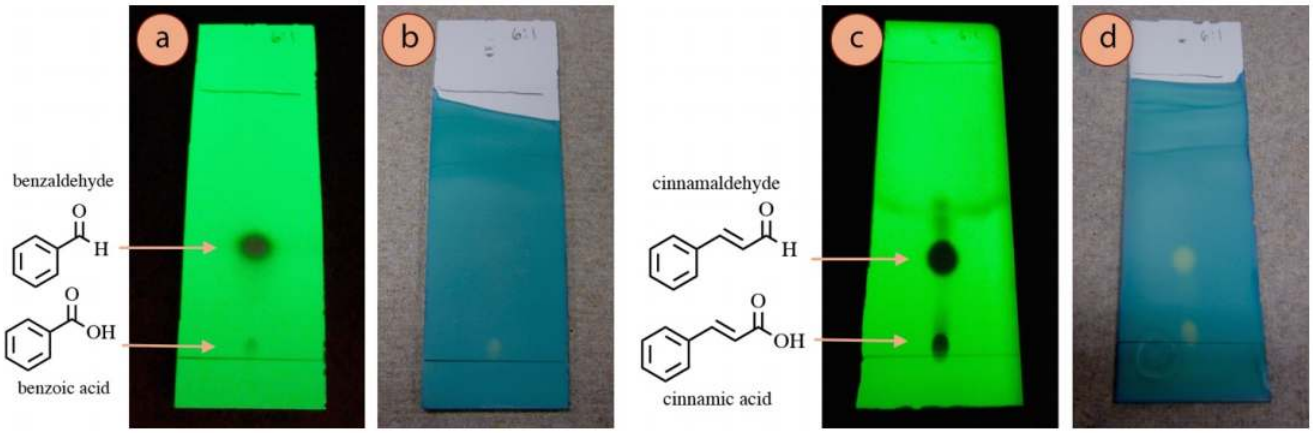


Figure 2.48: TLC plates of: a) Benzaldehyde with UV light, b) Benzaldehyde with bromocresol green stain, c) Cinnamaldehyde with UV light, d) Cinnamaldehyde with bromocresol green stain.

For example, a TLC of benzaldehyde visualized with UV light (Figure 2.48a) shows two spots, and based on relative R_f values, it would make sense that the dark spot is benzaldehyde and the fainter spot near the baseline is benzoic acid (caused by an oxidation of benzaldehyde). Staining of the plate with bromocresol green (a stain for acidic compounds), supports this hypothesis as the lower acidic spot is visualized with this method (Figure 2.48b). This is an example of when the staining results "make structural sense", and can even support the identification of unknown spots.

However, in a similar experiment with cinnamaldehyde, both aldehyde and carboxylic acid spots were strongly visualized with bromocresol green (Figure 2.48d), even though only one is an acidic compound. This result does not at first "make sense", and theories can only be postulated for why the aldehyde reacted with the stain.

The significance of Figure 2.48 is that interpretation of staining or lack of staining can *sometimes* be used to infer structure, but there may be exceptions that are difficult to explain.

[6]See *Nature* **165**, 1012 (24 June 1950); DOI: 10.1038/1651012b0

[7]The TLC plate was left in the I_2 chamber for only about 2 minutes, and the spots may have developed further with additional time.

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SECTION OVERVIEW

2.1.5: Gas Chromatography (GC)

Gas chromatography (GC) is a powerful instrumental technique used to separate and analyze mixtures. A gas chromatograph is a standard piece of equipment in forensics, medical, and environmental testing laboratories.

2.1.5A: Overview of GC

2.1.5B: Uses of Gas Chromatography

2.1.5C: Separation Theory

2.1.5D: Quantitating with GC

2.1.5E: GC Parameters

2.1.5F: Sample Preparation for Gas Chromatography

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2.1.5A: Overview of GC

Gas chromatography (GC) is a powerful instrumental technique used to separate and analyze mixtures. A gas chromatograph is a standard piece of equipment in forensics, medical, and environmental testing laboratories (Figure 2.75).

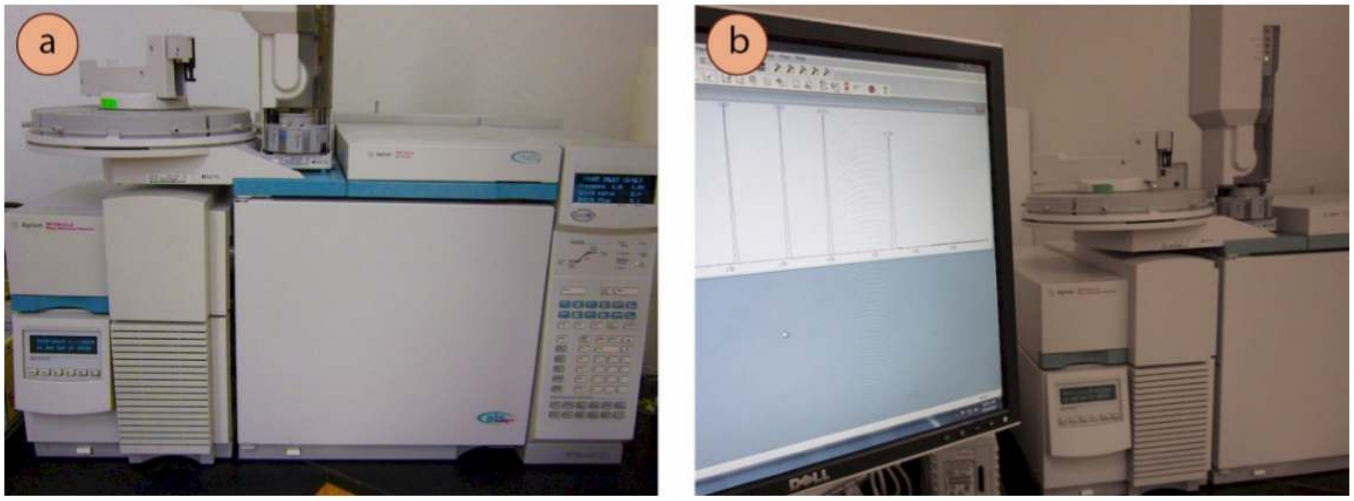


Figure 2.75: a) Gas chromatograph with mass spectrometer detector, b) GC-MS alongside a computer, which runs the instrument and can be used to manipulate the spectrum.

To run a GC, a sample is diluted then injected into the instrument where it is vaporized. The gaseous sample is pushed through a long, thin capillary column (typically 30 meters or approximately 100 feet long) by an inert carrier gas. The column separates components of a mixture, detects them, and a spectrum is generated displaying peaks that correspond to material that has exited the column at certain times. A GC spectrum of 87 octane gasoline is shown in Figure 2.76. Every peak represents one or more compounds, and since there are at least 50 peaks, this GC spectrum demonstrates that gasoline contains at least 50 different compounds!

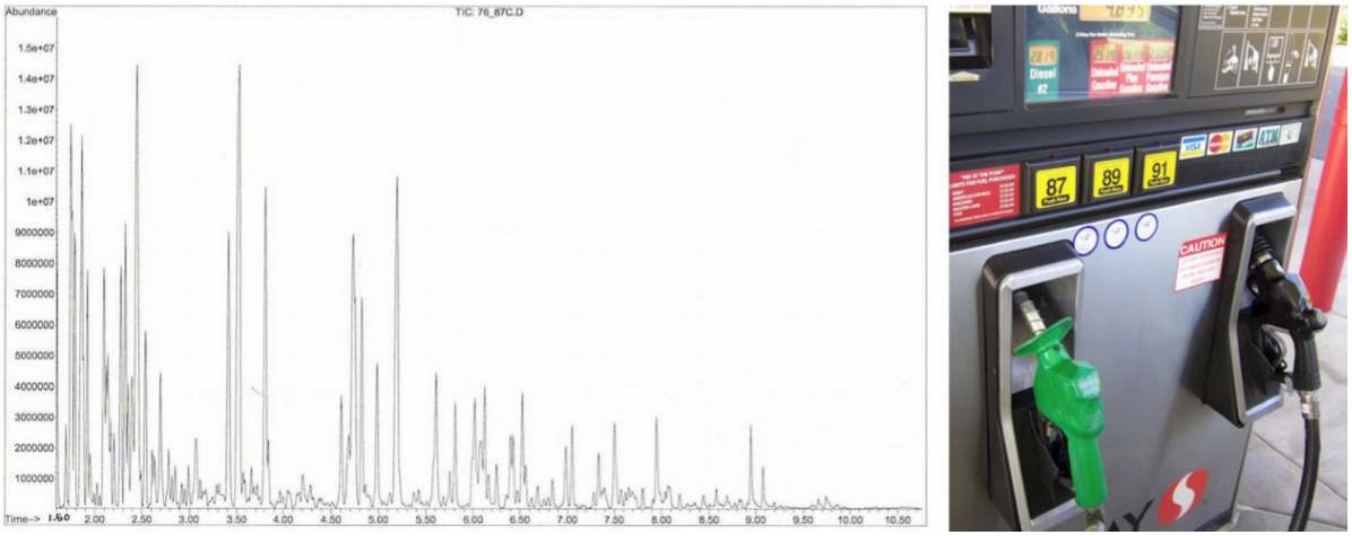


Figure 2.76: GC spectrum of 87 octane gasoline.

The quantity of time a compound spends inside a GC column before it is detected is called its "**retention time**," which represents the time a compound is "retained" on the column. This value is the x-axis of the GC spectrum in minutes. In many instruments, the retention time of each peak can be labeled on the spectra with the click of a button, and the value is displayed above each peak maxima. A compound's retention time is similar to R_f in thin layer chromatography, and should be reproducible between identical runs. Unlike R_f, however, retention times are very precise, and retention times typically vary by no more than 0.01 minute between identical runs (when the spectra have good peak shapes).

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2.1.5B: Uses of Gas Chromatography

Assessing Purity

A GC instrument is very good at verifying (or disproving) the purity of samples, and it can often spot trace quantities of impurity. In Figure 2.77, the GC spectra of "*n*-hexane" and "hexanes" are shown, two reagents that can often be found in a chemical stockroom. The GC spectrum of *n*-hexane (Figure 2.77b) shows one prominent peak, although there are hints of three other peaks on the baseline. The bottle of *n*-hexane claims it to be 95% pure, which is consistent with what is seen in its GC spectrum. "Hexanes" however, is a true mixture, as there are multiple significant peaks in its GC spectrum (Figure 2.77d). Hexanes contains *n*-hexane as the major component, but also contains closely related isomers (2-methylpentane, 3-methylpentane, and methylcyclopentane).[12] Hexanes is a commonly used solvent, where its lack of purity is not crucial, and it is considerably cheaper than pure *n*-hexane.

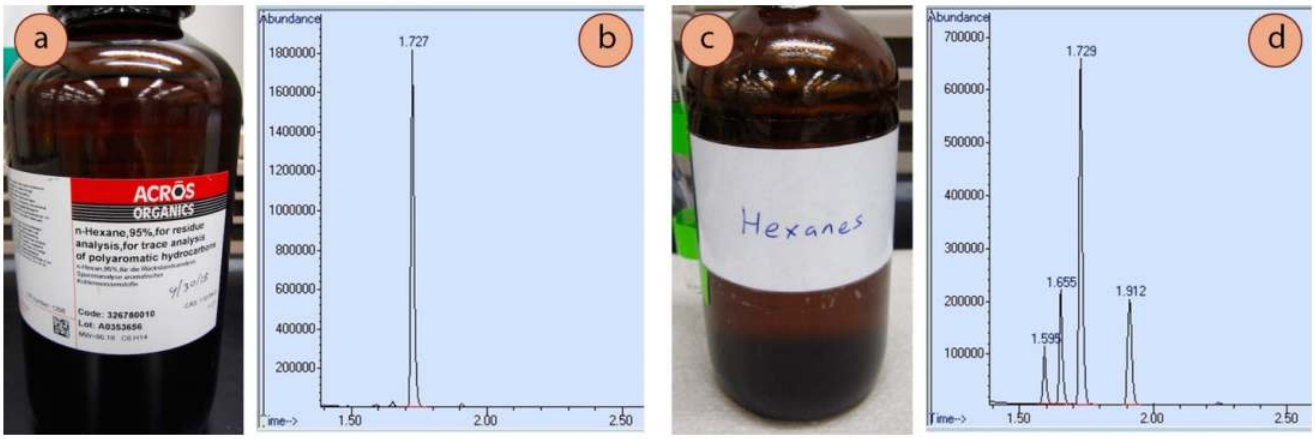


Figure 2.77: a) Bottle of n-hexane, b) GC spectrum of n-hexane, c) Bottle of "hexanes", d) GC spectrum of "hexanes". The compounds present in hexanes are: 2-methylpentane, 3-methylpentane, n-*hexane, and methylcyclopentane (in order of elution).*[13]

A sample that produces a GC spectrum with only one peak is not always pure. In Figure 2.78 is the GC spectrum of a sample containing *both* 2-pentanol and 3-pentanol, even though only a single peak is observed. The GC column used for this run separates based on differences in boiling point, and these isomers differ in boiling point by only 4°C, causing them to co-elute.

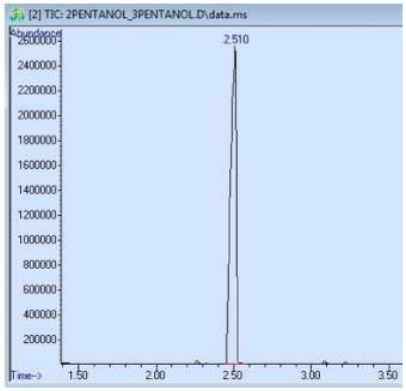


Figure 2.78: GC spectrum of a sample containing 2-pentanol and 3-pentanol. Both compounds are represented by the peak at 2.510 min.

An impure sample can also produce a GC spectrum with only one peak if some components elute outside of the window of time detected by the instrument. For example, the GC spectrum in Figure 2.78 begins collecting data at 1.50 min (the value on the x-axis), and any compounds that elute before that time will not be detected. Components of a mixture may also not exit the column before the run is ceased, in which case they remain on the column and sometimes elute overtop of a subsequent run!

Identifying Components

Due to the precision of retention times, GC can be used to identify components of a mixture if pure samples are acquired and if the components separate on the column.

For example, Figure 2.79a shows a GC spectrum of a sample containing both 3-pentanol and 1-pentanol. Boiling points can be used to predict which peak represents which isomer, but another definitive method is to run a GC of one of the pure components. Figure 2.79b shows a GC spectrum of 1-pentanol, and its retention time closely matches one of the two peaks in the original mixture, thus enabling its identification.

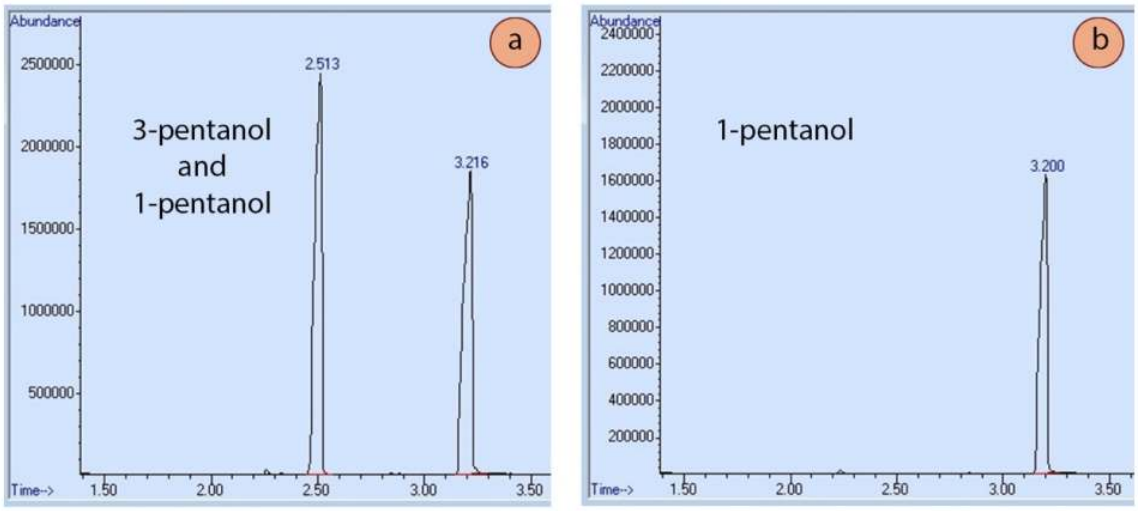


Figure 2.79: a) GC spectrum of a sample containing 3-pentanol and 1-pentanol, b) GC spectrum of pure 1-pentanol.

Injection of known standards can be helpful in deciphering confusing mixtures, and for identifying closely eluting components, such as *cis-trans* isomers, where the difference in boiling points may be minimal. If using a mass spectrometer detector, a mass spectrum computer database is also helpful in identifying components.

[12]Methylcyclopentane (C_6H_{12}) is not a true isomer of *n*-hexane (C_6H_{14}).

[13]Complete removal of hexanes by rotary evaporation is sometimes difficult, and evidence of its persistence can be seen in ^1H NMR samples by a doublet present around 0.9 ppm from the methyl of the methylcyclopentane impurity.

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2.1.5C: Separation Theory

General Theory

GC is an excellent analytical tool for separating mixtures in a sample. In this section are discussed the details of the separation, and expand upon the general discussion of Section 2.1B.

The GC column is what allows for the separation of a mixture's components by the instrument. It is composed of a thin, hollow tube approximately 0.5 mm thick, and is lined with a very thin polymeric coating 0.1-5 μm thick[14] (Figure 2.80a). Columns can be 15-100 meters long[14] (although commonly are 30 meters in length) and can be swapped in and out of an instrument depending on an experimenter's goals. There are columns specifically designed for analyzing poisons, biodiesel samples, or chiral compounds. An example of a typical academic capillary column is shown in Figure 2.80b, which is lined with a "dimethyl polysiloxane" polymer.

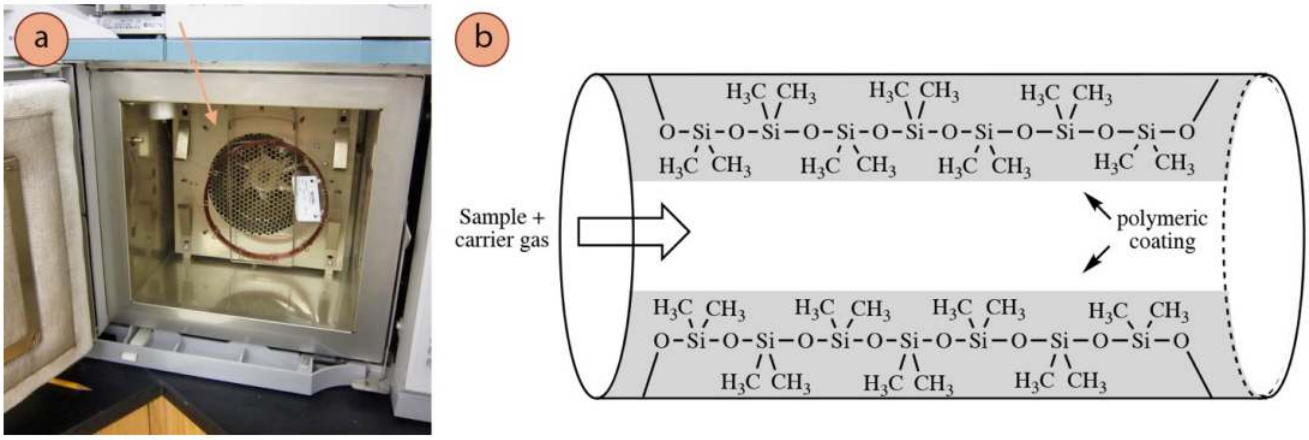


Figure 2.80: a) GC instrument opened to show the oven and column: the glass column is indicated with an arrow, and looks like a thin copper coil, b) Schematic of the dimethyl polysiloxane inner coating of a GC column.

Like all forms of chromatography, compounds equilibrate between a stationary phase and mobile phase. In GC, the stationary phase is the polymeric inner coating of the column, and compounds can interact with this high boiling liquid through various types of intermolecular forces (IMF's). The mobile phase is the carrier gas (usually helium), which is continually pushed through the column. Samples enter the column in the gas phase, subsequently adhere to the column coating, and establish an equilibrium between the stationary an mobile phases (equation 4).

$$X_{(\text{polymeric coating})} \rightleftharpoons X_{(\text{gas})} \tag{4}$$

Compounds move into the mobile phase if thermal energy from the oven provides sufficient energy to overcome the intermolecular forces between the compound and the column coating. When in the mobile phase, compounds are swept with the flow of the carrier gas, and re-adhere to the column coating further down the column. Compounds can be thought of as bouncing from one position to the next until they exit the column.

As all compounds have the same length to travel before they exit the column, they all spend the same amount of time in the mobile phase. Thus, **separation is due to the varying amount of time spent in the stationary phase**, or how long compounds adhere to the column coating. Compounds that have weak IMF's with the column coating spend little time "hung up" in the stationary phase, as heat from the oven allows for their IMF's to be broken. They quickly emerge from the column and thus have a short retention time. Conversely compounds that can form strong IMF's with the column coating will favor the stationary phase, and take a long time to emerge from the column (they will have a long retention time).

The type of IMF's experienced with the column coating often parallel the type of IMF's experienced in the pure liquid phase, meaning a compound that can hydrogen-bond in its liquid phase (Figure 2.81a) can also hydrogen bond with the column coating (Figure 2.81b). Therefore, **the strength of interaction with the column coating correlates closely with a compound's boiling point**, and boiling points can be used to predict the order of elution in GC.

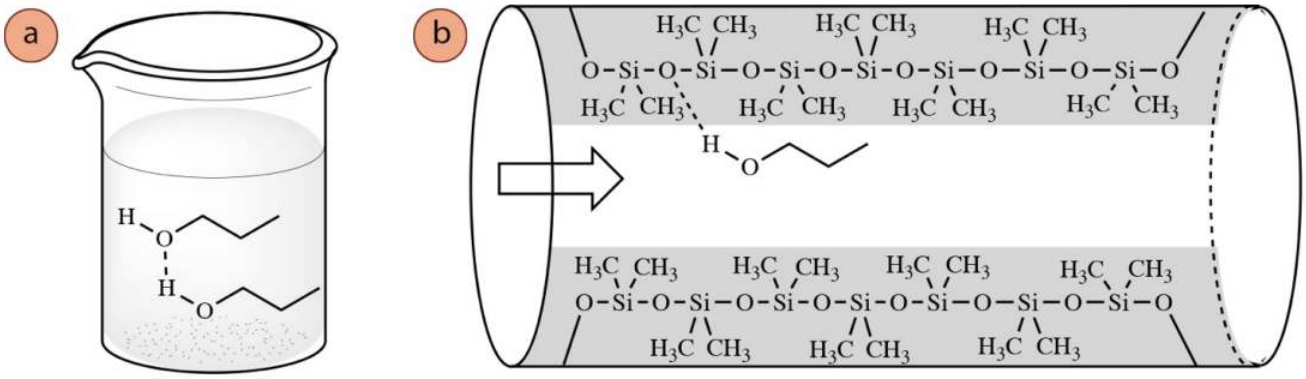


Figure 2.81: a) Hydrogen bonding shown for 1-propanol in the liquid phase, b) Hydrogen bonding shown between 1-propanol and the polymeric coating of the GC column.

In summary:

- Compounds that have weak IMF's with the column coating (low boiling points), spend little time in the stationary phase, exit the column early,and have shorter retention times.
- Compounds that have strong IMF's with the column coating (high boiling points), have longer retention times.

Structural Considerations

To demonstrate the effect of structural considerations, Figure 2.82 shows the GC spectrum of a mixture containing heptane, octane, nonane, and decane. The order of elution closely follows the trend in increasing boiling point. Heptane has the lowest boiling point of the series, and exits the column first (has the shortest retention time). As the chain length increases, so does the boiling point, and the retention times increase well (Table 2.9).

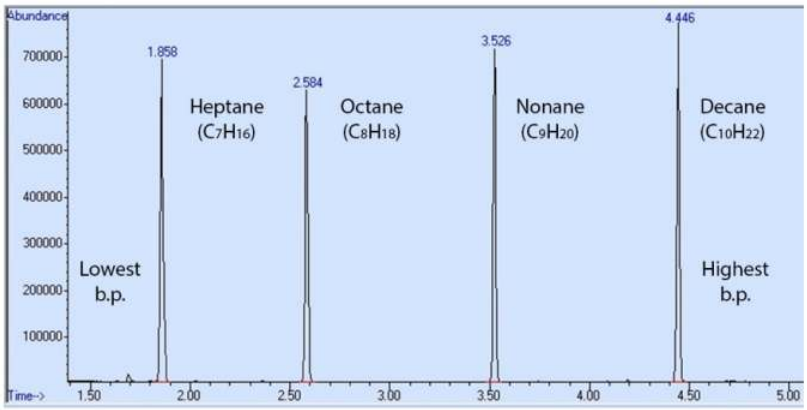


Figure 2.82: GC spectrum of a mixture containing heptane, octane, nonane, and decane (Method: held at **65°C** for **2 min**, then ramped **25°C/min**).

Table 2.9: Boiling point and retention time data for the GC spectrum in Figure 2.82.

Compound	Boiling Point (°C)	Retention Time (min)
Heptane (C_7H_{16})	98	1.858
Octane (C_8H_{18})	125	2.584
Nonane (C_9H_{20})	150	3.526
Decane ($C_{10}H_{22}$)	174	4.446

In another example, Figure 2.83 shows the GC spectrum of a mixture containing heptane, hexanal, and 1-hexanol. The order of elution again follows the trend in boiling point. 1-hexanol has the strongest IMF's, as it can interact with the column through both London dispersion forces (LDF's) and hydrogen bonds. This causes it to adhere to the stationary phase most strongly, resulting in

the longest retention time. Heptane interacts with the column coating through weaker LDF's, so spends the least amount of time in the stationary phase and elutes first (Table 2.10).

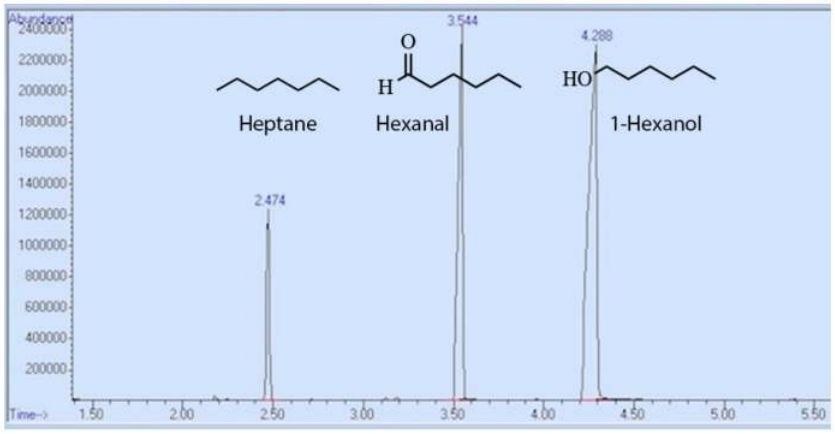


Figure 2.83: GC spectrum of a mixture containing heptane, hexanal, and 1-hexanol.

Table 2.10: Boiling point and retention time data for the GC spectrum in Figure 2.83.

Compound	Boiling Point (°C)	Retention Time (min)
Heptane	98	2.474
Hexanal	130	3.544
1-hexanol	155	4.288

[14]D.C. Harris, *Quantitative Chemical Analysis*, 5th edition, **1982**, p 676.

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2.1.5D: Quantitating with GC

Quantitative Challenges

Most modern GC instruments allow for integration of the peaks in a GC spectrum with the click of a button. If an older instrument is used, triangulation may be used to calculate the area under a peak, or the peaks may be cut out from a paper spectrum and weighed on an analytical balance to integrate. Peak integrations are useful because it is possible to correlate the area under a peak to the quantity of material present in a sample. Note it is the *area* of a peak that is relevant, not the height. A tall, narrow peak may have a smaller area than a short, wide one. It would be very useful if peak areas would *directly* reflect mixture composition, but that is unfortunately not always the case. The reason for this has to do with how compounds are detected upon exit from a column.

Common detectors at undergraduate institutions are flame-ionization detectors (FID) and mass spectrometry detectors (MS). With an FID, a sample is ignited upon exit from the column, and the ions produced in the flame are "counted" by the amount of electric current. Unfortunately, different compounds produce different amounts of ions when burned, meaning the ion count will not be directly equivalent to the molar quantity. Similarly, a mass spectrometer counts the number of ions produced from all the fragments detected in the instrument (called the "Total Ion Count", TIC, the y-axis on Figure 2.84), which does not always directly represent the quantity of the original material. Some compounds fragment more than others in a mass spectrometer, causing them to be detected in a manner that does not represent their true abundance.

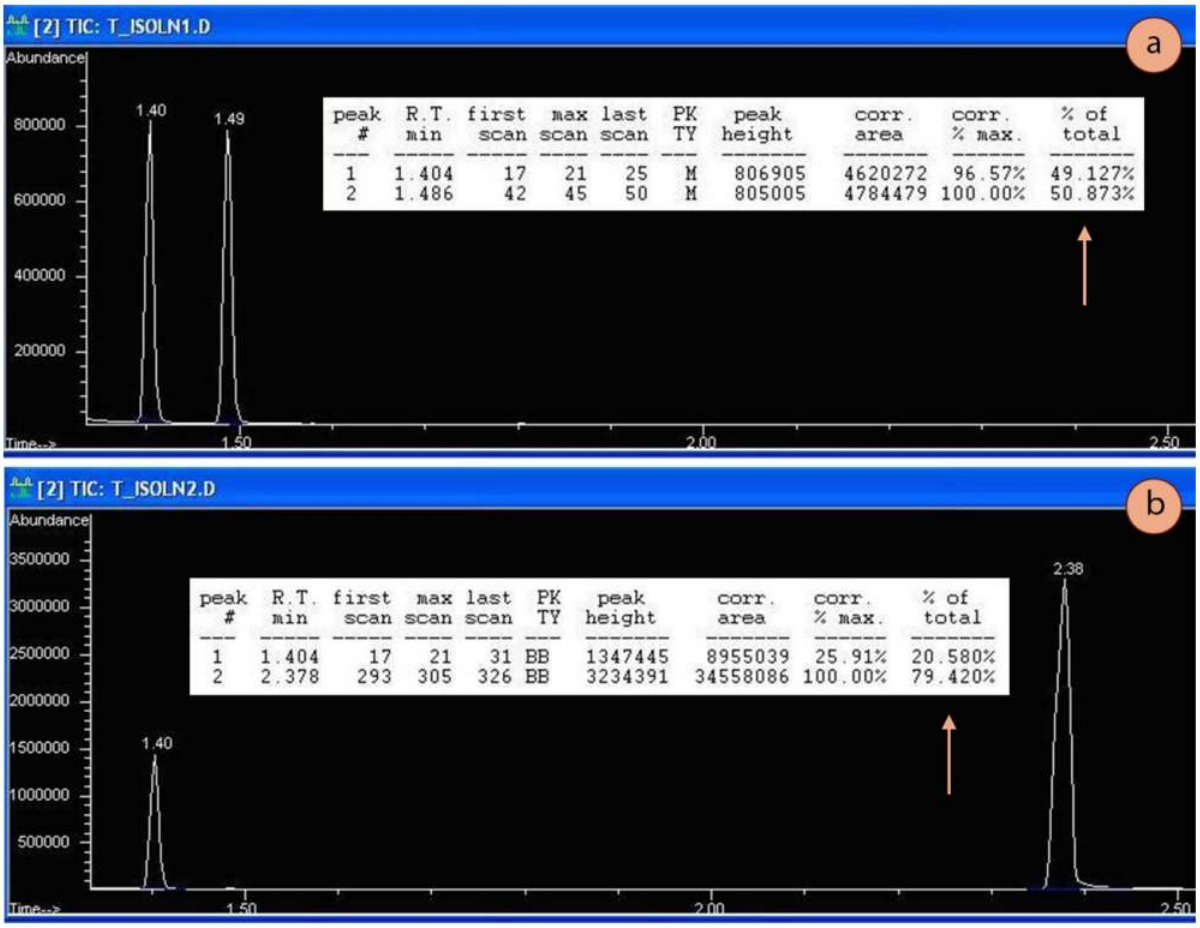


Figure 2.84: a) GC spectrum of a sample containing equimolar quantities of 1-butanol and 2-butanol, b) GC spectrum of a sample containing equimolar quantities of 2-butanol and 1-heptanol. Method for both runs: 60°C, ramp 20°C/min, MS detector. Arrows indicate the percentages reported by the GC for each spectrum.

To demonstrate how peak integration does not always correlate with actual abundance, GC spectra of two samples containing equimolar quantities of two compounds is shown in Figure 2.84. Figure 2.84a contains equal molar amounts of 1-butanol and 2-butanol, while Figure 2.84b contains equal molar amounts of 2-butanol and 1-heptanol.

The area under the peaks was tabulated by the mass spectrometer (represented by the column indicated by an arrow in each Figure), and was nearly 50% for each component in the butanol system (Figure 2.84a). In this case, the percentages generated by the instrument were nearly identical to the true composition (although not likely to five significant figures!).

However, the sample containing equimolar quantities of 2-butanol and 1-heptanol was reported as a ~20%-80% composition (Figure 2.84b). The true composition of the mixture *is* 50% of each component, but the compounds are "counted" disproportionately. In this situation, the integrations do not represent the true abundance as 1-heptanol forms more fragments in its mass spectrum than 2-butanol, so is "counted" more frequently.

It is a general rule that the integrations in a GC spectrum (the percentages) *can* be used directly as a first approximation of the true composition when comparing isomers (e.g. 1-butanol and 2-butanol). When compounds are compared that are of different sizes (e.g. 2-butanol and 1-heptanol), the reported percentages may need to be translated into actual percentages using either a calibration curve or response factors.

Using a Calibration Curve

One method to translate the integration values given by the GC instrument into meaningful percentages that reflect the mixture's composition is to use a calibration curve. To generate a calibration curve, standard samples of known molar or mass ratios are injected into the GC and the percentages reported by the instrument recorded. The graph in Figure 2.85 shows such a calibration curve for a 2-butanol/1-heptanol mixture, as detected by a mass spectrometer.

For example, if a mixture known to be 60 mol% **2-butanol** and 40 mol% 1-heptanol was injected into the instrument, and the resulting GC spectrum reported the mixture to be 42% **2-butanol** and 58% 1-heptanol, this data point would be recorded on the graph as **(60,42)**, using only the percentage of 2-butanol to simplify the situation. More data points could be analyzed using several known molar ratios of 2-butanol and 1-heptanol.

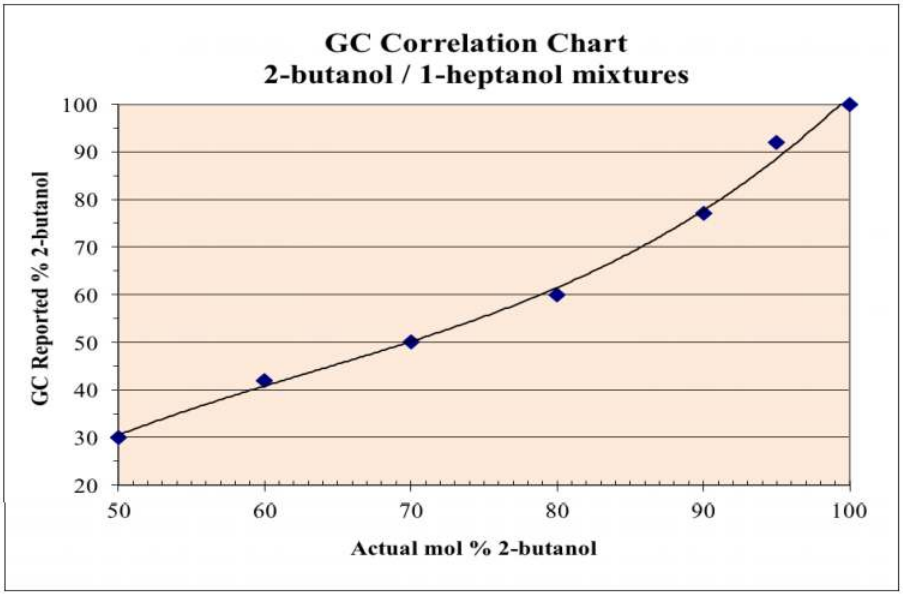


Figure 2.85: Known molar percentages of 2-butanol in a 2-butanol/1-heptanol mixture are correlated to the reported GC % of 2-butanol.

The calibration curve can then be used to correlate values reported by the GC instrument into true abundances. Imagine that a sample containing only 2-butanol and 1-heptanol is injected into the GC and reported by the instrument to be 70% 2-butanol. Using the calibration curve in Figure 2.85, a measured value of 70% 2-butanol (y-axis) correlates with an actual value of approximately 87 mol% 2-butanol (x-axis). Therefore, a sample reported by the GC instrument to be 70/30% 2-butanol/1-heptanol, is actually closer to 87/13% 2-butanol/1-heptanol.

Due to the approximate nature of this method, percentage values should never be reported with more precision than the one's place, and probably the true error is on the order of ±5%.

Using Response Factors

Another method that can be used to translate the integration values given by the GC instrument into meaningful percentages is to use a response factor. A sample containing equimolar quantities of the compounds to be analyzed is injected into the GC and the peak areas are numerically translated into compound sensitivities.

This process will be demonstrated with a mixture containing only 2-butanol and 1-heptanol. Figure 2.86 shows the GC spectrum of a sample that contains equimolar quantities of 2-butanol and 1-heptanol.

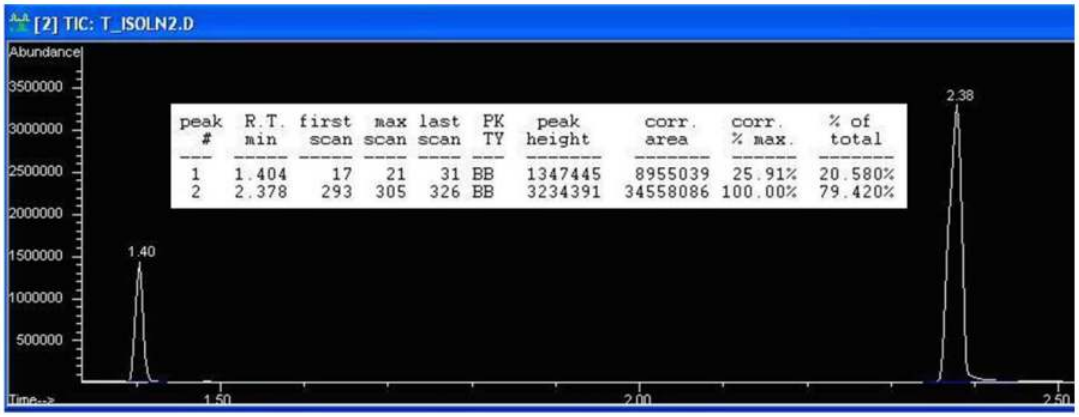


Figure 2.86: GC spectrum generated from a sample that contained equimolar quantities of 2-butanol and 1-heptanol.

The peaks *should* have equal integrations because the compounds are present in equal molar amounts, but the peak at **2.38 min** (1-heptanol) is "counting" more than it should. In the quantitative report, the column with the header "corr.area" can be used, as this shows the calculated area of each peak. The ratio of these area counts (see calculation below) gives a value of 3.86, which means that 1-heptanol is detected 3.86 times "better" than 2-butanol in these mixtures.

$$\text{Ratio of corrected areas} = \frac{\text{34558086 area counts for 1-heptanol}}{\text{8955039 area counts for 2-butanol}} = 3.86 \tag{2.1.5D.1}$$

To use this response factor in correlating values reported by the GC instrument into true abundances, imagine that a sample containing only 2-butanol and 1-heptanol is reported by the GC to be **30%** 1-heptanol (30 area counts of 1-heptanol for every 70 area counts of 2-butanol). As 1-heptanol is 3.86 times more *responsive* than 2-butanol, the true area counts would be more accurately represented as $30/3.86 = 7.77$ area counts of 1-heptanol for every 70 area counts of 2-butanol.[15]

$$\frac{\text{30 area counts for 1-heptanol}}{\text{70 area counts for 2-butanol}} \rightarrow \frac{\text{30/3.86 (1-heptanol)}}{\text{70 (2-butanol)}} = \frac{\text{7.77 (1-heptanol)}}{\text{70 (2-butanol)}} \tag{2.1.5D.2}$$

These hypothetical (and yet more accurate) area counts can then be turned into percentages, as follows:

$$\begin{aligned} \%\ \text{1-heptanol} &= \frac{\text{7.77 (1-heptanol)} \times 100\%}{70 + \text{7.77 (total)}} \\ &= 10\%\ \text{1-heptanol, (meaning 90\% 2-butanol)} \end{aligned} \tag{2.1.5D.3}$$

Therefore, a sample reported by the GC instrument to be **70/30%** 2-butanol/1-heptanol, is actually closer to **90/10%** 2-butanol/1-heptanol, which is a similar value to what could be found using a calibration curve.

[15]These calculations could be done more succinctly and with more precision using the actual area counts for each peak, found in the "corr.area" column of a quantitative GC report.

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2.1.5E: GC Parameters

There are many factors that affect the separation (and/or retention times) in gas chromatography, including the type of column, sample concentration, oven temperature, and flow rate of carrier gas. The factors controllable by a student are described in this section, and are related to concentration and temperature.

Dilution

GC runs must be conducted on very dilute samples. A dilute sample enables adequate stationary-mobile phase equilibrium inside the column, resulting in narrow Gaussian-shaped peaks. If samples are too concentrated, the peak shapes will often be broad and flattened on top (Figure 2.87a), indicating the column (and/or detector) has been overwhelmed. Appropriate abundances (the y-axis on GC spectra) using a mass-spectrometer detector should be in the low millions (e.g. 1,500,000 TIC's or so, see Figure 2.87b).

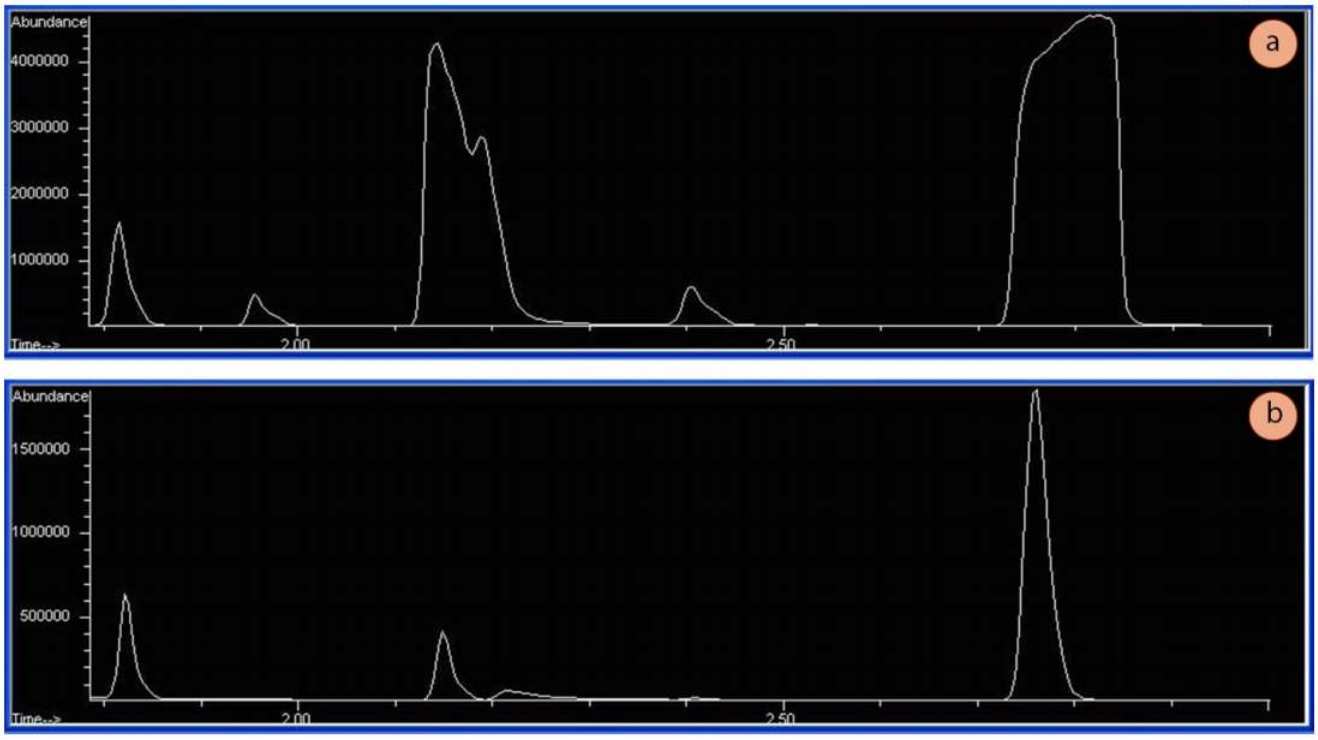


Figure 2.87: a) An overloaded sample with bad peak shape (note the y-axis has abundances around 4.5 million), b) The same sample diluted appropriately (abundances around 2 million). A too dilute sample will have abundances less than 100,000 (MS detector).

A GC should never be run on undiluted liquid. Overly concentrated samples do not only cause peaks to broaden and possibly overlap, they can also be harmful to detectors. Mass spectrometers require very small quantities of liquid, or over time, their filaments degrade.

To prepare a routine GC sample, $1.5\ \mathrm{mL}$ of a low-boiling solvent (e.g. methanol, clean acetone, diethyl ether, or dichloromethane) is added to a GC vial (Figure 2.88) along with one drop of compound. the instrument then injects roughly $1\ \mu\mathrm{L}$ of this dilute solution into the instrument, which is further diverted internally, resulting in *very* small quantities entering the narrow capillary column and detector. The normal function of a GC instrument *requires* tiny quantities of material, which is a major advantage to this technique.



Figure 2.88: GC vial.

Solvent Delay (With Mass Spectrometers)

A properly prepared GC sample contains a small amount of compound dissolved in a solvent, and yet GC spectra (when paired with a mass spectrometer detector) often do not show any solvent peaks. The reason is that GC methods often include a "**solvent delay**", where the detector is turned off until a certain amount of time has passed after injection. Even with the dilution inside the GC-MS instrument, the quantity of solvent reaching the detector would overwhelm and eventually degrade it. Therefore, the detector is left inactive until the solvent has passed through the column, and activated afterwards.

If you look at any GC-MS spectrum, the retention time (x-axis) never starts at zero minutes, which represents the time the sample is injected on the column. In the GC spectrum of hexanes, the spectrum starts at 1.40 minutes, (as is indicated with an arrow in Figure 2.89). The solvent would have eluted from the column before this time.

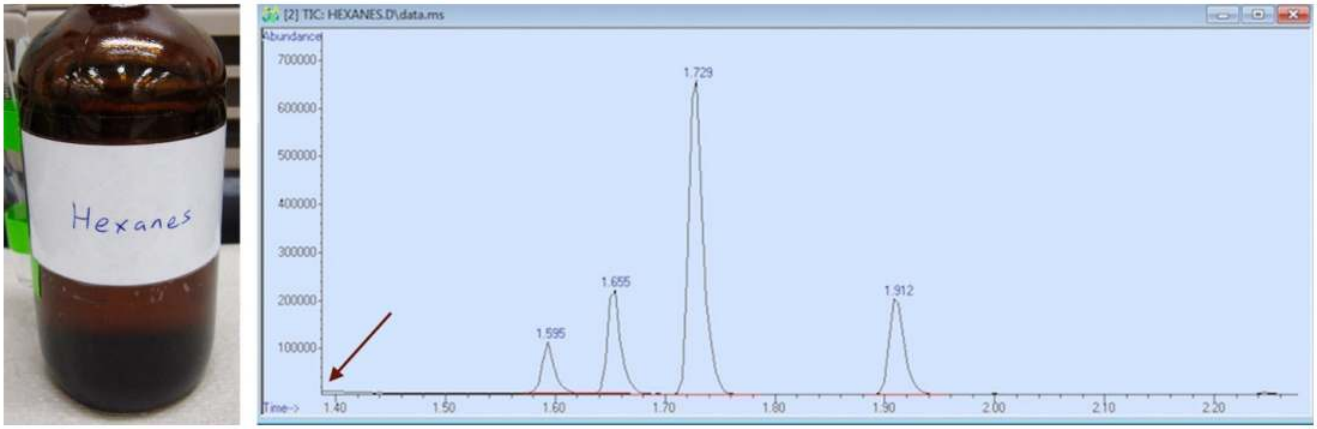


Figure 2.89: GC spectrum of hexanes, with arrow indicating the time the solvent delay is turned off.

The GC solvent must be chosen such that the solvent will elute before the compound of interest (the solvent must have a significantly lower boiling point than the compound), so that the solvent delay may be set between elution of the solvent and sample. For example, methanol (b.p. $65°C$) would have been an unsuitable solvent for the sample of hexanes (b.p. $68°C$). If the solvent delay was set such that the hexane signals could be detected, the GC spectrum would have been overwhelmed by signals from the methanol, as the two compounds have very similar boiling points and would elute rather closely. If the detector was activated after the methanol had eluted, the instrument would likely miss detection of the closely eluting hexanes. Therefore, a significantly lower boiling solvent was used (diethyl ether, b.p. $35°C$) to produce the GC spectrum of hexanes in Figure 2.89, and this solvent would have eluted before the solvent delay of 1.40 minutes.

Oven Temperature

The temperature of the GC oven is an easily adjusted variable (although it should be adjusted by an instructor, not student). The oven temperature has a dramatic effect on retention times, much in a similar way that changing the mobile phase in TLC has on R_f.

To demonstrate, a sample containing heptane, octane, nonane, and decane was run using three GC methods, differing only in their starting temperature ($65°C$, $45°C$, or $35°C$). The order of elution of the compounds was the same in all methods (Figure 2.90), but the components eluted *faster* with a hotter oven temperature (had lower retention times). This result can be explained in that the compounds were more able to overcome their intermolecular attraction with the stationary phase (the coating of the GC column)

when there was more available thermal energy. This resulted in compounds spending less time adhering to the stationary phase, and less time retained by the column.

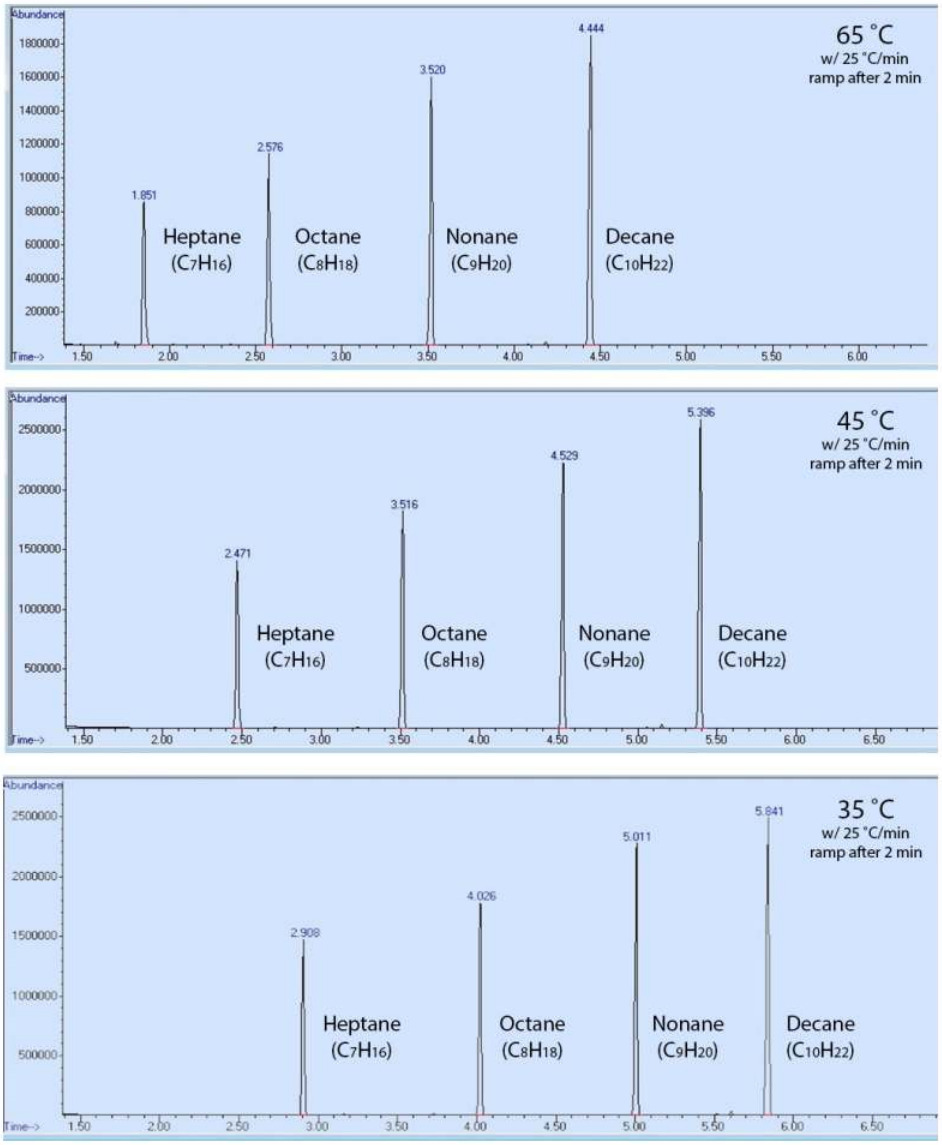


Figure 2.90: GC runs of a mixture containing heptane, octane, nonane, and decane at different oven temperatures. Each run was held at **65°C**, **45°C**, or **35°C** for **2 min**, then ramped **25°C/min**.

Using a Temperature Ramp

A GC can be run at one oven temperature the entire time (an "isothermal" run), or the method may include temperature programming. In a programmed method, the temperature may remain fixed for a certain length of time, and then may include a "**ramp**", where the temperature is increased at a steady rate during the run. A graphical display of a ramp generated by the GC instrument is shown in Figure 2.91.

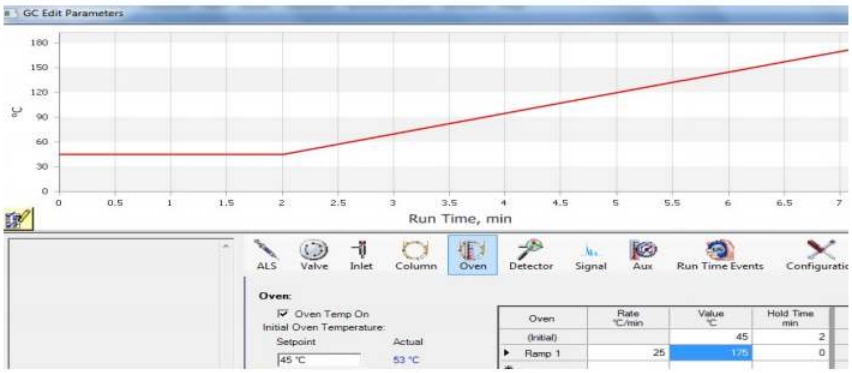


Figure 2.91: Graphical display of the GC method, which includes a "ramp".

Temperature programming is useful because the longer a compound stays in the column, the wider it elutes as diffusion broadens the sample (analogously to how spots broaden during elution in TLC). Figure 2.92a shows an isothermal GC run of four compounds, and the peak shape significantly broadens as the retention time increases. Figure 2.92b shows a GC run of the same four compounds eluted using a temperature ramp. The ramp allows the compounds to elute faster, and for peak shape to sharpen and improve. The optimal ramp for each situation often takes experimentation to achieve the best peak shape and separation of components.

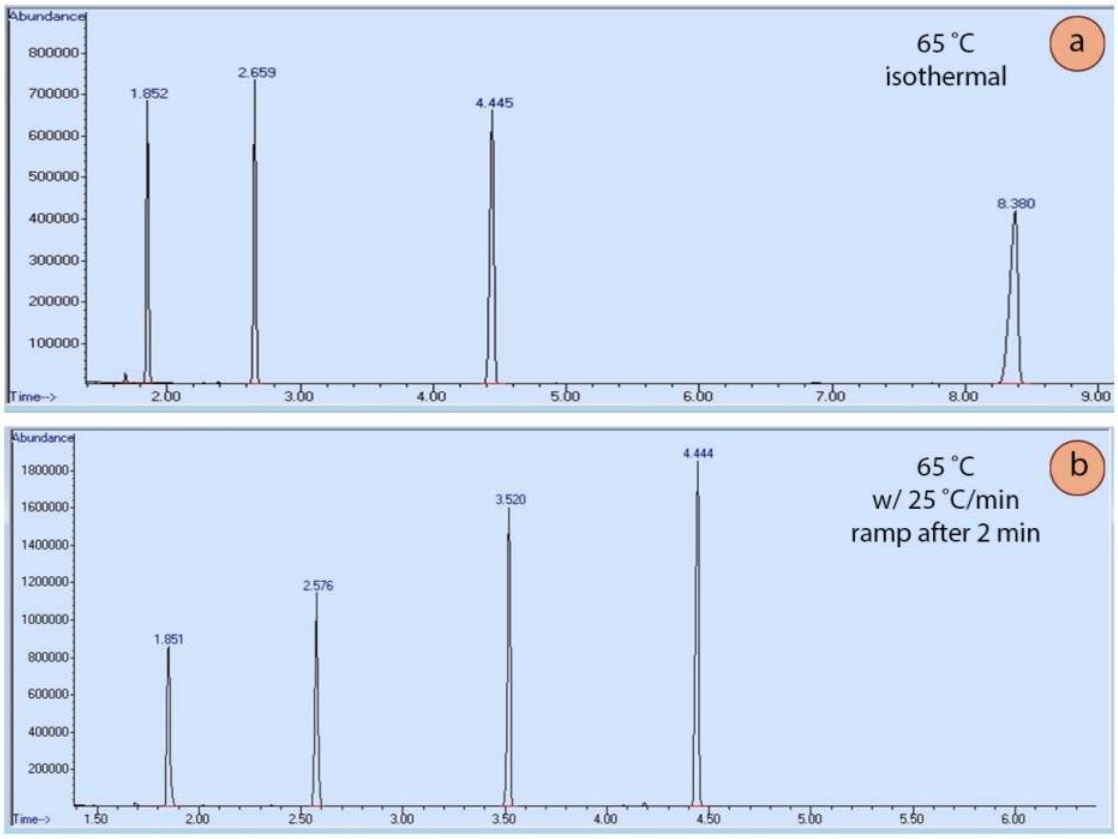


Figure 2.92: A sample composed of heptane, octane, nonane, and decane, run with two different GC methods. a) The run was kept under isothermal conditions, at a steady **65°C**, b) The method utilized a "ramp" after 2 minutes.

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2.1.5F: Sample Preparation for Gas Chromatography

Liquid GC Samples

1. Fill a GC vial to the **1.5 mL** mark (Figure 2.93a) with a low boiling solvent (e.g. methanol, clean acetone, diethyl ether, or dichloromethane). Add one drop of the sample to be analyzed. If you think you possibly only added a half-drop, it's probably enough. Two drops are really too much.
2. Cap the vial and invert once or twice to dissolve the sample. If it appears like the sample drop did not dissolve fully, prepare another sample using a different solvent.
3. Alternatively, if you have already prepared a high-field NMR sample, use one-third of this sample and dilute it further with a low-boiling solvent.
4. Run the GC, as demonstrated by your instructor. Procedures vary at each institution.



Figure 2.93: a) GC vial, b) GC-MS instrument, c) Small amount of solid in a GC vial.

Solid GC Samples

5. Some relatively volatile solids (never ionic solids!) can be analyzed by GC. Add one or two "specks" of solid[16] (a pile approximately **2 mm** in diameter), or a very small spatula-tip of solid to a GC vial (Figure 2.93c). Then add a low boiling solid (e.g. methanol, clean acetone, diethyl ether, or dichloromethane) to the **1.5 mL** mark.
6. Cap the vial and invert several times to fully dissolve the solid. If the solid dissolves, run the GC.
7. If the solid does not dissolve, do NOT run the GC anyway! Solids can plug the very small microliter syringes used by the instrument.
    a. If the quantity of solid does not appear to have changed at all after adding the solvent, try making another sample with a different low boiling solvent.
    b. If it appears the solid has decreased in quantity but is not *fully* dissolved, it is likely enough of it has dissolved to analyze. Use a pipette filter to filter the solution, and run the GC on the filtered liquid.

[16]The quantity of solid may need to be adjusted if the solid is "fluffy". A GC is at the ideal dilution when it produces abundances around one million using a mass spectrometer detector.

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SECTION OVERVIEW

2.2: Column Chromatography

Column chromatography is an extension of thin layer chromatography (TLC). Instead of applying a sample on a thin layer of silica or alumina, a sample is deposited on a cylinder of adsorbent and solvent is continually applied with pressure until the components completely drain from the cylinder. With this modification, components can be not only separated but collected into different containers, allowing for purification of mixtures. Column chromatography (also known as "flash chromatography"), is frequently used in research settings, as is evidenced by its common occurrence in the procedural sections of journal articles.

2.2.1: Macroscale Columns

2.2.2: Microscale (Pipette) Columns

2.2.3: 5.5 Polarimetry

2.2.4: Crystallization

2.2.4.1: Overview of Crystallization
2.2.4.2: Uses of Crystallization
2.2.4.2A: Reagent Purification
2.2.4.2B: Purification of Product Mixtures
2.2.4.3: Choice of Solvent
2.2.4.3A: Ideal Temperature Profile
2.2.4.3B: General Procedures for Removing Impurities
2.2.4.3C: Determining Which Solvent to Use
2.2.4.3D: Using Solubility Data
2.2.4.3E: Experimentally Testing Solvents
2.2.4.3F: Mixed Solvents
2.2.4.4: Crystallization Theory
2.2.4.4A: Purification
2.2.4.4B: Cooling Slowly
2.2.4.4C: Using the Minimum Amount of Hot Solvent
2.2.4.4D: The Unavoidable Loss of Recovery
2.2.4.4E: Quantitating Crystallization
2.2.4.4F: Second Crop Crystallization
2.2.4.5: Procedural Generalities
2.2.4.5A: General Procedure
2.2.4.5B: Heat Source and Bump Prevention
2.2.4.5C: Charcoal
2.2.4.5D: Cooling Slowly
2.2.4.5E: Initiating Crystallization
2.2.4.6: Step-by-Step Procedures
2.2.4.6A: Single Solvent Crystallization
2.2.4.6B: Crystallization Summary
2.2.4.6C: Using Solvents Other Than Water

2.2.4.6D: Mixed Solvent Crystallization
2.2.4.6E: Mixed Solvent Summary
2.2.4.6F: Troubleshooting

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2.2.1: Macroscale Columns

Procedural Generalities

The same underlying principles of thin layer chromatography (TLC) apply to column chromatography. In fact, a TLC is always run before performing a column to assess the situation and determine the proper solvent ratio. In order to get good separation, it is ideal if the desired component has an R_f **around 0.35** and is separated from other components by at least 0.2 R_f units.[8] If the spots to be separated are very close (if the difference in R_f is < 0.2), it's best if the middle of the spots has an R_f of 0.35. An R_f near 0.35 is ideal because it is slow enough that stationary-mobile phase equilibration can occur, but fast enough to minimize band widening from diffusion.

There are a few variables which aren't applicable to TLC, but which affect the separation of components in column chromatography. These include the column diameter, quantity of adsorbent used, and solvent flow rate. Table 2.5 summarizes variable recommendations based on the sample size and degree of separation between components. In all scenarios, the columns are to be prepped between 5-6 inches high.

Table 2.5: Summary of recommended values for column chromatography.[9]

Column diameter (mm)	Volume of eluent (mL)	Sample size (mg) If $\Delta R_f > 0.2$	Sample size (mg) If $\Delta R_f > 0.1$	Typical fraction size (mL)
10	100	100	40	5
20	200	400	160	10
30	400	900	360	20
40	600	1600	"600	30

For example, a column of one-inch diameter ($1\ \text{in}$ is $25.4\ \text{mm}$) should be able to purify around $400\ \text{mg}$ of material if the separation is good ($\Delta R_f > 0.2$, third column in Table 2.5), or around $160\ \text{mg}$ if the separation is difficult ($\Delta R_f > 0.1$). The column should be able to be prepared and eluted using around $200\ \text{mL}$ of solvent, and the fractions can be collected with approximately $10\ \text{mL}$ of solution each.[9]

There are multiple variations on how to physically run a column, and your instructor may prefer a certain method. One large difference in methods is how the column is prepared. In the "dry packing" method, dry silica or alumina is added directly to a column, and solvent is allowed to trickle through in portions, then with pressure. In the "wet packing" method, the column is filled with solvent first, then dry silica or alumina is lightly shaken in, then packed with pressure. In the "slurry" method, solvent is added to the silica or alumina in an Erlenmeyer flask, poured onto the column as a sludgy material, then packed with pressure.

It is important to know that heat is liberated when solvent is added to silica or alumina (they have an exothermic heat of solvation). The slurry method is presented in this section, with the main reason being that it allows this exothermic step to happen in an Erlenmeyer flask instead of on the column. If heat is liberated during the packing of the column, it may generate bubbles from the boiling of solvent. These can interfere with the separation of the column if they are not adequately removed, and can crack the adsorbent material in the column.

Step-by-Step Procedures

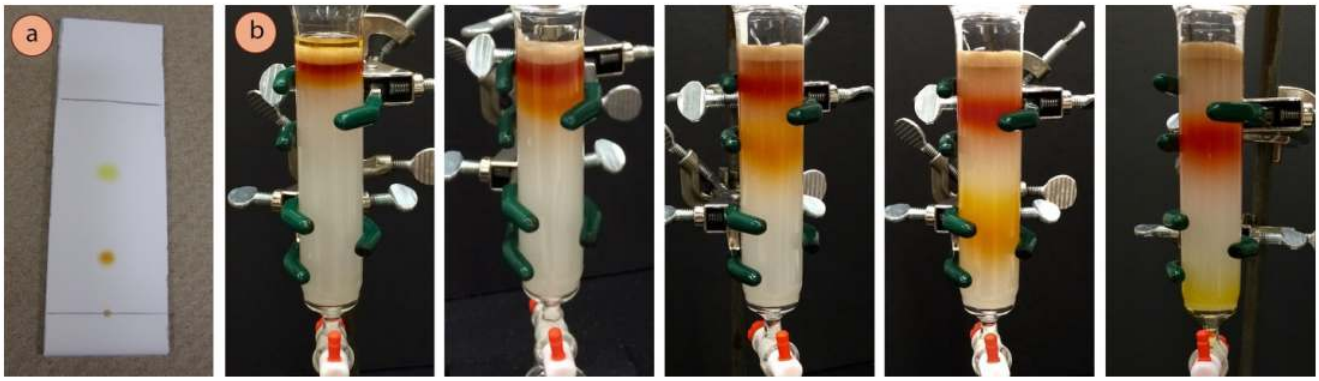


Figure 2.51: a) TLC of ferrocene/acetylferrocene mixture, b) Column chromatography.

The column pictured in this section shows purification of a $0.20\ \mathrm{g}$ sample containing a mixture of ferrocene and acetylferrocene (crude TLC is in Figure 2.51a). Roughly $8\ \mathrm{mL}$ fractions were collected into small test tubes, and roughly $400\ \mathrm{mL}$ of eluent was used.

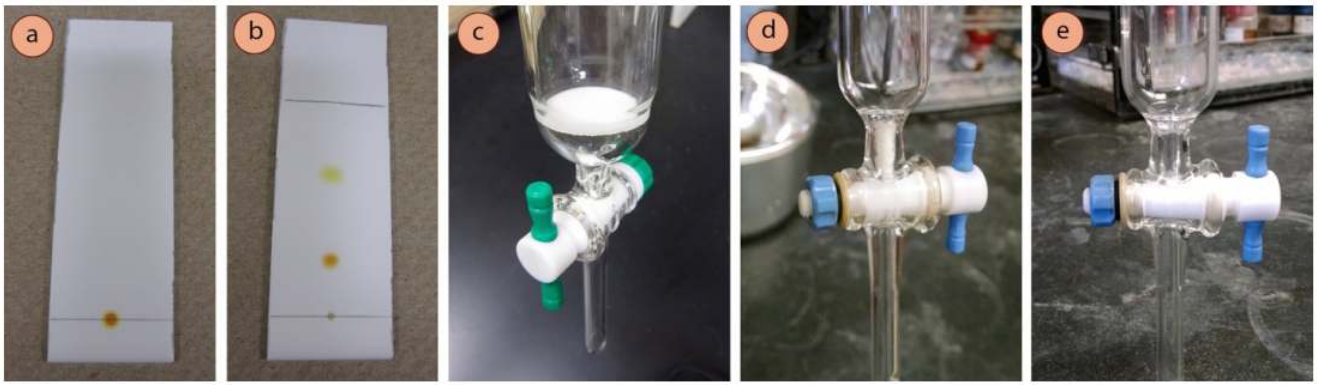


Figure 2.52: a) TLC plate of crude ferrocene/acetylferrocene mixture before elution, b) After elution, c) Column with frit, d) Column with cotton wedged in the bottom, e) Column lacking the cotton wedge (would need to be inserted before use).

Run a TLC

1. Run a TLC of the sample to be purified (Figures 2.52 a+b) to determine the appropriate solvent for chromatography. The desired component should have an R_f **around 0.35** and should ideally be separated from all other spots by at least 0.2 R_f units.
2. Prepare a batch of eluent that gives the proper R_f value. The quantity prepared depends on the quantity of sample, the size of the column, and whether or not the solvent composition is planned to be changed midway. (See Table 2.5 for guidelines and the eluotropic series for trends in "solvent power.")

Prepare the packed column

3. Obtain an appropriate column (see Table 2.5), and be sure there is something near the stopcock that will allow liquid to pass through, but not solid. Columns may have a sintered disk (also known as a "frit," Figure 2.52c), or a plug of cotton or glass wool remaining from the previous user (Figure 2.52d). If no disk or plug is present (Figure 2.52e), wedge a small wad of cotton or glass wool into the bottom of the column using a long rod.

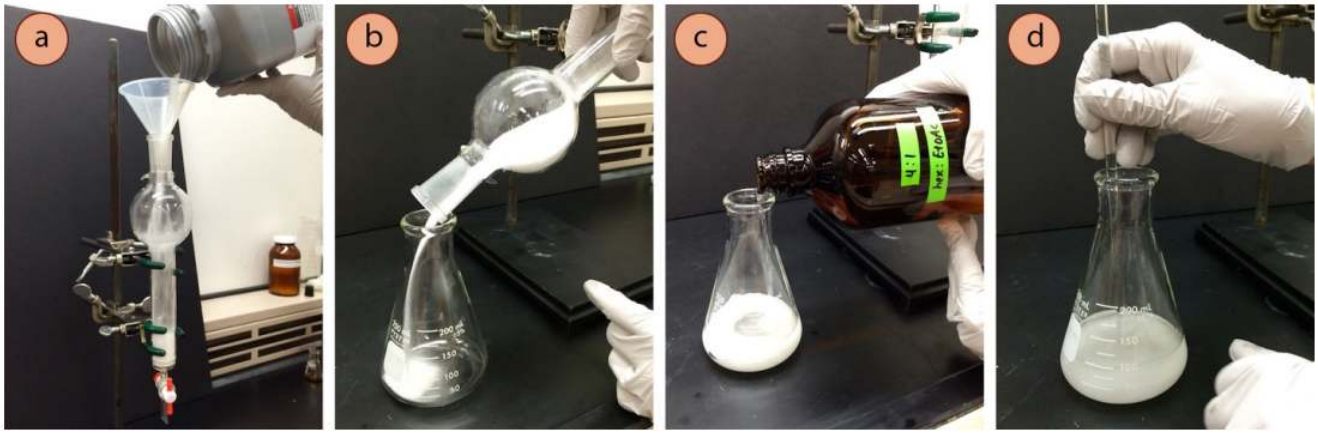


Figure 2.53: a) Pouring in silica to 5-6" high in the fume hood, b) Pouring the silica into an Erlenmeyer flask, c+d) Making a slurry.

4. Secure your column perfectly vertically to a ring stand or latticework, clamping it with three-fingered clamps in two locations. In the fume hood, pour silica gel or alumina adsorbent into the column to between 5-6 inches high (Figure 2.53a).
   Safety note: Powdered silica and alumina are lung irritants, and should always be handled carefully in a **fume hood**. Spilled dust should be disposed of by mopping it with a wet paper towel (if wet, the fine particles are less dispersive).
5. In the fume hood, pour the adsorbent measured in the column into an Erlenmeyer flask (Figure 2.53b), then add some eluent (Figure 2.53c). Make a loose slurry by swirling and stirring with a glass stirring rod (Figure 2.53d) until all of the adsorbent is completely wet, gas bubbles are released, and the consistency is somewhat thick but pourable.

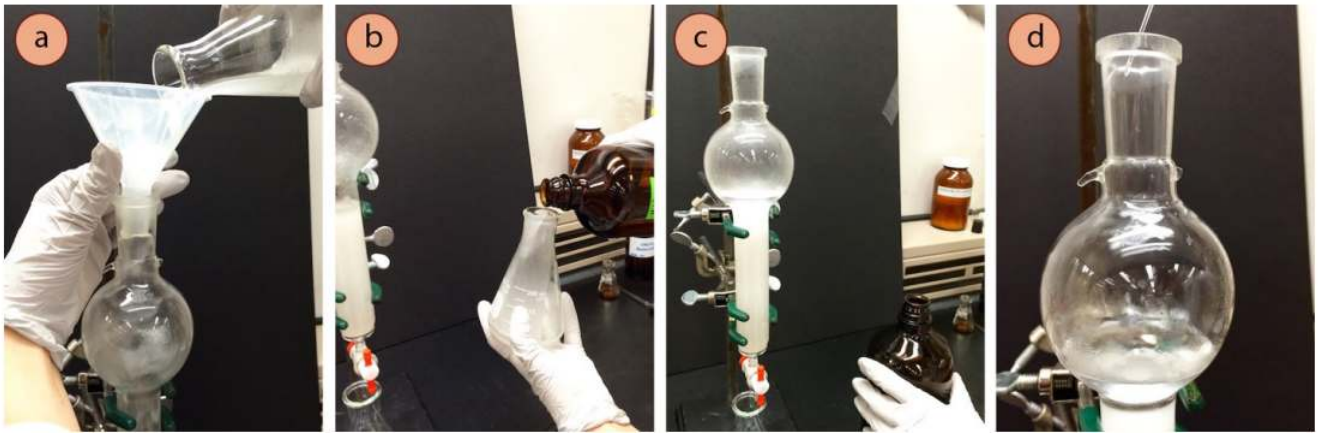


Figure 2.54: a) Pouring the slurry into the column, b) Rinsing the flask, c) Adsorbent adhered to the sides of the column, d) Rinsing off the clinging adsorbent.

6. Put a beaker or Erlenmeyer flask beneath the clamped column and open the stopcock. In one quick motion, swirl and pour the silica or alumina slurry into the column using a large-mouthed funnel (Figure 2.54a). Immediately use more eluent to rinse residual slurry out of the Erlenmeyer flask (Figure 2.54b) and onto the column.
7. Immediately rinse any silica or alumina off the sides of the column reservoir using eluent and a swirling motion from a Pasteur pipette (Figures 2.54 c+d). If allowed to dry, the adsorbent will cling to the glass and won't easily be rinsed down.



Figure 2.55: a) Jostling the column to remove air bubbles, b) Applying air pressure, c) Adding sand, d) Rinsing sand from the sides.

8. Jostle the column firmly using a cork ring or your knuckles (Figure 2.55a) to dislodge any air bubbles in the column (which could cause poor separation or cracking of the adsorbent in the column), and to promote an even deposition of adsorbent.
9. Apply gentle air pressure to the top of the column (Figure 2.55b) to compress it, stopping when the eluent level is $1\ \text{cm}$ from the top of the column. If a T-adapter is used with the air line as in Figure 2.55b, fine control of the airflow can be accomplished by adjustment of the pinch clamp on the rubber tubing.

   Throughout the entire elution process, keep the white column of adsorbent wet, with the eluent level above the top of the silica or alumina.

   Gently break the seal to cease application of pressure, and close the stopcock to prevent liquid from dripping out further.
10. Add a thin layer of sand (Figure 2.55c), approximately $0.5\ \text{cm}$ high. Rinse the sides of the column with eluent using a swirling motion to dislodge the sand off the sides of the glass (Figure 2.55d). Open the stopcock and allow liquid to drip out until the liquid is just above the sand layer. Apply air pressure if the dripping is too slow.

Add the sample

Once the sample is applied to the column, there is a race against time, as diffusion will start to broaden the material. A sample should not be applied until you are ready to complete the column immediately and in its entirety. This process may take between 15 and 90 minutes! If using test tubes to collect fractions, the test tubes should be arranged in a rack prior to adding the sample, and the column height should be adjusted so that the test tube rack can slide underneath.

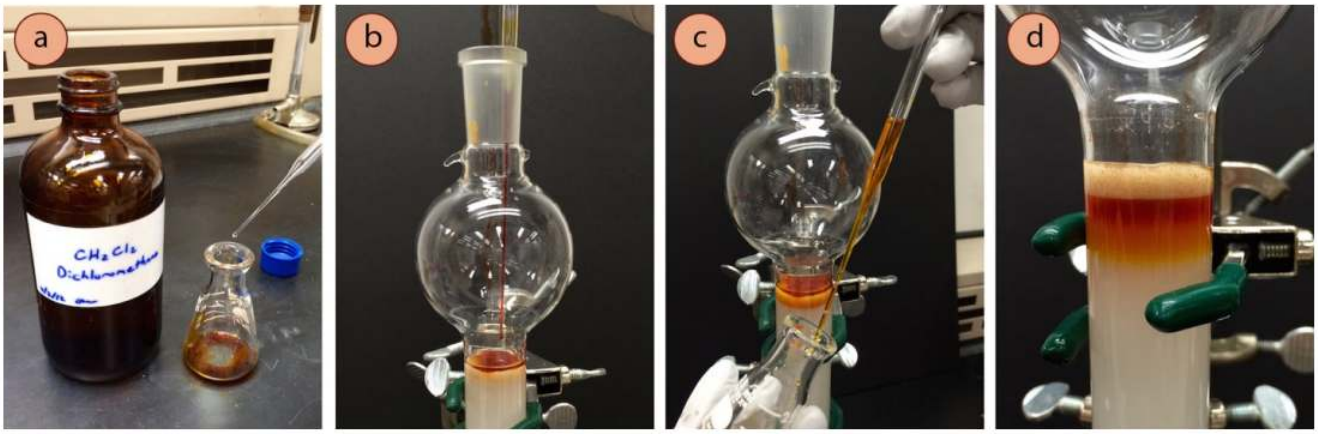


Figure 2.56: a) Dissolving a solid with a small amount of dichloromethane, b) Applying the sample, c) Rinsing the sample in its flask, d) Applying pressure to push the sample onto the column just past the sand layer.

11. If the crude sample is a liquid, use it directly (go on to step 13).
12. If the crude sample is a solid, do one of the following things:
    a. Ideal situation: dissolve the solid in the minimum amount of the eluent (a few **mL** at most).
    b. If the solid is not particularly soluble, or will not dissolve in a few **mL** of the eluent, dissolve it in the minimum amount of dichloromethane (few **mL** at most, Figure 2.56a).
    c. If the solid is insoluble in the eluent, an alternate procedure is also possible. Dissolve the solid in a round-bottomed flask using a few **mL** of a low-boiling solvent (e.g. dichloromethane or acetone). Add to the flask approximately **1 g** of silica or alumina, then remove the solvent on the rotary evaporator in order to leave a solid that contains the sample deposited on the adsorbent. With an inch of eluent resting atop the packed column (skip adding the sand layer if this method is used), pour the silica-adsorbed sample onto the column using a wide mouthed funnel. If any dust clings to the glass, rinse it down with more eluent (go on to step 15.)
13. Delicately add the sample to the column via pipette, dripping the liquid or solution directly onto the sand with the pipette tip as close as you can manage, not down the sides (Figure 2.56b). Take care to not squirt liquid in forcibly such that indentations would be caused in the sand or silica /alumina column.
14. Rinse the sample container with a little solvent (or dichloromethane if used, Figure 2.56c) and add the rinsing to the column using the same pipette (in order to rinse the pipette as well).
15. Open the stopcock and allow liquid to drip out until the sample is just past the sand layer (Figure 2.56d) and into the white area of the column (apply air pressure if this takes more than 20 seconds).
16. Gently rinse the sides of the column with a swirling motion using 1-2 pipettes-full of eluent to rinse any splashed sample. Again, allow liquid to drip out (or apply air pressure) until the sample is pushed into the white adsorbent.

    Repeat the rinsing step until you feel confident that the entire sample is deposited on the adsorbent. If some of the sample is still located in the sand layer, it may dissolve in the eluent when more solvent is added, leading to a loss of yield. If the compound is colored, the rinsing should be completely clear.

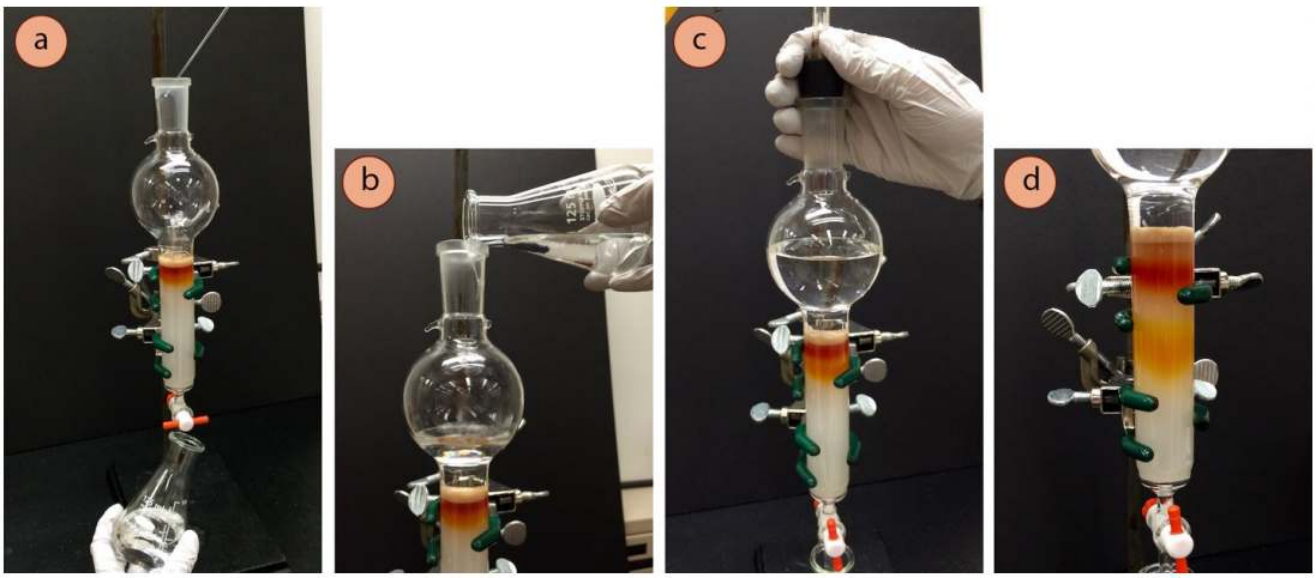


Figure 2.57: a+b) Filling the solvent reservoir, c+d) Eluting the column.

Fill with Eluent and Elute the Column

17. Delicately add more eluent via pipette (Figure 2.57a), swirling down the sides, and then when the sand layer would no longer be disturbed with the additions, carefully pour in larger quantities (Figure 2.57b) of the prepared eluent to fill the reservoir (or fill with as much as may be needed). Clean eluent collected during the packing of the column can be reused.
18. Use air pressure to gently and steadily elute the sample through the column (Figures 2.57 c+d). The more times the pressure is started and stopped, the more likely the column may crack. It's best if the pressure can be kept gentle and steady the entire time.

The optimal drip rate during elution depends on the size of the column. The ideal flow of eluent is when the solvent in the cylindrical section of the column above the adsorbent drops at a rate of 2.0 inches per minute.[10] Therefore, the drip rate should be slower with a narrow column compared to a wider column.

The drip rate for a one-inch column should be where individual drops can be barely distinguished. A stream of liquid pouring out the stopcock with this size of column is slightly too fast.

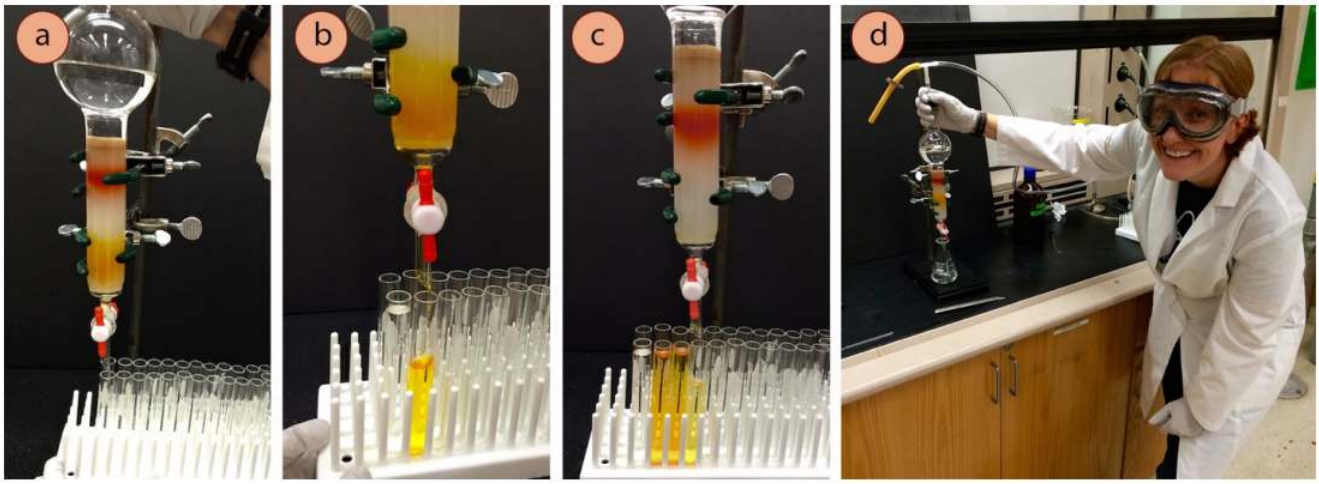


Figure 2.58: a-c) Collecting fractions, d) Author running a column.

Collect fractions

19. Immediately start collecting the eluting liquid into test tubes on a rack (Figure 2.58a). See Table 2.5 for recommendations on volumes to collect in each test tube.
20. When the first test tube fills, or if a certain height of liquid has been collected as recommended by your instructor or Table 2.5, move the rack over to start collecting into a different tube (Figures 2.58 b+c). Fill and keep the tubes in order on the rack.

    These different tubes are called "**fractions**". The goal of a column is to collect small enough fractions that most (or some) fractions contain pure material. If the separation of the mixture is difficult (if the ΔR_f of the components is low), it may be best to collect small fractions (e.g. half-filled tubes).

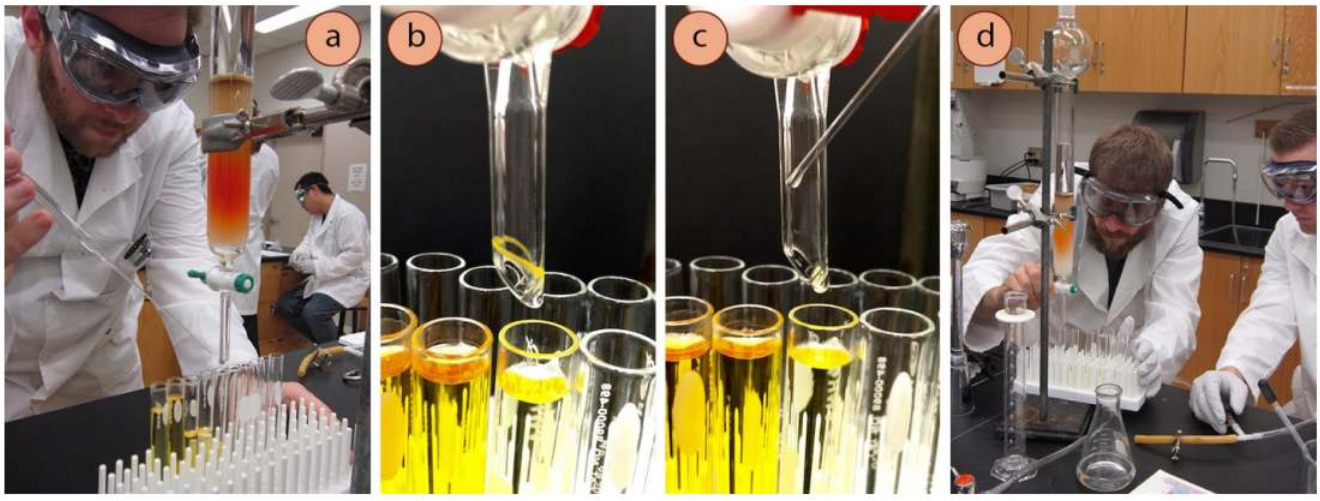


Figure 2.59: a-c) Rinsing material splashed onto the tip of the column, d) Students running a column.

21. As liquid drains off the column, it often splashes onto the outsides of the tip of the column, and when the solvent evaporates you may see a ring of material on the tip (you will see a ring of solid if the component is a solid as in Figure 2.59b, or oily

droplets if the component is a liquid). If the components are colored, the column tip should be rinsed (Figure 2.59c) when it appears as if one component has completely eluted and before the other component approaches.

22. **Periodically keep an eye on the eluent level**, and refill before it drops below the sand layer.

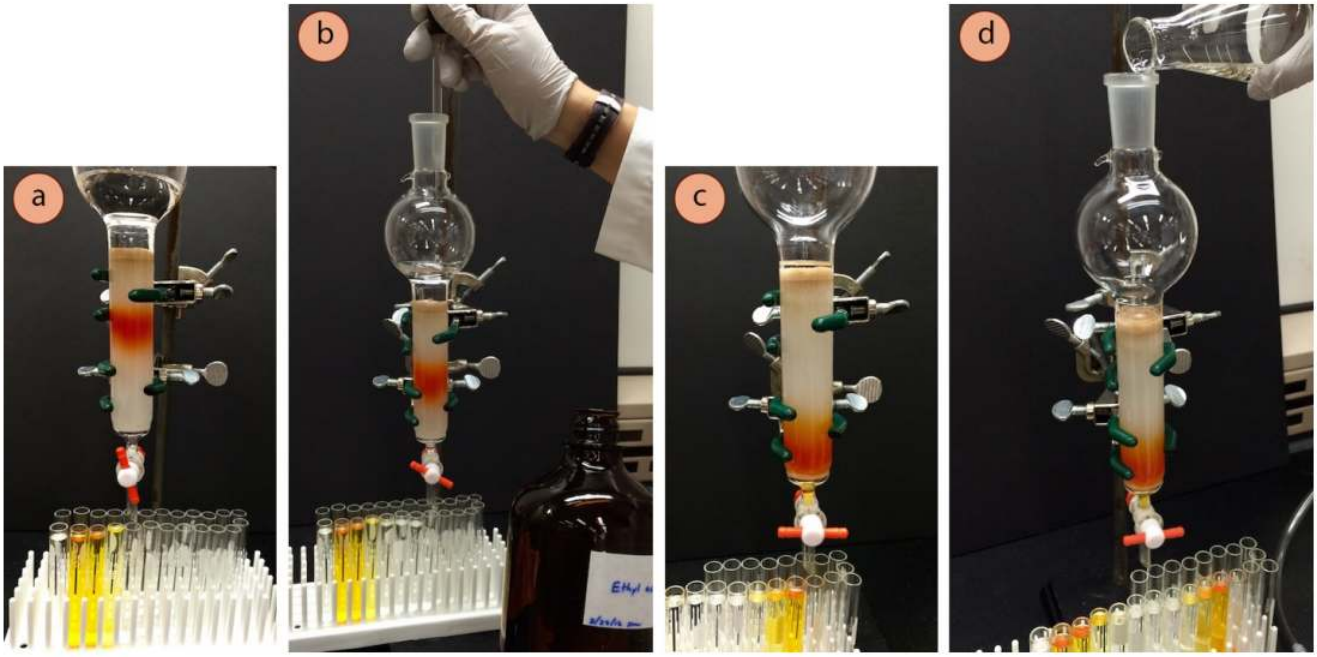


Figure 2.60: a) Elution, b) Addition of ethyl acetate to increase the solvent polarity, c) Solvent level nears the sand layer, d) Refilling.

Possibly Increase the Solvent Polarity

23. One eluent may be used throughout the entire column, especially if the components to be separated have similar R_f values. However, if the components have very different R_f values, the solvent polarity may be increased after one component has eluted from the column (Figure 2.60a).

    Increasing the solvent polarity will make components travel "faster." There are several reasons a faster elution is desired. First, if one component has already exited the column, the column has already done its job with separation, so speeding up the process will not affect the purity of the collected fractions. Second, the longer it takes to run a column, the wider will be the component bands (due to diffusion), and collecting a broad band of material will use (and waste) a lot of solvent.

    Table 2.6 contains a partial list of the **eluotropic series**, a list of common solvents ranked according to their "solvent power" in normal phase chromatography. The more polar solvent causes the most dramatic increase in R_f.

Table 2.6: Eluotropic series.

Eluotropic Series (from least to most polar)
Petroleum ether / hexanes
Dichloromethane
Diethyl ether
Ethyl acetate
Acetone
Methanol

24. To increase the solvent polarity, the polar solvent can be dripped directly into the eluent on the column reservoir (Figure 2.60b). For example, if using a hexanes:ethyl acetate mixture, addition of pure ethyl acetate to the eluent currently in the reservoir would increase its polarity. If the eluent level is running low, a solution could be prepared that contains a higher percentage of the more polar component. For example, if the column first used a 4:1 hexanes:ethyl acetate mixture, using a 1:1 mixture would be a more polar solvent.
25. Elute the column with the more polar solvent as before, and always remember **to watch the eluent level**, and refill (Figure 2.60d) before it drops below the sand layer.

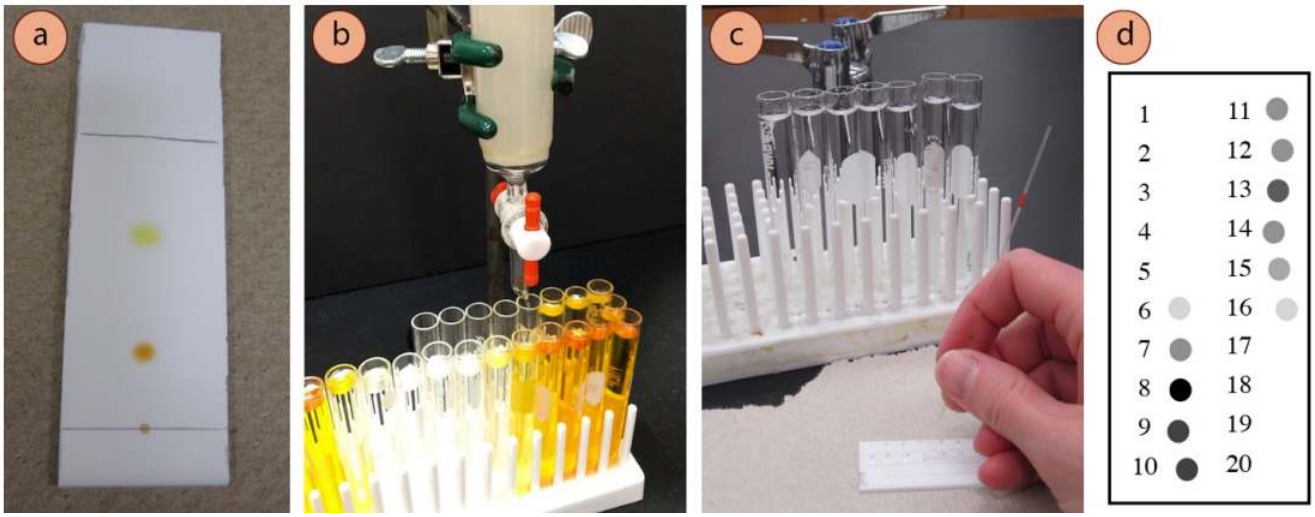


Figure 2.61: a) Original TLC plate, b) Fractions collected by the column, c) Spotting fractions onto a TLC plate, d) A visualized TLC plate of samples of each fraction.

Find and Concentrate the Desired Component

26. In finding the desired component in the test tube fractions, it is helpful to understand the relationship between R_f and elution order in column chromatography.

    In column chromatography, the sample is deposited on the top of the column and eluted down, while in thin layer chromatography the sample is spotted on the bottom of the plate and eluted up. Therefore, a column can be thought of like an upside-down TLC plate. A compound with a higher R_f runs "faster," meaning it will end up higher on a TLC plate, and will be collected *first* with a column.

    In the column pictured in this section, the component with the lower R_f (orange on the TLC plate in Figure 2.61a), is the component collected *second* from the column.
27. First determine which test tubes contain dissolved compound.
    a. Spot a sample of each fraction on a TLC plate labeled with fraction numbers corresponding to the order in which they were collected (Figure 2.61c). It may be best to spot each sample 2-3 times over top of one another in case the fractions are dilute.
    b. If *many* fractions have been collected, making you hesitant to sample *every* fraction, one method to identify colorless fractions that may contain compound is to look for a hint of residue on the top of the test tubes. After evaporation, a solid residue (Figure 2.62) or oily droplets are sometimes left on the top of the test tube, making obvious that those fractions contain more than just solvent. Sample all fractions near the tubes containing visible residue.



Figure 2.62: Ring of solid seen on tube rims after evaporation.

c. Visualize the spotted TLC plate using UV light and/or a stain to determine which fractions contain compound (Figure 2.61d).

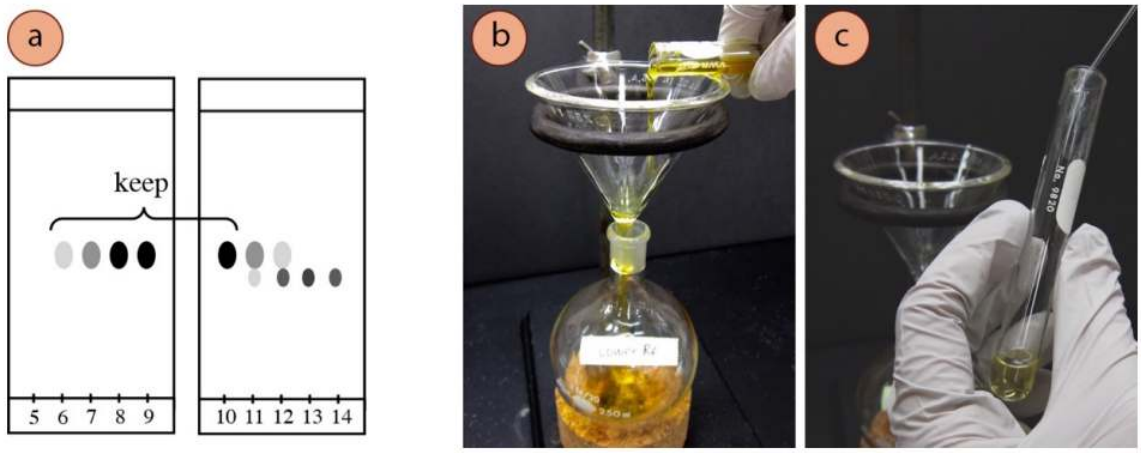


Figure 2.63: a) Eluted TLC plates of fractions containing possible compound, b) Combining fractions, c) Rinsing a fraction tube.

28. Run a TLC of all fractions that contain compound, spotting up to five samples per 1-inch wide TLC plate. Wider TLC plates may be used for this purpose if available.
29. Identify the compound with the desired R_f by comparison with the original crude TLC plate. Choose to retain the fractions that have the desired compound in pure form, as evidenced by the eluted TLC plate. For example, if the compound with the higher R_f is desired in Figure 2.63a, fractions 6-10 should be kept.
30. Combine the pure fractions into an appropriately sized round-bottomed flask (no more than half-full, Figure 2.63b). Rinse each test tube with a small amount of eluent (or other solvent if solubility is an issue), and add the rinsing to the round-bottomed flask (Figure 2.63c).
31. Evaporate the solvent on the rotary evaporator to leave the purified compound in the flask.



Figure 2.64: a) Using air pressure to dry the column, b) Allowing the column to dry upside-down, c) Collecting the waste silica.

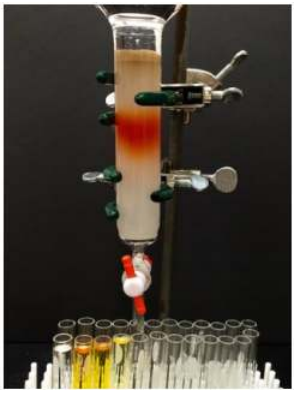
Clean Up the Column

32. To dry the column, apply air pressure to drain the majority of eluent from the column into a waste container. Then further dry the column using one of these methods:
    a. Leave connected a gentle stream of air running through the column to further dry it as you clean up other things (Figure 2.64a).
    b. Clamp the column upside down over a large waste beaker in the fume hood, so that the adsorbent will fall when it has dried (Figure 2.64b). This will take a long time (until the next class period), but is an option.
33. When dry, the adsorbent can be poured out of the column into a waste container in the fume hood (Figure 2.64c).

    Safety note: Powdered adsorbents are a lung irritant, and their hazard is exacerbated if the column contains residual compounds that can now make their way into your lungs. Pouring silica or alumina powders should always be done in the fume hood.
34. When the majority of the adsorbent has been collected in a waste container, use water to rinse any residual solid into the sink, and then rinse the column with acetone into a waste beaker. Further clean the column with soap and water and dry with the stopcock parts separated.

Macroscale Column Summary

Table 2.7: Procedural summary for macroscale column chromatography.

			
Make sure there is a frit or cotton plug in the bottom of the column. Fill the column with silica or alumina to 5-6 inches in the fume hood.	Pour the adsorbent into an Erlenmeyer flask and add eluent to make a pourable slurry. The eluent should give the desired component an R_f **of 0.35** by TLC.	Pour in the slurry and immediately rinse the sides of the column with eluent and a pipette. Jostle the column to remove air bubbles. Use air pressure to pack the column. Keep it perfectly vertical.	Add $0.5\ \text{cm}$ of sand. Rinse the sand off the sides carefully with a swirling motion. Don't disrupt the top surface of the silica or alumina with rinsing.
			
Adjust the eluent level to the sand layer, and then add the sample (pure liquid, dissolved in CH_2Cl_2, or solid adsorbed onto a portion of silica). Rinse the sides and use air pressure to force the eluent down onto the silica/alumina layer.	Fill the reservoir with eluent (carefully to not disrupt the top surface). Use steady air pressure to elute the column. Collect fractions in test tubes in a rack (keep in order).	Rinse the column tip if a component has finished coming off the column. Possibly increase the eluent polarity to make components elute faster. **Never allow the eluent to drop below the top of the adsorbent column.**	Use TLC to determine the purity of the fractions, and combine appropriate fractions. Remove the solvent with the rotary evaporator.

Troubleshooting

The Pipette Broke in the Column

It is quite common to break the tip of a Pasteur pipette while rinsing the column, which often falls and wedges itself into the delicate column. Unfortunately, a broken pipette in a column can cause problems with the separation of components.

For example, Figure 2.65 shows the effect of a broken pipette on the separation of two components. A broken pipette is embedded in the column and is the nearly vertical line of orange seen between the two bands on the column. Since stationary-mobile phase equilibration does not occur on the glass surface of the pipette, compounds stream down quickly and move faster than they should based on their R_f. The orange vertical line is the top component draining into the band of the bottom component, contaminating it.



Figure 2.65: Effect of a broken pipette on a column.

If a broken pipette pierces the column, and the sand or sample has *not* yet been applied, attempt to remove the pipette with long forceps. After removal, vigorously jostle the column to pack it again and continue on with the column. If the pipette cannot be removed with forceps, you may consider redoing the column.

If the sand *has* already been applied, removal of the pipette and jostling the column will often ruin the horizontal surface of the adsorbent, so it will be necessary to re-pack the column.

If the sample has already been applied, there isn't anything to do but continue on and hope for the best. If the column results in an unsuccessful separation, all fractions containing the compound of interest can be combined, solvent evaporated by the rotary evaporator, and another purification method (or a second column) can be attempted.

Air Bubbles are Seen in the Column

Like a broken pipette, an air bubble is an empty pocket where stationary-mobile phase equilibration does not happen, so components move quicker around an air bubble than they should. This may lead to uneven eluting bands, which can cause overlap if the separation of the mixture is difficult (if the components have very close R_f values, as in Figure 2.66).

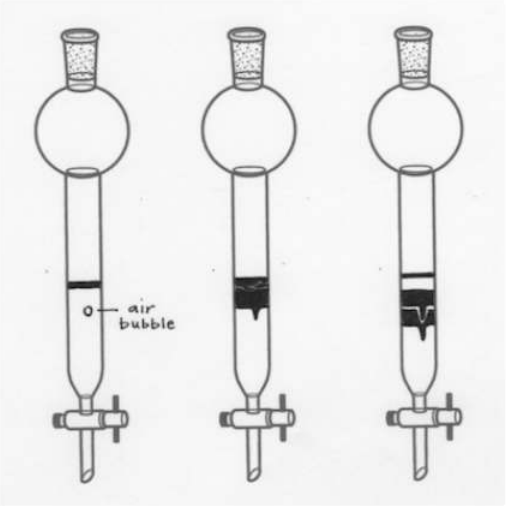


Figure 2.66: Effect of an air bubble on the separation in a column.

If air bubbles are seen in the column and the sand or sample has *not* yet been applied, give the column a good jostling during packing to remove all air bubbles. See your instructor if the bubbles are not budging as you may be approaching the task too delicately. If the sand or sample has already been applied, it's best to leave the column as is and hope the air bubbles do not affect the separation.

The Bands are Eluting Unevenly

If the components of a mixture are colored, it may be obvious when the bands elute in a crooked manner. This is most likely due to the column being clamped at a slight diagonal.

If the column is clamped in a slanted manner, components will travel in a slanted manner (Figure 2.67). This may cause separation problems if the components have a similar R_f.

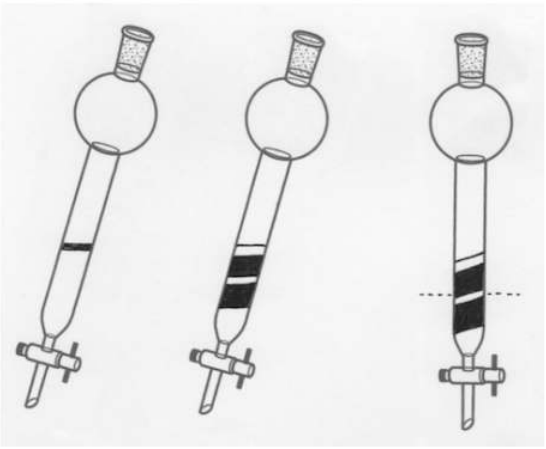


Figure 2.67: Effect of a crooked column on separation.

There is no way to fix this problem midway through a column, but if the components have very different R_f values, the slanted bands may have no effect on the separation. In the future, be sure to check that the column is perfectly vertical in both the side-to-side and front-back directions.

[8]W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, Vol. 43, No. 14, **1978**.

[9]A typical small test tube $(13x100\ \text{mm})$ has a capacity of $9\ \text{mL}$, and a typical medium test tube $(18x150\ \text{mm})$ has a capacity of $27\ \text{mL}$.

[10]W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, Vol. 43, No. 14, **1978**.

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2.2.2: Microscale (Pipette) Columns

A macroscale column is much too big for very small quantities of material (< 20 mg). Instead, a column can be constructed using a disposable Pasteur pipette.

In order to get good separation, it is ideal if the desired component has an R_f **around 0.35** and is separated from other components by at least 0.2 R_f units.[11] If the spots to be separated are very close (< 0.2 ΔR_f), it's best if the middle of the spots has an R_f of 0.35. An R_f near 0.35 is ideal because it is slow enough that stationary-mobile phase equilibration can occur, but fast enough to minimize band widening from diffusion.

Step-by-Step Procedures

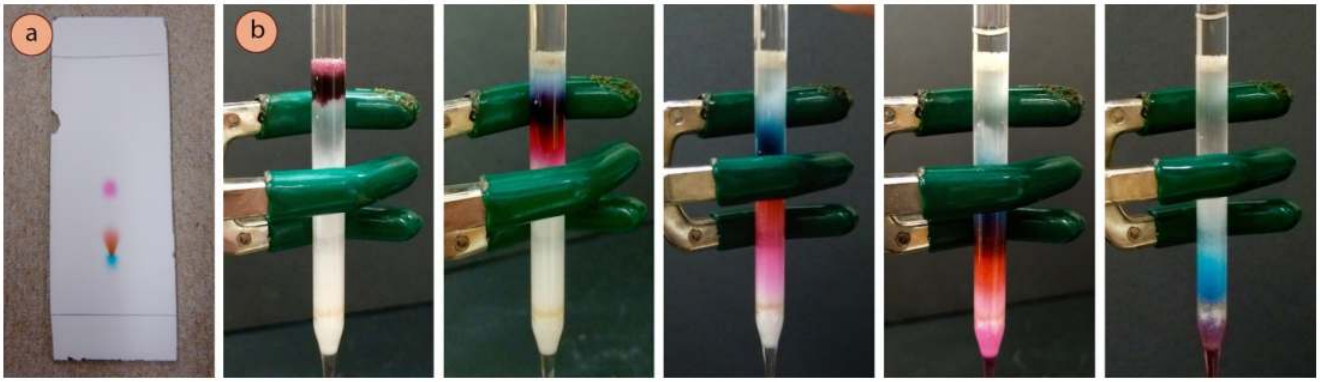


Figure 2.68: a) TLC plate of purple dye, b) Elution with a pipette column.

The column pictured in this section shows purification of a drop of dilute purple food dye (made from 1 drop red dye, 1 drop blue dye and 15 drops water). The dye is separated as best as possible into its three components: blue, red and pink (as seen in the TLC plate of Figure 2.68a). A 2.5" column of silica gel is used and eluted with a solution made from a 1:3:1 volume ratio of **6 M** NH_4OH:1-pentanol:ethanol.

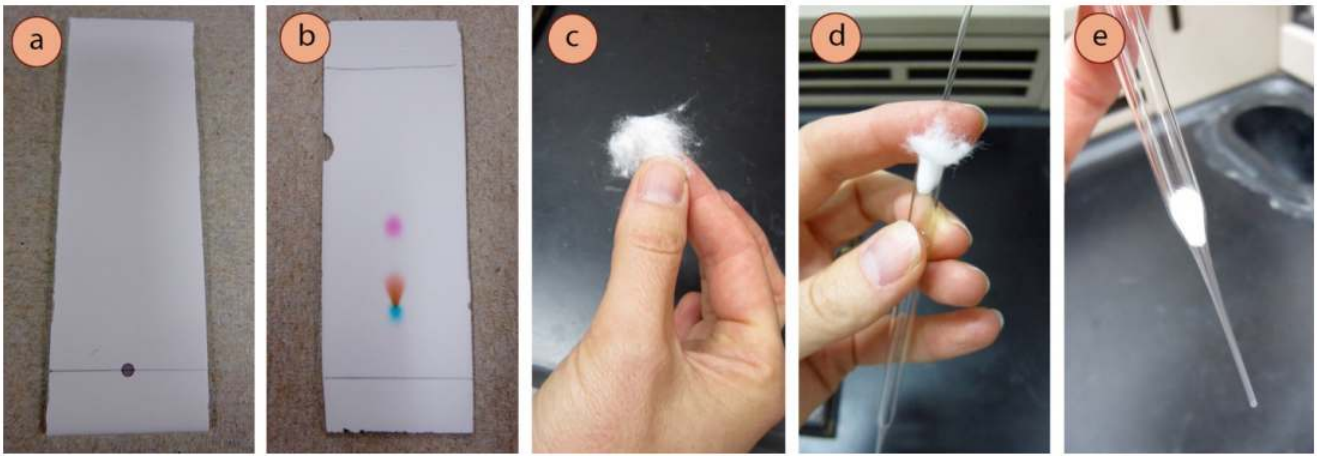


Figure 2.69: a) Purple dye spotted on the baseline of a TLC plate, b) after elution, c-e) Inserting cotton into the pipette tip.

1. Run a TLC of the sample to be purified (Figures 2.69 a+b) to determine the appropriate solvent for chromatography. The desired component should have an R_f **around 0.35**.

Prepare the dry column

2. Use a metal rod or hanger (Figure 2.69d) to wedge a bit of cotton or glass wool into the narrow end of a short-stemmed Pasteur pipette. The cotton should be moderately tight so liquid can trickle through, but not solid.

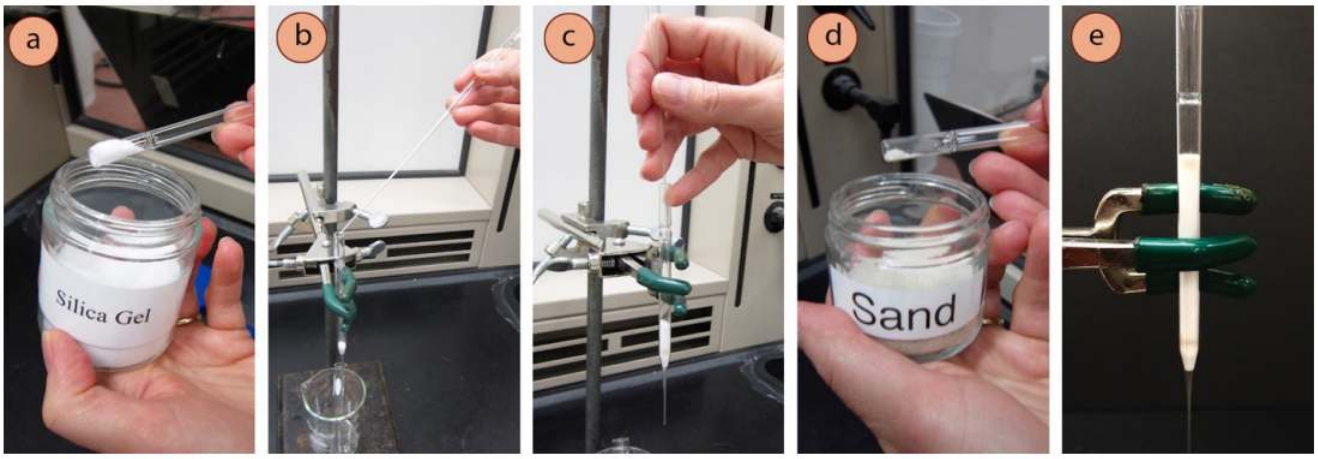


Figure 2.70: a) Scooping silica gel into the pipette column, b+c) Using a pipette as a funnel, d) Scooping sand, e) Complete dry column.

3. Scoop silica or alumina into the wide end of the pipette column (Figure 2.70a), then invert and raise the column so the powder falls to the bottom. Continue to use this scooping method to fill the pipette column to 2 - 2.5 inches high with silica or alumina (this quantity can be altered depending on the amount of sample).

   Alternatively, scoop adsorbent into the wide end of a fresh pipette and use it as a funnel to deliver adsorbent through the narrow tip and into the pipette column secured to a ring stand with a three-fingered clamp (Figures 2.70 a–c).

   Safety note: As silica and alumina are fine powders and lung irritants, be sure to work in a fume hood when handling silica or alumina. Also tap the pipette after scooping to dislodge adsorbent on the outside of the pipette (so it doesn't spill when vertical).
4. Gently clamp the pipette column to a ring stand or latticework using a three-fingered clamp (note: they are fragile!) and tap it to make sure the silica / alumina is settled and the top edge is horizontal.
5. Add approximately $0.5\ \text{cm}$ of sand atop the silica / alumina layer. If using very fine sand, use another pipette to act as a funnel, as described in step 3. For coarse sand, use a small scooper or the wide end of another pipette to aid in its delivery (Figure 2.70d). A complete pipette column is in Figure 2.70e.

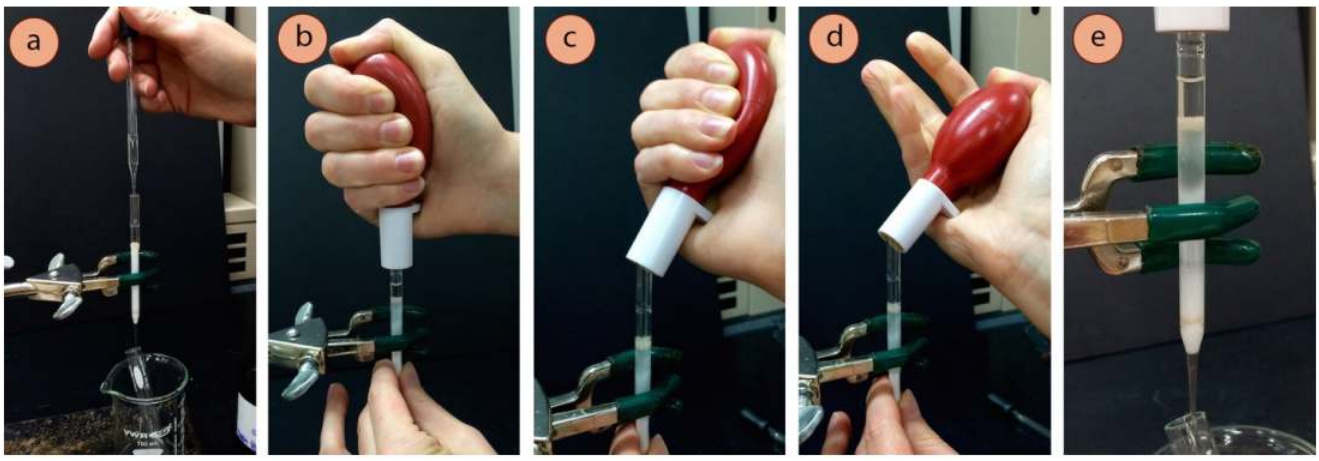


Figure 2.71: a) Adding eluent, b-d) Applying bulb pressure and correctly breaking the seal, e) Eluting the column.

Wet the column

6. Position a test tube supported in a small beaker beneath the column. Add a squirt-full of the appropriate eluent (previously determined by TLC in Step 1), gently above the sand layer of the pipette column (Figure 2.71a).
7. Use a pipette bulb (or dropper bulb) to apply gentle air pressure and push the eluent through the column (Figure 2.71b), stopping when the liquid level is in the sand layer. **Throughout the entire elution process, keep this white column section wet with eluent.**

To apply air pressure using a pipette bulb, create a strong connection between the column and the bulb, and then squeeze the bulb. It is important when releasing the pressure to first break the seal while still keeping your hand clenched (Figure 2.71c) and THEN release your hand (Figure 2.71d). If you release your hand while still connected to the column, the bulb will create suction that can violently pull liquid into the bulb and disrupt the column.

8. Add more eluent if needed, and use bulb pressure until the entire column is saturated with eluent (Figure 2.71e), and the eluent level is in the sand layer.

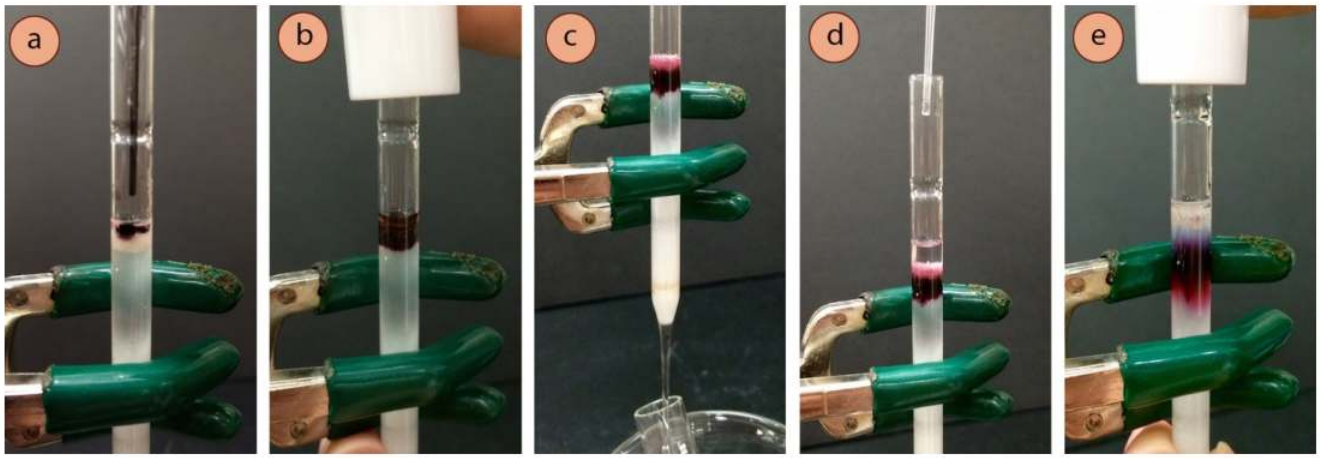


Figure 2.72: a) Adding sample, b) Applying pressure, c) Dye pushed onto the adsorbent, d) Filling with eluent, e) Eluting.

Add the sample

9. Use a pipette to add the entire sample to the sand layer. If the sample is a liquid, add it directly. If it is a solid, dissolve it in the smallest amount of solvent possible, preferably the eluent. If the solid is not soluble in the eluent, use the minimum amount of dichloromethane. Position the pipette tip near the sand layer and add the sample carefully, trying not to splash compound onto the sides (Figure 2.72a).
10. Rinse the original container with a little solvent and add the rinsing to the column using the same pipette (in order to rinse the pipette as well).
11. Apply pressure with the bulb to force the sample *just* past the sand layer (Figures 2.72 b+c).
12. Add more eluent (approximately $0.5\ \text{cm}$ high) to rinse the sides of the column (Figure 2.72d). Again use bulb pressure to force the dye onto the adsorbent (Figure 2.72e), and then fill the pipette above the sand layer as high as possible with eluent.

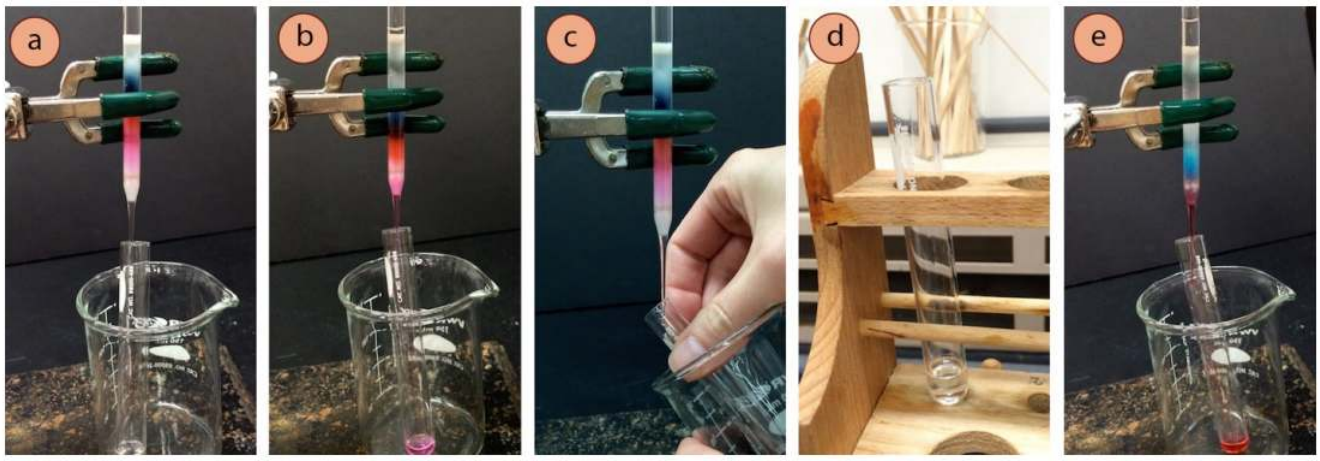


Figure 2.73: a) Eluting, b) Collecting the pink fraction, c) Changing the collection tube, d) Storing fractions in a rack, e) Collecting the red fraction.

Elute the Column and Collect Fractions

13. Apply gentle bulb pressure to begin eluting the sample through the column (Figure 2.73a), refilling the pipette whenever the solvent level nears the sand layer.
14. Immediately begin collecting the liquid eluting beneath the column into an empty test tube. Change the test tube for a fresh one periodically (Figure 2.73c), based on your judgment or your instructor's guidance (perhaps when a small test tube fills to about $1\ \text{cm}$ high).

    These different tubes are called "**fractions**". The goal of a column is to collect small enough fractions that most (or some) fractions contain pure material. If the separation of the mixture is difficult (if the ΔR_f of the components is low), it may be best to collect even smaller fractions (e.g. $0.5\ \text{cm}$ high).
15. Keep the test tubes in order on a test tube rack (Figure 2.73d).

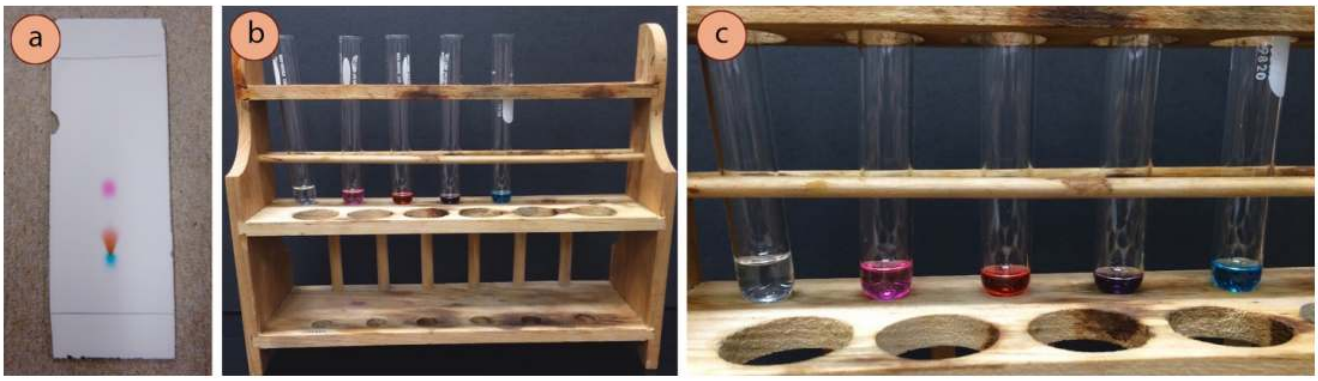


Figure 2.74: a) Original TLC plate, b+c) Resulting fractions (left to right in order of elution).

Find and Concentrate the Desired Component

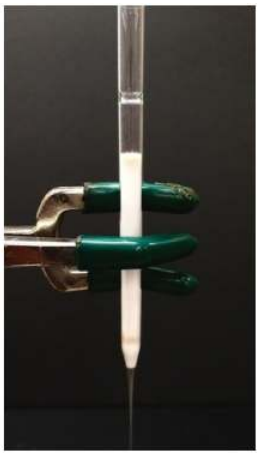
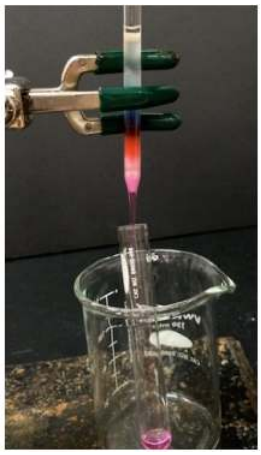
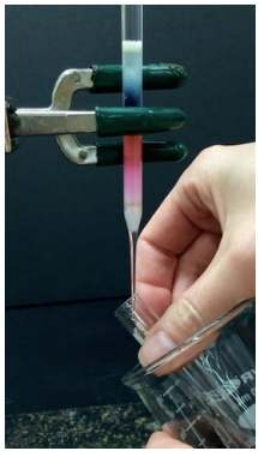
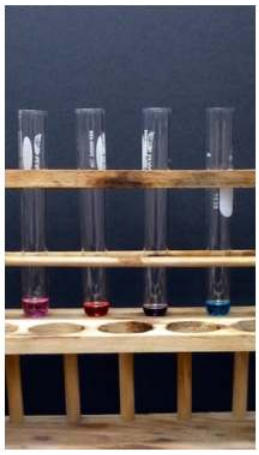
16. In finding the desired component in the test tube fractions, it is helpful to understand the relationship between R_f and elution order in column chromatography.

    In column chromatography, the sample is deposited on the top of the column and eluted down, while in thin layer chromatography the sample is spotted on the bottom of the plate and eluted up. Therefore, a column can be thought of like an upside-down TLC plate. A compound with a higher R_f runs "faster," meaning it will end up higher on a TLC plate, and will be collected *first* with a column.

    In the pipette column pictured in this section, the pink component had the highest R_f on the TLC plate (Figure 2.74a), and was collected *first* from the column (Figure 2.74b). A purple fraction was also collected (Figure 2.74c), due to incomplete separation of the red and blue components.
17. Use TLC as described in the section on macroscale columns to determine which tubes contain the desired component.
18. Combine the pure fractions into an appropriately sized round-bottomed flask using a funnel, rinse each tube with a small amount of eluent (or other solvent if solubility is an issue), and add the rinsing to the flask. Remove the solvent on the rotary evaporator.
19. To clean up the pipette column, use bulb pressure to force the excess liquid out of the pipette column, and dispose of the semi-dry column (silica gel and all) in the broken glass container.

Microscale (Pipette) Column Summary

Table 2.8: Procedural summary for microscale (pipette) column chromatography.

			
Wedge a bit of cotton into the bottom of a pipette. Use a scooping method to fill silica or alumina to 2-2.5 inches high.	Add a **0.5 cm** layer of sand.	Add eluent to the column and apply pressure with a pipette bulb to force eluent through the column to completely wet it.	Remember to break the seal before letting go of the pipette bulb, or suction will ruin the column. Refill the column with eluent as necessary.
			
Adjust the eluent level to the sand layer, and then delicately add the sample. Use pressure to push the eluent down onto the silica/alumina layer. Rinse with one portion of eluent and push the solvent onto the column.	Fill the pipette with eluent and apply pressure to elute the column. Collect liquid into test tubes. **Always keep the white column section wet** (refill whenever the eluent level nears the sand layer).	Switch test tubes periodically (perhaps when they are **1 cm** high in small test tubes) to collect different fractions.	Keep fractions organized in a test tube rack in the order they are eluted. Use TLC to determine the purity of the fractions, and combine appropriate fractions. Remove the solvent with the rotary evaporator.

[11]W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, Vol. 43, No. 14, **1978**.

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2.2.3: 5.5 Polarimetry

Objectives

After completing this section, you should be able to

1. describe the nature of plane-polarized light.
2. describe the features and operation of a simple polarimeter.
3. calculate the specific rotation of a compound, given the relevant experimental data.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- analyzer
- dextrorotatory
- levorotatory
- optically active
- plane-polarized light
- polarimeter
- polarizer
- specific rotation, $[\alpha]_D^{20}$

Study Notes

A *polarizer* is a device through which only light waves oscillating in a single plane may pass. A *polarimeter* is an instrument used to determine the angle through which plane-polarized light has been rotated by a given sample. You will have the opportunity to use a polarimeter in the laboratory component of the course. An *analyzer* is the component of a polarimeter that allows the angle of rotation of plane-polarized light to be determined.

Specific rotations are normally measured at 20°C, and this property may be indicated by the symbol $[\alpha]_D^{20}$. Sometimes the solvent is specified in parentheses behind the specific rotation value, for example,

$$[\alpha]_D^{20} = +12^o\,(\text{chloroform})$$

For liquids, the specific rotation may be obtained using the neat liquid rather than a solution; in such cases the formula is

$$[\alpha]_D^{\text{temp}}\,(\text{neat}) = \alpha \times l \times d$$

where α is the observed rotation, l is the path length of the cell (measured in decimetres, dm), and d is the density of the liquid.

Identifying and distinguishing enantiomers is inherently difficult, since their physical and chemical properties are largely identical. Fortunately, a nearly two hundred year old discovery by the French physicist Jean-Baptiste Biot has made this task much easier. This discovery disclosed that the right- and left-handed enantiomers of a chiral compound perturb plane-polarized light in opposite ways. This perturbation is unique to chiral molecules, and has been termed **optical activity**.

Polarimetry

Plane-polarized light is created by passing ordinary light through a polarizing device, which may be as simple as a lens taken from polarizing sun-glasses. Such devices transmit selectively only that component of a light beam having electrical and magnetic field vectors oscillating in a single plane. The plane of polarization can be determined by an instrument called a **polarimeter** (Figure 2.2.3.1).

Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source. A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an eyepiece through which the light intensity can be observed. In modern instruments an electronic light detector takes the place of the human eye. In the absence of a sample, the light

intensity at the detector is at a maximum when the second (movable) polarizer is set parallel to the first polarizer (α = 0º). If the analyzer is turned 90º to the plane of initial polarization, all the light will be blocked from reaching the detector.

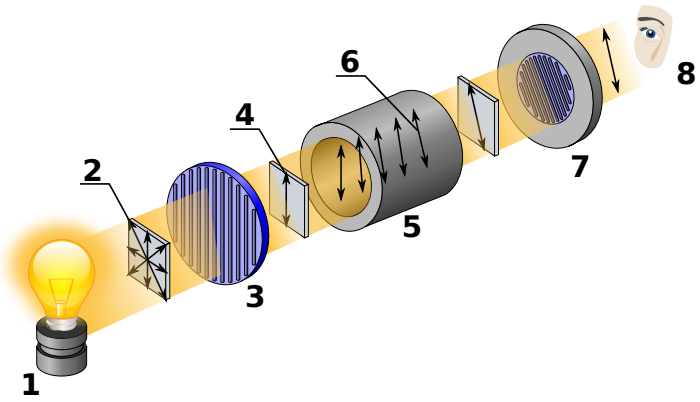


Figure **2.2.3.1**: Operating principle of an optical polarimeter. 1. Light source 2. Unpolarized light 3. Linear polarizer 4. Linearly polarized light 5. Sample tube containing molecules under study 6. Optical rotation due to molecules 7. Rotatable linear analyzer 8. Detector. (CC BY-SA 3.0 Unported; Kaidor via Wikipedia)

Chemists use polarimeters to investigate the influence of compounds (in the sample cell) on plane polarized light. Samples composed only of achiral molecules (e.g. water or hexane), have no effect on the polarized light beam. However, if a single enantiomer is examined (all sample molecules being right-handed, or all being left-handed), the plane of polarization is rotated in either a clockwise (positive) or counter-clockwise (negative) direction, and the analyzer must be turned an appropriate matching angle, **α**, if full light intensity is to reach the detector. In the above illustration, the sample has rotated the polarization plane clockwise by +90º, and the analyzer has been turned this amount to permit maximum light transmission.

The observed rotations (α) of enantiomers are opposite in direction. One enantiomer will rotate polarized light in a clockwise direction, termed **dextrorotatory** or (+), and its mirror-image partner in a counter-clockwise manner, termed **levorotatory** or (–). The prefixes dextro and levo come from the Latin *dexter*, meaning right, and *laevus*, for left, and are abbreviated *d* and *l* respectively. If equal quantities of each enantiomer are examined , using the same sample cell, then the magnitude of the rotations will be the same, with one being positive and the other negative. To be absolutely certain whether an observed rotation is positive or negative it is often necessary to make a second measurement using a different amount or concentration of the sample. In the above illustration, for example, α might be –90º or +270º rather than +90º. If the sample concentration is reduced by 10%, then the positive rotation would change to +81º (or +243º) while the negative rotation would change to –81º, and the correct α would be identified unambiguously.

Since it is not always possible to obtain or use samples of exactly the same size, the observed rotation is usually corrected to compensate for variations in sample quantity and cell length. Thus it is common practice to convert the observed rotation, α, to a **specific rotation**, by the following formula:

$$[\alpha]_D = \frac{\alpha}{lc} \tag{5.3.1}$$

where

- $[\alpha]_D$ is the specific rotation
- l is the cell length in dm
- c is the concentration in g/ml
- D designates that the light used is the 589 line from a sodium lamp

Compounds that rotate the plane of polarized light are termed **optically active**. Each enantiomer of a stereoisomeric pair is optically active and has an equal but opposite-in-sign specific rotation. Specific rotations are useful in that they are experimentally determined constants that characterize and identify pure enantiomers. For example, the lactic acid enantiomers have the following specific rotations:

- Carvone from caraway: $[\alpha]_D^{20} = +62.5^o$ (this isomer may be referred to as (+)-carvone or d-carvone)
- Carvone from spearmint: $[\alpha]_D^{20} = -62.5^o$ (this isomer may be referred to as (–)-carvone or l-carvone)

and carvone enantiomers have the following specific rotations:

- Lactic acid from muscle tissue: $[\alpha]_D^{20} = +2.5^o$ (this isomer may be referred to as (+)-lactic acid or d-lactic acid)
- Lactic acid from sour milk: $[\alpha]_D^{20} = -2.5^o$ (this isomer may be referred to as (–)-lactic acid or l-lactic acid)

A 50:50 mixture of enantiomers has no observable optical activity. Such mixtures are called **racemates** or racemic modifications, and are designated (±). When chiral compounds are created from achiral compounds, the products are racemic unless a single enantiomer of a chiral co-reactant or catalyst is involved in the reaction. The addition of **HBr** to either cis- or trans-2-butene is an example of racemic product formation (the chiral center is colored red).

$$CH_3CH{=}CHCH_3 + HBr \longrightarrow (\pm)\ CH_3CH_2\color{red}{C}HBrCH_3$$

Chiral organic compounds isolated from living organisms are usually optically active, indicating that one of the enantiomers predominates (often it is the only isomer present). This is a result of the action of chiral catalysts we call enzymes, and reflects the inherently chiral nature of life itself. Chiral synthetic compounds, on the other hand, are commonly racemates, unless they have been prepared from enantiomerically pure starting materials.

There are two ways in which the condition of a chiral substance may be changed:

1. A racemate may be separated into its component enantiomers. This process is called **resolution**.
2. A pure enantiomer may be transformed into its racemate. This process is called **racemization**.

Enantiomeric Excess

The "optical purity" is a comparison of the optical rotation of a pure sample of unknown stereochemistry versus the optical rotation of a sample of pure enantiomer. It is expressed as a percentage. If the sample only rotates plane-polarized light half as much as expected, the optical purity is 50%.

$$\%\ \text{optical purity} = \frac{\text{specific rotation of mixture}}{\text{specific rotation of pure enantiomer}} \times 100\%$$

Because *R* and *S* enantiomers have equal but opposite optical activity, it naturally follows that a 50:50 racemic mixture of two enantiomers will have no observable optical activity. If we know the specific rotation for a chiral molecule, however, we can easily calculate the ratio of enantiomers present in a mixture of two enantiomers, based on its measured optical activity. When a mixture contains more of one enantiomer than the other, chemists often use the concept of **enantiomeric excess (ee)** to quantify the difference. Enantiomeric excess can be expressed as:

$$ee = \frac{(\%\ \text{more abundant enantiomer} - 50) \times 100\%}{50}$$

For example, a mixture containing 60% *R* enantiomer (and 40% *S* enantiomer) has a 20% enantiomeric excess of R: ((60-50) x 100) / 50 = 20 %.

? Exercise 2.2.3.1

The specific rotation of (*S*)-carvone is (+)61°, measured 'neat' (pure liquid sample, no solvent). The optical rotation of a neat sample of a mixture of *R* and *S* carvone is measured at (-)23°. Which enantiomer is in excess, and what is its ee? What are the percentages of (*R*)- and (*S*)-carvone in the sample?

Answer

The observed rotation of the mixture is levorotary (negative, counter-clockwise), and the specific rotation of the pure *S* enantiomer is given as dextrorotary (positive, clockwise), meaning that the pure *R* enantiomer must be levorotary, and the mixture must contain more of the *R* enantiomer than of the *S* enantiomer.

Rotation (*R*/*S* Mix) = [Fraction(*S*) × Rotation (*S*)] + [Fraction(*R*) × Rotation (*R*)]

Let Fraction (*S*) = x, therefore Fraction (*R*) = 1 – x.

Rotation (*R*/*S* Mix) = x[Rotation (*S*)] + (1 – x)[Rotation (*R*)].

$$-23 = x(+61) + (1 - x)(-61)$$

Solve for x: x = 0.3114 and (1 – x) = 0.6885

Therefore the percentages of (*R*)- and (*S*)-carvone in the sample are 68.9% and 31.1%, respectively.

ee = [(% more abundant enantiomer – 50) × 100]/50. = [68.9 – 50) × 100]/50 = 37.8%.

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration.

Separation of Chiral Compounds

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used of this technique is known as chiral resolution.

? Exercise 2.2.3.2

A 3.20 g sample of morphine ($[\alpha]_D$ = -132) was dissolved in 10.0 mL of acetic acid ($[\alpha]_D$ = 0). If it is put into a sample tube with a path length of 2.00 cm, what would be its observed rotation (α)?

Answer

The specific rotation, $[\alpha]_D$ = (observed rotation, α (degrees))/ [(pathlength, *l* (dm)) x (concentration, c (g/cm^3))] = α/(*l* x c)

Solving for α, α = $[\alpha]_D$ x *l* x c

($[\alpha]_D$ = -132) x (*l* = 2.00 cm = 0.200 dm) x (c = 3.20 g / 10.0 cm^3 = 0.320 g/cm^3)

α = -132 x 0.200 dm x 0.320 g/cm^3 = -8.45 °

? Exercise 2.2.3.3

Is the morphine in the previous excercise dextrorotatory or levorotatory?

Answer

Since morphine has a (-) rotation, it indicates that it rotates light to the left (counterclockwise) and morphine is levorotatory.

? Exercise 2.2.3.4

Label the following compounds as dextrorotatory or levorotatory.

a. sucrose ($[\alpha]_D$ = + 66.7)
b. cholesterol ($[\alpha]_D$ = - 31.5)

c. cocaine ($[\alpha]_D$ = - 16)
d. chloroform ($[\alpha]_D$ = 0)

Answer

a. sucrose ($[\alpha]_D$ = + 66.7) dextrorotatory
b. cholesterol ($[\alpha]_D$ = - 31.5) levorotatory
c. cocaine ($[\alpha]_D$ = - 16) levorotatory
d. chloroform ($[\alpha]_D$ = 0) neither, not optically active

? Exercise 2.2.3.5*a*

The specific rotation of (*S*)-carvone is (+) 61° when measured neat (pure liquid sample with no solvent). The optical rotation of a neat sample of a mixture of R and S carvone is measured at (-) 23 ^{o}.

a) Which enantiomer is in excess?

Answer

Since the pure *S* enantiomer ((+) 61°) is dextrorotatory (positive, clockwise), the *R* enantiomer must be levorotatory. The observed rotation of the mixture is levorotatory since its negative (counterclockwise). This means the mixture must contain more of the *R* enantiomer than the *S* enantiomer.

? Exercise 2.2.3.5*b*

b) What are the percentages of (*S*)- and (*R*)- carvone in the sample mixture?

Answer

Optical rotation (α) of the (*R*/*S* mixture) = [fraction (*S*) x $[\alpha]_D$ (*S*)] + [fraction (*R*) x $[\alpha]_D$ (*R*)]

To determine the fraction of S and R, we make y = fraction (*S*) and 1 – y = fraction (*R*)

-23° = y x (61°) + (1 – y) x (-61°) solving for y: y = 0.3114 and (1-y) = 0.6885

Therefore the percentage of (*S*)-carvone is 31.1 % and (*R*)-carvone is 68.9 %

? Exercise 2.2.3.5*c*

c) What is the ee (enantiomeric excess)?

Answer

ee = [(% more abundant isomer – 50) x 100]/50 = [(68.9 – 50) x100]/50 = 37.8 % ee

? Exercise 2.2.3.6*a*

Determine the ee's of the following from the percentages

- 95 % (*R*)- tartaric acid and 5.0 % (*S*)- tartaric acid

Answer

[(95 – 50) x 100] / 50 = 90 % ee (*R*)-tartaric acid

Exercise 2.2.3.6b

Determine the ee's of the following from the percentages

- 75 % (*S*)- limonene and 25 % (*R*)- limonene

Answer

[(75 – 50) x 100] / 50 = 50 % ee (*S*)- limonene

Exercise 2.2.3.6c

Determine the ee's of the following from the percentages

- 85 % (*R*) cysteine

Answer

(85 – 50) x 100] / 50 = 70 % ee (*R*)-cysteine

Exercise 2.2.3.6d

Determine the ee's of the following from the percentages

- 50 % (*S*) alanine

Answer

(50 – 50) x 100] / 50 = 0 % ee, racemic mixture

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SECTION OVERVIEW

2.2.4: Crystallization

Crystallization is used in the chemistry laboratory as a purification technique for solids. An impure solid is completely dissolved in a minimal amount of hot, boiling solvent, and the hot solution is allowed to slowly cool. The developing crystals ideally form with high purity, while impurities remain in the saturated solution surrounding the solid (called the "mother liquor"). The crystallized solid is then filtered away from the impurities.

2.2.4.1: Overview of Crystallization

2.2.4.2: Uses of Crystallization

2.2.4.2A: Reagent Purification
2.2.4.2B: Purification of Product Mixtures

2.2.4.3: Choice of Solvent

2.2.4.3A: Ideal Temperature Profile
2.2.4.3B: General Procedures for Removing Impurities
2.2.4.3C: Determining Which Solvent to Use
2.2.4.3D: Using Solubility Data
2.2.4.3E: Experimentally Testing Solvents
2.2.4.3F: Mixed Solvents

2.2.4.4: Crystallization Theory

2.2.4.4A: Purification
2.2.4.4B: Cooling Slowly
2.2.4.4C: Using the Minimum Amount of Hot Solvent
2.2.4.4D: The Unavoidable Loss of Recovery
2.2.4.4E: Quantitating Crystallization
2.2.4.4F: Second Crop Crystallization

2.2.4.5: Procedural Generalities

2.2.4.5A: General Procedure
2.2.4.5B: Heat Source and Bump Prevention
2.2.4.5C: Charcoal
2.2.4.5D: Cooling Slowly
2.2.4.5E: Initiating Crystallization

2.2.4.6: Step-by-Step Procedures

2.2.4.6A: Single Solvent Crystallization
2.2.4.6B: Crystallization Summary
2.2.4.6C: Using Solvents Other Than Water
2.2.4.6D: Mixed Solvent Crystallization
2.2.4.6E: Mixed Solvent Summary

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2.2.4.1: Overview of Crystallization

In many people's opinion, crystals are beautiful specimens of nature (Figure 3.1). Many crystals have long lines and edges, form geometric patterns, and have sheer surfaces that reflect light and cause them to sparkle. The macroscopic appearance of a crystal is a direct result of its microscopic structure, where a regular, repeating unit forms a three-dimensional crystal lattice. The uniformity and structural repetition differentiate a crystal from an amorphous solid. For this reason, there is a difference between precipitation (the rapid formation of a solid), and crystallization (the slow growth of a solid with regular microscopic structure). Precipitated solids tend to have lower purity than crystals, which is why crystallization is of interest to organic chemists (and geologists!).



Figure 3.1: Various crystals.

Crystallization is used in the chemistry laboratory as a purification technique for solids. An impure solid is completely dissolved in a minimal amount of hot, boiling solvent, and the hot solution is allowed to slowly cool. The developing crystals ideally form with high purity, while impurities remain in the saturated solution surrounding the solid (called the "**mother liquor**"). The crystallized solid is then filtered away from the impurities. A diagram of the crystallization procedure is shown in Figure 3.2.

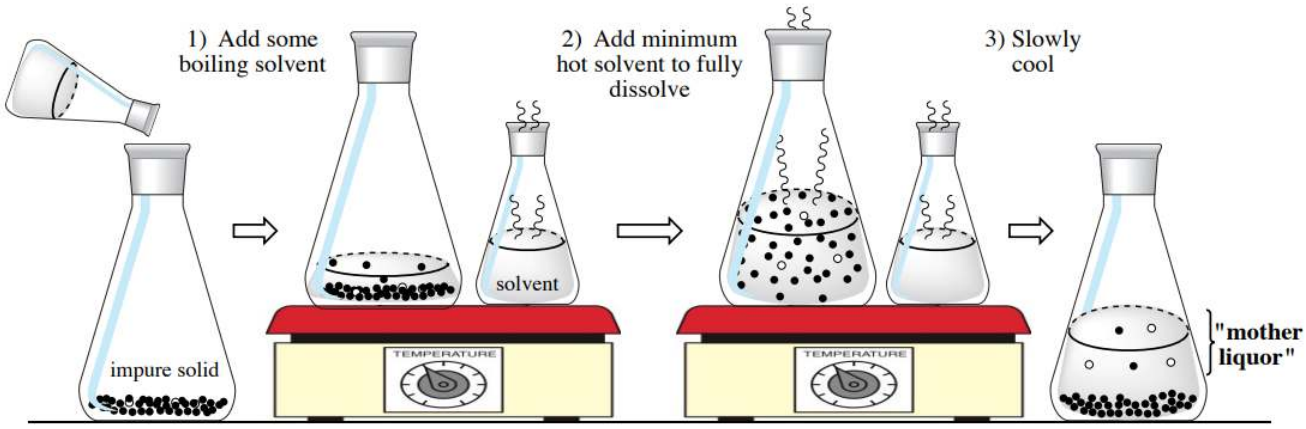


Figure 3.2: Procedural sequence for crystallization.

As an impure solid may have originally formed through partial crystallization, some call this procedure a "recrystallization", as the solid is allowed to crystallize a second time under more careful conditions. In this chapter the technique will be referred to as crystallization, which does not imply any previous process.

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SECTION OVERVIEW

2.2.4.2: Uses of Crystallization

The main use of crystallization in the organic chemistry laboratory is for purification of impure solids: either reagents that have degraded over time, or impure solid products from a chemical reaction.

2.2.4.2A: Reagent Purification

2.2.4.2B: Purification of Product Mixtures

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2.2.4.2A: Reagent Purification

N-bromosuccinimide (NBS) is a reagent used for benzylic and allylic radical bromination, among other things. It is commonly found in its reagent jar as a yellow or orange solid (Figure 3.3a), as over time the solid degrades and generates $\mathbf{Br_2}$, the source of the color. Before use, NBS should be crystallized from hot water, and the resulting crystals are pure white (Figure 3.3c). If NBS were used without previous crystallization, yields would undoubtedly suffer as the quantity of active reagent would be unknown, and side produces might form due to the presence of excess bromine.

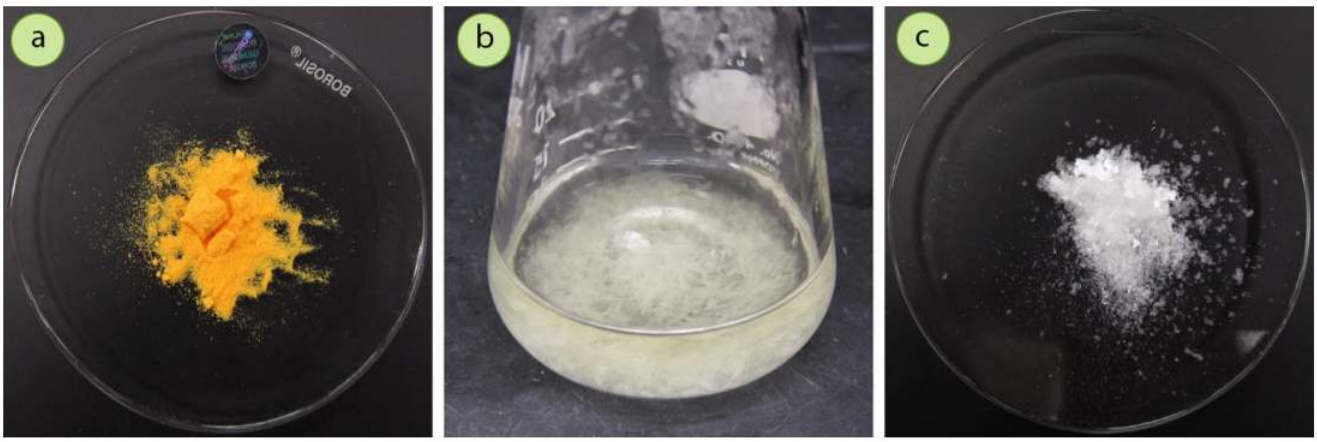


Figure 3.3: a) An old sample of **N**-bromosuccinimide (NBS), b) Crystallization of NBS using hot water, c) Crystallized NBS.

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2.2.4.2B: Purification of Product Mixtures

If the crude product of a chemical reaction is a solid, it may be crystallized in order to remove impurities. For example, benzoic acid can be brominated to produce *m*-bromobenzoic acid (Figure 3.4). The crude solid product could very likely contain unreactive benzoic acid, and this impurity could be removed through crystallization.

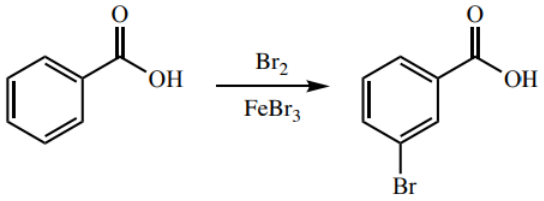


Figure 3.4: Bromination of benzoic acid to produce m-bromobenzoic acid.

To demonstrate, a mixture containing roughly **85 mol%** *p*-bromobenzoic acid[1] (a solid) contaminated with **15 mol%** benzoic acid (another solid) had a yellow tint (Figure 3.5a), and after crystallization the resulting solid was pure white (Figure 3.5c). The crystallization appeared to purify the mixture based on the slight improvement in color.

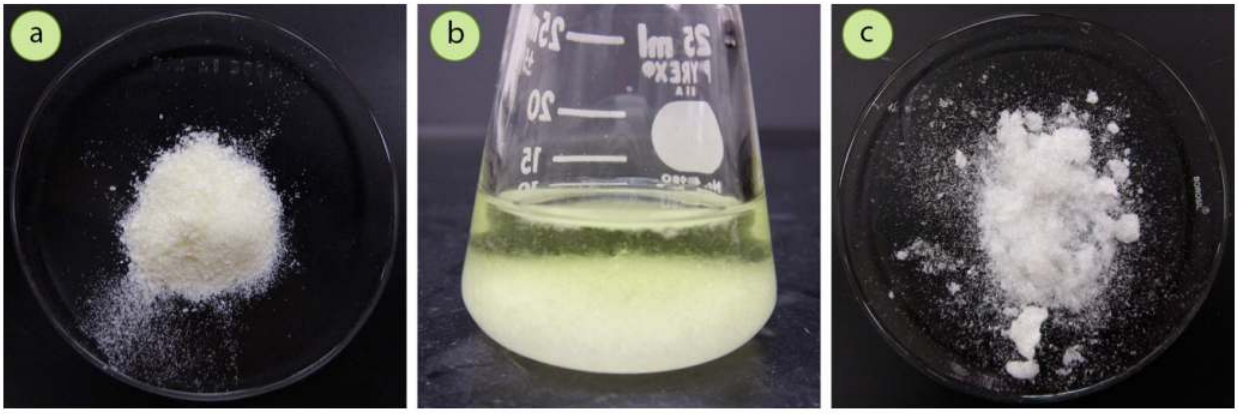


Figure 3.5: a) A mixed solid containing **85 mol%** p-bromobenzoic acid and **15 mol%** benzoic acid, b) Crystallization of the mixture using ethanol, c) Crystallized solid.

More reliable than appearance, the crystallization was proven to have indeed purified the mixture through melting point and **^{1}H** NMR analysis of the crude and crystallized solids. The melting point of the crude solid was **221-250°C** while the melting point of the purified solid was **248-259°C** (literature melting point of *p*-bromobenzoic acid from Aldrich is **252-254°C**). The melting point of the crystallized solid sharpened significantly, indicating greater purity. Additionally, in the crude solid's **^{1}H** NMR spectrum (Figure 3.6a), there are signals from both *p*-bromobenzoic acid and benzoic acid, and the integrations correlate reasonably well with the original composition of the mixture. In the crystallized solid's **^{1}H** NMR spectrum (Figure 3.6b), the benzoic acid signals are entirely gone, demonstrating that the crystallization successfully purified the *p*-bromobenzoic acid. An analogous purification could be done if a bromination reaction produced a mixture of *m*-bromobenzoic acid and benzoic acid.

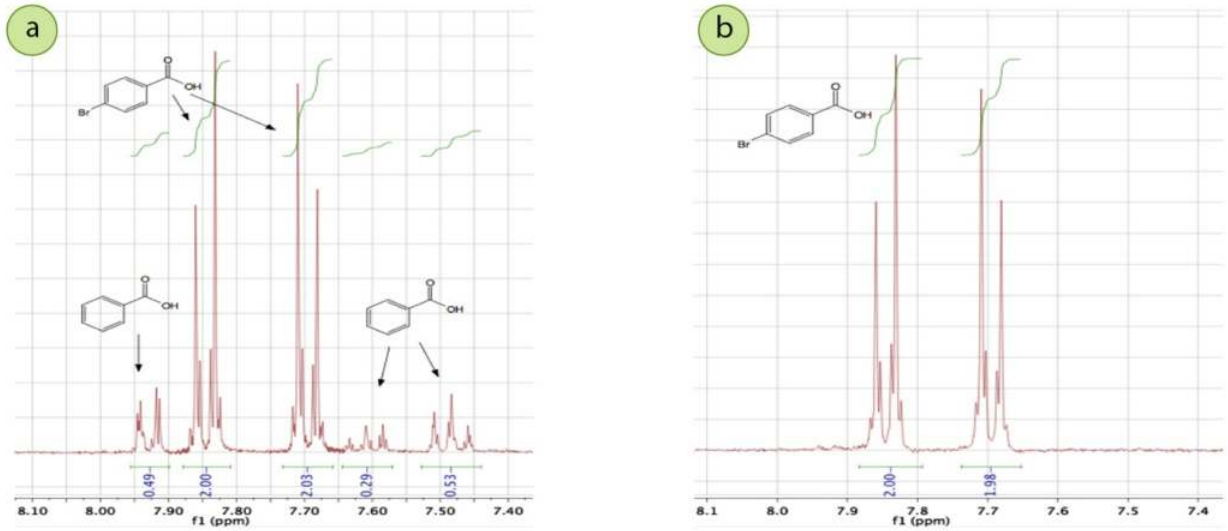


Figure 3.6: a) **300 MHz ^{1}H** NMR spectrum of the crude mixture of benzoic acid and p-bromobenzoic acid (taken in DMSO-d_6; carboxylic acid hydrogen is at **13.0 ppm** and is not shown), b) **^{1}H** NMR spectrum of solid after crystallization from ethanol, showing the sample is mostly p-*bromobenzoic acid*.

[1]*p*-Bromobenzoic acid was used instead of *m*-bromobenzoic acid for analysis purposes.

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SECTION OVERVIEW

2.2.4.3: Choice of Solvent

The crystallization procedure is possible as most solids tend to **become more soluble in solvents as their temperature is increased.**

2.2.4.3A: Ideal Temperature Profile

2.2.4.3B: General Procedures for Removing Impurities

2.2.4.3C: Determining Which Solvent to Use

2.2.4.3D: Using Solubility Data

2.2.4.3E: Experimentally Testing Solvents

2.2.4.3F: Mixed Solvents

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2.2.4.3A: Ideal Temperature Profile

The crystallization procedure is possible as most solids tend to **become more soluble in solvents as their temperature is increased** (Figure 3.7 shows a yellow solid dissolving in ethanol as the temperature increases on a hotplate).

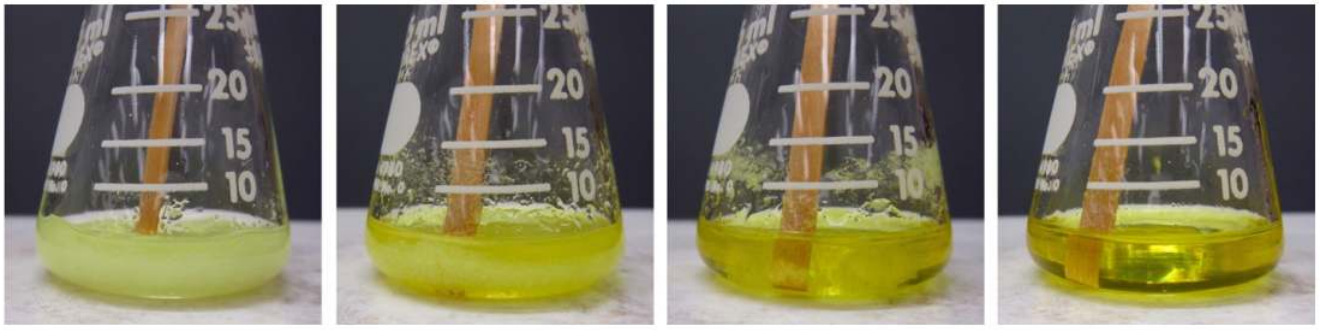


Figure 3.7: Time-lapse dissolving of benzil (yellow solid) in ethanol as the temperature increases on a hotplate. The boiling stick is used for bump prevention.

Caffeine is a white solid that follows this usual patter, as 1 gram of caffeine dissolves in **46 mL** of room temperature water, **5.5 mL** of **80°C** water, and **1.5 mL** of boiling water.[2] If you have ever had a difficult time cleaning solidified starch residue from a kitchen colander (perhaps after you have strained pasta water), you may have learned that the colander is more easily cleaned in hot water than cold. Starch has an increased solubility in hot water, and this trend in solubility is partly what makes a dishwasher so effective.

The solubility profile of compounds is an empirical determination. Some solids increase solubility regularly with temperature (Figure 3.8a), and others increase in an exponential fashion (Figure 3.8b). In unusual cases, a solid's solubility can decrease with temperature. For the best crystallization, **the compound should be very soluble in the hot solvent and minimally soluble (or insoluble) in the cold solvent**.

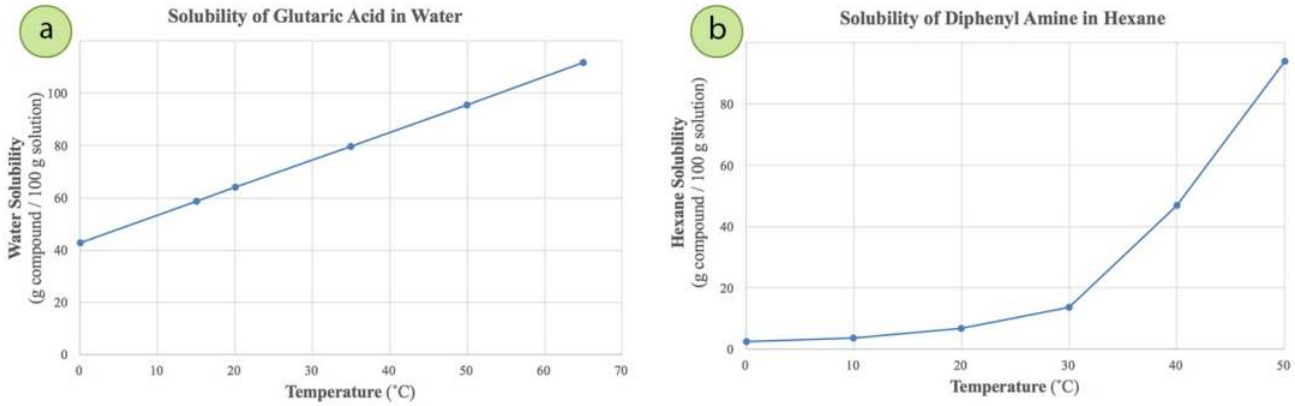


Figure 3.8: Graphs of solubility versus temperature data for glutaric acid in water (left) and diphenyl amine in hexane (right).[3] In both sets, solubility increases with temperature. Note that glutaric acid could not be crystallized from water, as it is highly soluble even at cold temperatures.

[2]From: *The Merck Index*, 12th edition, Merck Research Laboratories, **1996**.

[3]Data from: A. Seidell, *Solubilities of Inorganic and Organic Substances*, D. Van Nostrand Company, **1907**.

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2.2.4.3B: General Procedures for Removing Impurities

Crystallization works well as a purification technique if impurities are present in very small quantities (less than 5 mol% of the solid), or if the impurities have a very different solubility profile from the desired compound. Impurities can be easily removed if they are either *much more* soluble or *much less* soluble in the solvent than the compound of interest.

Figure 3.9 shows the procedural sequence used to remove a "**soluble impurity**" from an impure soled, meaning an impurity that is embedded in the crystalline matrix, but would be completely soluble in the crystallization solvent. The impure solid is first fully dissolved in the minimum amount of hot solvent to liberate impurities trapped in the solid's interior. Upon cooling, a completely soluble impurity will remain dissolved in the mother liquor while the desired compound crystallizes. The crystallized solid can then be collected by suction filtration.

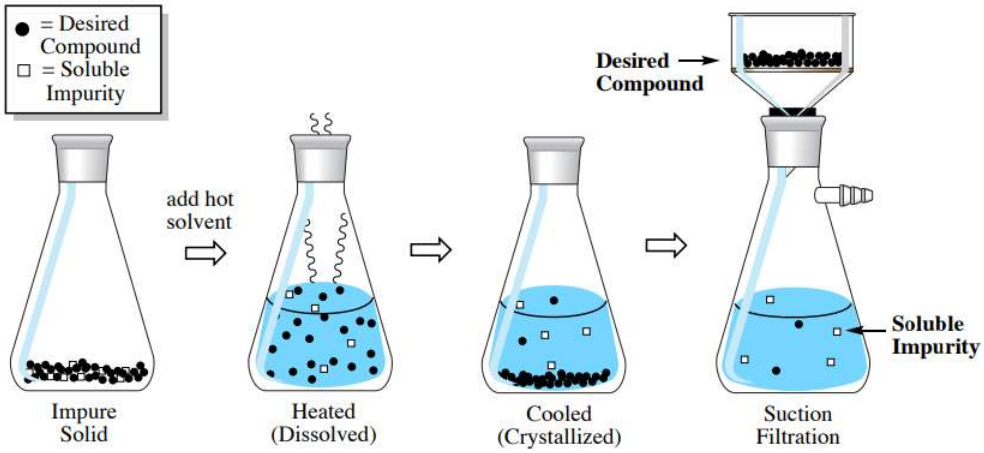


Figure 3.9: Crystallization sequence in order to remove a soluble impurity, using black circles and white squares to represent individual particles. As in reality individual particles are too small to see, the liquids in each of these scenarios would appear completely transparent.

Figure 3.10 shows the procedural sequence used to remove an "**insoluble impurity**" from an impure solid, meaning an impurity that is embedded in the crystalline matrix, but would be insoluble in the crystallization solvent. The impure solid is heated in the minimum amount of hot solvent needed to dissolve the desired compound. The insoluble material is then filtered while the solution is kept hot (called "hot filtration"), and then the desired compound is crystallized and collected by suction filtration.

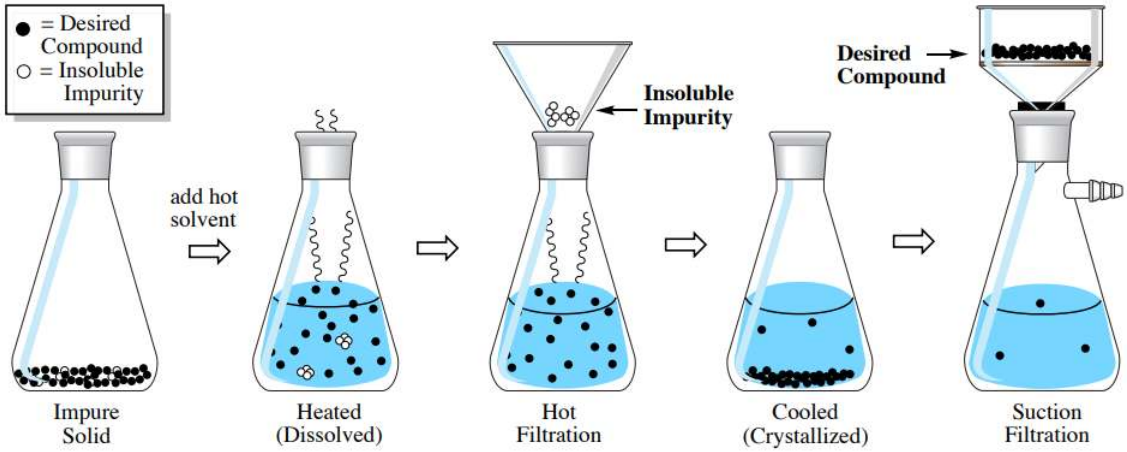


Figure 3.10: Crystallization sequence to remove an insoluble impurity. In the second flask, the white circles aggregate as an insoluble material, while the black circles are dispersed and therefore dissolved and invisible.

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2.2.4.3C: Determining Which Solvent to Use

The most important factor in the success of crystallization is probably the chosen solvent. Besides having the crucial solubility properties for crystallization (the compound should be soluble in the hot solvent and as insoluble as possible in the cold solvent), there are other factors that determine an appropriate solvent.

An ideal crystallization solvent should be unreactive, inexpensive, and have low toxicity. It is also important that the solvent have a relatively low boiling point (b.p. often $< 100°C$ as it's best if the solvent readily evaporates from the solid once recovered. Table 3.1 shows a list of common solvents used with crystallization. Toluene has the highest boiling point ($111°C$) of the list, and should be avoided if alternatives exist for this reason (as well as its toxicity and smell). Along with fast evaporation, a relatively low boiling solvent is also ideal for crystallization as it minimizes the probability of a compound "oiling out", where material comes out of solution above its melting point and forms a liquid instead of a solid. When a compound liquefies first, it rarely crystallizes well.

Table 3.1: Boiling point of common solvents in crystallization. Note: petroleum ether is a mixture of hydrocarbons, and is very nonpolar. The term "ether" comes from its volatility, not the functional groups present.

Solvent	Boiling Point (°C)
Diethyl ether	35
Acetone	56
Petroleum Ether (low boiling)	30-60
Ligroin (high boiling petroleum ether)	60-90
Methanol	65
Hexanes	69
Athyl acetate	77
Ethanol	78
Water	100
Toluene	111

Solvents with very low boiling points (e.g. diethyl ether, acetone, and low-boiling petroleum ether) are highly flammable and can be difficult to work with as they readily evaporate. They can still be used with care, but if alternatives exist, they are often preferable.

There are some general trends in predicting the appropriate solvent for a particular compound. As the compound needs to be soluble in the boiling solvent, it helps if the compound and solvent have similar intermolecular forces. For example, if a compound can hydrogen bond (alcohols, carboxylic acids, and amines), it sometimes can be crystallized from water. If a compound has moderate polarity it sometimes is crystallized from ethanol. If a compound is mostly nonpolar, it sometimes is crystallized from petroleum ether or hexanes, or may require a mixed solvent.

As it can be difficult to predict the ideal solvent for crystallization, often a published procedure from a journal article will indicate the appropriate solvent. If no solvent is listed, an appropriate solvent can be predicted using solubility data (next section), determined experimentally, or chosen from Perrin's *Purification of Organic Chemicals*,[4] a reference book which lists purification procedures for roughly 5700 known compounds.

[4]D.D. Perrin, W.L.F. Armarego, *Purification of Organic Chemicals*, Pergamon Press, 3rd edition, **1988**.

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2.2.4.3D: Using Solubility Data

If you are not following a procedure where a crystallization solvent has been specified, it may be helpful to consult solubility data for the desired compound. Qualitative (and sometimes quantitative) solubility data can be found for many compounds in the CRC[5] and Merck Index.[6]

If the goal is to use just one solvent for crystallization, it's best to look for a solvent in which the desired compound is slightly soluble. Although the percent recovery will be less than 100% (a portion will remain in the mother liquid), there is a good chance that a slightly soluble solid will dissolve when heated. It is possible that solvents listed as insoluble will not dissolve the compound at any temperature.

For example, below are entries in the CRC and Merck Index for the compound 1,4-dinitrobenzene:

- *CRC Handbook:* "i $\mathbf{H_2O}$; sl $\mathbf{EtOH}$, chl; s ace, bz, tol" Translation: The compound is insoluble in water; slightly soluble in ethanol and chloroform; and soluble in acetone, benzene, and toluene.
- *Merck Index:* "White crystals. . . one gram dissolves in $\mathbf{12,500\ mL}$ cold water, $\mathbf{555\ mL}$ boiling water, $\mathbf{300\ mL}$ alcohol; sparingly soluble in benzene, chloroform, ethyl acetate." Translation: The compound is very insoluble in cold water, but much more soluble in hot water. It is slightly soluble in ethanol, and basically insoluble in benzene, chloroform, and ethyl acetate.

1,4-dinitrobenzene is slightly soluble in ethanol, making it a good "first guess" as a crystallization solvent. Indeed Perrin's *Purification of Organic Chemicals*[7] recommends crystallization of 1,4-dinitrobenzene using ethanol or ethyl acetate.

[5]*Handbook of Chemistry and Physics*, CRC Press, 84^\text{th}\) edition, **2003-2004**.

[6]*The Merck Index*, Merck Research Laboratories, 12$^{\mathbf{th}}$ edition, **1996**.

[7]D.D. Perrin, W.L.F. Armarego, *Purification of Organic Chemicals*, Pergamon Press, 3$^{\mathbf{rd}}$ edition, **1988**.

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2.2.4.3E: Experimentally Testing Solvents

To experimentally determine a single solvent for crystallization, use the following procedure. A flow chart describing this process is shown in Figure 3.11.

- Place **100 mg** of the solid to be crystallized in a test tube and add **3 mL** of solvent. (These quantities correspond with the usual guideline of solubility, where a compound is deemed "soluble" if **3 g** of compound dissolves in **100 mL** solvent.) Note: quantities may be scaled back depending on compound availability.
- While holding the test tube by the top, flick the tube to vigorously mix the contents.
- If the solid completely dissolves at room temperature, the solvent will not work for crystallization since it needs to be insoluble when cold. If the solid appears to remain insoluble, the solvent may work.
- Bring the solid suspended in the solvent to a boil using a steam bath or hot water bath. If the solid dissolves when the solvent is boiling, it may work for crystallization since it needs to be soluble when hot. If it never dissolves in the hot solvent, the solvent won't work.
- If the solid dissolves in the hot solvent, allow it to cool to room temperature, and then submerge it in an ice bath for 10-20 minutes. If most of the crystals return, the solvent should work for crystallization. If few or no crystals return, try to scratch the flask with a glass stirring rod to initiate crystallization. If crystals still don't return, the solvent won't work for crystallization.

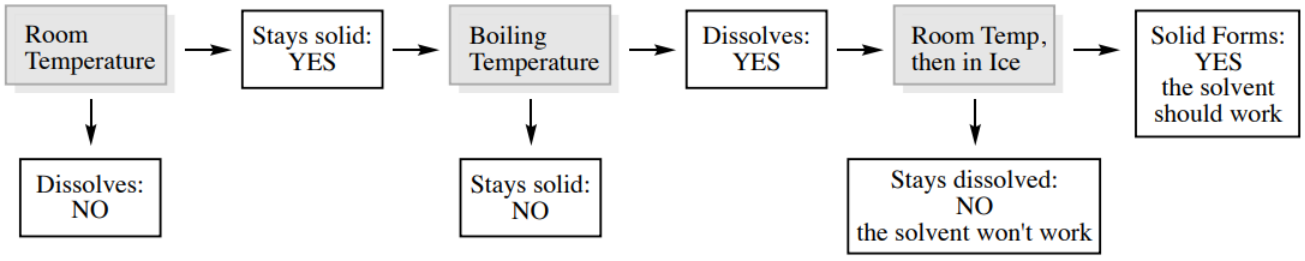


Figure 3.11: Flow chart for testing a crystallization solvent by mixing solid and solvent, as described on this page.

This testing procedure is shown for **N**-bromosuccinimide in Figure 3.12, using water as the solvent.

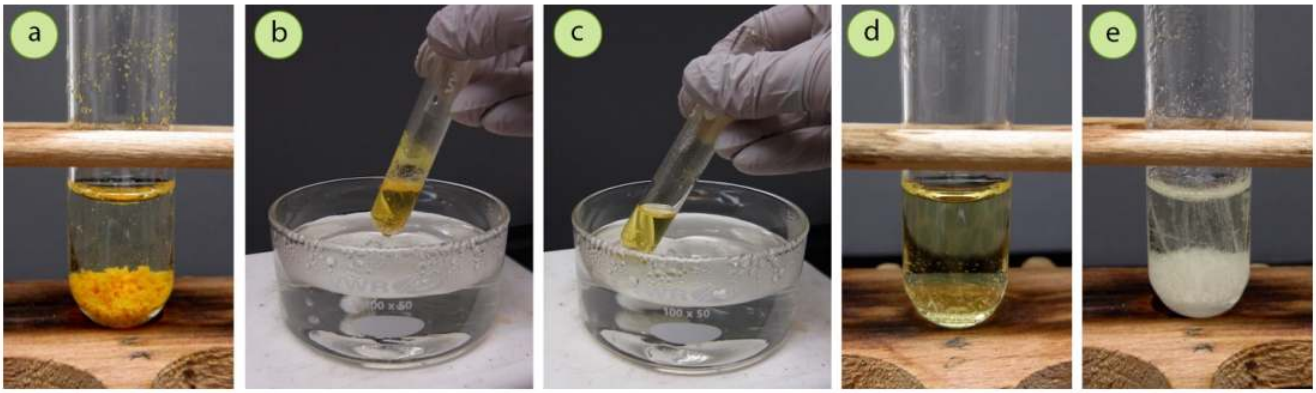


Figure 3.12: Testing the crystallization of **N**-bromosuccinimide (NBS) using water: a) NBS insoluble in cold water, b+c) Dissolving NBS in hot water, d+e) Cooling and crystallization (ice bath was not needed, as crystals returned).

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2.2.4.3F: Mixed Solvents

When no single solvent can be found that meets all of the criteria for crystallization, it may be possible to use a mixed solvent. A pair of solvents is chosen: one in which the compound is soluble (called the "**soluble solvent**"), and one in which the compound is insoluble (called the "**insoluble solvent**"). The two solvents must be miscible in one another so that their solubility with one another does not limit the proportions used. Table 3.2 shows a list of common mixed solvents used in crystallization.

Table 3.2: Common mixed solvent pairs in crystallization.

Solvent Pair
Methanol / Water
Ethanol / Water
Acetone / Water
Methanol / Diethyl ether
Petroleum Ether (or hexanes) / Diethyl ether
Hexanes / Ethyl acetate

To perform a crystallization using a mixed solvent, the solid to be crystallized is first dissolved in the minimum amount of hot "soluble solvent", then hot "insoluble solvent" is added dropwise until the solution becomes slightly cloudy. An additional small portion of hot soluble solvent is then added to clarify the solution, and the solution is set aside to slowly cool and crystallize. A diagram describing this process is shown in Figure 3.13.

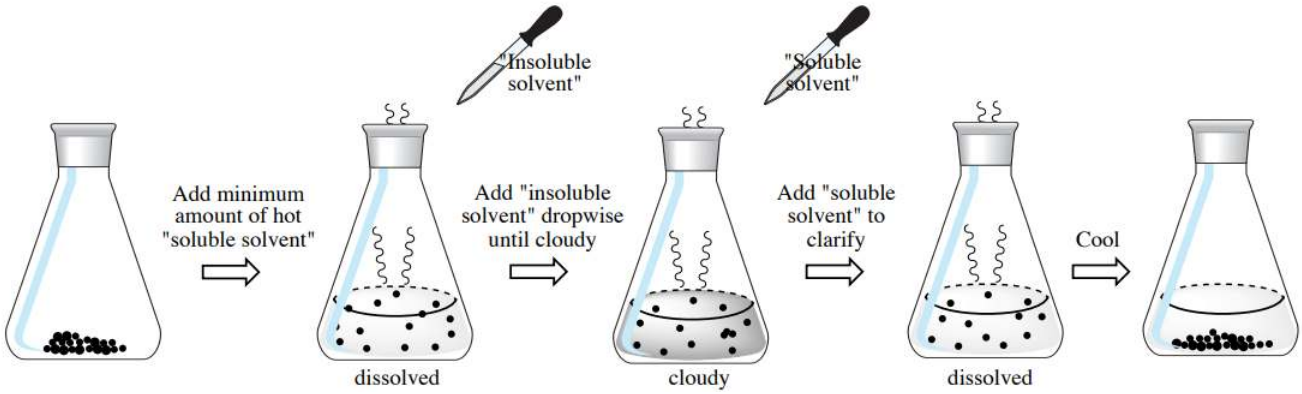


Figure 3.13: Schematic for using a mixed solvent in crystallization.

Although this procedure can produce good results, when possible it is often best to use a single solvent for crystallization. As a mixed solvent is heated, the composition can change as the solvents evaporate at different rates, which can affect the solubility of the compound in the mixed solvent. Also, crystallizations from mixed solvents sometimes "oil out", where the dissolved compound comes out of solution above its melting point and forms a liquid instead of a solid.

To test a mixed solvent for crystallization, use the procedure that follows. This process is demonstrated by crystallizing *trans*-cinnamic acid from a mixed solvent of water and methanol (Figures 3.14 + 3.15).

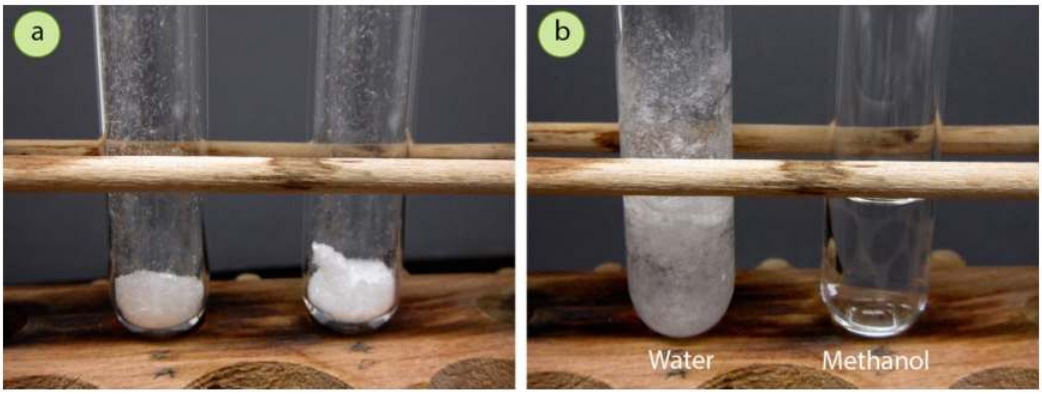


Figure 3.14: a) **100 mg** of trans-cinnamic acid in each test tube, b) Left tube contains trans-*cinnamic acid with water (insoluble) and right tube contains* trans-*cinnamic acid with methanol (soluble).*

1. Use the previously described method (**100 mg** compound in **3 mL** solvent), to find a pair of solvents: one solvent in which the compound is soluble and one solvent in which the compound is insoluble (Figure 3.14). The solvents must be miscible with one another.
2. Place a fresh **100 mg** of the solid to be crystallized in a test tube and add the "soluble solvent" dropwise while heating (with a steam bath or hot water bath, Figure 3.15a) until the solid just dissolves. The suspension should be immersed in the heat source after each drop, and some time should be allowed in between additions for the sometimes slow dissolving process.
3. Add the "insoluble solvent" dropwise while heating until the solution becomes faintly cloudy (Figure 3.15c).
4. Add the "soluble solvent" dropwise while heating until the solution is clarified (clear).
5. Allow the system to cool to room temperature (Figure 3.15e), and then submerge in an ice bath for 10-20 minutes. If crystals return, the mixed solvent may work for the crystallization.

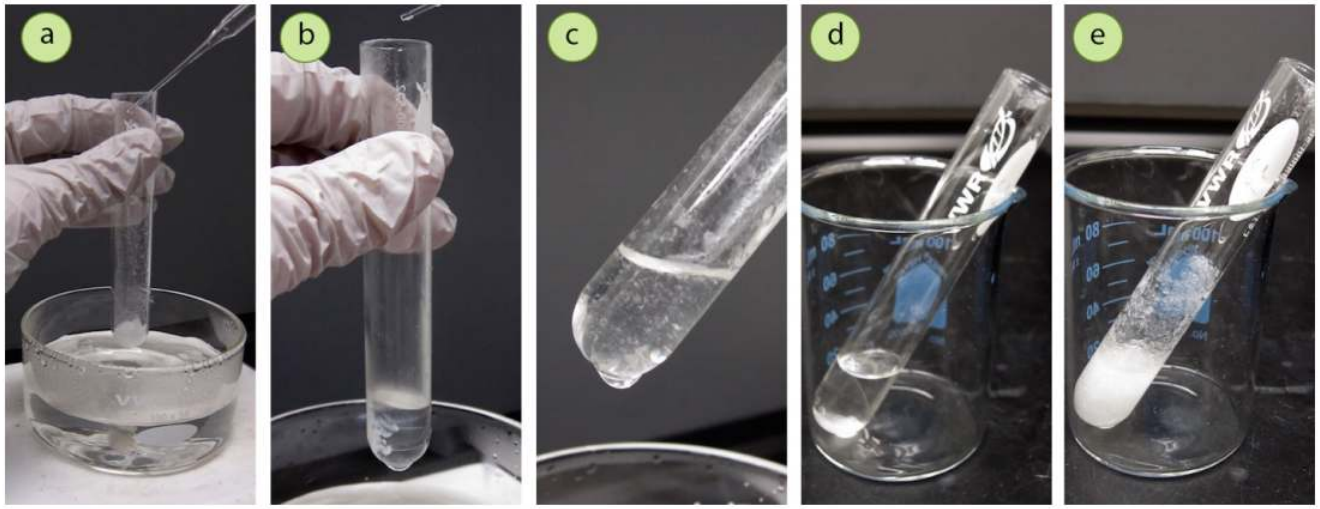


Figure 3.15: a) Addition of methanol (soluble solvent) to trans-cinnamic acid, b) Addition of water (insoluble solvent) to the solution, c) Sustained cloudiness/fine crystals after enough water was added, d) Tube set aside to cool after a few drops of methanol were added to clarify the solution, e) The return of crystals after cooling.

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SECTION OVERVIEW

2.2.4.4: Crystallization Theory

2.2.4.4A: Purification

2.2.4.4B: Cooling Slowly

2.2.4.4C: Using the Minimum Amount of Hot Solvent

2.2.4.4D: The Unavoidable Loss of Recovery

2.2.4.4E: Quantitating Crystallization

2.2.4.4F: Second Crop Crystallization

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2.2.4.4A: Purification

Crystallization is an excellent purification technique for solids because a crystal slowly forming from a saturated solution tends to selectively incorporate particles of the same type into its crystal structure (a model of a crystal lattice is in Figure 3.16a). A pure crystal is often slightly lower in energy than an impure crystal (or has a higher lattice energy), as packing identical particles into a lattice allows for maximized intermolecular forces.

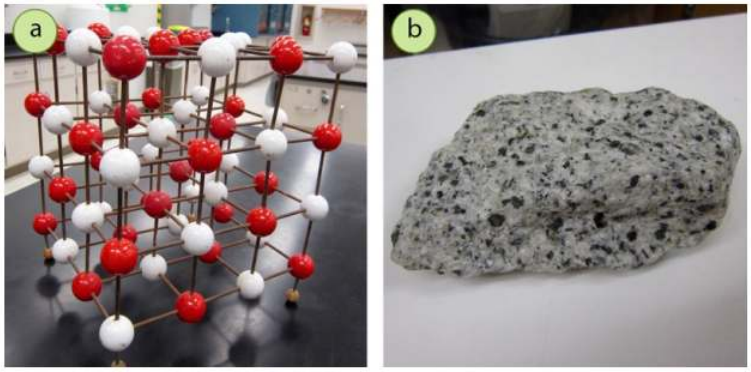


Figure 3.16: a) An example of a crystal lattice (this model is of NaCl), b) Granite, a heterogeneous rock.

If an impurity is smaller than the majority of particles in a crystal lattice, there may be a "dead space" around the impurity, resulting in a region with unrealized intermolecular forces. If the impurity is larger than the other particles, it may instead disrupt intermolecular forces by forcing other particles in the lattice out of alignment.

A developing solid will tend to incorporate particles of the same type in order to create the lowest energy solid, and exclude impurities that disrupt the idealized packing of the solid. This process works best if the impurity is present as a minor component of the crude solid. When higher quantities of impurities are present, the resulting crystal tends to be heterogeneous, with pure regions of compound and pure regions of "impurity" intermixed with impure regions. This sort of heterogeneity is often seen in the crystallization of minerals (Figure 3.16b).

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2.2.4.4B: Cooling Slowly

The difference in crystal lattice energy between pure and impure solids is marginal, so a solution must be cooled SLOWLY to allow for differentiation. If a hot solution is plunged immediately into an ice bath, the system will favor the formation of a solid (any solid!) so strongly that there may be little preference for purity. Impurities can become engulfed in the developing solid and trapped as solutes are deposited unselectively onto the growing solid. It is only when enough time is allowed for equilibration between the developing solid and the solution that the lowest energy pure solid is formed.

As a metaphor for the slow crystallization process, imagine that you have won a prize and are allowed to go into a tube, where money in the form of $1 and $100 bills will be blown around for you to grab. The prize rules state that you're only allowed to keep a total of twenty bills. Imagine you are given just 30 seconds in the money tube to grab twenty bills: you would likely grab whatever bills you can get your hands on, and hope that most of them are $100 bills. If instead given more time in the money tube (perhaps 10 minutes), you could be less frenzied and more selective about choosing $100 bills while excluding $1 bills.

In a similar way, the crystallization process can be though of as the crystal lattice "grabbing" solutes from solution. If the process is hurried, solutes may be "grabbed" indiscriminately, and once embedded in the interior of the solid they become trapped as the equilibrium between solid and solution happens only on the surface.

Along with increased purity, a slow crystallization process also encourages the growth of larger crystals. Figure 3.17 shows crystallization of acetanilide from water with two different rates. The crystals grown in Figure 3.17a were formed much more quickly, and are smaller than the slower grown, larger crystals in Figure 3.17b.



Figure 3.17: a) These crystals of acetanilide formed from water are perfectly acceptable, but small, b) These crystals of acetanilide were grown much more slowly, and are larger (note crystal indicated with the arrow).

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There are several benefits to larger crystals. Most importantly they tend to be purer than small crystals. They also have a lower surface area exposed to the mother liquid, which makes washing of the crystals more effective. Finally, they are more easily collected by suction filtration (Figure 3.18), as very small crystals may pass through or wedge themselves into the pores of the filter paper, preventing solvent from easily trickling through and leading to crystals that are irrecoverable.



Figure 3.18: Suction filtration.

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2.2.4.4C: Using the Minimum Amount of Hot Solvent

The quantity of solvent used in crystallization is usually kept to a minimum, to support the goal of recovering the **maximum amount of crystals**.

Every solid has partial solubility in the solvents used, even at cold temperatures. In Figure 3.19 the cold solvent surrounding a yellow solid is tinted yellow as some compound dissolves. Solids that appear insoluble in a solvent do in fact have a (normally small) portion of material that dissolves. This is analogous to how "water-insoluble" ionic compounds (such as AgCl have a non-zero solubility product constant (K_{sp}).



Figure 3.19: Yellow solid (benzil) in contact with cold ethanol.

Crystallization is most common with solids that have moderate solubility at low temperatures, so that heat can "tip them over the edge" to completely dissolve. This means that in practice there *will* be a quantity of compound that dissolves in the mother liquor at low temperatures, which can be significant depending on the compound's solubility profile. Use of the minimal amount of hot solvent lessens the quantity of compound that is lost to the mother liquor.

To demonstrate the importance of using the minimum amount of hot solvent during a crystallization, **imagine you are to crystallize 5.0 g 2-furoic acid using hot water**.[8] The calculations from this example are described below, and summarized in Figure 3.21.

2-furoic acid has an increased solubility in boiling water compared to cold water, as shown by the solubility data in Figure 3.20. The quantity of hot solvent needed to dissolve this sample can be calculated using the compound's solubility in hot water, as shown below. This represents the "minimum amount of hot solvent" needed for the crystallization.

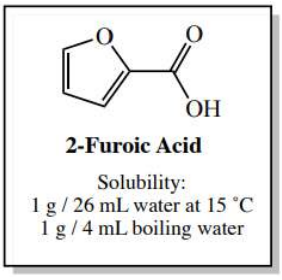


Figure 3.20: Solubility data for 2-furoic acid (Merck Index).

$$\mathbf{5.0\ g\ 2\text{-furoic acid\ (FA)} \times \frac{4\ mL\ hot\ water}{1\ g\ FA} = 20.\ mL\ hot\ water} \qquad (2.2.4.4C.1)$$

When the 2-furoic acid is dissolved in $\mathbf{20\ mL}$ of hot water and is allowed to cool, the compound will crystallize as it has a lower solubility in the cold solvent. Ideally the solution would be placed in an ice bath ($\mathbf{0°C}$), but as $\mathbf{0°C}$ solubility data is not provided, let's imagine the solution is cooled to $\mathbf{15°C}$. The solubility of 2-furoic acid in this cold water is as follows.

$$\mathbf{20.\ mL\ cold\ water \times \frac{1\ g\ FA}{26\ mL\ cold\ water} = 0.77\ g\ FA\ dissolves\ in\ 15°C\ water} \qquad (2.2.4.4C.2)$$

This calculation shows that a portion of the 2-furoic acid will remain dissolved in the mother liquor even when placed in the cold bath. Any compound present that exceeds this quantity will crystallize, in this case $4.2\ \text{g}$ of 2-furoic acid $(5.0\ \text{g} - 0.77\ \text{g})$. Note that because of the loss of material to the mother liquor, the maximum theoretical recovery from this process is only 84% $(100 \times 4.2\ \text{g}/5.0\ \text{g})$.

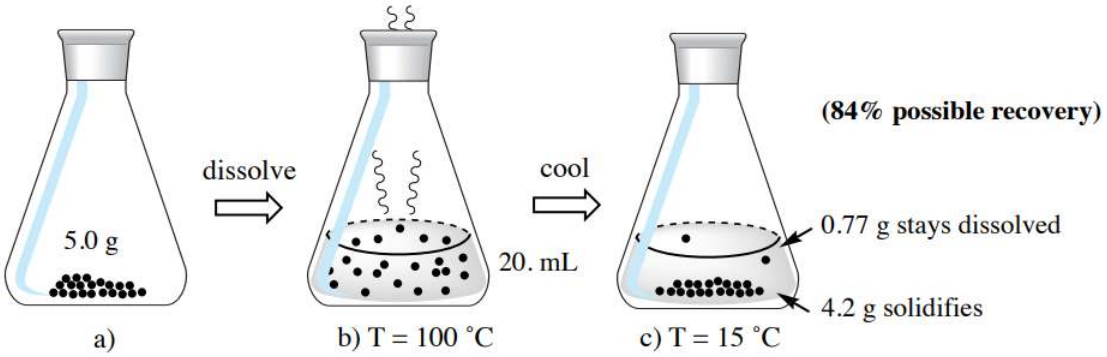


Figure 3.21: Calculations using the minimum amount of hot water to dissolve $5.0\ \text{g}$ of 2-furoic acid.

Next imagine that instead of using the minimum amount of hot solvent, we use **double the volume of hot solvent** ($40\ \text{mL}$ in this example). The calculations from this example are described below, and summarized in Figure 3.22.

When the solvent volume is doubled, the quantity of material dissolved in the mother liquor also doubles, as shown in the calculation below.

$$40.\ \text{mL cold water} \times \frac{1\ \text{g FA}}{26\ \text{mL cold water}} = 1.5\ \text{g FA dissolves in } 15^{\circ}\text{C water} \qquad (2.2.4.4\text{C}.3)$$

If a $5.0\ \text{g}$ sample of 2-furoic acid were instead dissolved in $40\ \text{mL}$ (double the minimal amount of hot solvent necessary), only $3.5\ \text{g}$ would crystallize $(5.0\ \text{g} - 1.5\ \text{g})$. The maximum theoretical recovery for this process is only 70%.

Notice when additional solvent is used than the minimum, more compound is soluble in the solvent and lost to the mother liquor, leading to a lower theoretical recovery.

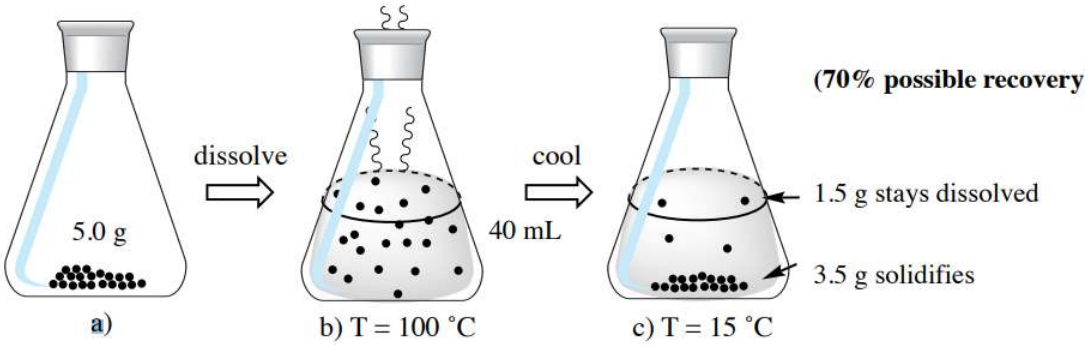


Figure 3.22: Calculations using twice the volume of hot water as the minimum amount needed to dissolve $5.0\ \text{g}$ of 2-furoic acid.

As you might imagine, there is also a quantity of solvent in which the *entire* $5.0\ \text{g}$ sample of 2-furoic acid dissolves (in this case $130\ \text{mL}$, see calculation below). If $130\ \text{mL}$ were used for the crystallization instead of the minimal amount of hot solvent, *no* crystals would form at all when cooled to 15°C (0% recovery). Thus the quantity of solvent used in crystallization should be monitored and restricted when possible.

$$5.0\ \text{g FA (2-furoic acid)} \times \frac{26\ \text{mL cold water}}{1\ \text{g FA}} = 130\ \text{mL of } 15^{\circ}\text{C water dissolves the whole sample} \qquad (2.2.4.4\text{C}.4)$$

To demonstrate the importance of using the minimum amount of hot solvent, two samples of benzil (each roughly $1.8\ \text{g}$), were crystallized from hot ethanol (Figure 3.23). The first was dissolved in the minimum amount of hot solvent (approximately $8\ \text{mL}$), and resulted in a 92% recovery after crystallization. The second was dissolved in roughly double the quantity of hot solvent

(approximately **15 mL**) and resulted in an **87%** recovery. The solubility profile of benzil led to an excellent recovery in both trials, but the recovery was compromised somewhat when an excess of solvent was used.

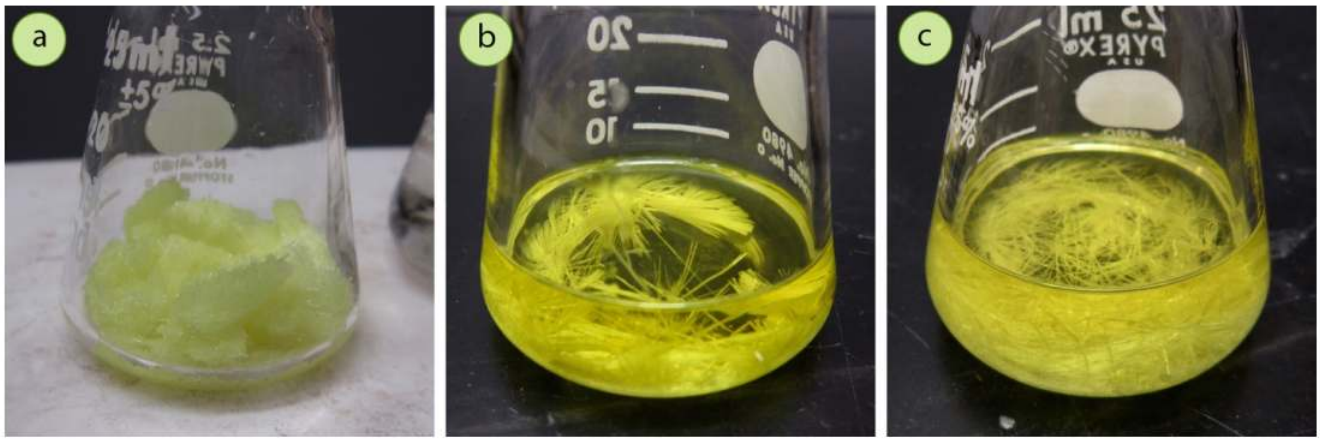


Figure 3.23: a) Original sample of benzil **(1.8 g)**, b) Crystallization using the minimum amount of hot ethanol needed to dissolve the sample, c) Crystallization using double the minimal amount of hot solvent.

[8] As recommended in D.D. Perrin, W.L.F. Armarego, *Purification of Organic Chemicals*, Pergamon Press, 3rd edition, **1988**.

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2.2.4.4D: The Unavoidable Loss of Recovery

A loss of recovery should be expected when performing a crystallization. Although there are ways to maximize the return of crystals, a portion of the desired compound will always be lost. The reasons for this are both inherent to the design of the process and mechanical.

As previously discussed, a portion of the compound of interest will remain dissolved in the mother liquor and be filtered away. Figure 3.24 shows suction filtration in order to recover benzil (a yellow solid) that had been crystallized from ethanol. In Figure 3.24c it is apparent that the **filtrate** is also yellow (the liquid that has passed through the filter paper), making it obvious that some benzil remained dissolved in the solvent. Further evidence that some compound is always lost to the mother liquor can be seen when solvent evaporates from drips on glassware or the benchtop, revealing residual solid (Figure 3.25a+b).

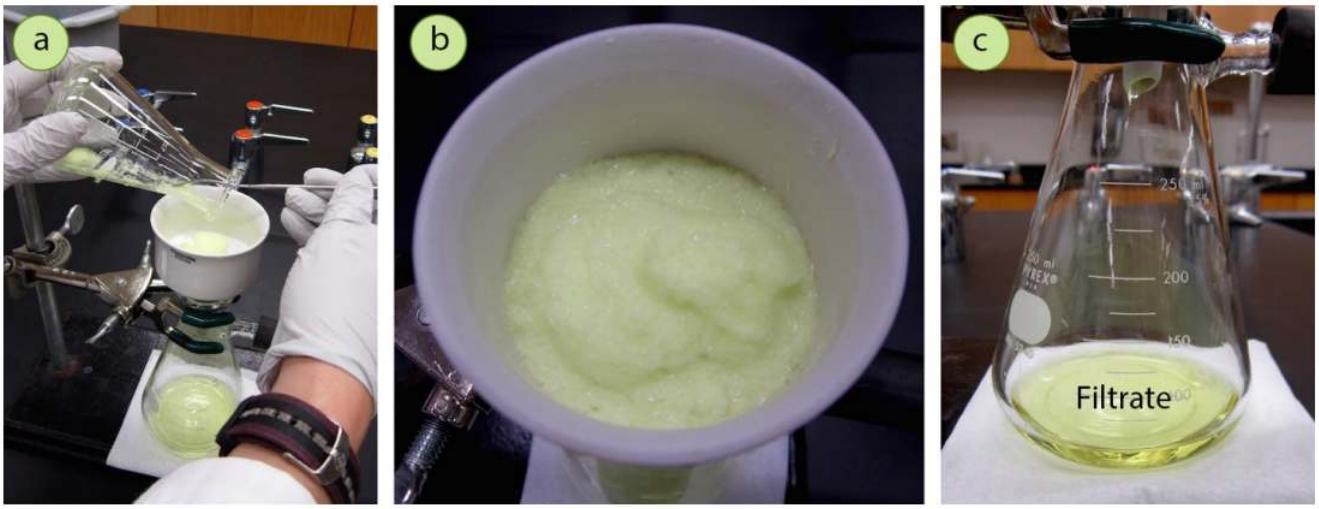


Figure 3.24: Loss of yield due to the solubility of compound in the cold solvent: a) Suction filtration, b) Recovered yellow solid, c) Yellow filtrate, indicating some yellow compound remained dissolved in the mother liquor.

The loss of solid material can also be witnessed with every manipulation of the solid. Only the *majority* of the crystals can be delicately scraped off the glassware, Buchner funnel, and filter paper, and there will always be a residue that is left behind (Figure 3.25c).



Figure 3.25: a) Streak of solid (benzoic acid) from an evaporated drip on the outside of a flask, b) A magnificent crystal pattern from an evaporated drip on the benchtop, c) Residual solid (benzil) on a flask after collection by suction filtration.

When there is such an obvious loss of yield from solid clinging to glassware, it may seem wise to use solvent to rinse additional solid out of the flasks. A few rinses with cold solvent are indeed recommended, but it is not recommended to use solvent

excessively in an attempt to recover every granule of solid. The more solvent that is used, the more compound will dissolve in the cold mother liquor, decreasing the yield. The loss of material due to residue on the glassware is an unfortunate, but accepted aspect of this technique.

To demonstrate the loss of yield with crystallization, several pure samples of acetanilide and benzil were crystallized. Using pure samples allowed for any loss of material to be only due to the solubility in the mother liquor and adhesion to the glassware, not by the exclusion of impurities, which also have mass. From many trials of crystallizing acetanilide from hot water using different scales (between **0.5 g-1.5 g** each time), the recoveries were surprisingly consistent, between **60-65%** (Figure 3-26). From many trials of crystallizing benzil from hot ethanol using different scales (between **0.5 g-4.5 g** each time), the recoveries were also quite consistent, between **87-92%** (benzil is the yellow solid in Figure 3.24). In all situations, the recovery of solid was never **100%**. Also, the typical recovery for the two systems was different, with the most logical explanation being that there was a larger percentage of compound lost to the mother liquor with acetanilide than with benzil.



Figure 3.26: Crystallized acetanilide.

It is common for new organic chemistry students to be disappointed by a low yield (anything less than **95%**!), and to worry that it is somehow their fault. Students are often inclined to cite "user error" as a main cause for a loss of yield in any process. Although spilling solid on the benchtop or addition of too much solvent will of course compromise the yield, the modest recovery of acetanilide in this section should demonstrate that sometimes low yields are inherent to the process and the chosen solvent.

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2.2.4.4E: Quantitating Crystallization

In this section, real solubility data for compounds is used to quantitatively describe the purification of impure solids that contain either a "soluble impurity" or an impurity with similar solubility to the compound of interest.

With a "Soluble Impurity"

The simplest crystallization in terms of purification is when an impurity is very soluble in the cold solvent while the compound of interest is not (see procedural sequence in Figure 3.27). In this situation, the impurity is trapped in the crystal matrix of the impure solid, and needs only be liberated by dissolution. After adding hot solvent to dissolve the impure solid then cooling, the soluble impurity remains dissolved in the mother liquor while the compound of interest crystallizes and can be collected by suction filtration.

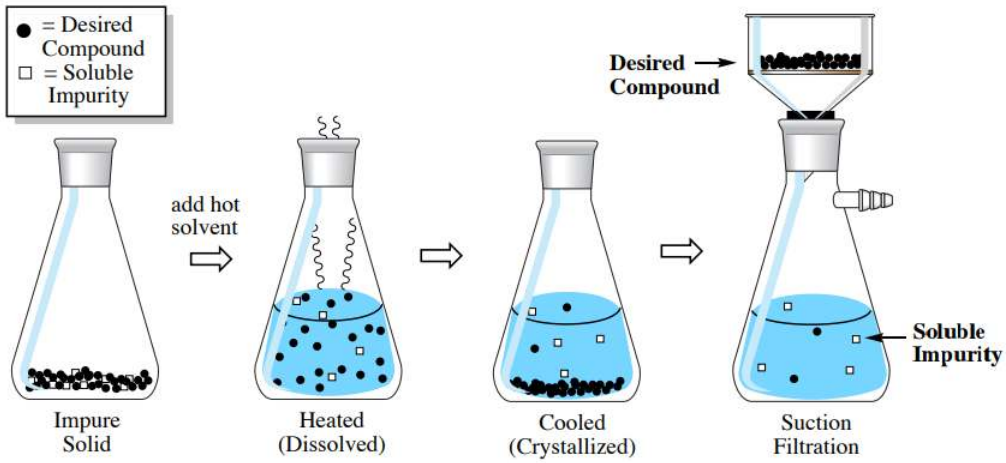


Figure 3.27: Crystallization sequence to remove a soluble impurity.

An example of this type of system is a sample containing **4.00 g acenapthene and 0.50 g acetanilide**. According to Perrin's *Purification of Organic Compounds*,[9] acenapthene can be purified by crystallization using ethanol, and even though this sample contains a considerable quantity of acetanilide impurity (**13 mol%**), the calculations in this section will show that this process should work well.

The solubility values of acenapthene and acetanilide in ethanol are shown in Figure 3.28.

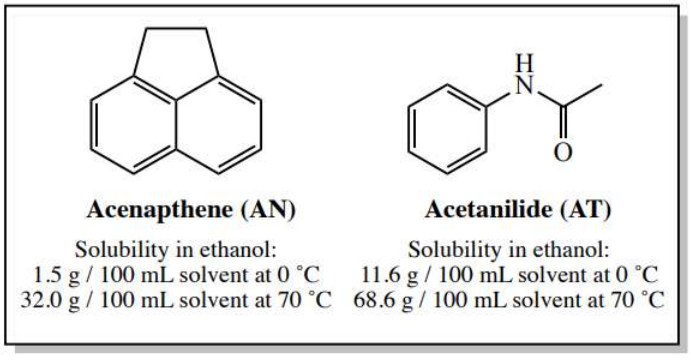


Figure 3.28: Ethanol solubility for acenapthene and acetanilide.[10]

4.00 g of pure acenapthene (AN) should completely dissolve in **12.5 mL** (see calculation below) of nearly boiling ethanol (the boiling point of ethanol is **78°C**).[11]

$$\mathbf{4.00\ g\ Acenapthene\ (AN)} \times \frac{\mathbf{100\ mL\ hot\ ethanol}}{\mathbf{32.0\ g\ AN}} = \mathbf{12.5\ mL\ hot\ ethanol\ (70°C)\ to\ dissolve} \qquad (2.2.4.4E.1)$$

Since acetanilide (AT) is more soluble than acenapthene at this temperature (see Figure 3.28), it should also completely dissolve in **12.5 mL** of hot ethanol.

If the hot ethanolic solution containing these two components is then cooled in an ice bath, acenapthene should crystallize as it has low solubility in cold ethanol. The calculation below shows how much acenapthene would remain dissolved in the cold ethanol (**0.19 g**). Any quantity of acenapthene present greater than **0.19 g** would form a solid, in this case **3.81 g** (**4.00 g − 0.19 g**).

$$\begin{aligned} &12.5\ \text{mL cold ethanol} \times \frac{1.5\ \text{g acenapthene (AN)}}{100\ \text{mL cold ethanol}} \\ &= \mathbf{0.19\ g\ AN}\ \text{remains dissolved in 0°C ethanol} \end{aligned} \tag{2.2.4.4E.2}$$

The acetanilide impurity, however, should not crystallize. The calculation below shows that **1.45 g** of acetanilide can dissolve in the cold ethanol, and since only **0.50 g** was originally present, the entire portion would remain dissolved.

$$\begin{aligned} &12.5\ \text{mL cold ethanol} \times \frac{11.6\ \text{g AT}}{100\ \text{mL cold ethanol}} \\ &= \mathbf{1.45\ g\ AT}\ \text{can dissolve in 0°C ethanol} \end{aligned} \tag{2.2.4.4E.3}$$

This process is summarized in Figure 3.29. As only the acenapthene crystallizes, it could be collected through filtration and separated from the acetanilide impurity in the mother liquor.

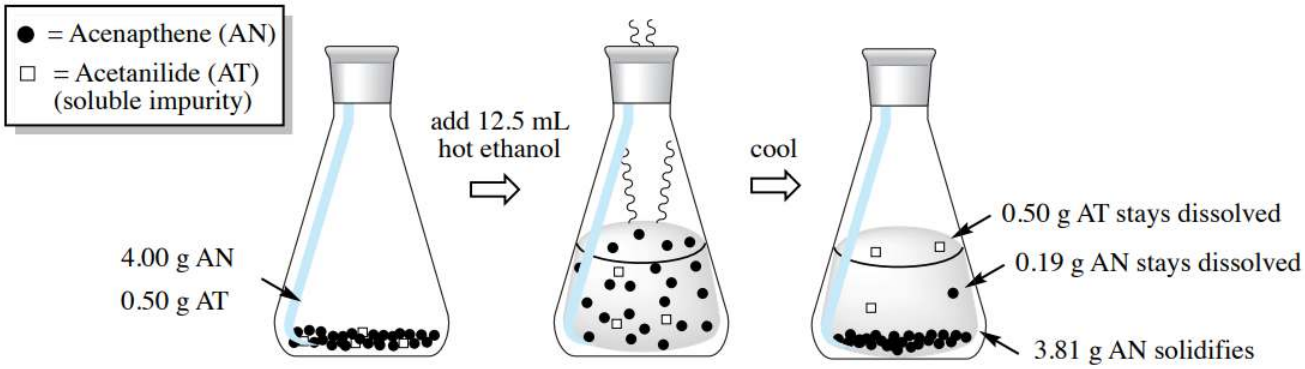


Figure 3.29: Crystallization of an impure sample containing **4.00 g** acenapthene and **0.50 g** acetanilide from nearly boiling ethanol. This represents a crystallization with a "soluble" impurity.

Purification of this mixture works well in theory because the acetanilide is so much more soluble (approximately ten times as much) in the cold ethanol than the acenapthene, and so can be removed. In practice if the crystallization is done too quickly, there is still the possibility of acetanilide being incorporated into the developing solid.

With an Impurity of Similar Solubility

If an impure solid contains an impurity that has similar solubility properties as the desired compound, it is still possible to purify the mixture through crystallization if the impurity is present in a small amount. An example is a sample containing **4.00 g acenapthene and 0.30 g phenanthrene** (phenanthrene is **6 mol%** of the sample). The solubility of these compounds in ethanol is shown in Figure 3.30.

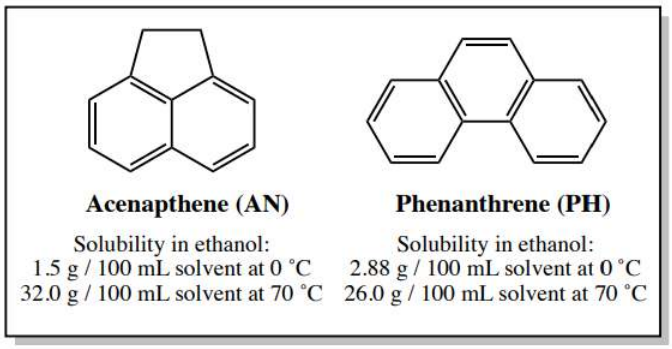


Figure 3.30: Ethanol solubility for acenapthene and phenanthrene.[12]

4.00 g of pure acenapthene (AN) should completely dissolve in **12.5 mL** (see calculation below) of nearly boiling ethanol (the boiling point of ethanol is **78°C**. **0.30 g** of pure phenanthrene (PH) would dissolve in **1.2 mL** of hot ethanol (see calculation below), and so would also dissolve in **12.5 mL** were used.

$$\text{4.00 g Acenapthene (AN)} \times \frac{\text{100 mL hot ethanol}}{\text{32.0 g AN}} = \textbf{12.5 mL hot ethanol (70°C) to dissolve AN} \tag{2.2.4.4E.4}$$

$$\text{0.30 g Phenanthrene (PH)} \times \frac{\text{100 mL hot ethanol}}{\text{26.0 g PH}} = \textbf{1.2 mL hot ethanol (70°C) to dissolve PH} \tag{2.2.4.4E.5}$$

If this hot solution is then cooled in an ice bath, the calculations below show the quantity of each compound that would remain dissolved in the cold ethanol.

$$\text{12.5 mL cold ethanol} \times \frac{\text{1.5 g acenapthene (AN)}}{\text{100 mL cold ethanol}} = \textbf{0.19 g AN remains dissolved in 0°C ethanol} \tag{2.2.4.4E.6}$$

$$\text{12.5 mL cold ethanol} \times \frac{\text{2.88 g phenanthrene (PH)}}{\text{100 mL cold ethanol}} = \textbf{0.360 g PH remains dissolved in 0°C ethanol} \tag{2.2.4.4E.7}$$

Since greater than this quantity of acenapthene is present, most of it will crystallize **(3.81 g)**. However, since only **0.30 g** of phenanthrene is present, the entire portion should remain in the mother liquor. The two components can then be separated through filtration.

In essence, impurities that have a similar solubility to the compound of interest can be removed like soluble impurities as long as they are present in small enough quantities. **It is a general guide that solids containing less than 5 mol% of impurity can be purified in this manner.** The crystallization process essentially "sacrifices" a portion of each component to the mother liquor in order to produce a pure crystal.

[9]D.D. Perrin, W.L.F. Armarego, *Purification of Organic Chemicals*, Pergamon Press, 3rd edition, **1988**.

[10]Adapted from data found in: A. Seidell, *Solubilities of Inorganic and Organic Substances*, D. Van Nostrand Company, **1907**.

[11]It is very possible that the acenapthene/acetanilide *mixture* might require a slightly different quantity of hot ethanol to dissolve than pure samples, but the calculations in this section provide a rough estimate of the solvent volumes needed.

[12]Adapted from data found in: A. Seidell, *Solubilities of Inorganic and Organic Substances*, D. Van Nostrand Company, **1907**.

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2.2.4.4F: Second Crop Crystallization

As previously discussed, a portion of the compound of interest always remains dissolved in the mother liquor and is filtered away. This is not to say that this portion is *lost*, as it is possible to recover additional compound from the mother liquor. The solvent can be concentrated in the original vessel or on a rotary evaporator, and a second crystallization can be attempted. A second crystallization from the mother liquor of the first crystallization is called a "**second crop crystallization**".

To demonstrate this process, a **1.16 g** sample of *trans*-cinnamic acid was crystallized from a methanol/water mixed solvent system (Figure 3.31). **0.95 g** of a "first crop" of crystals was collected, representing an **82%** recovery.



Figure 3.31: Crystallization of trans-cinnamic acid from water and methanol.

To collect a second crop of crystals, the filtrate was pipetted into an Erlenmeyer flask (Figure 3.32a) and boiled to reduce the volume by half (Figures 3.32b+c). When this solution was cooled, another **0.08 g** of compound crystallized out (Figure 3.32d), making the combined recovery of *trans*-cinnamic acid **1.03 g**, or **89%**.

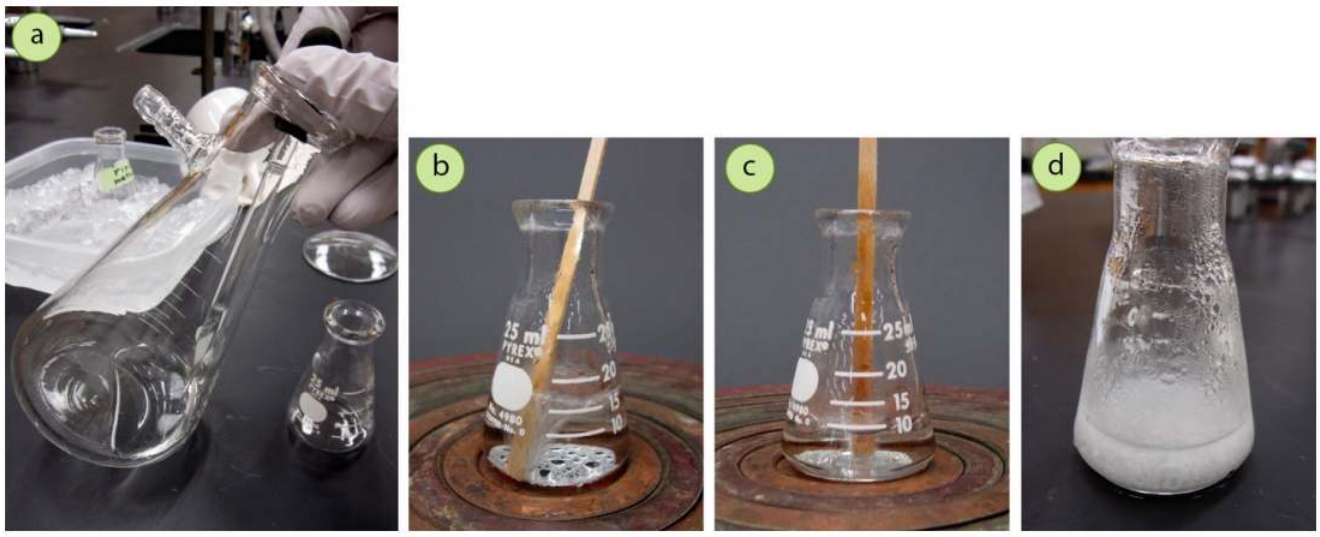


Figure 3.32: Crystallization of a "second crop" of trans-cinnamic acid from water and methanol.

A "second crop" solid should always be kept separate from a "first crop" solid until its purity can be verified. **A second crop crystal is usually more impure than a first crop crystal**, as it crystallizes from a solution that contains a higher percentage of impurities (the first crop removed more compound, leaving more impurities behind).

To demonstrate the relative purity of first crop and second crop crystals, a **1.5 g** mixture of 4-bromoacetophenone contaminated with a small amount of acetophenone was crystallized using ethanol. A GC spectrum of the original mixture (Figure 3.33b) shows the sample to have approximately **7 mol%** acetophenone impurity.

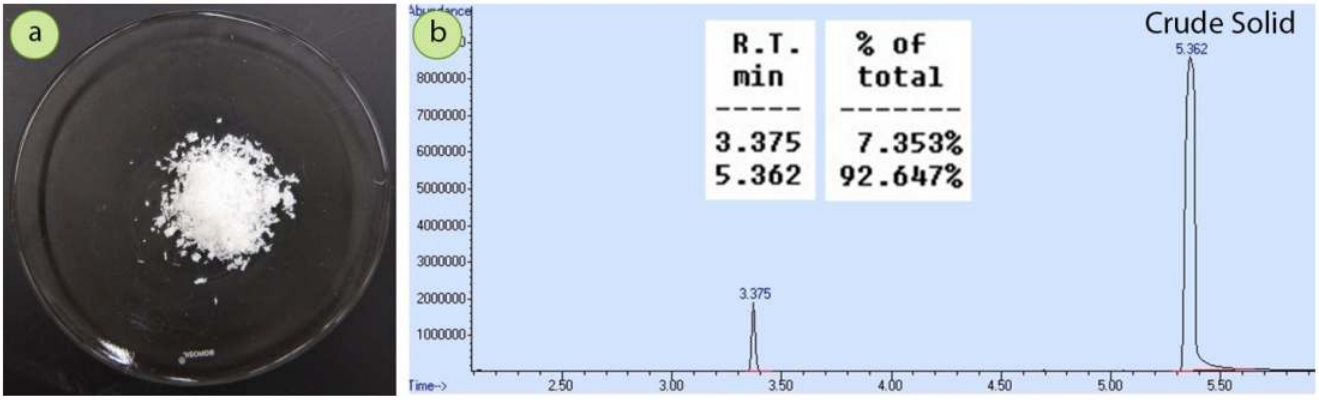


Figure 3.33: a) Initial solid mixture, b) GC spectrum of solid mixture.[13]

Quantitation by a GC-MS instrument can sometimes be inaccurate, so the composition was also calculated through ^{1}H NMR integrations. The partial ^{1}H NMR spectrum of this sample is in Figure 3.34, and integrations indicate the sample is 5.6 mol% acetophenone. There is good agreement between the two quantitative methods.

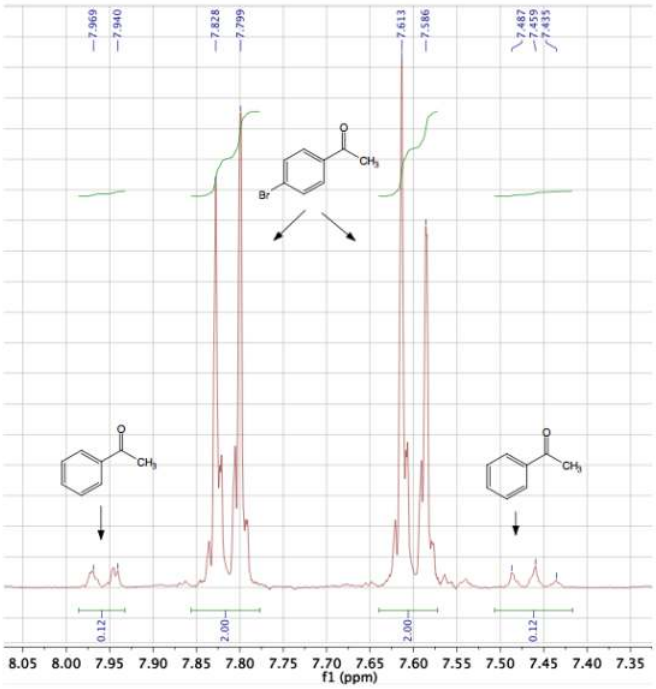


Figure 3.34: Partial 300 MHz ^{1}H NMR spectrum of the original mixture of 4-bromoacetophenone and acetophenone (two signals for the methyl groups are at 2.58 and 2.61 ppm). The integrations show a similar composition as the GC data.

After the mixture was crystallized from ethanol, a GC spectrum of the resulting solid (0.93 g, 63% recovery) showed a dramatic reduction in the acetophenone impurity, to almost negligible amounts (Figure 3.35b). The crystallization purified the 4-bromoacetophenone very well.

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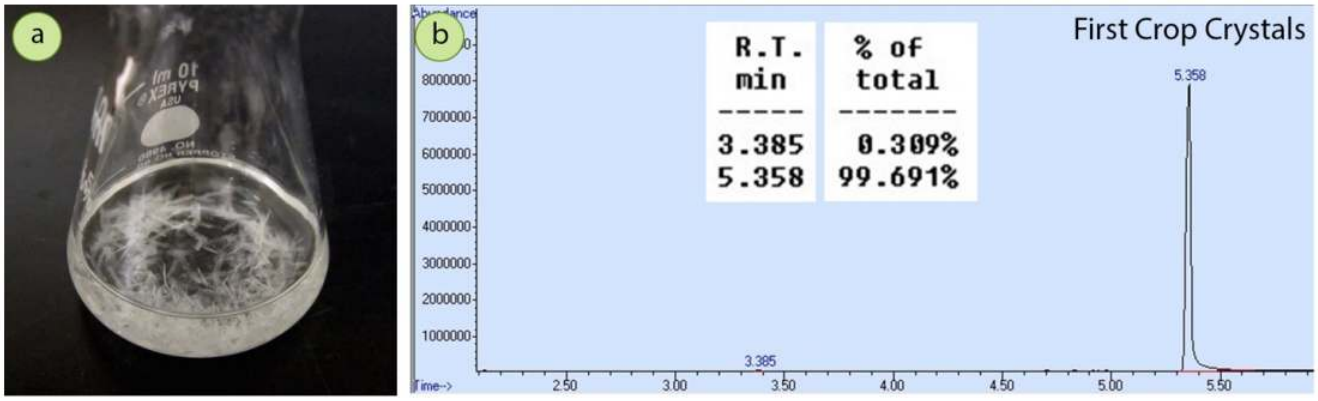


Figure 3.35: a) First crop of 4-bromoacetophenone crystals coming out of solution, b) GC spectrum of the crystallized mixture.

The filtrate from the first crystallization was boiled to reduce the solvent level, and a second crop of crystals was obtained (0.18 g, combined recovery of 77%). The second crop crystals had a noticeable yellow tint while the first crop crystals were pure white. A GC spectrum of the second crop crystals (Figure 3.36b) showed the acetophenone had incorporated somewhat into the crystalline solid, demonstrating that second crop crystals are less pure than first crop crystals.

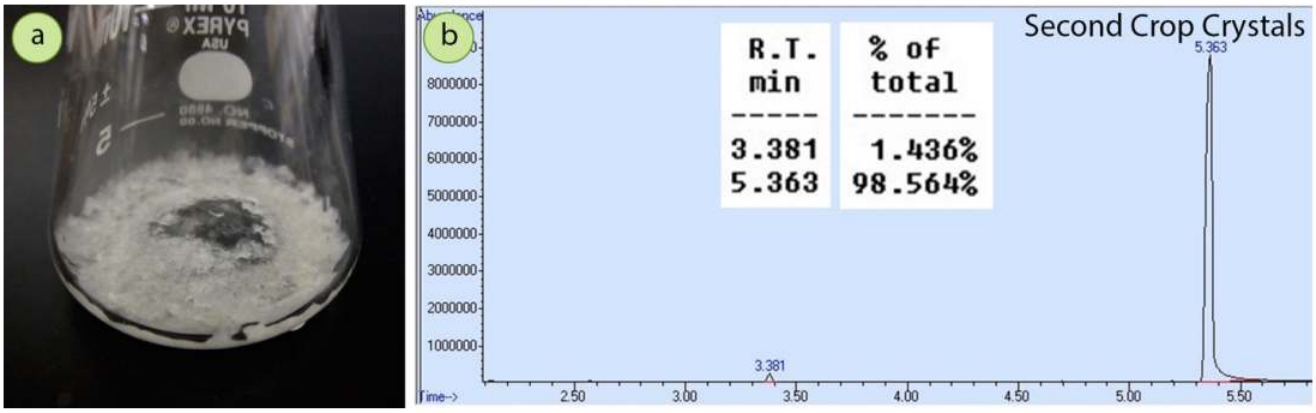


Figure 3.36: a) Second crop of 4-bromoacetophenone crystals coming out of solution, b) GC spectrum of the second crop solid.

Recovery of a second crop of crystals is not commonly done in undergraduate settings as the additional recovery from a second crop is usually modest (Figure 3.37). However, the process may be done if the material is quite expensive, or if a large amount remains dissolved in the mother liquor. For the latter reason, it is a good idea to save the mother liquor until a yield can be calculated. If the recovery is quite low, a second crystallization might be attempted.



Figure 3.37: First crop crystals of 4-bromoacetophenone (left) and second crop crystals (right).

[13]GC method: 100°C hold for 2 min, 25°C ramp per min to 210°C (6.4 min), solvent delay 2.00 min.

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SECTION OVERVIEW

2.2.4.5: Procedural Generalities

2.2.4.5A: General Procedure

2.2.4.5B: Heat Source and Bump Prevention

2.2.4.5C: Charcoal

2.2.4.5D: Cooling Slowly

2.2.4.5E: Initiating Crystallization

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2.2.4.5A: General Procedure

Most often you will be asked to follow a published crystallization procedure that may be written in one of two varieties:

- Solid A was crystallized using Y solvent, or
- Solid A was crystallized using *X mL* of Y solvent

When no volume of solvent is specified, the process should be conducted using the minimum volume of boiling solvent to dissolve the solid. If a volume *is* specified, it probably means the crystallization is tricky and previous trials have shown that a greater than minimal solvent volume produce higher quality crystals, or attempting to dissolve common impurities leads to using too great a quantity of solvent.

The standard crystallization process (Figure 3.38a) is summarized as follows:

1. Dissolve the impure solid in the minimum amount of hot solvent.
2. Slowly cool the solution to induce crystallization.
3. Further cool the solution in an ice bath.
4. Collect the solid by suction filtration.

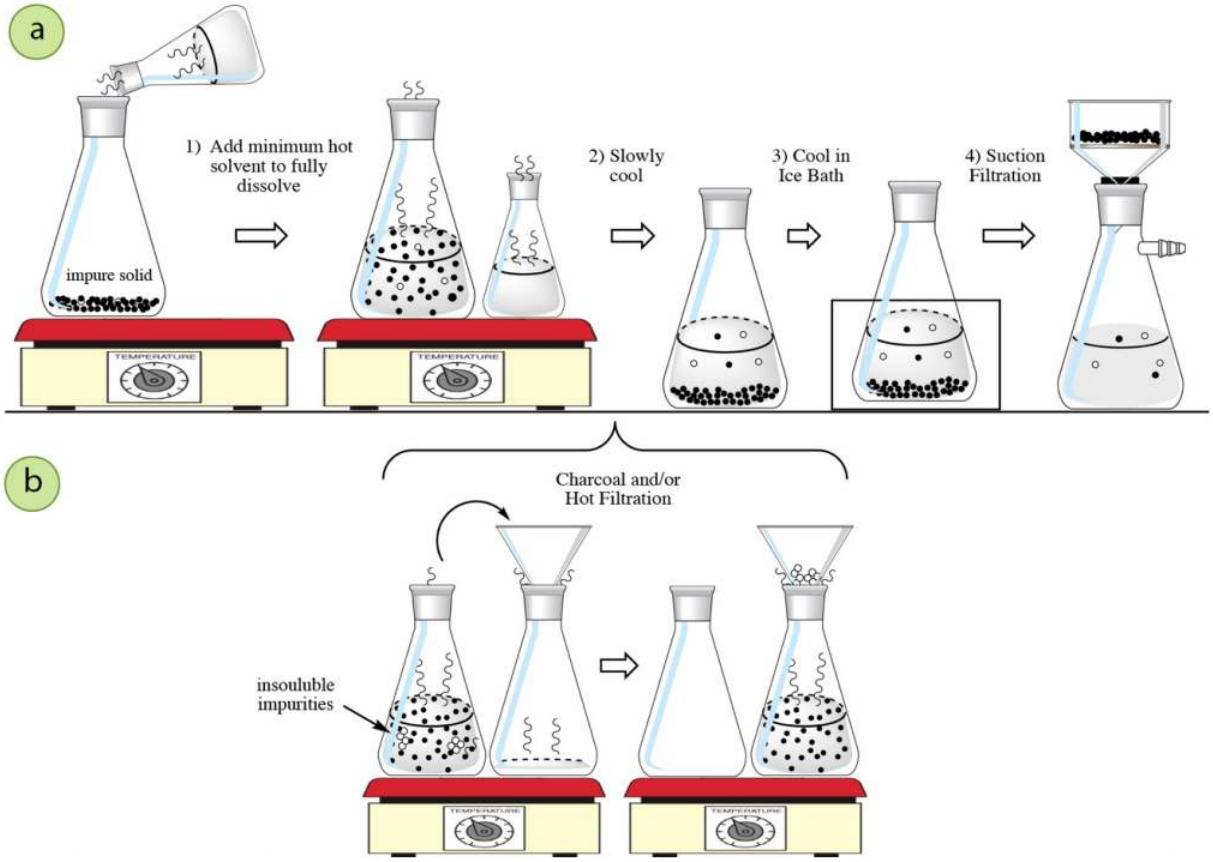


Figure 3.38: a) General procedure for crystallization, b) Modification when insoluble impurities are present.

An additional step may be inserted into this general process (between steps 1 and 2) if insoluble impurities are present, or if impurities will be removed with charcoal (Figure 3.38b). After the compound is dissolved in the minimal amount of hot solvent, charcoal can be used, or insoluble impurities removed with hot filtration. The general process can then be continued on to next cool the solution and induce crystallization.

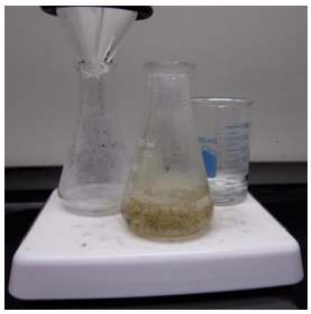
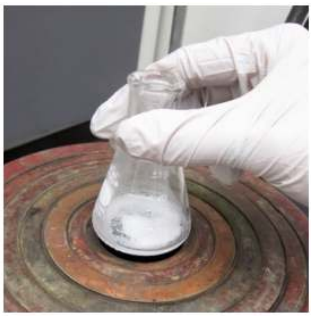
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2.2.4.5B: Heat Source and Bump Prevention

Crystallizations are generally conducted using a hotplate or steam bath, and the crystallization solvent may affect which heat source is appropriate (Table 3.3). If the crystallization solvent is water, a hotplate can be used as there is no issue with flammability. If the crystallization solvent is highly flammable or volatile (e.g., diethyl ether, low-boiling petroleum ether, or acetone), the vapors produced during boiling could ignite on the hot surface of a hotplate, and it is therefore *essential* to use a steam bath. Solvents with moderate volatility (e.g., ethanol or ethyl acetate), should be preferably heated with a steam bath, but can be safely heated with a hotplate if extreme care and caution is utilized.

Table 3.3: Solvent and preferred heat source.

Solvent	**Water**	**Diethyl ether, Acetone, Petroleum Ether (low-boiling)**	**Ethanol, Methanol, Ethyl Acetate, Hexanes**
Photo of Substance			
Heat source	Use a hotplate.	Use steam bath, never a hotplate	Use steam bath preferably. Can use hotplate with caution.

Boiling stones, boiling sticks, or stir bars must be used for "bump" protection as crystallization involves heating solutions to a boil. Boiling stones are often used for solvents, and may be used with solutions if a hot filtration step is planned (or if the plan is to pick the stones out of the crystallized solid). If no filtration step is planned, it may be easier to use a boiling stick or stir bar for bump protection, as these can be easily removed from the hot solution before crystallization.

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2.2.4.5C: Charcoal

Activated charcoal is sometimes used to **remove small amounts of colored impurities** from solution. Activated charcoal has a high affinity for conjugated compounds, whose flat structures wedge themselves well between the graphene sheets. The quantity used should be limited, as charcoal adsorbs all compounds to some extent and could lead to a lower recovery of the desired compound. Charcoal should of course not be used if the product itself is colored.

Decolorizing charcoal (Norit) is added after a solid has been dissolved in the minimum amount of hot solvent. A small portion should be used at first; just as much that can fit on the tip of a spatula (the size of half a pea, see Figure 3.39b). **When adding charcoal, it's recommended to temporarily remove the solution from the heat source** or the charcoal's high surface area may cause superheated areas to immediately boil. Superheated areas are regions where the temperature is above the boiling point of the solvent, but lack a nucleation site to create a bubble and initiate the phase change. If charcoal is added directly to a near boiling solution, the solution may boil over.

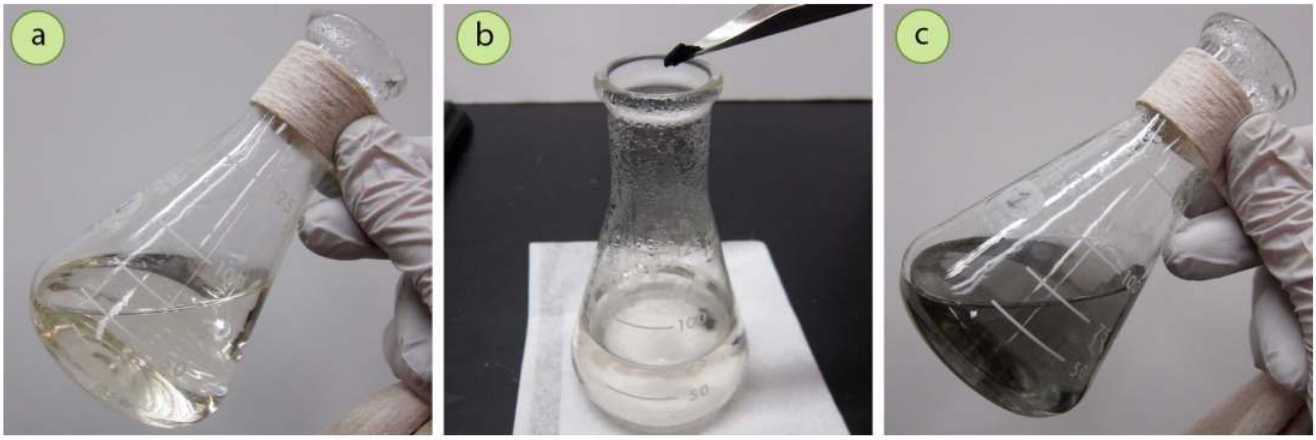


Figure 3.39: a) Solution before addition of charcoal, b) An appropriate quantity of charcoal to start with (tip of the spatula), c) Solution after swirling with charcoal.

For fairly colored solutions, the first portion of charcoal is likely all that is necessary, and the resulting solution should be a faint grey (Figure 3.39c). Additional charcoal can be added if the color remains (Figure 3.40c). Charcoal particles are so fine that hot filtration is necessary to remove them before crystallization.

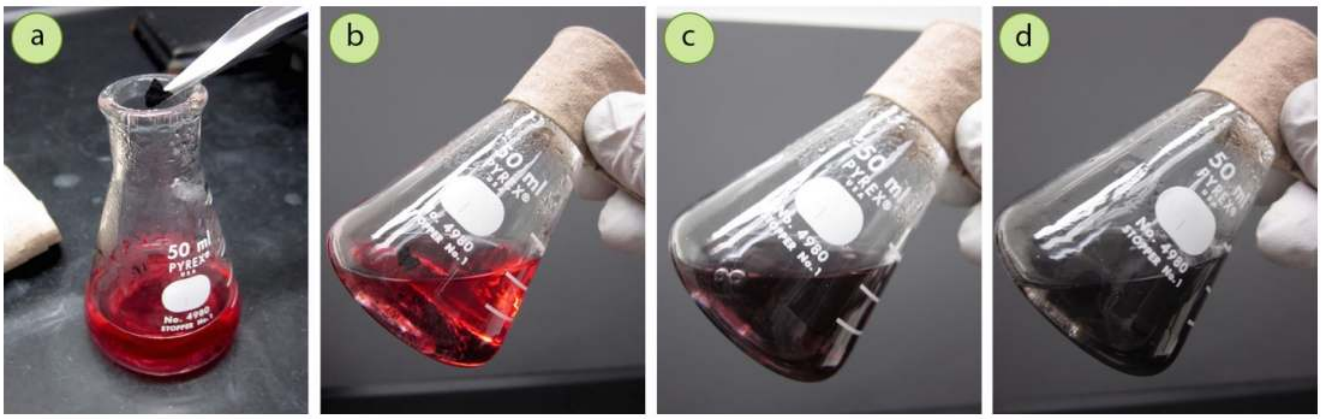


Figure 3.40: Use of charcoal with a highly-colored impurity (acetanilide contaminated with methyl red): a) Addition of charcoal to the aqueous solution, b) Pre-swirling, c) After swirling (color remains), d) Addition of another small scoop of charcoal to fully decolorize.

Charcoal does not need to be used with every solution that's colored, even if the desired compound is white. Colored impurities may remain in the mother liquor after filtration. For example, the sequence in Figure 3.41 shows the purification of acetanilide (a white solid) that has been contaminated with several drops of methyl red solution to produce an orange solid (Figure 3.41a). The solid was crystallized from hot water without the use of charcoal, and even though the mother liquor was yellow (Figure 3.41b), the

crystallized solid was still a pure white color (Figure 3.41c). The methyl red "impurity" remained in the mother liquor and was not obviously incorporated into the crystal lattice of acetanilide.

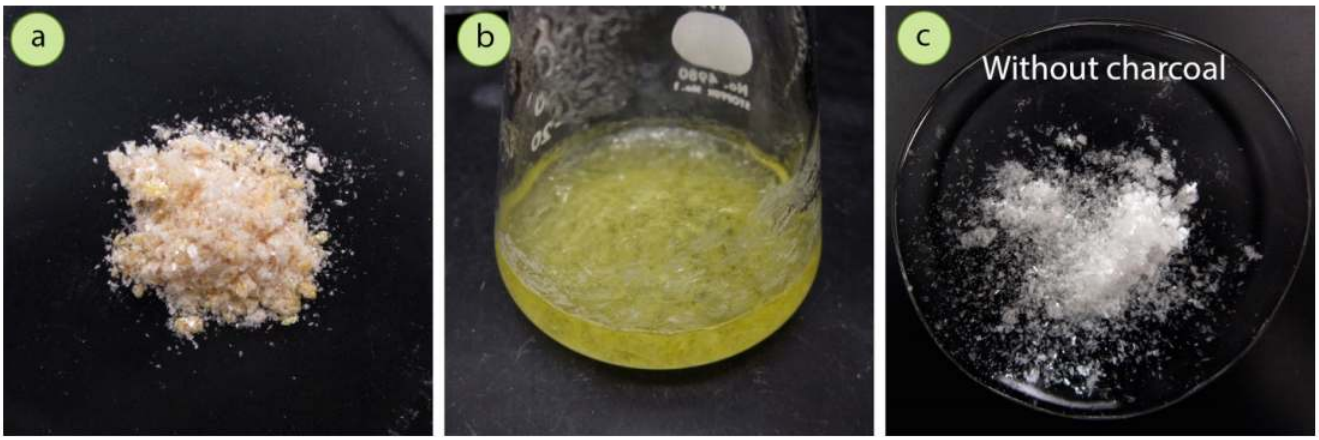


Figure 3.41: a) Crude solid of acetanilide mixed with several drops of methyl red, b) Crystallization, noting the mother liquor is highly colored, c) Crystallized solid with no obvious color.

As a comparison, the same solid was decolorized with charcoal, filtered and crystallized, as shown in Figure 3.42. The charcoal removed the methyl red color, and the mother liquor was colorless (as indicated with an arrow in Figure 3.42b), but there was no obvious improvement of color in the resulting crystallized solid (Figure 3.42c). Additionally, there was a loss of yield when using charcoal. When charcoal was not used, the recovery was **63%**, which was consistent with various other trials of acetanilide. However, when charcoal was used, the recovery was **53%**. The loss of yield may be attributed to charcoal's absorption of the target compound along with the colored impurity, as well as loss of compound on the filter paper during the hot filtration. For this reason, charcoal should only be used if specified in a procedure, or if previous crystallization trials failed to remove colored impurities.

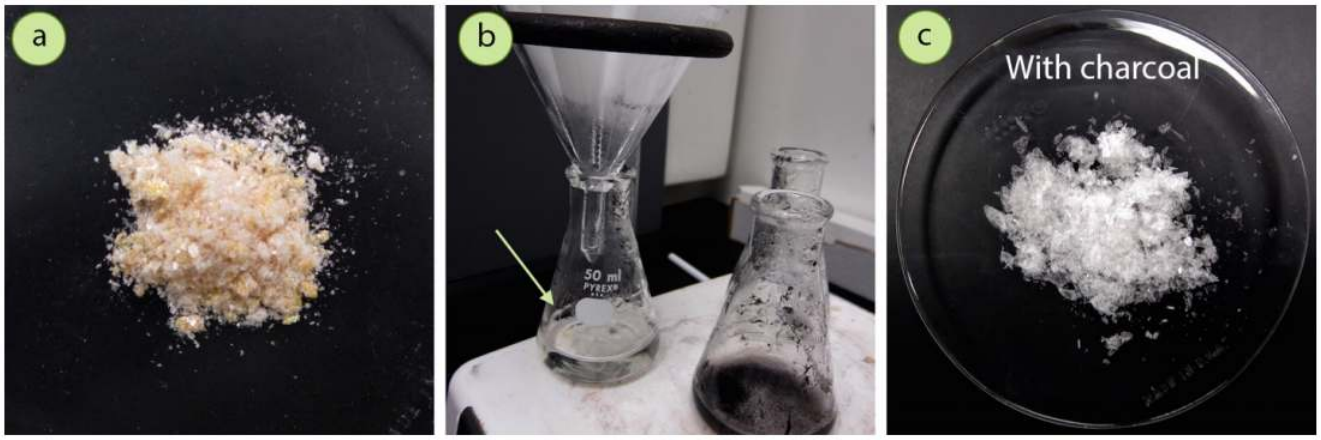


Figure 3.42: a) Crude solid, b) Hot filtration of the solution after addition of decolorizing charcoal (mother liquor is colorless, as indicated by the arrow), c) Crystallized solid with no obvious color.

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2.2.4.5D: Cooling Slowly

After a solution is dissolved in the minimum amount of hot solvent and filtered (if applicable), the solution should be cooled as slowly as possible (keeping in mind time limitations in a lab). To achieve this goal:

The mouth of the Erlenmeyer flask should be covered with a watch glass (Figure 3.43a). This retains heat just like placing a lid on a boiling pot. The watch glass also prevents excess evaporation of low-boiling solvents. Condensation can often be seen on the watch glass as the solution cools, which is evidence that warm vapors are trapped with this method.

The flask should be placed on a non-conductive surface so heat is not wicked away from the bottom of the flask. The flask can be placed atop a paper towel folded several times, a wood block, or on an inverted cork ring (Figure 3.43a-c). For solutions that cool very quickly (e.g., when using solvents with low boiling points like diethyl ether and acetone), the flask may also be covered by an inverted beaker (Figure 3.43d) to create an insulating atmosphere around the flask. This is not generally necessary for solvents with relatively high boiling points like water and ethanol.

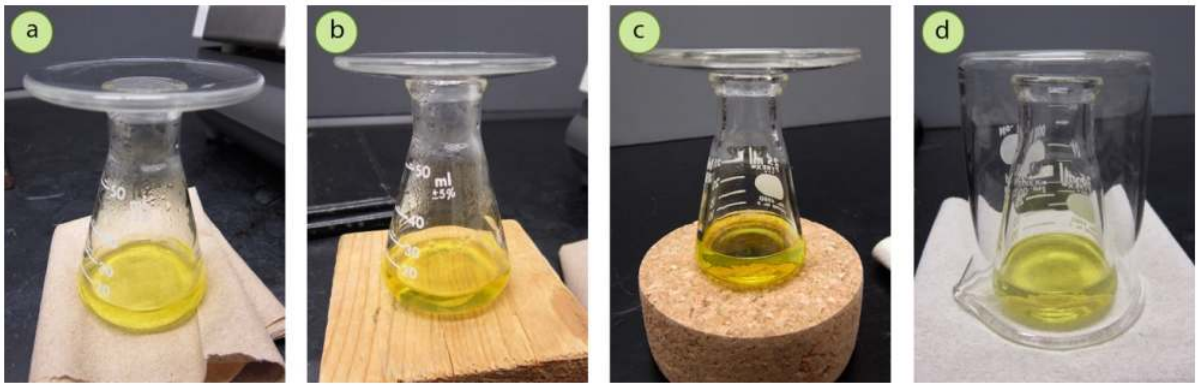


Figure 3.43: Methods to prevent a flask from cooling too quickly: a) Paper towel, b) Wood block, c) Cork ring, d) Inverted beaker.

The correct flask size should be used so that the quantity of hot solvent used reaches a height of more than $1\ \text{cm}$ in the flask. If the solvent level is too shallow during crystallization, the high surface area will cause the solution to cool and evaporate too quickly (Figure 3.44b). It will also be difficult to filter a shallow volume. Ideally the solution should be to a height of at least $2\ \text{cm}$ in the flask, which allows for maintenance of heat by the solution's interior (Figure 3.44d). It is common to use between 10-50 times as much solvent as sample, and a rough guide is to use a flask where the sample just covers the bottom in a thin layer.

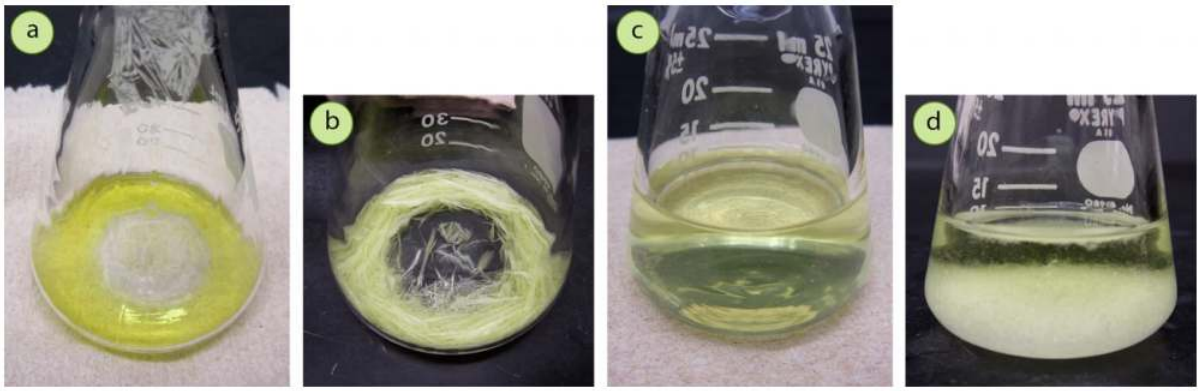


Figure 3.44: a) The flask is too large for the sample, and the solvent is too shallow, b) After crystallization the solvent is completely adsorbed (or evaporated), c) The flask is the correct size for the amount of sample, d) The solvent is an appropriate height in the flask.

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2.2.4.5E: Initiating Crystallization

At times, crystals will not form even when a solution is supersaturated, as there is a kinetic barrier to crystal formation. At times crystallization may need to be initiated, for example if the solution becomes faintly cloudy as it cools, or if the solution fails to produce crystals even when it is noticeably cooler than originally. The methods described in this section preferably should be used on solutions that are still warm, as initiating crystallization on already cool (or cold) solutions will cause too rapid a crystallization.

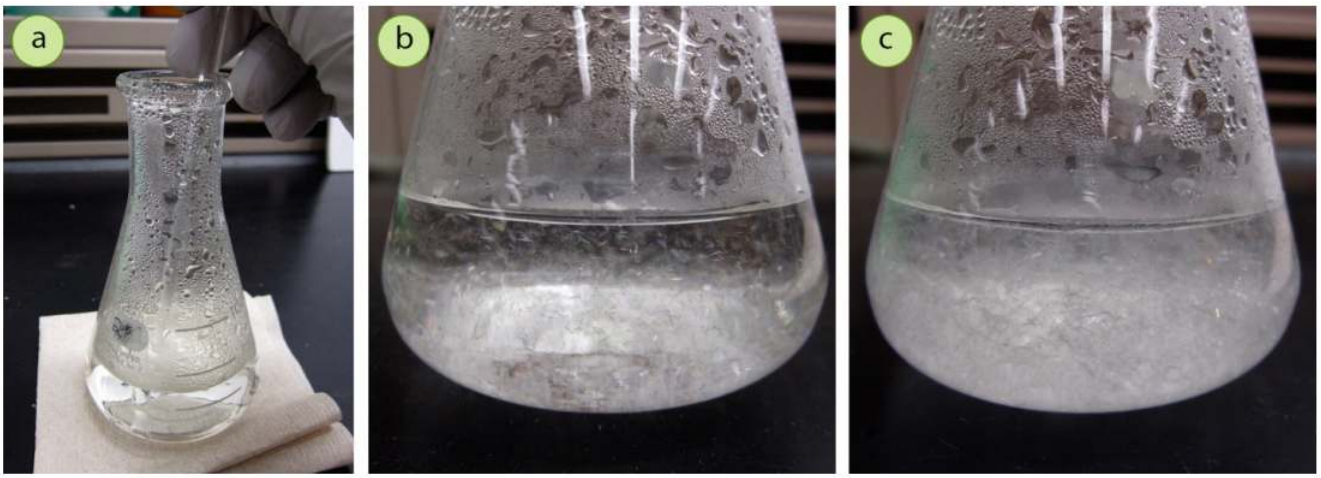


Figure 3.45: a) Scratching to initiate crystallization for acetanilide in water, b+c) Crystallization.

The easiest method to initiate crystallization is to scratch the bottom or side of the flask with a glass stirring rod (Figure 3.45a), with enough force that the scratching is audible (but of course not so much that you break the glass!). Crystallization often begins immediately after scratching, and lines may be visible showing crystal growth in the areas of the glass that were scratched (Figure 3.46).

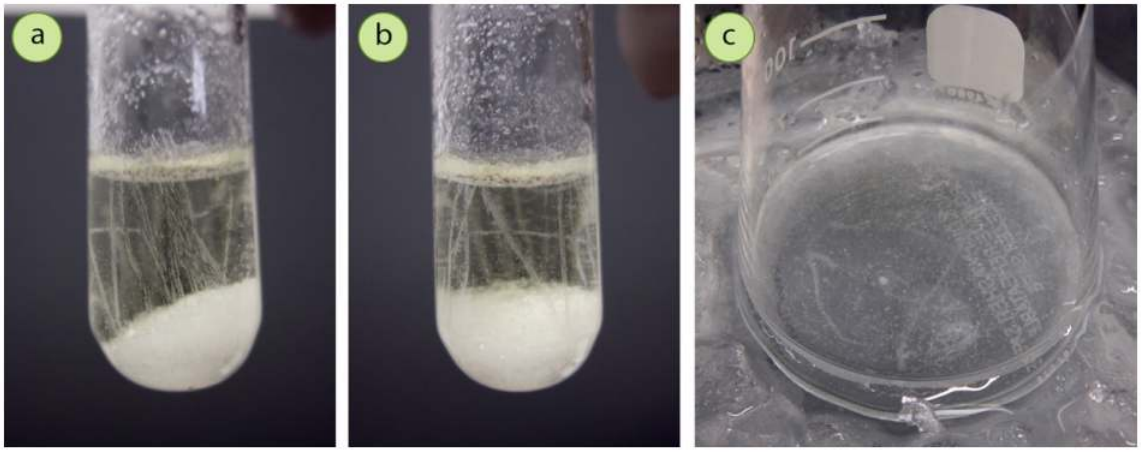


Figure 3.46: Lines of crystals seen in the initial stages of crystal growth, originating from where the glass was scratched: a+b) **N**-bromosuccinimide crystallizing from water, c) Acetanilide crystallizing from water.

Although there is no doubt that this method works, there are differences in opinion as to the mechanism of action. One theory is that scratching initiates crystallization by providing energy from the high-frequency vibrations. Another theory is that tiny fragments of glass are dislodged during scratching that provide nucleation sites for crystal formation. Another hypothesis is that the solvent may evaporate from the glass stirring rod after it is removed, and a speck of solid may fall into solution and act as a "seed crystal" (see next paragraph). It is not well understood how scratching initiates crystallization, but it is in every chemist's arsenal of "tricks".

There are a few other methods that can be used to initiate crystallization when scratching fails:

- Add a "seed crystal": a small speck of crude solid saved from before the crystallization was begun, or a bit of pure solid from a reagent jar. Seed crystals create a nucleation site where crystals can begin growth.

- Dip a glass stirring rod into the supersaturated solution, remove it, and allow the solvent to evaporate to produce a thin residue of crystals on the rod (Figure 3.47a). Then touch the rod to the solution's surface, or stir the solution with the rod to dislodge small seed crystals.

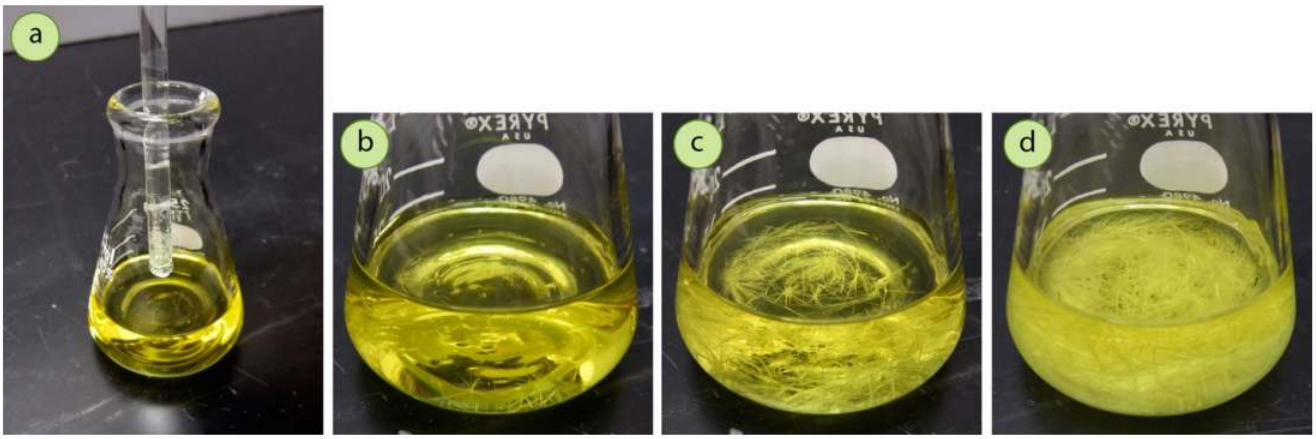


Figure 3.47: a) A glass stirring rod dipped into a solution of benzil, and residual solid formed on the rod after evaporation of the ethanol solvent, b-d) Crystallization, which began after the rod was stirred in the solution to dislodge the seed crystals.

- If scratching and seed crystals do not initiate crystallization, it's possible there is too much solvent present that the compound remains completely soluble (Figure 3.48). To test if this is the case, return the solution to a boil and reduce the volume of solvent, perhaps by half (Figure 3.48c). Allow the reduced solution to cool and see if solid forms. If it does (Figure 3.48d), the quantity of solvent was definitely the problem, and solvent volumes can be experimented with to achieve the best growth of crystals.

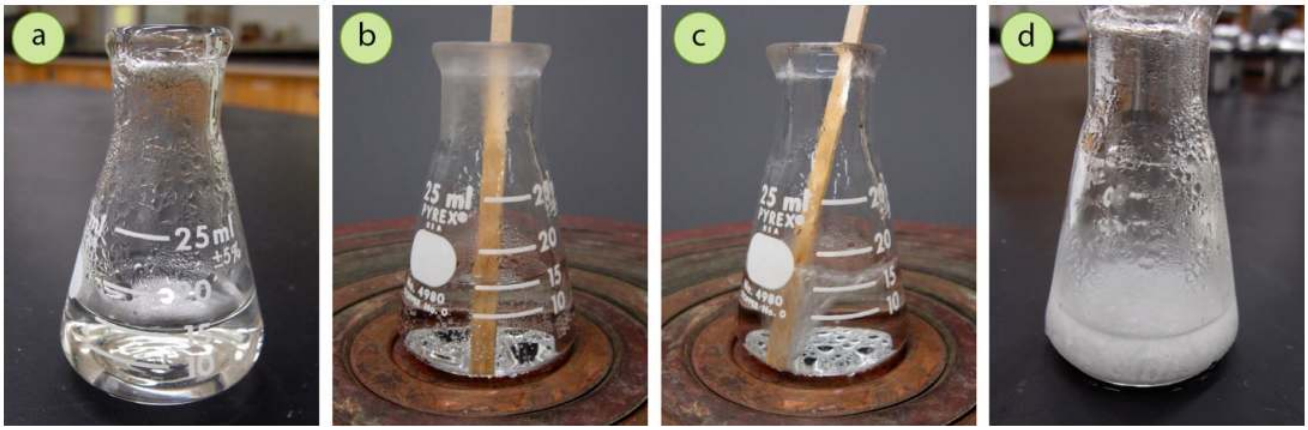


Figure 3.48: a) No crystals formed when cooled, b+c) Reducing the solvent volume on a steam bath, d) Crystals then formed when cooled.

- Use a lower temperature bath to try and encourage crystal formation. A salt water-ice bath ($-10°C$) or chemical freezer are some options.

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SECTION OVERVIEW

2.2.4.6: Step-by-Step Procedures

If a crystallization is to be performed using flammable organic solvents, a steam bath is recommended and in some situations necessary (when using diethyl ether, acetone, or low-boiling petroleum ether).

2.2.4.6A: Single Solvent Crystallization

2.2.4.6B: Crystallization Summary

2.2.4.6C: Using Solvents Other Than Water

2.2.4.6D: Mixed Solvent Crystallization

2.2.4.6E: Mixed Solvent Summary

2.2.4.6F: Troubleshooting

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2.2.4.6A: Single Solvent Crystallization

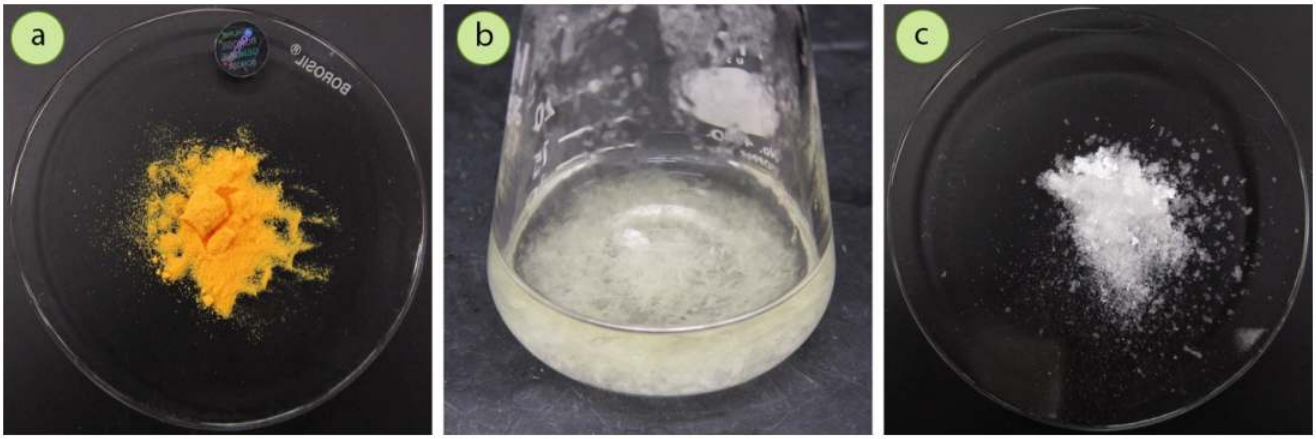


Figure 3.49: a) An old sample of **N**-bromosuccinimide (NBS), b) Crystallization of NBS using hot water, c) Crystallized NBS.

The crystallization pictured in this section shows purification of a roughly **1 g** sample of old **N**-bromosuccinimide (NBS), which was found in its reagent bottle as an orange powder. The crystallization uses water as the solvent, which has no flammability issues, and so a hotplate is used.

If a crystallization is to be performed using flammable organic solvents, a steam bath is recommended and in some situations necessary (when using diethyl ether, acetone, or low-boiling petroleum ether). The following procedure should be used as a guideline for the process, and some key differences between using water and organic solvents are discussed in a future section.

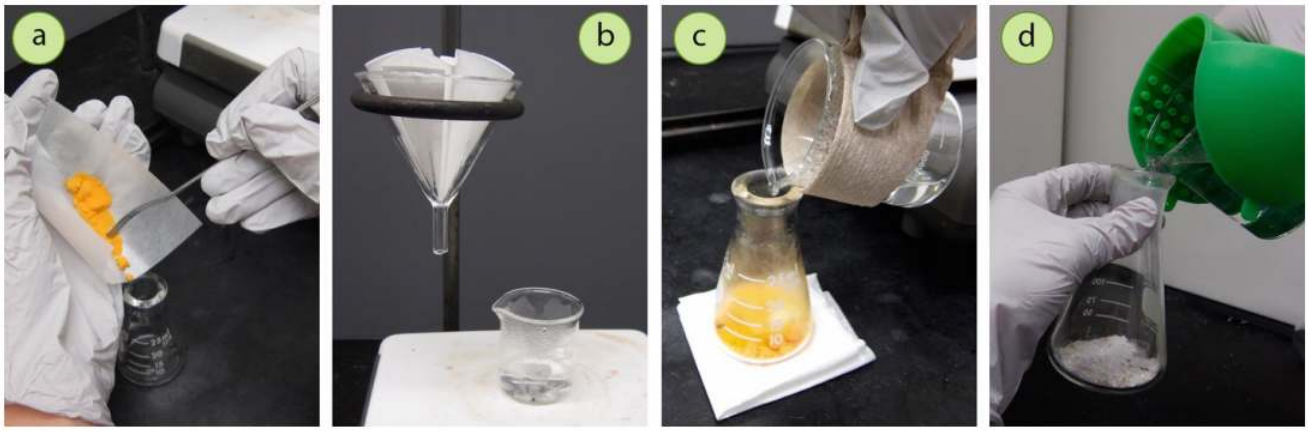


Figure 3.50: a) Impure NBS added to the flask, b) Heating water on a hotplate, c) Addition of hot water to the solid, using a paper towel holder to hold the beaker, d) Addition of hot water to the solid (not NBS, a different system) using a silicone hot hand protector.

Prepare the Setup

1. Transfer the impure solid to be crystallized into an appropriately sized **Erlenmeyer flask** (Figure 3.50a). If the solid is granular, first pulverize with a glass stirring rod.
   It is not recommended to perform crystallizations in a beaker. The narrow mouth of an Erlenmeyer flask allows for easier swirling and minimized evaporation during the process as solvent vapors instead condense on the walls of the flask (they "reflux" on the sides of the flask). The narrow mouth of an Erlenmeyer also allows for a flask to be more easily covered during the cooling stage, or even potentially stoppered for long crystallizations. A round-bottomed flask is also not ideal for crystallization as the shape of the flask makes it difficult to recover solid at the end of the process.
   It is important that the flask be not too full or too empty during the crystallization. If the flask will be greater than half-full with hot solvent, it will be difficult to prevent the flask from boiling over. If the flask will contain solvent to a height less than **1 cm**, the solution will cool too quickly. It is common to use between 10-50 times as much solvent as sample, and a rough guide is to use a flask where the sample just covers the bottom in a thin layer.

2. Place some solvent in a beaker or Erlenmeyer flask along with a few boiling stones on the heat source, and bring to a gentle boil. Use a beaker if the solvent will be poured and an Erlenmeyer flask if the solvent will be pipetted. If a hot filtration step is anticipated for later in the procedure, also prepare a ring clamp containing a funnel with fluted filter paper (Figure 3.50b).

Add the Minimum Amount of Hot Solvent

3. When the solvent is boiling, grasp the beaker with a hot hand protector (Figure 3.50d), cotton gloves, or a paper towel holder made by rolling a sheet of paper towel into a long rectangle (Figure 3.50c). To the side of the heat source, pour a small portion of boiling solvent into the flask containing the impure solid, to coat the bottom of the flask. If the crystallization is being performed on a small scale (using a **50 mL** Erlenmeyer flask or smaller), it may be easier to use a pipette to transfer portions of the solvent to the flask.
   It's customary to not place the dry solid atop the heat source before adding solvent or the solid may decompose. When the solid is dispersed in a small amount of solvent, it can then be placed on the heat source.

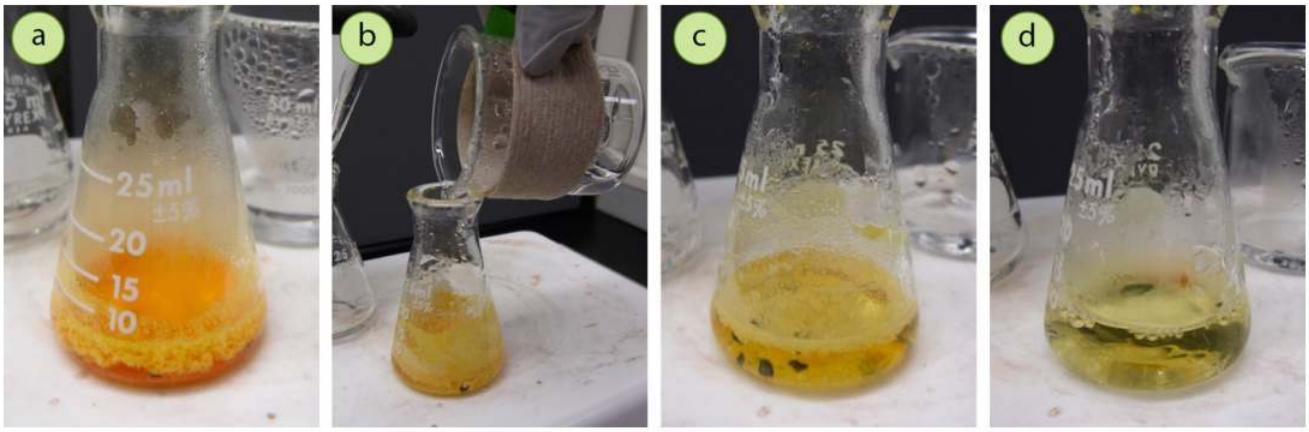


Figure 3.51: Dissolving NBS in the minimum amount of hot water (boiling stones are also present).

4. Place the flask containing the impure solid and solvent atop the heat source. Use some method to prevent bumping (boiling stones if you plan to "hot filter", a boiling stick or stir bar if you don't), and bring the solution to a gentle boil (Figure 3.51a).
5. Add solvent in portions (Figure 3.51b), swirling to aid in dissolution, until the solid just dissolves (Figure 3.51d). For **100 mg-1g** of compound, add **0.5-2 mL** portions at a time. Note that it may take time for a solid to completely dissolve as there is a kinetic aspect to dissolution. Each addition should be allowed to come completely to a boil before adding more solvent, and some time should be allowed between additions. Not allowing time for dissolution and consequently adding too much solvent is a main source of error in crystallization.
   It is not uncommon for droplets of liquid to be seen during the heating process (Figure 3.52). This is when the material "oils out", or melts before it dissolves. If this happens, the liquid droplets are now the compound you are crystallizing, so continue adding solvent in portions until the liquid droplets fully dissolve as well.
   Watch the solution carefully to judge whether the size of the solid pieces (or liquid droplets) change with additional solvent: if they don't they may be an insoluble impurity. Addition of excess solvent in an attempt to dissolve insoluble impurities will negatively affect the recovery. If insoluble solid impurities are present, the solution should be filtered (insert a hot filtration step at this point). Colored impurities can also be removed at this point with charcoal.

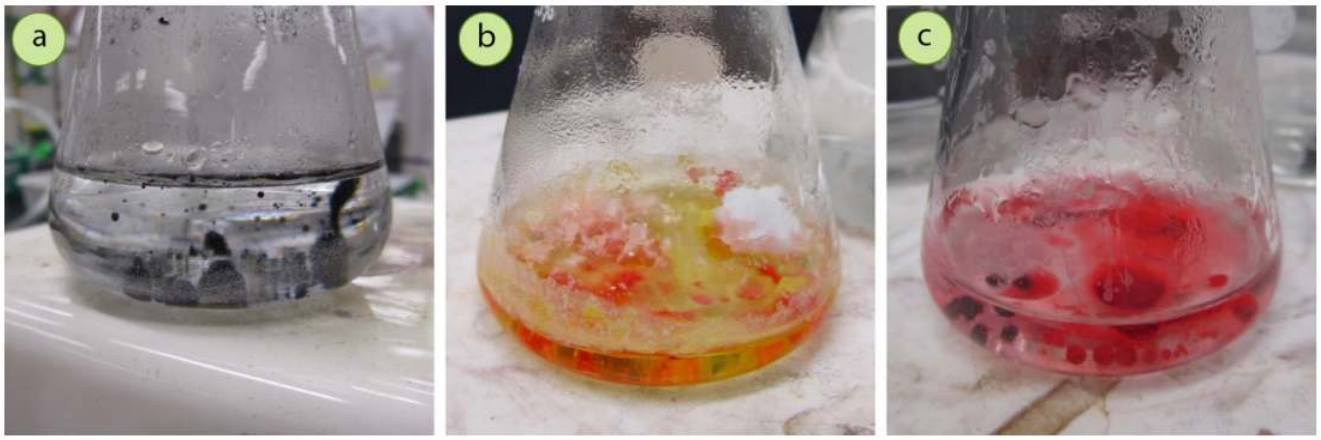


Figure 3.52: *Examples of samples "oiling out" during dissolving: a) Oily droplets of acetanilide in a solution decolorized with charcoal, b+c) Oily droplets containing methyl red and acetanilide in water.*

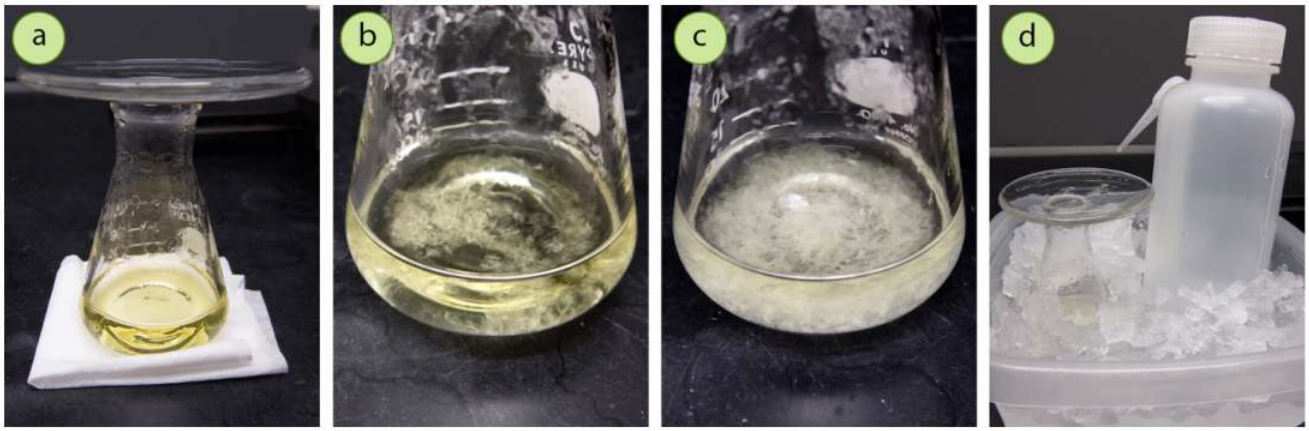


Figure 3.53: a-c) Cooling and crystallization of NBS, d) Further cooling in an ice bath along with some solvent (in the bottle) for rinsing.

Allow the Solution to Slowly Cool

6. When the solid is just dissolved, remove the flask from the heat source using a hot hand protector, paper towel holder, or glove, and set it aside to cool. Remove the boiling stick or stir bar if used for bump protection (boiling stones can be picked out of the solid at a later point if used).
   To encourage slow cooling, set the flask atop a surface that does not conduct heat well, such as a folded paper towel. Cover the mouth of the Erlenmeyer flask with a watch glass to retain heat and solvent (Figure 3.53a). Allow the solution to slowly come to room temperature.
7. As the solution cools, eventually solid crystals should form (Figure 3.53b). If the solution is only warm to the touch or cloudy and no crystals have formed, use a glass stirring rod to scratch the glass and initiate crystallization.
   After crystallization has begun, the crystals should slowly grow as the temperature decreases. An ideal crystallization takes between 5-20 minutes to fully crystallize, depending on the scale. Complete crystallization in less than 5 minutes is too quick (see Troubleshooting section for advice on how to slow it down).
8. When the solution is at room temperature, place the flask into an ice bath (ice-water slurry) for 10-20 minutes to lower the compound's solubility even more and maximize crystal formation (Figure 3.53d). Also place a portion of solvent in the ice bath, to be used later for rinsing during suction filtration.
9. Use suction filtration to recover the solid from the mixture.

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2.2.4.6B: Crystallization Summary

Table 3.4: Procedural summary for single solvent crystallization.

			
Heat some solvent on a heat source to a boil (include boiling stones). To the impure solid in an **Erlenmeyer flask**, add a small portion of hot solvent. If a hot filtration step is expected, use boiling stones with the impure solid, or a boiling stick or stir bar if a filtration is not expected. Put both flasks on the heat source and bring to a boil.	Add the minimum amount of boiling solvent needed to dissolve the impure solid, with swirling. For **100 mg-1 g** quantities, add **0.5-2 mL** solvent each time. For smaller scales, add solvent dropwise. Wait for each portion of solvent to come to a boil before adding more. Possibly use charcoal and hot filtration at this point if colored or insoluble impurities are present.	When dissolved, remove the solution from the heat source and remove the boiling stick or stir bar if used. Allow the solution to slowly cool atop some paper towels, and with a small watch glass over the mouth of the Erlenmeyer. If a hint of cloudiness is seen in the solution, or if the solution has cooled a good deal without crystallizing, scratch with a glass stirring rod to initiate crystallization.	A proper crystallization takes between 5-20 minutes to complete. When the solution is at room temperature, place it in an ice bath for at least 10 minutes to maximize crystal formation. Also chill a rinse solvent in the ice bath. Collect the crystals by suction filtration.

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2.2.4.6C: Using Solvents Other Than Water

This section describes a few key differences between a crystallization using water and one using volatile organic solvents. It is expected that readers have previously read or performed a crystallization using water as the solvent.

Ethanol, Methanol, Ethyl Acetate, and Hexanes

Ethanol, methanol, ethyl acetate, and hexanes are flammable and have moderate volatility, thus these solvents necessitate some different approaches than when using water as the crystallization solvent.

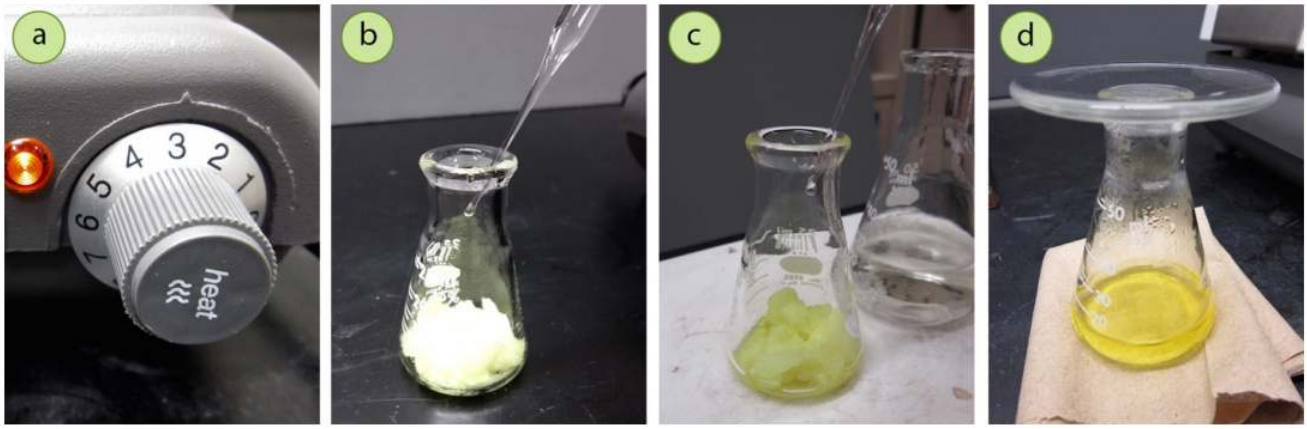


Figure 3.54: a) Hotplate set to low (for ethanol), b+c) Adding solvent via pipette, d) Crystallizing atop some paper towels to encourage slow cooling.

1. Although a steam bath is the preferred heat source for these solvents, if a hotplate is chosen to be used carefully it's essential that you:
   a. Keep the hotplate on **low** (Figure 3.54a) and monitor the temperature of the solvent with a thermometer, being sure to patiently wait for the solvent to come to a boil instead of "cranking" up the heat.
   b. Use the hotplate in a fume hood to prevent a "blanket" of solvent vapors from forming around the hotplate, which have the potential to ignite.
   c. Monitor the hotplate the entire time while the solvent is heating.
2. It may be more controllable to use a pipette to transfer portions of hot solvent to the solid instead of pouring (Figure 3.54b+c). Pouring has a greater possibility of spilling, and if solvent drips onto the hotplate surface, it has the potential to ignite. Since solvent tends to cool in a pipette, care must be taken to be sure the solution is returned to a boil before adding more solvent.
3. All organic solvents have lower heat capacities than water, so tend to cool more quickly. Be sure to set the cooling sample atop several paper towels to encourage a slow crystallization (Figure 3.54d).

Diethyl Ether, Acetone, and Petroleum Ether (Low-Boiling)

Diethyl ether, acetone, and low-boiling petroleum ether are flammable and highly volatile, and thus necessitate further considerations than when using water or other organic solvents as the crystallization solvent.

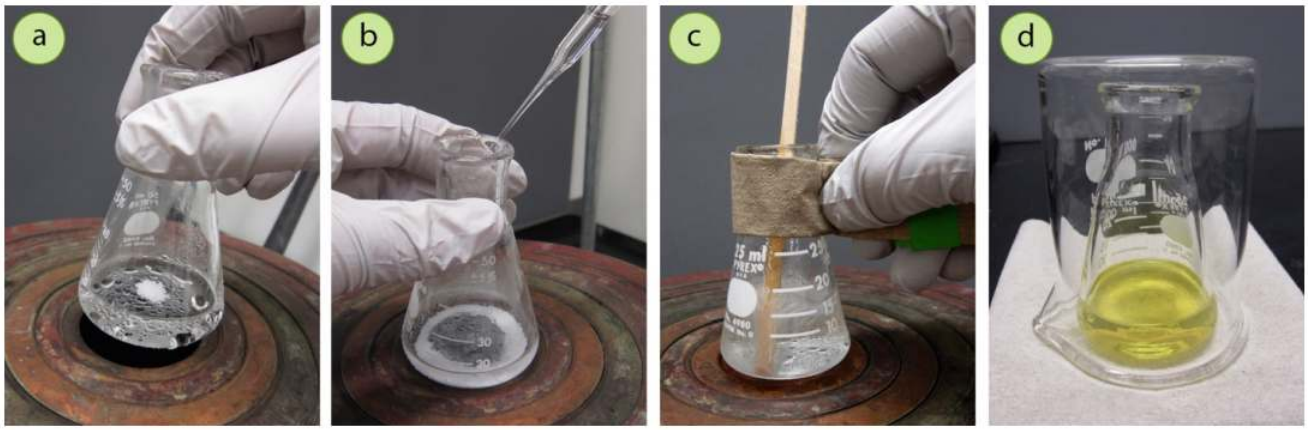


Figure 3.55: *a) Hovering a flask above the steam bath, b) Adding solvent by pipette, c) Inevitable vigorous boiling, d) Using an inverted beaker during crystallization.*

- As these solvents have very low boiling points, they MUST be heated with a steam bath (Figure 3.55a), not a hotplate, or ignition may occur on the hotplate's surface.
- Steam is much hotter than is necessary to bring these solvents to a boil, and they must therefore be *closely* monitored during heating. To prevent too vigorous boiling, flasks may need to be lifted periodically off the steam bath, or simply *hovered* above the steam bath (Figure 3.55a) instead of resting directly atop the bath (Figure 3.55c). To control boiling, the steam rate should also be turned down.
- Using a Pasteur pipette with warm solvent is impractical with very volatile solvents, as liquid will undoubtedly drip out the end of the pipette before it is able to be delivered. Instead of heating the solvent beforehand, simply add cold solvent to the solid by pipette each time (Figure 3.55b), and then be sure to allow each portion to come to a boil before adding more.
  Liquid may drip out the tip of a pipette even when dispensing cold solvent, which happens as solvent evaporates into the pipette's headspace, and the additional vapor causes the headspace pressure to exceed the atmospheric pressure. To prevent a pipette from dripping, withdraw and expunge solvent into the pipette several times. Once the headspace is saturated with solvent vapors, the pipette will no longer drip.
- These solvents boil so readily that it's possible they will vaporize as quickly as a new portion of solvent is added (Figure 3.55c shows vigorous boiling). It may feel as if you keep adding solvent and are "getting nowhere" with the additions. It is important to be watchful of the solvent volume in the flask, and if the additions appear to be quickly "disappearing", raise the flask above the steam bath or turn down the steam to moderate the rate of heating.
- As these solvents are not much warmer than room temperature when boiling, they will cool very quickly. Thus, it may be helpful to cover the flask with an inverted beaker to create an insulating atmosphere in addition to setting the cooling flask atop several paper towels (Figure 3.55d).

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2.2.4.6D: Mixed Solvent Crystallization

The crystallization pictured in this section shows purification of a roughly **1 g** sample of *trans*-cinnamic acid. *Trans*-cinnamic acid is soluble in methanol and insoluble in water, and this crystallization uses a mixed solvent of methanol and water to give a **74%** recovery.

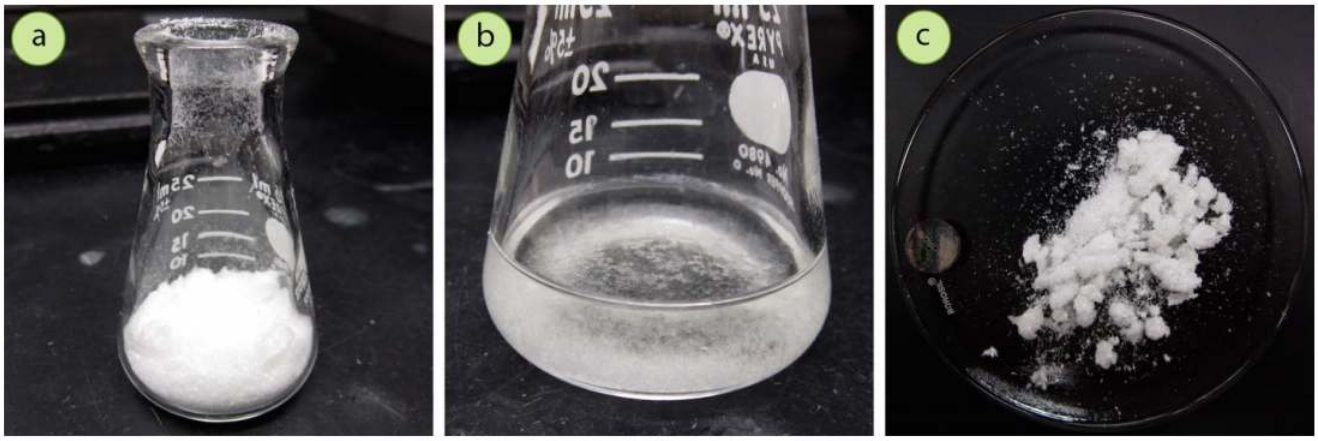


Figure 3.56: a) Initial sample of trans-cinnamic acid, b) Crystallization using methanol/water, c) Crystallized trans-*cinnamic acid*.

It is assumed that students performing this technique have previously performed or read about a single-solvent crystallization.

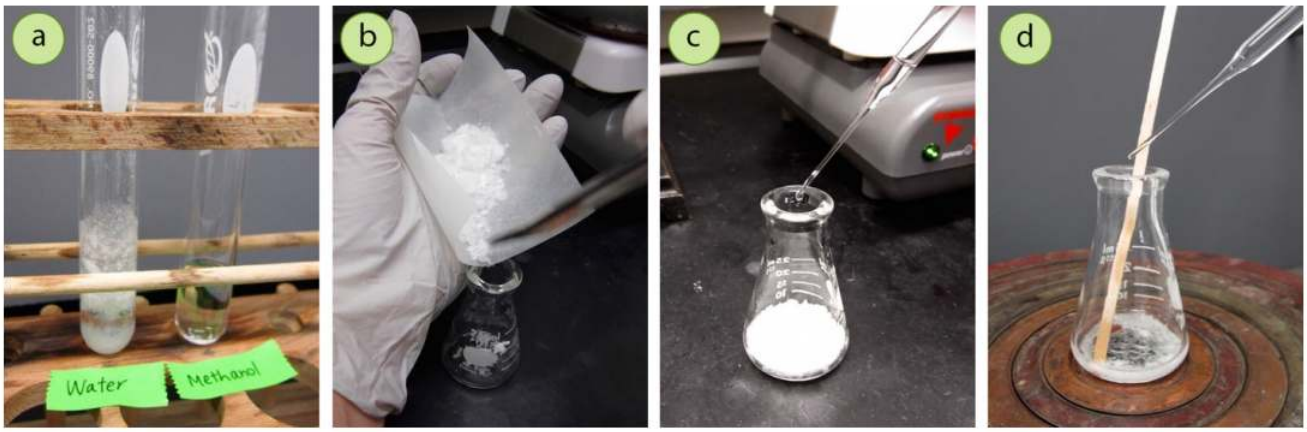


Figure 3.57: a) Trans-cinnamic acid is insoluble in water and soluble in methanol, b) Adding solid to the flask, c) Adding methanol off the heat source, d) Adding enough methanol to dissolve the solid.

1. Determine two miscible solvents that can be used for the crystallization (Figure 3.57a): the desired compound should be soluble in one solvent (called the "**soluble solvent**") and insoluble in the other solvent (called the "**insoluble solvent**").
2. Transfer the impure solid to be crystallized into an appropriately sized Erlenmeyer flask (Figure 3.57b).
3. Place some of the "soluble solvent" into the flask (Figure 3.57c), add a boiling stick (or boiling stones if preferred), then heat atop a steam bath (Figure 3.57d). A hotplate can be used cautiously if using the mixed solvents methanol/water or ethanol/water.

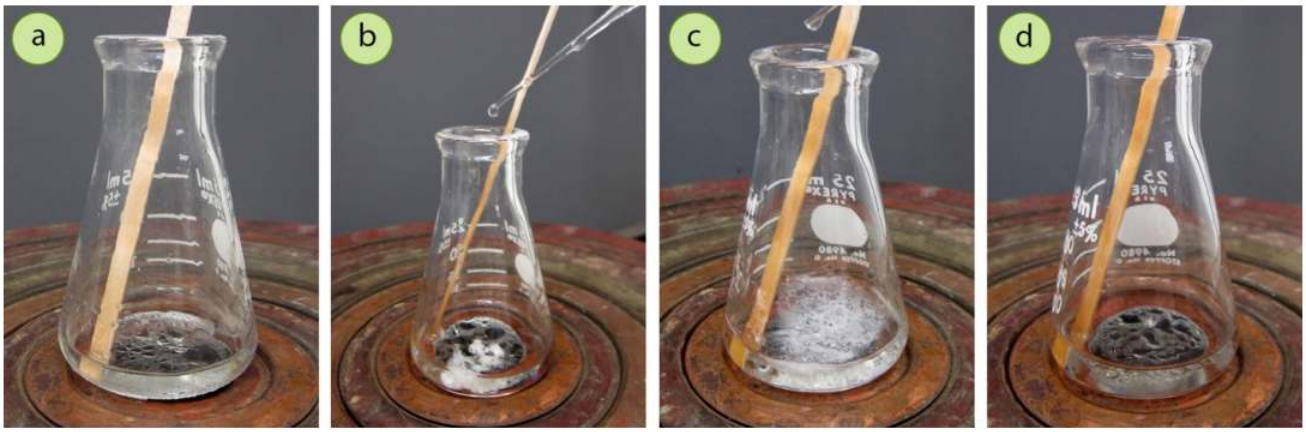


Figure 3.58: a) Addition of just enough soluble solvent (methanol) to dissolve the solid, b) Addition of the insoluble solvent (water) dropwise, c) Sustained cloudiness after addition of enough insoluble solvent, d) Addition of soluble solvent to clarify.

4. Add more of the "soluble solvent" in portions until the solid just dissolves (Figure 3.58a). Be sure to allow time in between additions, and allow each addition to come completely to a boil before adding more.
5. Add the "insoluble solvent" in portions with heating until the solution becomes just cloudy (Figure 3.58c).
6. Add the "soluble solvent" dropwise with heating until the solution again clarifies (Figure 3.58d).

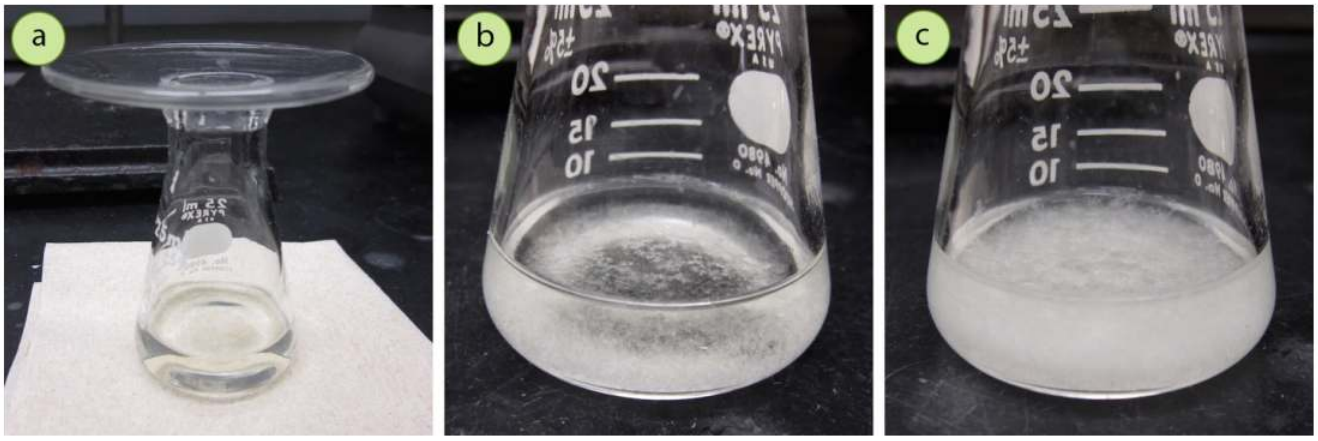


Figure 3.59: a) Cooling solution in flask, b+c) Crystallization in solution.

7. Remove the flask from the heat source, remove the boiling stick and set the flask atop a paper towel folded several times. Cover the mouth of the Erlenmeyer flask with a watch glass, and allow the solution to slowly cool to room temperature (Figure 3.59a).
8. As the solution cools, eventually solid crystals should form (Figure 3.59b). Use a glass stirring rod to scratch the flask and initiate crystallization if necessary. Place the crystals in an ice-water bath for 10-20 minutes and collect the solid by suction filtration.

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2.2.4.6E: Mixed Solvent Summary

Table 3.5: Procedural summary for mixed solvent crystallization.

			
Find a miscible pair of solvents: one in which the desired compound is soluble (called the "**soluble solvent**") and one in which the compound is insoluble (called the "**insoluble solvent**").	Place the impure solid in an Erlemeyer flask along with a boiling stick (or boiling stones if preferred). Add the soluble solvent in portions while heating until the solvent just dissolves. Allow time in between additions, and allow each addition to come completely to a boil before adding more.	Add the insoluble solvent in portions with heating until the solution becomes faintly cloudy.	Add the "soluble solvent" dropwise with heating until the solution is clarified (transparent).
Remove the boiling stick (if used) and allow the system to come to room temperature while sitting atop some paper towels and with the flask's mouth covered by a watch glass.		Scratch with a glass stirring rod to initiate crystallization if necessary. Submerge in an ice bath for 10-20 minutes. Collect the crystals by suction filtration.	

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2.2.4.6F: Troubleshooting

Crystallization is Too Quick

Rapid crystallization is discouraged because impurities tend to become incorporated into the crystal, defeating the purpose of this purification technique. It may be acceptable for crystallization to *start* immediately after removing the flask from the heat source, but if a large amount of solid is formed then the compound is crystallizing too fast.

An ideal crystallization has some crystals forming in approximately 5 minutes, and growth continuing over a period of 20 minutes. Below are methods that can be used to slow the growth of crystals:

1. Place the solid back on the heat source and add extra solvent (perhaps **1-2 mL** for **100 mg** of solid), so that you have exceeded the minimum amount of hot solvent needed to dissolve the solid. Although more compound will dissolve in the mother liquor, the compound will stay soluble longer once set aside to cool.

   For example, in the crystallization of *trans*-cinnamic acid with a mixed solvent of methanol and water, use of the minimum amount of hot solvent to dissolve the solid (Figure 3.60a) resulted in the solid immediately crashing out of solution when the solution was taken off the heat source (Figure 3.60b). To remedy this problem, the solid was placed back on the steam bath, additional methanol (soluble solvent) was added, brought to a boil to dissolve the solid, and then cooled. The solid then began to crystallize much more slowly (Figure 3.60c), taking a period of 15 minutes to fully crystallize.

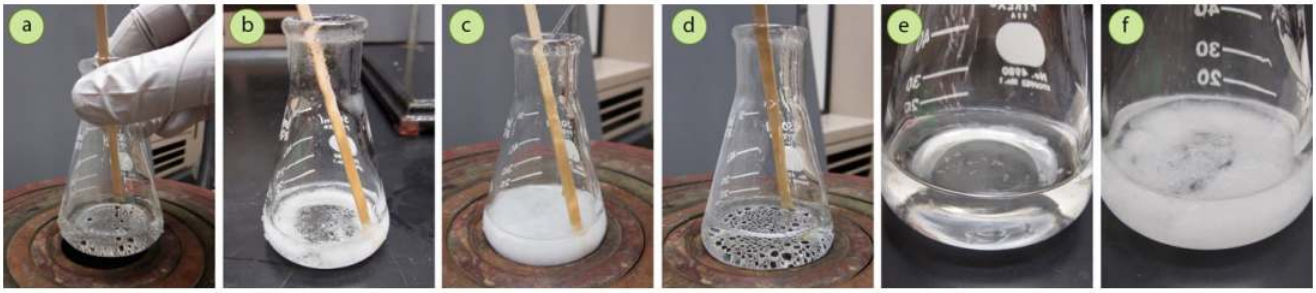


Figure 3.60: a) The minimal amount of methanol/water was used to dissolve a sample of trans-cinnamic acid, b) Upon cooling, the solid immediately crashed out, c) The cloudy solution was placed back on the heat source and extra methanol was added, d) The solid dissolved, e+f) The solid crystallized more slowly when using more solvent.

2. If the minimal amount of hot solvent needed to dissolve the solid reached a height of less than **1 cm** in the flask, the flask may be too big for the crystallization. A shallow solvent pool has a high surface area, which leads to fast cooling. Transfer the solution to a smaller flask (using some solvent to rinse the flask, and then boil away the same amount of solvent used for rinsing) and repeat the crystallization.
3. Be sure to use a watch glass over the top of the Erlenmeyer flask to trap heat, and set the flask atop some material to insulate the bottom (several paper towels, a wood block, or cork ring). An inverted beaker could also be tried to create an insulating atmosphere around the cooling flask.

Crystallization Doesn't Happen

It can be quite frustrating to set aside the dissolved solution to cool and have no crystals form at all. Methods to initiate crystallization were discussed in great detail previously. To summarize, here are the methods that can be tried (in hierarchical order) to form crystals depending on the appearance of the solution:

1. If the solution is cloudy, scratch the flask with a glass stirring rod.
2. If the solution is clear,
   a. First try scratching the flask with a glass stirring rod.
   b. Add a seed crystal (a small speck of crude solid saved from before the crystallization was begun, or a bit of pure solid from the reagent jar).
   c. Dip a glass stirring rod into the solution, remove it, and allow the solvent to evaporate to produce a thin residue of crystals on the rod (Figure 3.61). Then touch the rod to the solution's surface, or stir the solution with the rod to dislodge small seed

crystals.

d. Return the solution to the heat source an boil off a portion of solvent (perhaps half), then cool again.
e. Lower the temperature of the cooling bath.

3. If very few crystals are seen, there is likely too much solvent. Return the solution to the heat source and boil off a portion of solvent, then cool again.
4. If all else fails, the solvent can always be removed by rotary evaporation to recover the crude solid. Another crystallization can be attempted, perhaps with a different solvent system.



Figure 3.61: A glass stirring rod dipped into a solution of benzil in ethanol, to initiate crystallization.

The Yield is Poor

A crystallization may result with a really poor yield (e.g. less than 20%). There are several reasons why this might happen:

1. Too much solvent may have been used during the crystallization, and therefore large quantities of compound were lost to the mother liquor. If the mother liquor (the filtrate after suction filtration) has not been disposed of, this can be tested by dipping a glass stirring rod into the mother liquor and letting it dry. If the solvent evaporates to leave a large residue on the rod, there is a lot of compound left in solution. Additional compound may be recovered by boiling away some of the solvent and repeating the crystallization (this is called "second crop crystallization"), or by removing all of the solvent by rotary evaporation and repeating the crystallization with a different solvent.
2. Too much solvent may have been used while attempting to dissolve semi-insoluble impurities. If this may have been the case, a hot filtration could have been attempted to remove the impurities. (The solid would have to be recovered from the mother liquor first through rotary evaporation in order to attempt the crystallization again.)
3. Too much charcoal may have been used to decolorize the solution (a pitch black solution has too much charcoal). Too much charcoal decreases the yield as charcoal can adsorb the desired compound along with impurities. There is no way to recover the product once it is adsorbed by charcoal.
4. If a hot filtration step was used, compound may have been lost in the filter paper and/or on the stem of the funnel. Additionally, too much solvent may have been used when adding a portion to get the system hot before filtration. The extra solvent before filtration adds to the "minimum amount of hot solvent" and if in substantial excess, can cause a loss of compound to the mother liquor.
5. If the impure solid was the product of a chemical reaction, the reaction may not have worked well. This could be assessed if a crude mass had been obtained: if the crude mass was very low to begin with, then the low crystallized yield was due to problems with the reaction, not the crystallization.

   If a crude mass was not obtained, assessment of the rough volumes of solid before and after crystallization can be used. If the volumes were similar, the loss of yield may not be due to problems with the crystallization. Note that crystallized solids tend to be a lot "fluffier" than crude solids (Figure 3.62), so "eyeballing" solid volumes is only a very rough assessment of quantity.



Figure 3.62: Two **6.5 mg** samples of benzil: (left) from reagent jar, (right) crystallized sample.

Liquid Droplets Form (The Solid "Oils Out")

When cooling, a compound may come out of solution as a liquid rather than a solid (Figure 3.63). This process is called "oiling out" and happens when the melting point of the solid is lower than the solution's temperature. This is a problem in crystallization because when compounds liquefy first, they rarely form pure crystals. This is due to the fact that impurities often dissolve *better* in the liquid droplets than they do in the solvent. Figure 3.63c shows a sample of crude acetanilide that has oiled out (the droplets are impure liquid acetanilide), and the sample is contaminated with a methyl red impurity (which appears red in the low pH of the solution, an artifact of how the crude solid was synthesized). The oily acetanilide droplets appear more colored than the solution, indicating a higher quantity of dissolved methyl red impurity. If an oiled out liquid eventually solidifies, it often forms an impure glass-like non-crystalline solid.

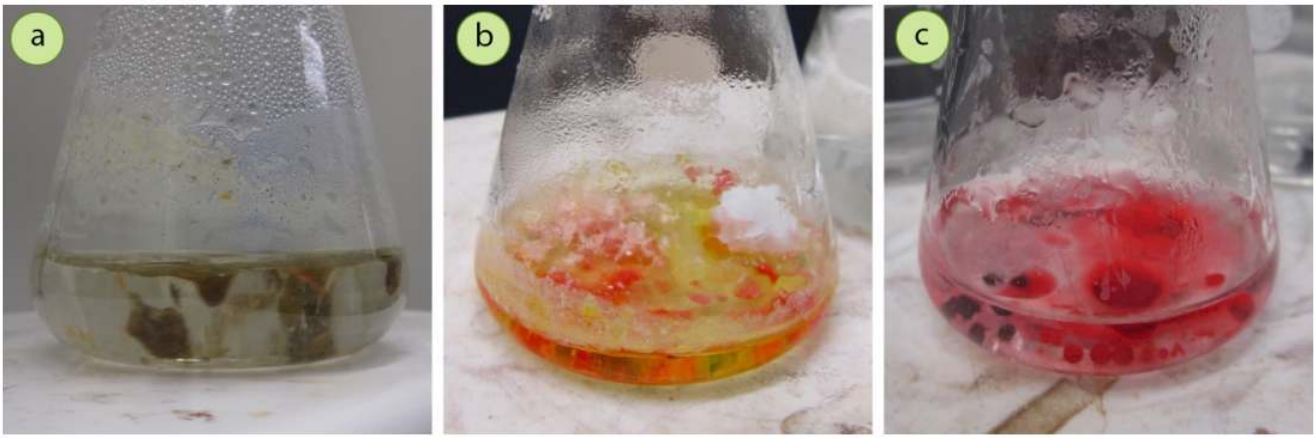


Figure 3.63: Examples of a sample "oiling out" during the heating process (which would look similar as a sample cools): a) Oily droplets in a tan acetanilide crude solid, b+c) Oily droplets containing methyl red and acetanilide in water.

The reasons for oiling out are several, and it can happen while dissolving the solid and during crystallization. It may be that the melting point of the solid is naturally low. It may also be that a solid is so impure that its melting point is dramatically lowered (as impurities lower the melting point).

There are several ways to attempt to fix an oiled out solution:

1. Return the sample to the heat source and add a bit more solvent, then cool the solution again. (If using a mixed solvent system, add more of the "soluble solvent"). The solid may have been coming out of solution too quickly (and thus at a temperature above its melting point), so it may stay soluble longer if there is more solvent.
2. Add a charcoal step if it was not already a part of the crystallization. The solid may be melting because there are large quantities of impurities, which charcoal can remove. This especially might work if a colored tint is noticed in the hot solution.

If either of these methods fail, recover the crude solid by rotary evaporation and attempt another crystallization. If the failed attempt used a mixed solvent, try a single solvent if possible. Or choose another solvent with similar solubility properties, but with

a lower boiling point. For example, if ethanol were used as the solvent the first time, repeat the crystallization using methanol. Methanol has similar solubility properties as ethanol, but its lower boiling point may allow for the solid to come out of solution above its melting point.

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CHAPTER OVERVIEW

3: Alcohols, Ethers, Thiols, Sulfides, and Amines

3.1: Alcohols and Phenols

3.1.1: Introduction

3.1.2: Naming Alcohols and Phenols

3.1.3: Properties of Alcohols and Phenols

3.1.4: Preparation of Alcohols- A Review

3.1.5: Alcohols from Carbonyl Compounds- Reduction

3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents

3.1.7: Reactions of Alcohols

3.1.8: Oxidation of Alcohols

3.1.9: Protection of Alcohols

3.1.10: Phenols and Their Uses

3.1.11: Reactions of Phenols

3.1.12: Spectroscopy of Alcohols and Phenols

3.1.S: Alcohols and Phenols (Summary)

3.2: Ethers and Epoxides; Thiols and Sulfides

3.2.1: Introduction

3.2.2: Names and Properties of Ethers

3.2.3: Preparing Ethers

3.2.4: Reactions of Ethers- Acidic Cleavage

3.2.5: Reactions of Ethers- Claisen Rearrangement

3.2.6: Thiols and Sulfides

3.3: Amines and Heterocycles

3.3.1: Naming Amines

3.3.2: Structure and Properties of Amines

3.3.3: Synthesis of Amines

3.3.4: Reactions of Amines

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SECTION OVERVIEW

3.1: Alcohols and Phenols

Learning Objectives

When you have completed Chapter 17, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using any of the reactions introduced in this chapter, together with any number of the reactions discussed in *Chemistry 350*.
3. solve "road-map" problems that require a knowledge of the chemistry of alcohols and phenols, in addition to the chemistry of the other classes of compounds discussed in *Chemistry 350*.
4. define, and use in context, the key terms introduced in this chapter.

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

The discussion begins with an outline of the nomenclature of alcohols and phenols. We review the physical properties of these compounds, and discuss methods used to obtain the lower members of the series on an industrial scale. A detailed discussion of the laboratory preparation of alcohols follows, with particular emphasis on those methods that involve either the reduction of a carbonyl compound or the use of a Grignard reagent.

Certain reactions of alcohols were discussed in previous chapters. In this chapter, we concentrate on the oxidation of alcohols to carbonyl compounds. We also introduce the concept of protecting a sensitive functional group during an organic synthesis. The discussion then turns to the uses of phenols, their preparation and their chemical reactivity.

Infrared, nuclear magnetic resonance and mass spectroscopy each can provide valuable information about alcohols and phenols, and we illustrate the application of these techniques to the identification of unknown alcohols and phenols with a number of examples.

3.1.1: Introduction

3.1.2: Naming Alcohols and Phenols

3.1.3: Properties of Alcohols and Phenols

3.1.4: Preparation of Alcohols- A Review

3.1.5: Alcohols from Carbonyl Compounds- Reduction

3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents

3.1.7: Reactions of Alcohols

3.1.8: Oxidation of Alcohols

3.1.9: Protection of Alcohols

3.1.10: Phenols and Their Uses

3.1.11: Reactions of Phenols

3.1.12: Spectroscopy of Alcohols and Phenols

3.1.S: Alcohols and Phenols (Summary)

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3.1.1: Introduction

Objectives

After completing this section, you should be able to

1. describe the structural differences among alcohols, phenols and enols.
2. write equations describing the industrial preparation of the two simplest alcohols: methanol and ethanol.

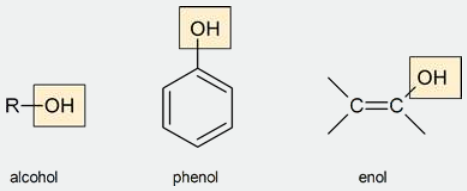
Key Terms

Make certain that you can define, and use in context, the key terms below.

- alcohol
- enol
- phenol

Study Notes

Alcohols and phenols are organic compounds with at least one hydroxyl group attached to a saturated or an aryl carbon, respectively. Enols are a related third class of compounds, with the hydroxyl group attached to a vinylic carbon. We will discuss enols in more detail in Chapter 22.



The reading correctly points out the toxicity of methanol, and describes the adverse effects of its consumption. These effects have not been exaggerated; you may recall reading about the deaths of six residents of Peerless Lake, Alberta, in 1986, brought about by drinking photocopier fluid which contained methanol (or methyl hydrate as it is often called in press reports). In 2000, more than 100 people died in El Salvador after black marketeers sold discarded liquor bottles that had been refilled with a methanol mixture. Indeed the problem has repeated itself globally and so often that in 2014 the World Health Organization released an information note warning of methanol poisoning outbreaks which “occur when methanol is added to illicitly- or informally-produced alcoholic drinks.”

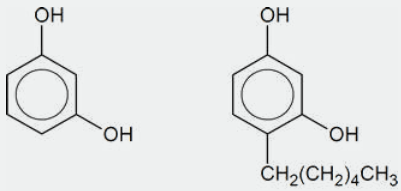
Almost everyone is aware that the alcohol present in alcoholic beverages is ethanol (also called ethyl alcohol or grain alcohol). However, many people do not realize that in its pure state, or in solutions of high concentration, this substance is poisonous. In the laboratory one may find containers labelled “absolute ethanol,” “95% ethanol” and “denatured ethanol.” The acquisition of ethanol by laboratories, and its subsequent disposal, is carefully monitored by provincial authorities. On no account should one consider drinking laboratory ethanol, even after it has been diluted to a concentration equivalent to that found in beer. Denatured alcohol is ethanol to which appropriate quantities of poisonous or nauseating substances (such as methanol) have been added.

A third commonly encountered alcohol, isopropyl alcohol (“rubbing alcohol” or 2-propanol), is also toxic. It has the ability to kill germs and has a temporary lubricating effect during the rubbing process. Unlike methanol, 2-propanol is not absorbed through the skin; therefore it poses less of a health hazard.

The use of alcohols as fuels is well established. In 2010, the Canadian federal government joined several of the provinces in requiring that all gasoline must include an average of five per cent ethanol. Some gasoline producers, notably Husky/Mohawk, average ten per cent ethanol content in their products. Some especially modified vehicles can use fuel that consists of 85 per cent ethanol (E85).

A phenol is an organic compound in which a hydroxyl group is directly bonded to one of the carbon atoms of an aromatic ring.

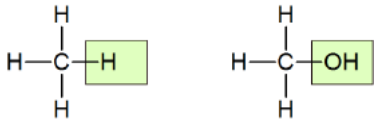
Until the late nineteenth century, a person undergoing surgery had to face the fact that he or she might suffer the consequences of what we now know to be bacterial infection, contracted during the course of the operation. The physicians of the time did not know that bacteria existed, and had no way to counter the problems that bacteria caused. In 1867, Joseph Lister, who had learned of the existence of bacteria as a result of research done by Louis Pasteur, began using solutions of phenol to clean wounds and surgical instruments. The phenol solution was an effective antiseptic, killing bacteria, and as a result, a patient's chances of surviving surgery improved greatly. Phenol itself was rather strong for these purposes—it burns healthy tissue—and substitutes were eventually found. One such substitute, used today in throat lozenges and mouthwashes, is 4-*n*-hexylresorcinol.



resorcinol 4-*n*-hexylresorcinol

Alcohols

Molecules of alcohols contain one or more hydroxyl groups (OH groups) substituted for hydrogen atoms along the carbon chain. The structure of the simplest alcohol, methanol (methyl alcohol), can be derived from that of methane by putting an OH in place of one of the H's:



methane methanol

The name, too, is derived from the name methane by replacing the final *e* with *ol* (for alcoh*ol*). The general formula for an alcohol may be written as R—OH, where R represents the hydrocarbon (alkane) portion of the molecule and is called an **alkyl group**. In methanol, R is the methyl group CH_3.

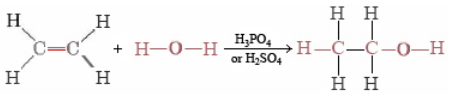
Methanol is also called wood alcohol because it can be obtained by heating wood in the absence of air, a process called **destructive distillation**. Methanol vapor given off when the wood is heated can be condensed to a liquid by cooling below its boiling point of 65°C. The effect of polarity and especially hydrogen bonding due to the OH group is evident when this is compared with the temperature of –85°C at which ethane, C_2H_6, boils. Both molecules contain 18 electrons and are nearly the same size, and so London forces should be about the same, but the OH group in one methanol molecule can form strong hydrogen bonds with an OH in another molecule. Methanol is an important industrial chemical—nearly 3×10^{10} kg was produced worldwide in 2003[1]. Some was made by destructive distillation, but most was synthesized from hydrogen and carbon monoxide:

$$2\,H_2\,(g) + CO\,(g) \longrightarrow CH_3OH\,(l)$$

This reaction is carried out at pressures several hundred times normal atmospheric pressure, using metal oxides as catalysts. Methanol is mainly used to make other compounds from which plastics are manufactured, but some is consumed as fuel in jet engines and racing cars. Methanol is also a component of nonpermanent antifreeze and automobile windshield-washer solvent.

The second member of the alcohol family is ethanol (ethyl alcohol)— the substance we commonly call *alcohol*. Ethanol is also known as grain alcohol because it is obtained when grain or sugar ferments. **Fermentation** refers to a chemical reaction which is speeded up by enzymes and occurs in the absence of air. (Enzymes, catalysts which occur naturally in yeasts and other living organisms, are discussed in more detail elsewhere.)

Ethanol can also be synthesized by adding H_2O to ethene, obtained during petroleum refining:



This is a typical example of an **addition reaction**. The H and OH from H_2O are added to the ethene molecule and held there by electrons made available when one-half of the double bond breaks.

Ethanol is used as a solvent, in some special fuels, in antifreeze, and to manufacture a number of other chemicals. You are probably most familiar with it as a component of alcoholic beverages. Ethanol makes up 3 to 6 percent of beer, 12 to 15 percent of most wines, and 49 to 59 percent of distilled liquor. (The “proof” of an alcoholic beverage is just twice the percentage of ethanol.) Alcohol’s intoxicating effects are well known, and it is a mild depressant. Prolonged overuse can lead to liver damage. Methanol also produces intoxication but is much more poisonous than ethanol—it can cause blindness and death. Denatured alcohol is ethanol to which methanol or some other poison has been added, making it unfit for human consumption. Most of the ethanol not used in alcoholic beverages is denatured because in that form its sale is taxed at a much lower rate.

Phenols

Compounds in which a hydroxyl group is bonded to an aromatic ring are called phenols. The chemical behavior of phenols is different in some respects from that of the alcohols, so it is sensible to treat them as a similar but characteristically distinct group. A corresponding difference in reactivity was observed in comparing aryl halides, such as bromobenzene, with alkyl halides, such as butyl bromide and tert-butyl chloride. Thus, nucleophilic substitution and elimination reactions were common for alkyl halides, but rare with aryl halides. This distinction carries over when comparing alcohols and phenols, so for all practical purposes substitution and/or elimination of the phenolic hydroxyl group does not occur.

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3.1.2: Naming Alcohols and Phenols

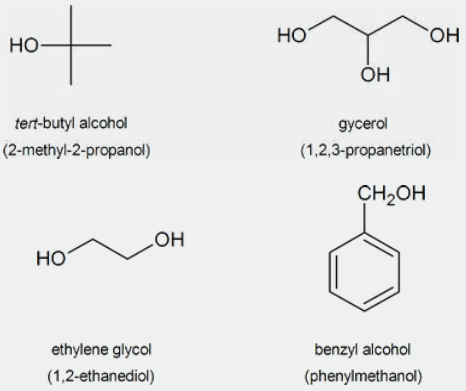
Objectives

After completing this section, you should be able to

1. identify an alcohol as being primary, secondary or tertiary, given its structure, its IUPAC name or its trivial name.
2. write the IUPAC name of an alcohol or phenol given its Kekulé, condensed or shorthand structure.
3. draw the structure of an alcohol or phenol given its IUPAC name.
4. identify a number of commonly occurring alcohols (e.g., benzyl alcohol, *tert*-butyl alcohol) by their trivial names.

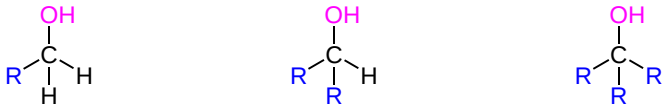
Study Notes

The following are common names of some alcohols (with IUPAC name).



Alcohol Classifications

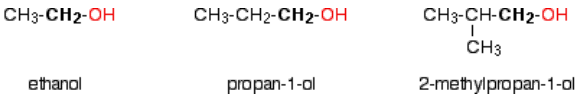
Alcohols can be classified as primary (**1°**), secondary (**2°**), or tertiary (**3°**) depending on the number of alkyl substituents attached to the carbon bonded to the O-H group.



Primary (1°) Alcohol **Secondary (2°) Alcohol** **Tertiary (3°) Alcohol**

Primary alcohols

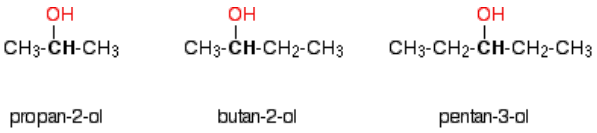
In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the -OH group. There is an exception to this. Methanol, CH_3OH, is counted as a primary alcohol even though there are no alkyl groups attached to the carbon with the -OH group on it.

Secondary alcohols

In a secondary (2°) alcohol, the carbon with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples:



propan-2-ol butan-2-ol pentan-3-ol

Tertiary alcohols

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



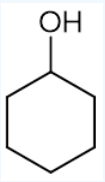
2-methylpropan-2-ol 2-methylbutan-2-ol

? Exercise 3.1.2.1

Indicate if the following molecules are 1°, 2°, or 3° alcohols:

1)

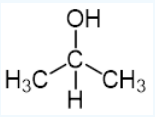
a)



b) $(CH_3)_3COH$

c) $CH_3CH_2CH_2OH$

d)



Answer

1)

a) Secondary

b) Tertiary

c) Primary

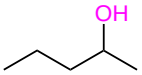
d) Secondary

Naming Alcohols

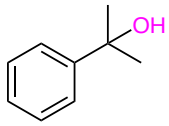
The IUPAC naming of alcohols is based off the name of the parent alkane chain:

1. The longest chain containing the hydroxyl group (OH) is considered the parent chain. Remove the final **-e** from the parent alkane chain name and add the suffix **-ol**.
2. Number the parent alkane chain such that the hydroxyl group get the lowest possible number. Older IUPAC rules origianlly place the hydroxyl group number before the name of the parent chain. However, the newer rules places the number before the **-ol** suffix.

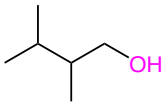
3. Number the substituents according to their position on the parent chain. Then list the substituents in alphabetical order.



2-Pentanol
(New: Pentan-2-ol)



2-Phenyl-2-propanol
(New: 2-Phenylpropan-2-ol)

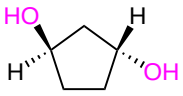


2,3-Dimethyl-1-butanol
(New: 2,3-Dimethylbutan-1-ol)

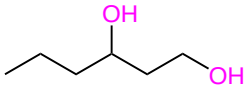
4. When naming a cyclic structure with a hydroxyl group, the -OH is assumed to be on the first carbon.

5. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. Also, when a prefix is used the **-e** is not removed from the parent chain name ex. 2,3-hexanediol

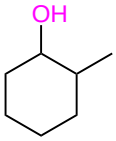
6. When an alkene and alcohol are present in a molecule it is named as follows **(location of the alkene)-(prefix for the parent chain + en)-(location of the hydroxyl)-ol**



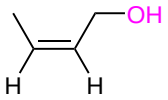
trans-1,3-Cyclopentanediol
(trans-Cyclopentane-1,3-diol)



1,3-Hexanediol
(Hexane-1,3-diol)



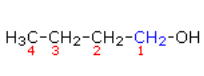
2-Methylcyclohexanol



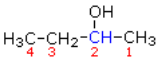
(Z)-2-Buten-1-ol

Common Names of Alcohols

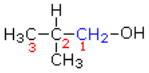
The common system of naming is often used when the alcohol only contains a few carbons. As discussed in **Section 3-3**, the common system names alcohols as if the hydroxyl group (-OH) is attached to a single substituent with the word alcohol added at the end **(Name of the substituent + Alcohol)**. Also, some simple alcohols are given their own generic name such ethylene glycol or glycerol.



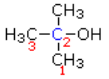
1-butanol
(butyl alcohol)



2-butanol
(*sec*-butyl alcohol)



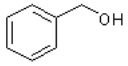
2-methyl-1-propanol
(isobutyl alcohol)



2-methyl-2-propanol
(*tert*-butyl alcohol)



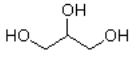
2-propen-1-ol
(allyl alcohol)



phenylmethanol
(benzyl alcohol)



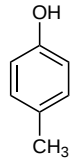
1,2-ethanediol
(ethylene glycol)



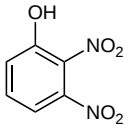
1,2,3-propanetriol
(glycerol)

Naming phenols

Phenols are named using the rules for aromatic compounds discussed in **Section 15-1**. Note that *-phenol is used* as the ending rather than *-benzene*.



p-methylphenol



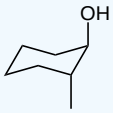
2,3-dinitrophenol

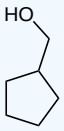
Exercises

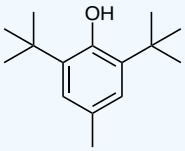
Exercise 3.1.2.1

Give IUPAC names for the following structures.





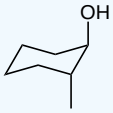




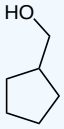
Answer



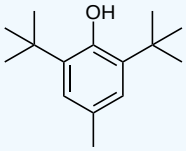
butan-2-ol



(1*R*, 2*R*)-2-mthylcyclohexan-1-ol



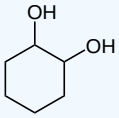
cyclopentylmethanol

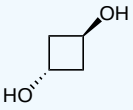


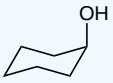
2,6-di-tert-butyl-4-methylphenol

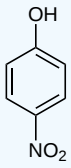
Exercise 3.1.2.2

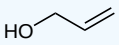
Name the following structures.







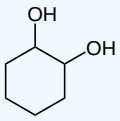




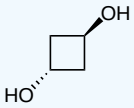


Answer

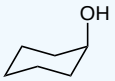
https://chem.libretexts.org/@go/page/413180



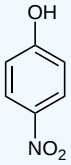
cyclohexane-1,2,-diol



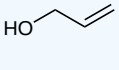
trans-cyclobutane-1,3-diol



cyclohexanol



4-nitrophenol



prop-2-en-1-ol



cycloproanol

Exercise 3.1.2.3

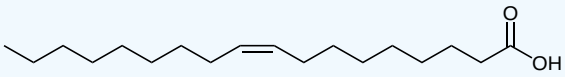
Draw and name all the alcohol isomers of C_3H_9O

Answer

Add texts here. Do not delete this text first.

Exercise 3.1.2.4

Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.

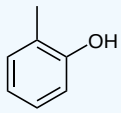


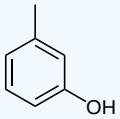
Answer

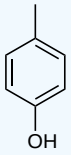
(9Z)-Octadec-9-enoic acid

Exercise 3.1.2.5

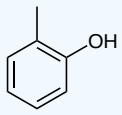
Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.



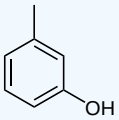




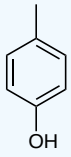
Answer



2-methylphenol



3-methylphenol



4-methylphenol

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3.1.3: Properties of Alcohols and Phenols

Objectives

After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

Key Terms

Make certain that you can define, and use in context, the key terms below.

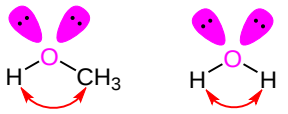
- acid ionization constant (K_a)
- alkoxide ion (RO^-)
- phenoxide ion (ArO^-)

Study Notes

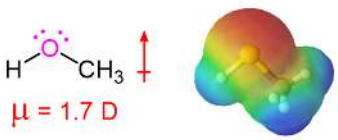
You may wish to review the concept of hydrogen bonding, which should have been discussed in your first-year general chemistry course.

Boiling Points of Alcohols

The oxygen in alcohols and phenols is sp^3 hybridized which gives the roughly the same tetrahedral geometry as water. The bond angle of methanol (108.5 º) is slightly less than the tetrahedral value mainly due to the presence of its lone pair electrons.



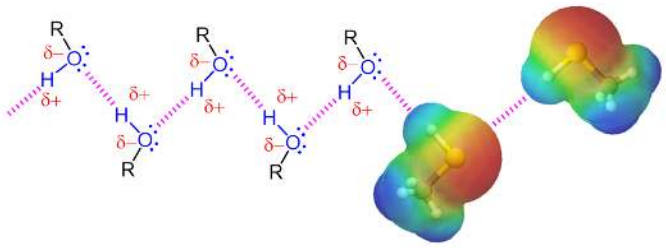
The presence of a highly electronegative oxygen confers a measure of polar character to alcohols. Much of the electron density of an alcohol is drawn towards the oxygen, giving alcohols a relatively high dipole momeny (1.7 D for Methanol).



The Dipole Moment of Methanol

Alcohols contain an extremely polar covalent O-H bond. The electrons in this bond are strongly drawn towards the oxygen giving it a partial negative charge (delta-) while the electrons are drawn away from the hydrogen giving is a partial positive charge

(delta+). The polar character of this bond leads to an interaction between alcohol molecules where the positively polarized hydrogen of one alcohol molecule is attracted to the lone pair electrons on the electronegative oxygen atom of a different alcohol molecule. This creates a type of intramolecular attraction is called “hydrogen bonding.” Although the strength of such attractions are much less than most conventional chemical bonds, they are still significant (about 5 to 10 kcal per bond). For an alcohol to vaporize, these intramolecular hydrogen bonding attractions must be broken making alcohols substantially less volatile, have higher boiling points, and greater water solubility than molecules with a similar molecular weight (Table **3.1.3.1**). An example of this is seen when comparing 1-propanol (MW = 60.1), Chloroethane (MW = 64.5), and butane (MW = 58.1) which have boiling points of 94.7 ºC, 12.3 ºC, and -1 ºC respectively.



A Representation of Hydrogen Bonding in Alcohols

This table shows that alcohols (in blue) have higher boiling points than haloalkanes and alkanes with the equivalent molecular weight. It also shows that the boiling points of alcohols increase with the number of carbon atoms.

Table **3.1.3.1**: Physical Properties of Selected Alcohols, Haloalkanes, and Alkanes

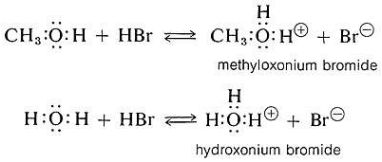
Compound	IUPAC Name	Molecular Weight (g/mol)	Melting Point (^{o}C)	Boiling Point (^{o}C)
CH_3OH	Methanol	32.0	-97.8	65.0
CH_3Cl	Chloromethane	50.5	-97.7	-24.2
CH_3CH_2OH	Ethanol	46.1	-114.7	78.5
$CH_3CH_2CH_2CH_3$	Butane	58.1	-140.	-1
$CH_3CH_2CH_2OH$	1-Propanol	60.1	-126.5	97.4
CH_3CH_2Cl	Chloroethane	64.5	-136.4	12.3
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72.2	-130	36.3
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74.1	-89.5	117.3
$CH_3(CH_2)_4OH$	1-Pentanol	88.1	-79	138

Solubility of Alcohols in Water

Alcohols and water have the ability to form hydrogen bonds with one another which tends to make the two liquids miscible. Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

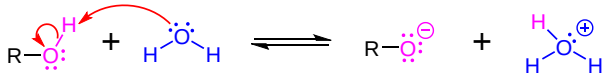
Basic Properties of Alcohols

Alcohols are weak bases similar in strength to water and can accept protons from strong acids to form the conjugate acid called oxonium ions (ROH_2^+). An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide from the reaction of hydrogen bromide and water:

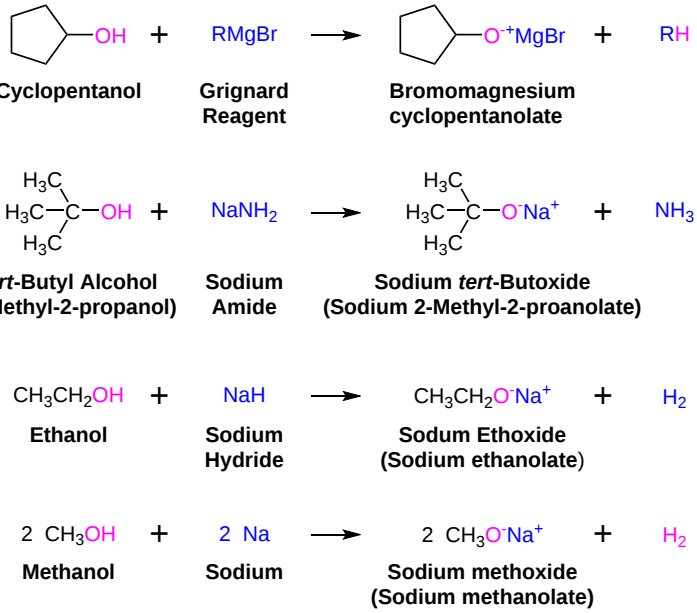


Acidic Properties of Alcohols

Alcohols, like water, are both weak bases and weak acids. In aqueous solutions, alcohols dissociate slightly by donating a hydrogen to water. This creates the alcohol's conjugate base, called an alkoxide ion (RO^-), along with hydronium (H_3O^+). The acid ionization constant (K_a) of ethanol is about 10^{-18}, which is slightly less than that of water. Alcohols, such as ethanol, can be deprotonated to form its conjugate base by reaction with a stronger base, such as sodium amide ($NaNH_2$), sodium hydride (NaH), or Grignard reagents (RMgBr). Alkoxides can also be formed using sodium or potassium metal which reacts vigorously but controllably with alcohols.



Once created, alkoxides act as bases and are often used as reagents in organic chemistry. Alkoxide's systematic names are based of the corresponding alcohol with the suffix *-ate* added. For example, ethanol becomes ethanolate. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance. Common names are often used for small alkoxides. Common names are generated as: (Name of the positive counter ion) (Prefix for the parent chain + oxide). Example: ethanol becomes ethoxide.



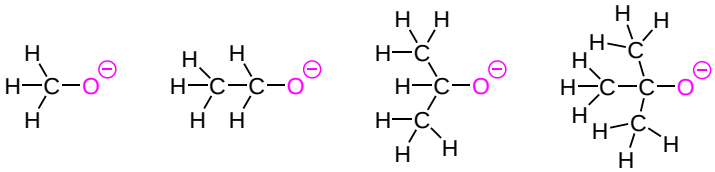
As discussed in **Section 2.8**, the strength of an acid in water can be expressed either by its K_a or its pK_a. Compounds with a lower K_a and a higher pK_a are considered less acidic than compound with a higher K_a and a lower pK_a.

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{3.1.3.1}$$

$$pK_a = -\log K_a$$

In general, alcohols in aqueous solution are slightly less acidic than water. The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the pK_a is increased as R is changed from primary to secondary to tertiary; therefore, *tert*-butyl alcohol is less acidic than ethanol. This trend is explained by the importance of solvation

in equilibrium. In solution, the larger alkoxide ions, are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions. Acidity of alcohols therefore decreases as the size of the conjugate base increases. This trend can be clearly seen when comparing alkoxide size to the pKa of the corresponding alcohol listed in Table **3.1.3.2**.



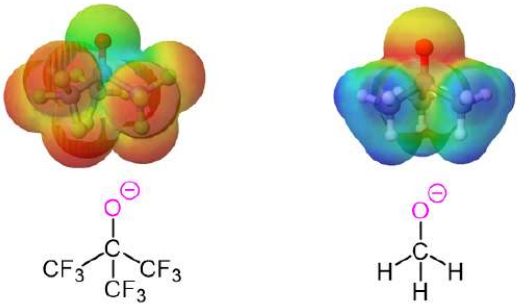
Methoxide **Ethoxide** **Isopropoxide** ***tert*-Butoxide**

$$ROH + OH^- \rightleftharpoons RO^- + HOH$$

Table **3.1.3.2**: The pKa's of various alcohols

R	Name	pK_{a1}
H	water	14.0
CH_3	methanol	15.5
CH_3CH_2	ethanol	15.9
$(CH_3)_2CH$	propan-2-ol (isopropyl alcohol)	16.5
$(CH_3)_3C$	2-methylpropan-2-ol (*tert*-butanol)	17
C_6H_5 (phenyl)	phenol	9.95

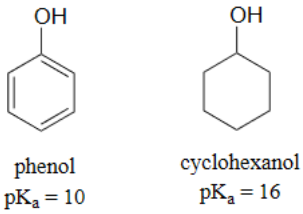
The addition of an electron-withdrawing group, such as an electronegative halogen, can increase the acid strength of an alcohol by stabilizing its alkoxide conjugate base through induction (**Section 2.10**). The electron-withdrawing group helps to spread out the electron density of the alkoxide's negative charge, which has a stabilizing effect. The inductive effect is cumulative such that the acid strength of an alcohol becomes stronger (Lower pK_a) as the number of halogens increases. The presence of nine fluorines in nonafluoro-*tert*-butyl alcohol decreases its pK_a to 5.4 which is significantly more acidic than *tert*-butyl alcohol (pK_a = 18). The electron-withdrawing effect of the fluorines is clearly seen when comparing the electrostatic potential maps of the corresponding alkoxides. In *tert*-butoxide the molecule's electron density is firmly centered around the oxygen as shown by the orange/yellow color. In nonafluoro-*tert*-butoxide the molecule's electron density is almost completely removed from the oxygen and shifted to the fluorines.



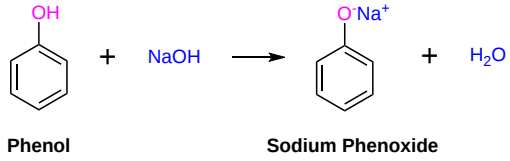
Nonafluoro-*tert*-butoxide (pK_a = 5.4) ***tert*-Butoxide (pK_a = 18)**

Acidity of Phenol

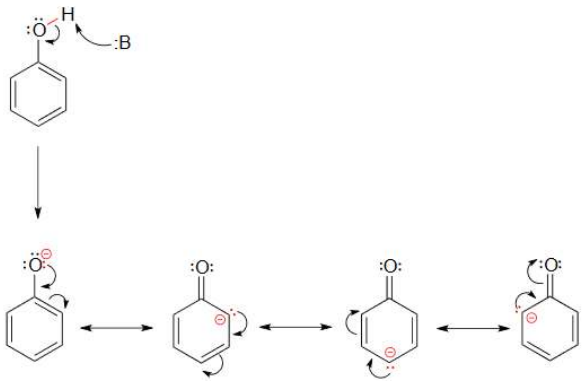
Another method for increasing acidity is through stabilizing a conjugate base through resonance effects. An excellent example of this effect is shown through phenol being roughly a million times more acidic than cyclohexanol.



Phenol is acidic enough to be deprotonated by weaker bases, such as sodium hydroxide (NaOH), to form the phenoxide ion.

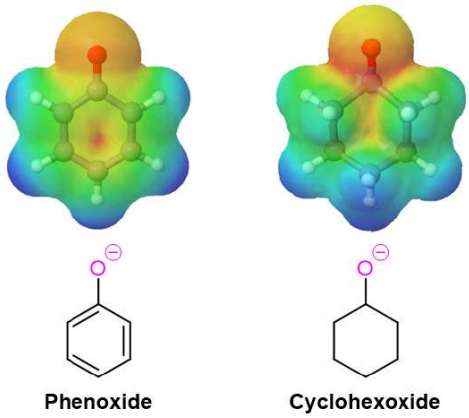


The increased acidity of phenol is caused by the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread throughout the whole ion allowing it to be highly stabilized.



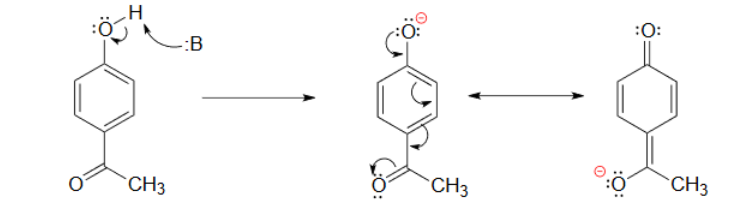
Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton. Essentially, the benzene ring is acting as an electron-withdrawing group by resonance.

The electrostatic potential maps below compare the phenoxide ion to an unconjugated alkoxide. The negative charge of the phenoxide ion, show as a yellow/orange color, is delocalized from oxygen into the aromatic ring (seen by the growing red color in the phenoxide ring).



Acidity of Substituted Phenols

Phenolic acidity is further enhanced by the presence of an additional electron-withdrawing substituent, such as a nitro or carbonyl, on the aromatic ring. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.

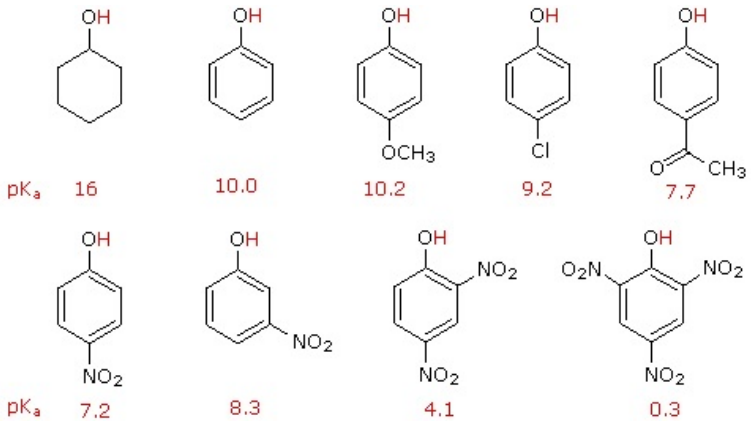


para-hydroxyacetophenone
(pKa = 4.2)

Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen atoms. The ketone group on the aromatic ring is acting as an electron withdrawing group and 'pulling' electron density towards itself, through both inductive and resonance effects.

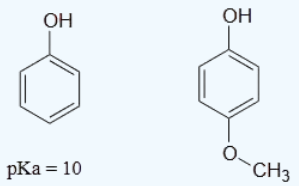
It is noteworthy that the influence of a nitro substituent is over ten times stronger in the *para*-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. This occurs since nitro groups at the meta position cannot accept the negative charge through resonance. Furthermore additional nitro groups have an additive influence if they are positioned *ortho* or *para* locations to the hydroxide. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Lastly, if an electron donating group is attached to aromatic ring, as in *p*-methoxyphenol, the phenoxide ion is destabilized which causes a decrease in acidity in the corresponding phenol.



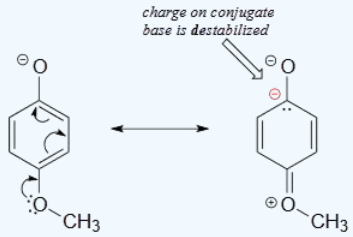
? Worked Example 3.1.3.1

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer

The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.

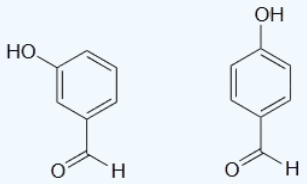


Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

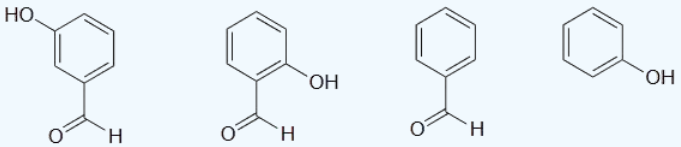
Exercise 3.1.3.1

1.

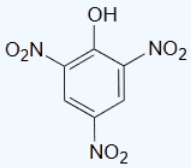
The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



2) Rank the four compounds below from most acidic to least.



3) Use a resonance argument to explain why picric acid has such a low pKa.



picric acid
pKa = 0.25

4) Predict which compound of each pair is more soluble in water and explain your reasoning.

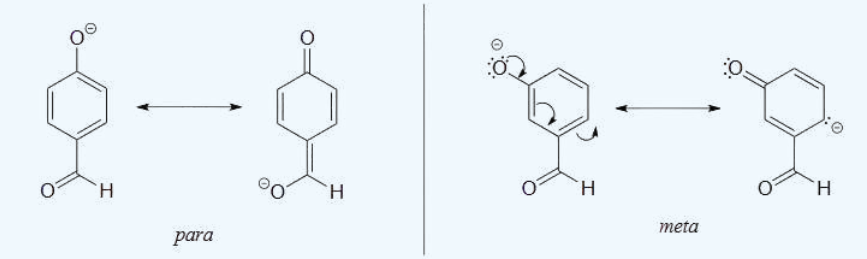
a. Butan-1-ol or pentan-1-ol
b. Phenol or cyclohexanol
c. Octan-1,3-diol or octan-1-ol
d. 1-Chlorohexane or hexan-1-ol

5) Predict which compound has the higher boiling point and explain your reasoning.

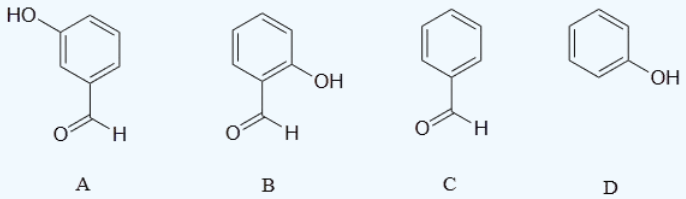
a. Water or ethanol
b. Butan-1-ol or octan-1-ol
c. Hexan-2-ol or hexan-2-one

Answer

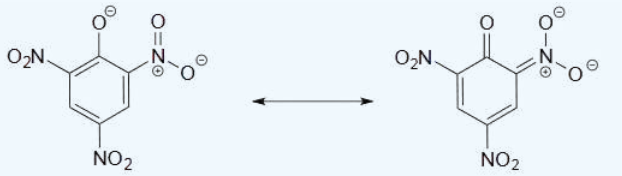
1) The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position



2) Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.



3) The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



4)

a. Butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
b. Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.
c. Octan-1,3-diol is more soluble in water as it has two hydroxy groups, allowing it to form more hydrogen bonds and interact with water better than octan-1-ol.
d. Hexan-1-ol is more soluble in water as it can hydrogen bond compared to alkyl halides, such as 1-chlorohexane, which are insoluble in water.

5)

a. Water has a higher boiling point compared to ethanol as it participates in more hydrogen bonding with other water molecules, thus requiring more energy to break the intermolecular attractions between water molecules.
b. Octan-1-ol has the higher boiling point compared to butan-1-ol. Both alcohols can H-bond, however the longer hydrophobic carbon chain tail of octan-1-ol experiences more van der Waal interactions compared to the shorter hydrophobic region of butan-1-ol leading to a higher boiling point.
c. Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

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3.1.4: Preparation of Alcohols- A Review

Objectives

After completing this section, you should be able to describe in detail the methods of preparing alcohols and diols, which you encountered in previous chapters.

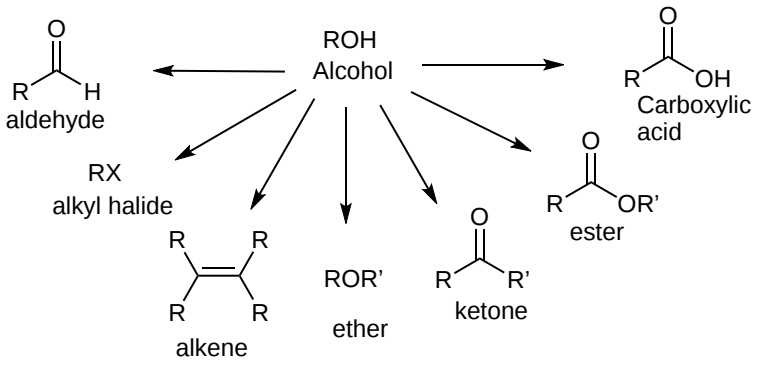
Study Notes

If necessary, you should review Sections 8.4 and 8.5 describing direct hydration of alkenes, and Section 8.7 describing preparation of cis and trans diols from alkenes. Section 8.7 also gives more details on the formation of the respective osmate and epoxide intermediates of these reactions.

Introduction

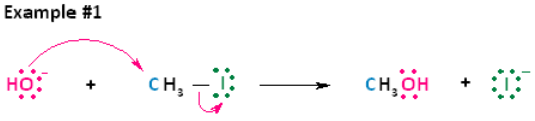
Alcohols are considered on of the more important functional groups in organic chemistry. They can be prepared from compounds containing a wide assortment of functional groups. Also, the can be used to create compounds with a wide variety of functional groups such as: alkenes, ketones, carboxylic acids, and others. Many functional group conversions can be accomplished through the preparation of an alcohol giving them an important central position in organic synthesis. ex. Alkene → Alcohol → Ketone.

Many methods for the preparation of alcohols have been discussed in previous chapter of this textbook and will be review in this section.



Alcohols from Substitution Reactions

Methyl and primary alkyl halides can be converted to alcohols by using an S_N2 reaction with OH^- as a nucleophile (Section 11.5). Also, secondary and tertiary alkyl halides can be converted to alcohols by an S_N1 reaction using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents (Section 11.7).

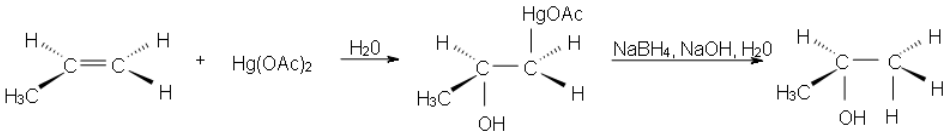


The Synthesis of Methanol Using an S_N2 Reaction

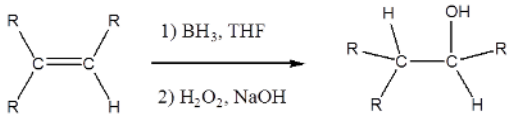
Alcohols from Alkenes

Oxymercuration - demercurationis a special electrophilic addition (Section 8.5). It is anti-stereospecific and regioselective. This reaction involves mercury undergoing electrophilic addition to the alkene double bond forming a *Mercurinium Ion Bridge*. A water molecule then attacks the most substituted carbon to open the mercurium ion bridge, followed by proton transfer to form a hydroxyl group (-OH). The organomercury intermediate is then reduced by sodium borohydride. Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's Regioselectivity with the OH group attached to the most

substituted carbon and the H is attached to the least substituted carbon. Also, the H and OH species will be anti to each other in the product.

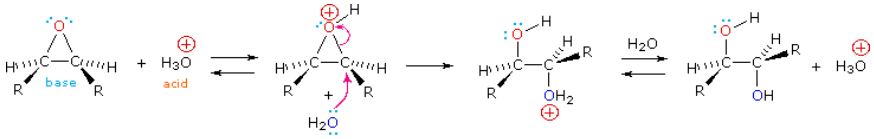


Hydroboration-Oxidation is a two step pathway used to produce alcohols (Section 8.6). It is syn-stereospecific and regioselective. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. The organoborane intermediate is then converted to an alcohol by reaction with hydrogen peroxide (H_2O_2) and sodium hydroxide (NaOH). The hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific ***(syn addition)***, meaning that the addition of the H and OH species takes place on the same face of the double bond leading to their ***cis*** configuration in the product. Because the BH_3 can attack either face of the alkene, this reaction can product a racemic mixture of enantiomers in the product.

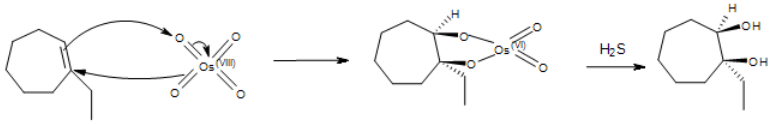


Diols from alkenes

Epoxides may be cleaved by aqueous acid to give anti-1,2-diols which are also called glycols. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by a water nucleophile. Because the nucleophilic attach utilizes an S_N2 mechanism the result is an anti-stereospecific configuration of the diol product. The water nucleophile prefers to attack the more substituted carbon on the epoxide which allows for regioselectivity in the reaction.



Osmium tetroxide oxidizes alkenes to give 1,2-diols through syn addition. The reaction with OsO_4 is a concerted process that creates a cyclic intermediate with no rearrangements. The intermediate osmium compound is reduced to the diol product by reduction with H_2S or $NaHSO_4$ with H_2O.

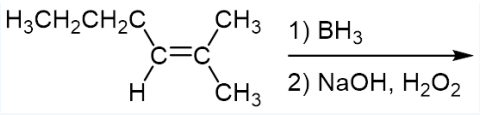


This *syn*-dihydroxylation complements the epoxide-hydrolysis sequence which creates an *anti*-dihydroxylation product. This reaction lack regioselectivity so an alkene reacts with osmium tetroxide there is a possibility of a reaction producing a racemic mixture as the product. In general for this reaction, cis alkenes produce a meso product while trans alkenes produce a racemic mixture as the product.

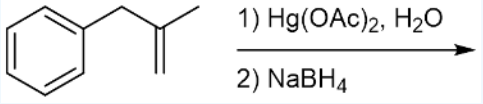
? Exercise 3.1.4.1

1) Predict the products of the following reactions:

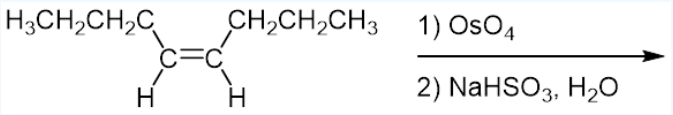
a)



b)



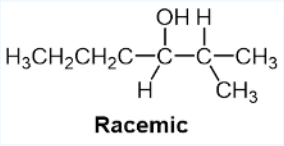
c)



Answer

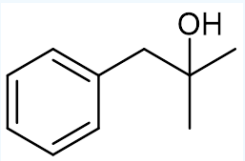
1)

a)

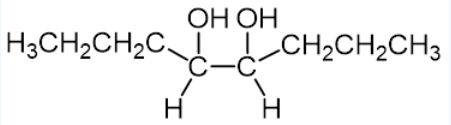


Racemic

b)



c)



Meso

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3.1.5: Alcohols from Carbonyl Compounds- Reduction

Objectives

After completing this section, you should be able to

1. determine whether a given reaction should be classified as an oxidation or a reduction.
2. write an equation to represent the reduction of an aldehyde or ketone using sodium borohydride or lithium aluminum hydride.
   a. discuss the relative advantages and disadvantages of using sodium borohydride or lithium aluminum hydride to reduce aldehydes or ketones to alcohols.
   b. identify the product formed from the reduction of a given aldehyde or ketone.
   c. identify the aldehyde or ketone that should be used to produce a given alcohol in a reduction reaction.
   d. identify the best reagent to carry out the reduction of a given aldehyde or ketone.
3. write an equation to represent the reduction of an ester or a carboxylic acid to an alcohol.
   a. identify the product formed from the reduction of a given ester or carboxylic acid.
   b. identify the esters or carboxylic acids that could be reduced to form a given alcohol.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- (organic) oxidation
- (organic) reduction

Study Notes

In your course in first-year general chemistry, you probably discussed oxidation-reduction reactions in terms of the transfer of electrons and changes in oxidation numbers (oxidation states). In organic chemistry, it is often more convenient to regard reduction as the gain of hydrogen or loss of oxygen, and oxidation as the gain of oxygen or the loss of hydrogen. There is no contradiction in using these various definitions. For example, when hydrogen is added across the double bond of ethene to reduce it to ethane, the oxidation number of the doubly bonded carbon atoms decreases from −II to −III. Similarly, when 2-propanol



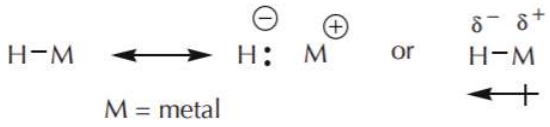
is oxidized to acetone



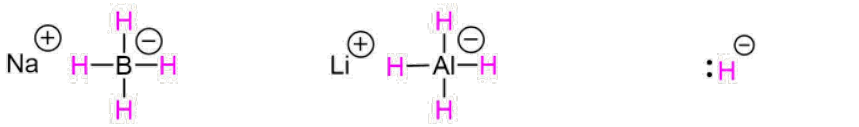
hydrogen is removed from the compound and the oxidation number of the central carbon atom increases from 0 to +II. If necessary, review the concept of oxidation number.

Reduction of Aldehydes and Ketones

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion (˙:H).** How much of the negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.

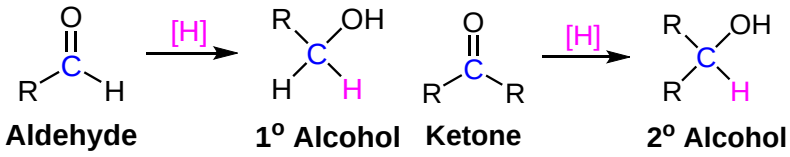


The most common sources of the hydride nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.

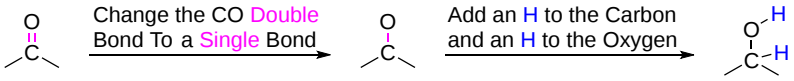


Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 1º-alcohols and ketones produce 2º-alcohols. These reactions will be discussed in more detail in **Chapter 19**.

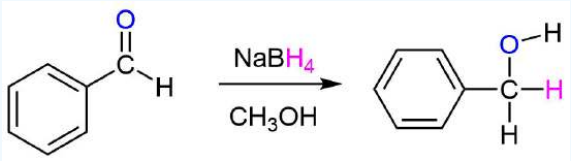


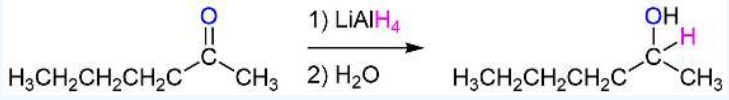
Predicting the Product of a Hydride Addition to a Carbonyl

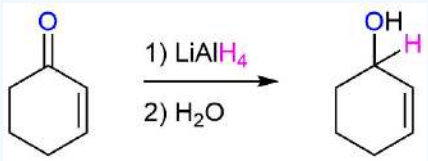


During the reduction the C=O double bond in the reactant and forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which originally in the carbonyl. Both of these single bonds will be attached to an "H" in the product formed.

Example 3.1.5.1





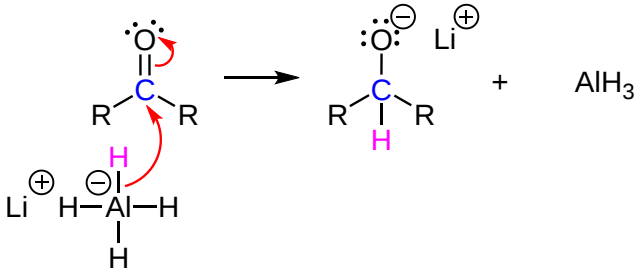


Mechanism

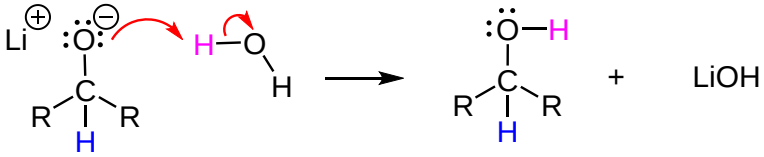
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of the hydride anion nucleophile. They hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source. In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding..

1) Nucleophilic attack to form a tetrahedral alkoxide intermediate



2) Protonation to form an alcohol



In metal hydride reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

Biological Reduction

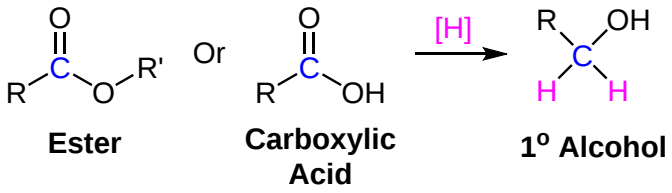
Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Instead of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

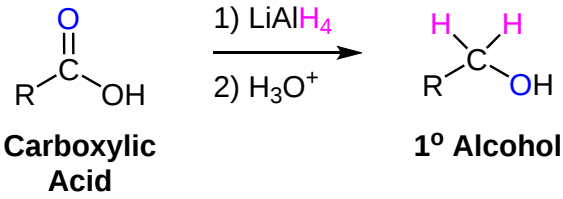
 CONADH2.png

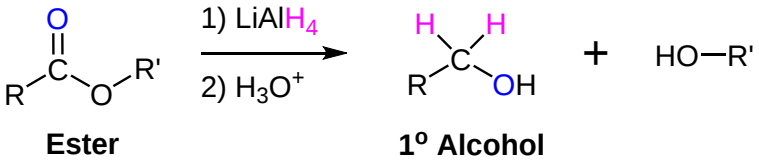
Reduction of Carboxylic Acids and Esters

Carboxylic acids and esters can be converted to 1° alcohols using Lithium aluminum hydride ($LiAlH_4$).

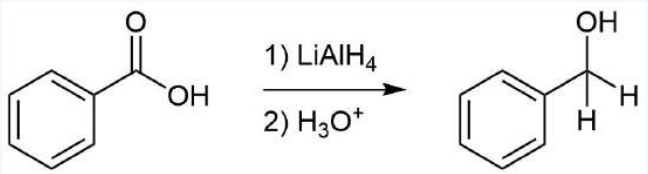


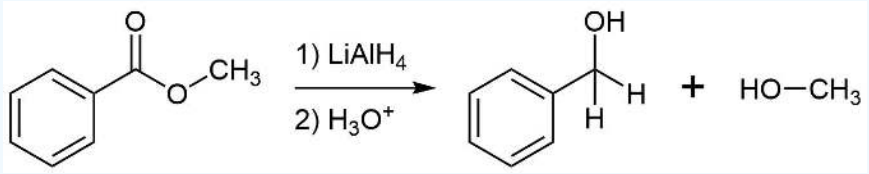
Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. Notice that during these reaction two hydrogen atoms are added the to carbonyl carbon whereas only one hydrogen atom was added during aldehyde and ketone reductions. These reactions will be discussed in more detail in **Chapter 21**.





Example 3.1.5.2

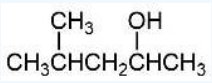




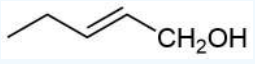
Worked Example

How would you prepare the following molecules using a hydride reduction?

a)



b)

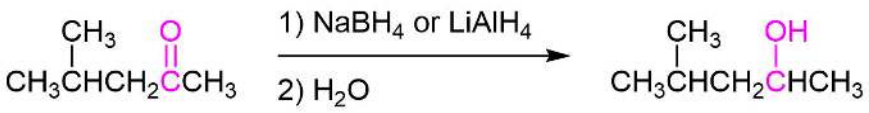


Answer

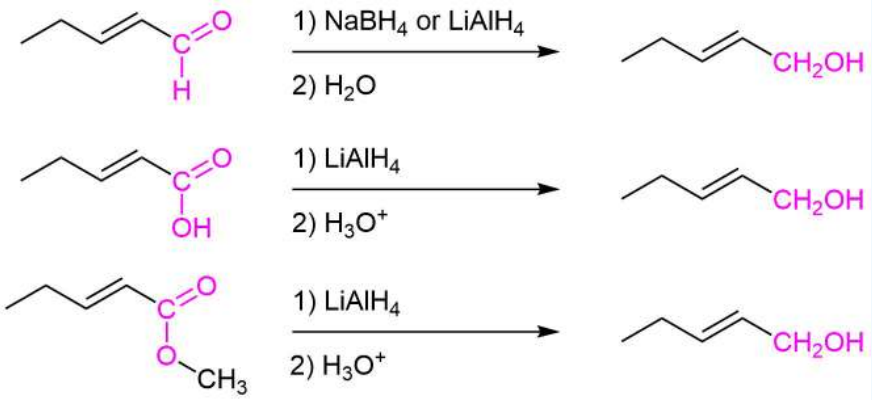
Analysis: The first step is to note if the target molecule is a 1° or 2° alcohol. Primary alcohols can be made by the hydride reduction of an aldehyde, carboxylic acid, or ester while secondary alcohols are made by the reduction of ketones. A 3°

alcohol cannot be made by a hydride reduction. Also, it is important to remember than aldehydes and ketones can be reduced by both $NaBH^4$ and $LiAlH_4$ whereas carboxylic acids and ester can only be reduced by $LiAlH_4$.

a) Because the target molecule is a secondary alcohol the starting material must be a ketone.



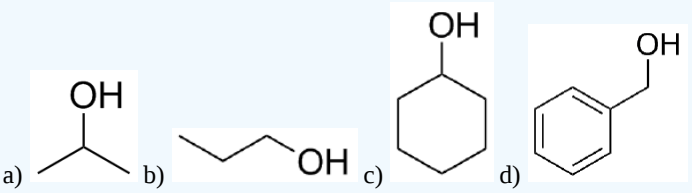
b) Because the target molecule is a primary alcohol the starting material could be an aldehyde, a carboxylic acid, or an ester.



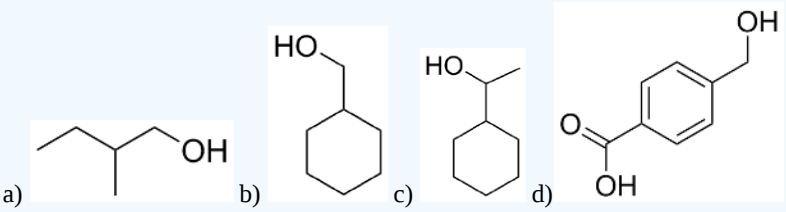
Exercises

Exercise 3.1.5.1

1) Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

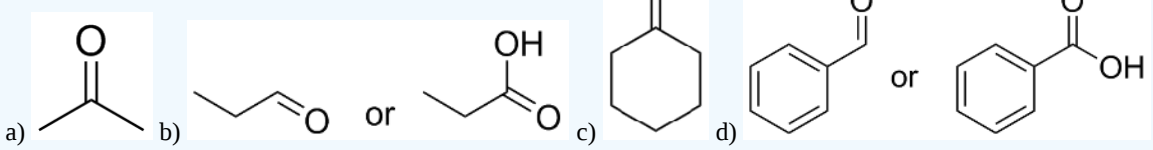


2) Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$

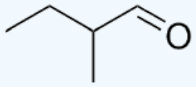


Answer

1)



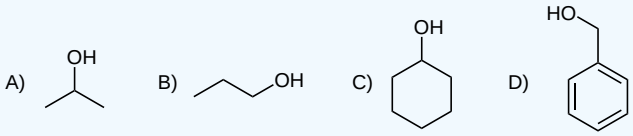
2) Note, $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



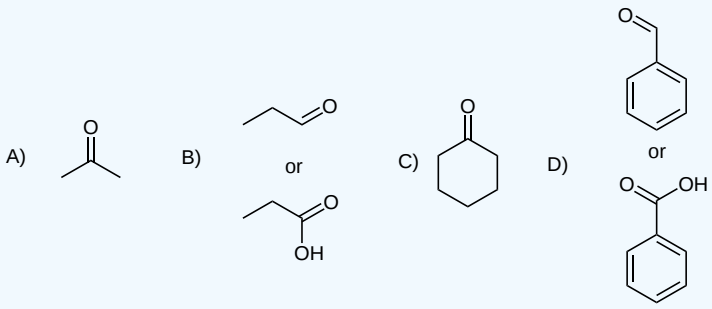
a) b)

Exercise 3.1.5.2

Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

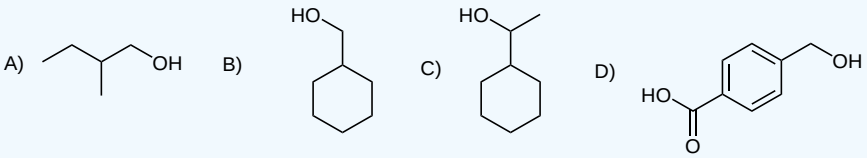


Answer



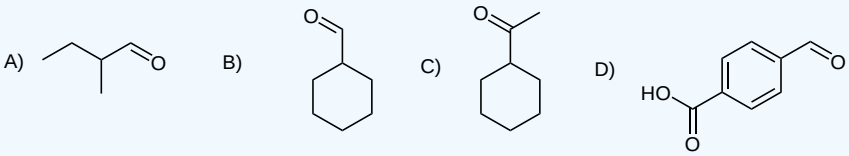
Exercise 3.1.5.3

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$.



Answer

Note: $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



3.1.5: Alcohols from Carbonyl Compounds- Reduction is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Dietmar Kennepohl.

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3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents

Objectives

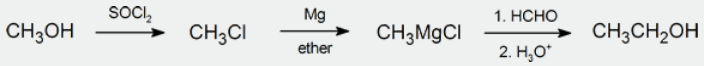
After completing this section, you should be able to

1. write an equation to illustrate the formation of a Grignard reagent.
2. write a general equation to represent the reaction of an aldehyde or ketone with a Grignard reagent.
3. write the detailed mechanism for the reaction of an aldehyde or ketone with a Grignard reagent.
4. identify the product formed from the reaction of a given aldehyde or ketone with a given Grignard reagent.
5. identify the carbonyl compound, the Grignard reagent, or both, needed to prepare a given alcohol.
6. write the equation to describe the reaction of an ester with a Grignard reagent.
7. identify the product formed from the reaction of a given ester with a given Grignard reagent.
8. discuss the limitations of Grignard reagent formation, and determine whether a given compound can be used to form such a reagent.

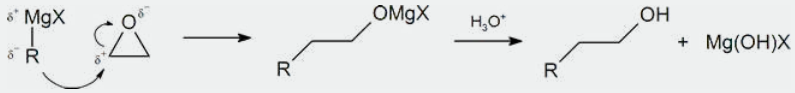
Study Notes

Before you begin this section, you may wish to review Section 10.8 which discusses the formation of Grignard reagents. Link to section 10.8

Grignard reagents are among the most frequently used reagents in organic synthesis. They react with a wide variety of substrates; however, in this section, we are concerned only with those reactions that produce alcohols. Notice that in a reaction involving a Grignard reagent, not only does the functional group get changed, but the number of carbon atoms present also changes. This fact provides us with a useful method for ascending a homologous series. For example:



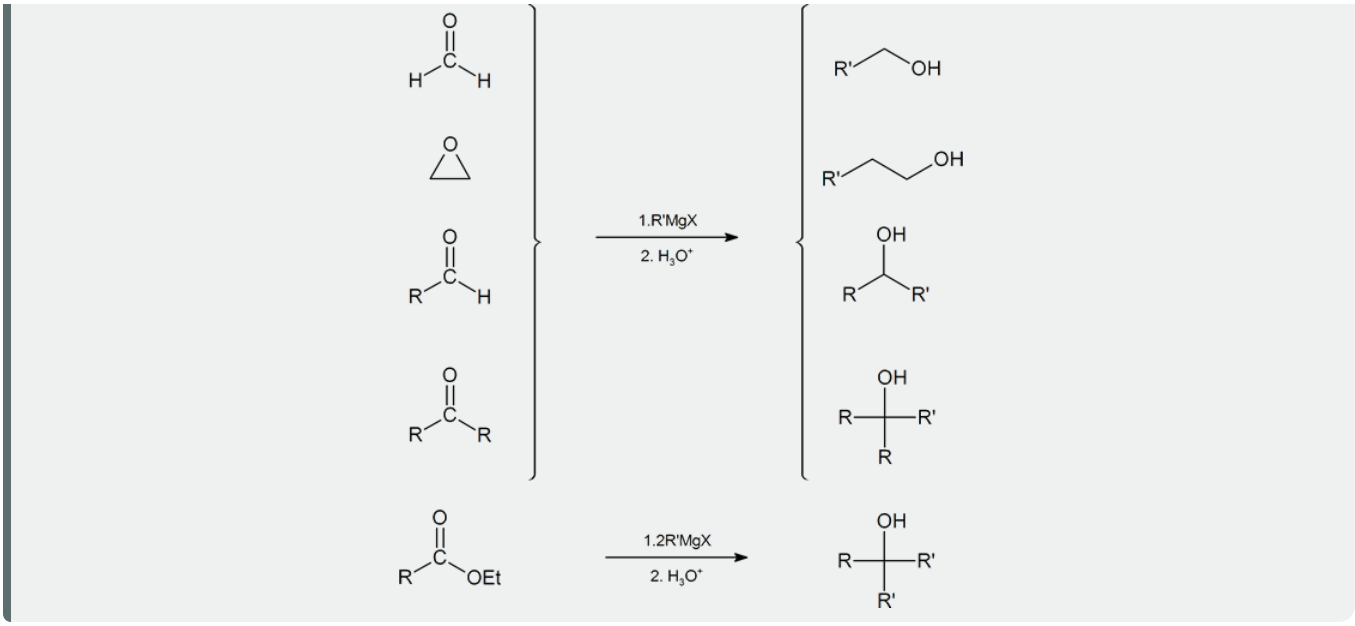
One important route for producing an alcohol from a Grignard reagent has been omitted from the discussion in the reading. It involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.



As mentioned in the reading, both organolithium and Grignard reagents are good nucleophiles. They also act as strong bases in the presence of acidic protons such as $-CO_2H$, $-OH$, $-SH$, $-NH$ and terminal alkyne groups. Not only do acidic protons interfere with the nucleophilic attack on the carbonyl of these organometallic reagents, if the starting materials possess any acidic protons, reagents cannot be generated in the first place. They are also the reason these reactions must be carried out in a water-free environment.

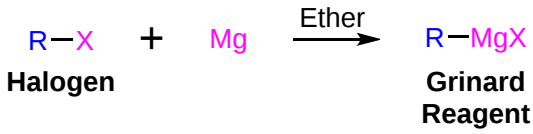
Another limitation of preparing Grignard and organolithium reagents is that they cannot already contain a carbonyl group (or other electrophilic multiple bonds like C=N, nitriles, N=O, S=O) because it would simply react with itself.

A summary of the methods used to prepare alcohols from Grignard reagents is provided below.



Formation of Grignard Reagents

Grignard reagents (RMgX) can be prepared through the reaction of halogens with magnesium metal (**Section 10-6**). Grignard reagents are a source of carbanion nucleophiles (R:$^{-}$ $^{+}$MgX) which add to carbonyl compounds to yield alcohols. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent. This complex helps stabilize the organometallic and increases its ability to react.

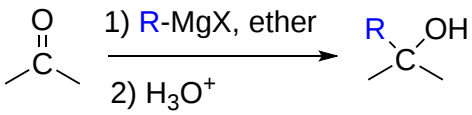


R = 1°, 2°, or 3° alkyl, aryl, or vinylic groups
X = Cl, Br, or I

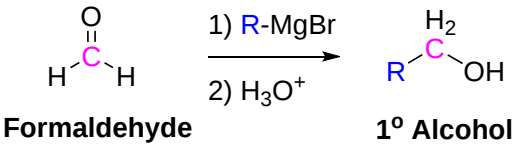
Reaction of Grignard Reagents with Carbonyls

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes, ketones, and other carbonyl containing compounds will undergo nucleophilic addition with Grignard reagents. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation by an acid. The type of alcohol produced depends on the number of alkyl substituents attached to the electrophilic carbonyl carbon. Reacting a Grignard reagent with formaldehyde (H_2C=O) produces 1° alcohols, aldehydes produce 2° alcohols, and ketones produce 3° alcohols. These reactions will be discussed in greater detail in **Section 19.7**.

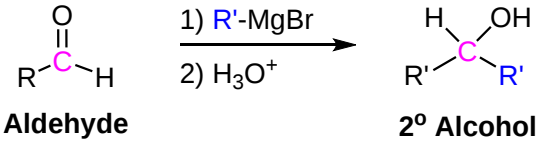
General Reaction



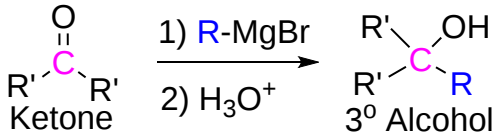
Addition to Formaldehyde gives 1° Alcohols



Addition to Aldehydes gives 2° Alcohols

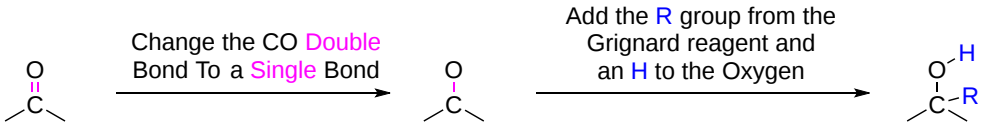


Addition to Ketones gives 3° Alcohols

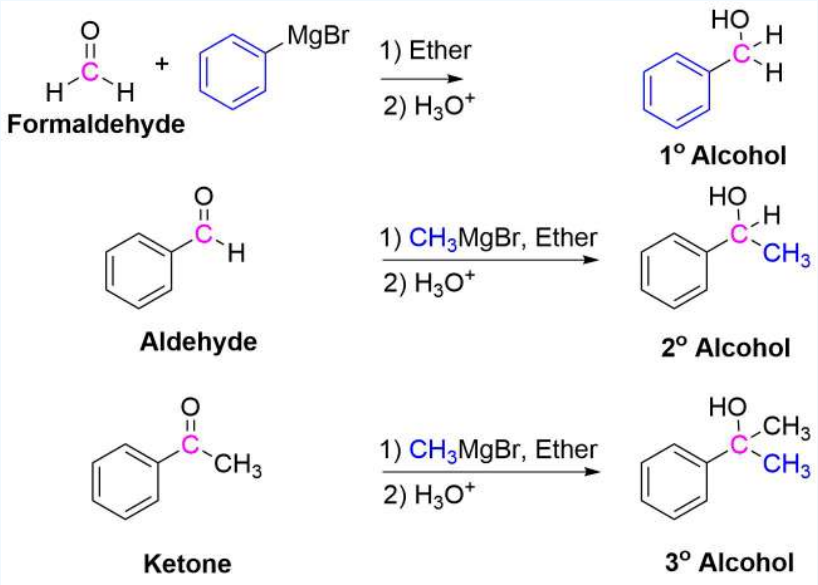


Predicting the Product of the Addition of Grignard Reagent to Carbonyl

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally in the carbonyl. The carbon will gain whatever R group was contained in the Grignard reagent and the oxygen will gain a hydrogen.



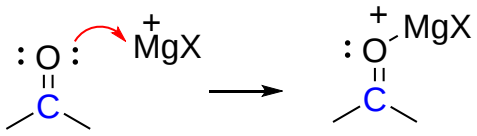
Example 3.1.6.1



Mechanism for the Addition of Grignard Reagents to Carbonyls

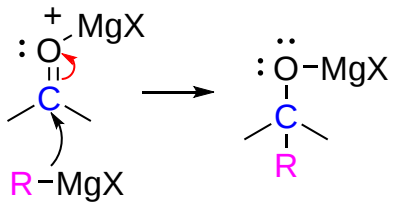
The mechanism starts with the formation of a acid-base complex between $^{+}$MgX and the carbonyl oxygen. The $^{+}$MgBr of the Grignard reagent acts as a Lewis acid and accepts a set of lone pair electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing its susceptibility to nucleophilic attack.

Step 1: Lewis acid-base formation



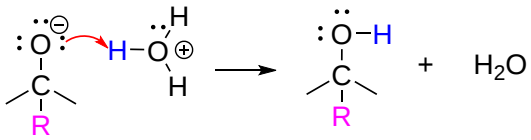
Step 2: Nucleophilic attack

The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral Magnesium alkoxide intermediate.



Step 3: Protonation

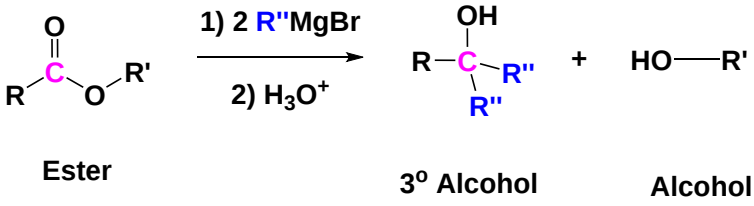
The alkoxide intermediate is converted to an alcohol through addition of a acidic aqueous solution. The $^{+}$MgX ion is also converted to HOMgX.'



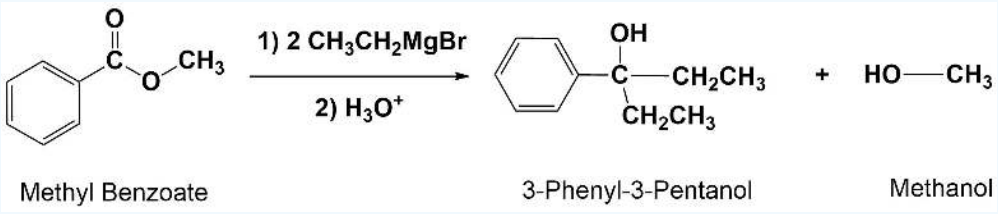
Grignard Reagents Convert Esters to 3° alcohols

With esters, after the first Grignard reaction, the carbonyl reforms creating a ketone which can then react with a second molecule of the Grignard. In effect, the Grignard reagent adds twice. This reaction will be discussed in greater detail in **Section 21.6**.

General Reaction

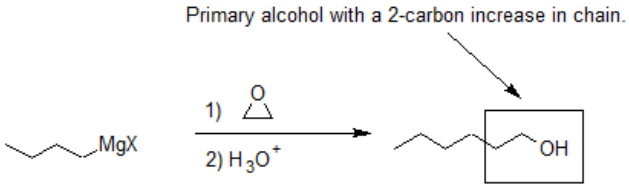


Example 3.1.6.2

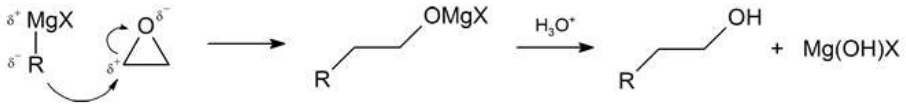


Grignard Reagents Convert Epoxides to 1o alcohols

Another important route for producing an alcohol from a Grignard reagent involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent. This reaction will be discussed in greater detail in **Section 18.6**.

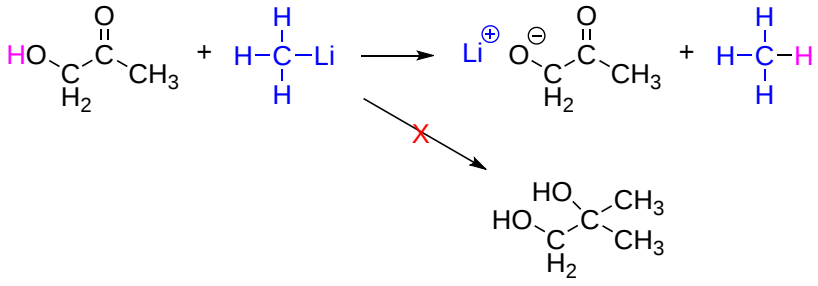


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section.



Limitation of Organometallic Reagents

Grignard and organolithium reagents are powerful bases. Because of this they cannot be prepared using halogen compounds which contain an additional functional group that has acidic hydrogens. If there are acidic hydrogens present, the organometallic reagent will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used are: alcohols (ROH), carboxylic acids (RCO_2H), thiols (RSH), and terminal alkynes (RCCH). Additionally, amides ($RCONH_2$) and amines (RNH_2) that have NH bonds cannot be used with organometallic reagents.

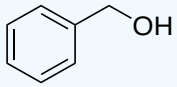


Planning an Alcohol Synthesis Using a Grignard Reaction

The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because if forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

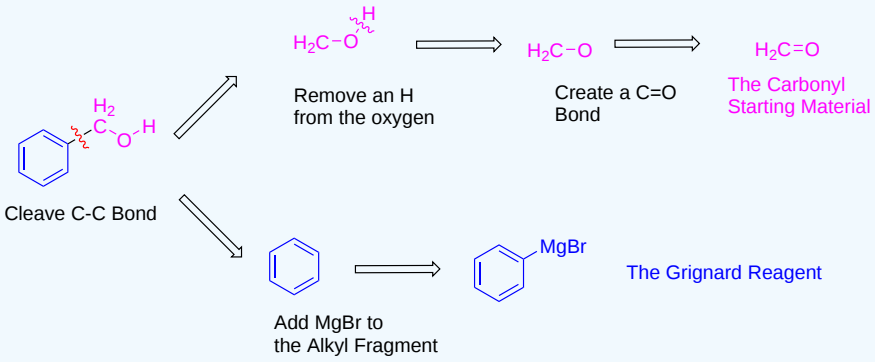
Worked Example 3.1.6.1

What reagents are required to make the following molecule using a Grignard Reaction?



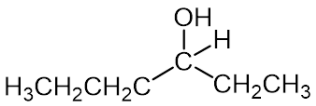
Answer

Analysis: Because the target molecule is a 1o alcohol there is only one C-C bond which can be cleaved to generate possible starting materials. The only possible reagents which would provide the target molecule would be formaldehyde and phenylmagnesium bromide.



Worked Example 3.1.6.2

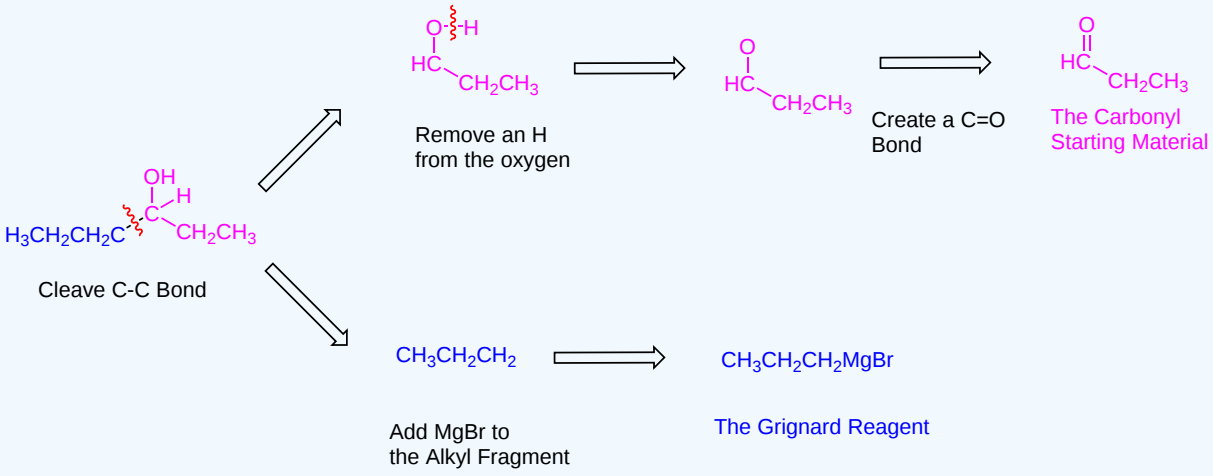
What reagents are required to make the following molecule using a Grignard Reaction?



Answer

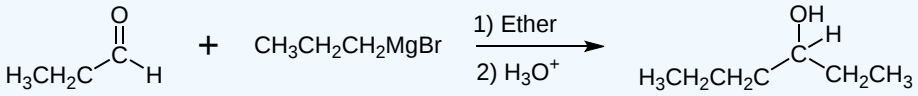
Analysis: Because the target molecule is an asymmetrical 2º alcohol there are two different C-C bond cleavage points. Each of these will provide a unique set of reagents which should be considered in terms of their reactivity and availability.

Pathway 1)

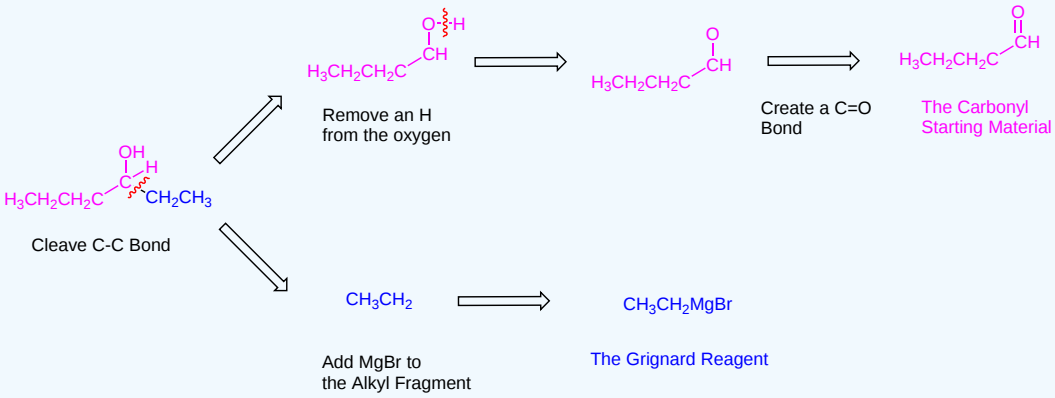


Pathway 1 synthesis)

Pathway 1 shows that propanal and propylmagnesium bromide can be reacted to create the target molecule.

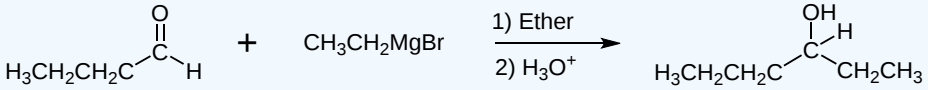


Pathway 2)



Pathway 2 synthesis)

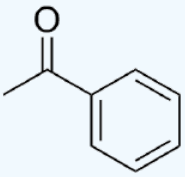
Pathway 2 shows that butanal and ethylmagnesium bromide can be reacted to create the target molecule.



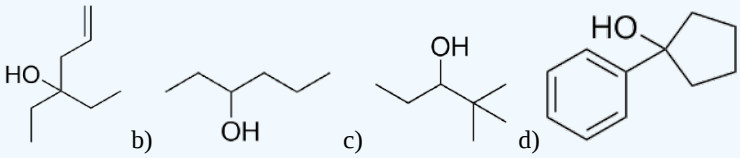
Exercises

? Exercise 3.1.6.1

1) If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.



2) What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?



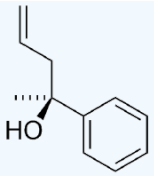
3) If the following compounds were reacted with methylmagnesium bromide what would be the products?

a) Cyclohexanone b) Acetophenone c) 2-Hexanone

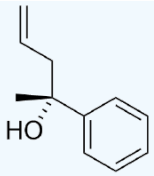
Answer

1) The result would be a racemic mixture of the following.

https://chem.libretexts.org/@go/page/413184



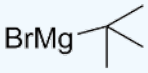
s enantiomer

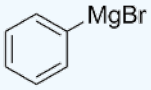


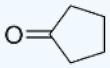
r enantiomer

2)

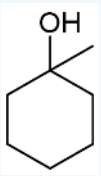
c) 

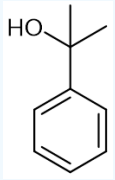


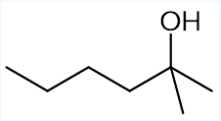
d) 



3)

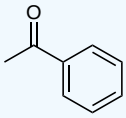
a) 

b) 

c) 

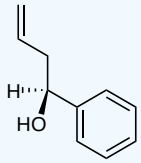
Exercise 3.1.6.2

If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.

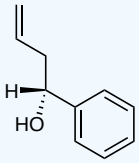


Answer

The result would be a racemic mixture of the following.



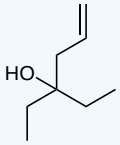
(*S*)-enantiomer

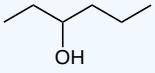


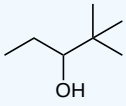
(*R*)-enantiomer

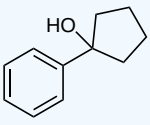
Exercise 3.1.6.3

What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

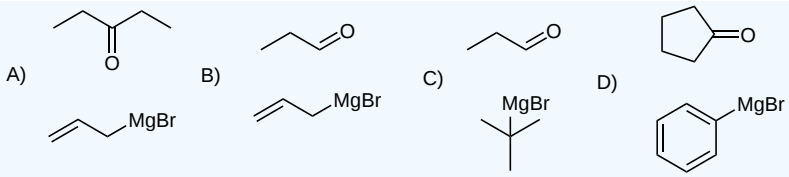
A) 

B) 

C) 

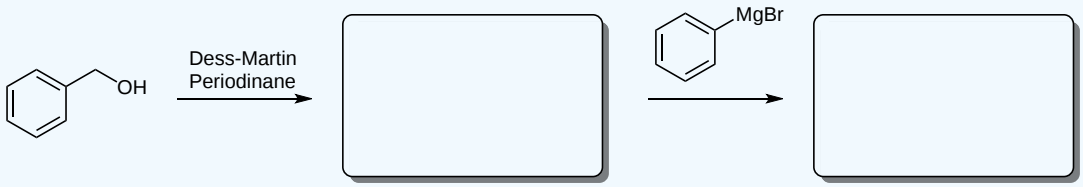
D) 

Answer

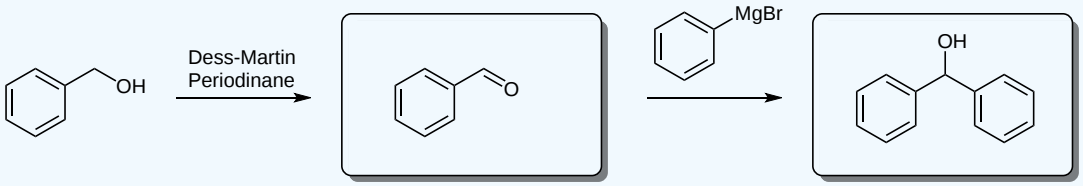


Exercise 3.1.6.4

Fill in the blanks of the following reaction scheme.



Answer



3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Dietmar Kennepohl.

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3.1.7: Reactions of Alcohols

Objectives

After completing this section, you should be able to

1. discuss the reactions of alcohols that have been introduced in previous units. These reactions include
   a. conversion of alcohols into alkyl halides.
   b. conversion of alcohols into tosylates.
   c. dehydration of alcohols to yield alkenes.
   d. conversion of alcohols into esters.

Study Notes

As you read through Section 17.6 you should be prepared to turn back to those earlier sections in which some of the reactions of alcohols were discussed:

- dehydration to alkenes—Section 8.1.
- conversion to alkyl halides—Section 10.5.

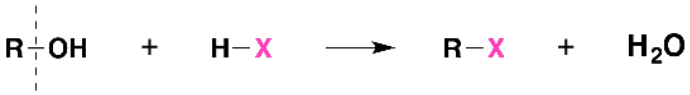
You may also wish to review the discussion of acidity constants, which can be found in Section 2.8.

Remember that when an alcohol reacts with tosyl chloride to form a tosylate, it is the O-H bond of the alcohol that is broken, not the C-O bond. This means that the absolute configuration of the carbon atom attached to the hydroxyl group remains unchanged throughout the reaction. The reading illustrates how this fact can be exploited to control the stereochemistry in an organic synthesis.

Finally, the reading shows the production of an ester from an alcohol and and an acid chloride. In Section 21.3 we will discuss the Fischer esterification, a famous reaction that uses an alcohol and a carboxylic acid to form the ester.

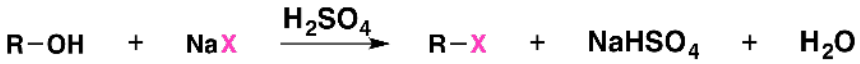
Conversion of Alcohols into Alkyl Halides

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:



- The order of reactivity of alcohols is 3° > 2° > 1° methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:

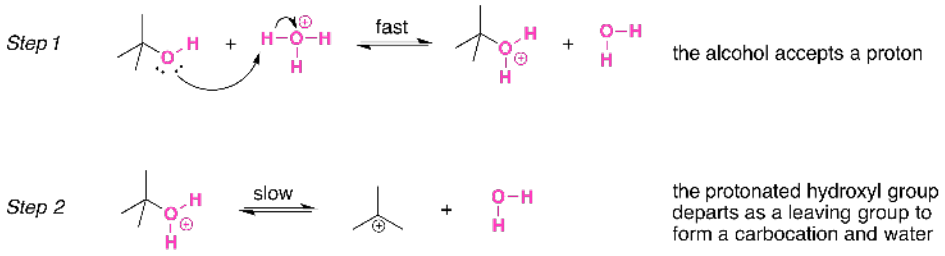


Mechanisms of the Reactions of Alcohols with HX

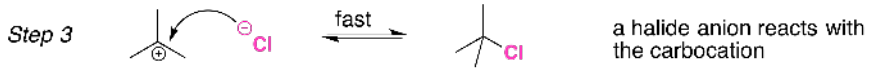
Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as a leaving group.

The S_N1 mechanism is illustrated by the reaction of tert-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-). The first two steps in this S_N1 substitution mechanism are protonation of the alcohol to form an oxonium ion. Although the oxonium ion is formed by protonation of the alcohol, it can also be viewed as a Lewis acid-base complex between the cation R^+ and H_2O.

Protonation of the alcohol converts a poor leaving group (OH-) to a good leaving group H_2O, which makes the dissociation step of the S_N1 mechanism more favorable.

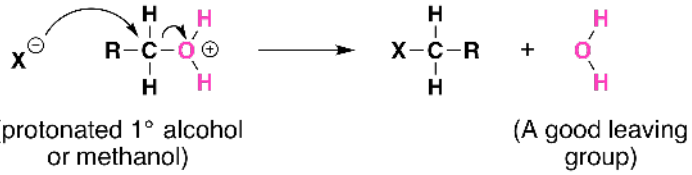


In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.

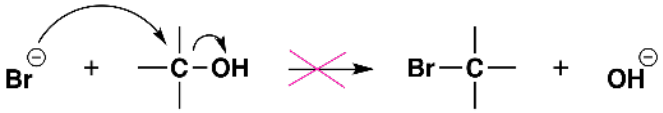


When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_N1 reaction.

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism. In these reactions the function of the acid is to produce a *protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:



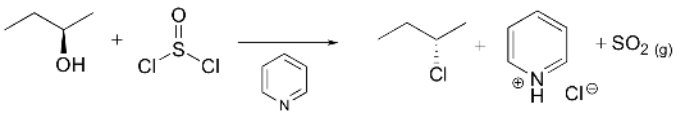
Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:



Conversion of Alcohols into Alkyl Halides Using $SOCl_2$ or PBr_3

The most common methods for converting 1º- and 2º-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use.

Synthetic organic chemists, when they want to convert an alcohol into a better leaving group, have several methods to choose from. One common strategy is to convert the alcohol into an alkyl chloride or bromide, using thionyl chloride or phosphorus tribromide:



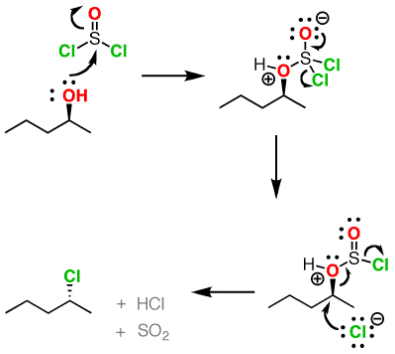


Mechanisms

Both of these reagents form an alkyl halide through an S_N2 mechanism. The mechanism for both reactions start by making the alcohol's -OH a better leaving group through conversion to an intermediate. Thionyl chloride creates an intermediate chlorosulfite ($-OSOCl_2$) compound and phosphorus tribromide makes an intermediate dibromophosphite ($-OPBr_2$) compound. These intermediate compounds can subsequently be eliminated as a leaving group during an S_N2 reaction with the corresponding nucleophilic halide ion. Since these reactions proceeds through a backside attack, there is inversion of configuration at the carbon.

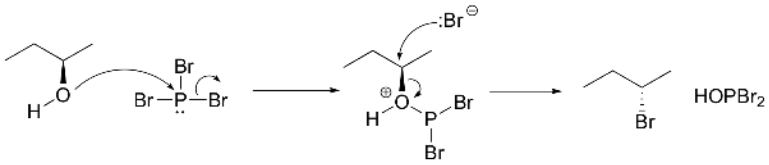
Thionyl Chloride

Notice that during the reaction with thonyl chloride hydrochloric acid (HCl) and sulfurdioxide (SO_2) are produced as byproducts.



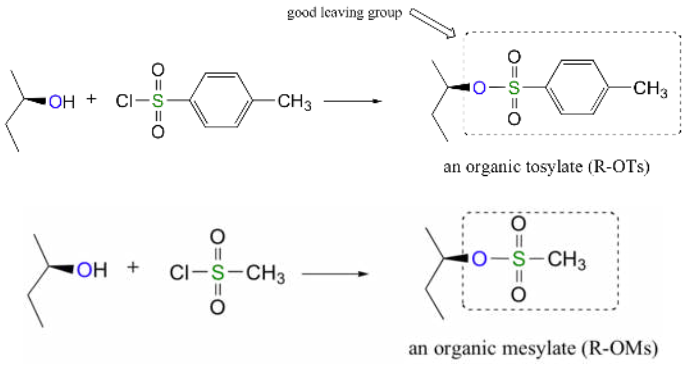
Phosphorustribromide

During this reaction $HOPBr_2$ is made as biproducts.



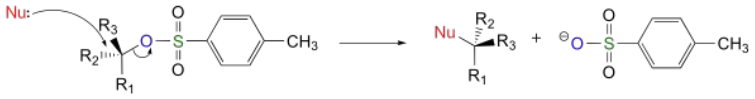
Conversion of Alcohols into Tosylates

Alternatively, we can transform an alcohol group into sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate.** Notice that unlike the halogenation reactions above, the C-O bond of the alcohol is not broken during the conversion to a tosylate or mesylate so the reaction proceeds with retention of configuration at the electrophilic carbon.

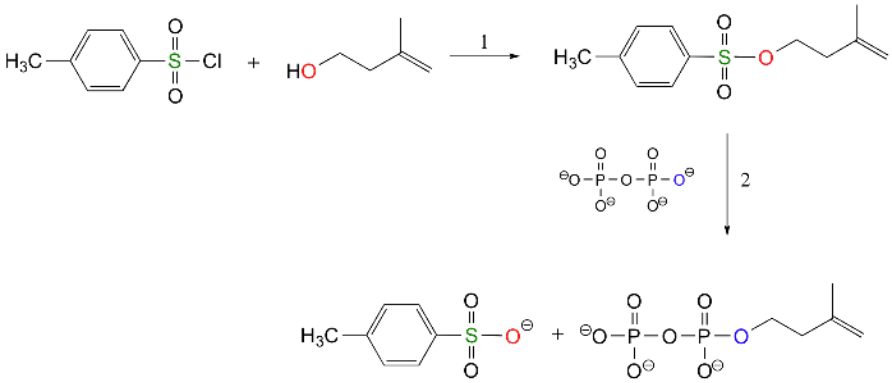


Tosylate and mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen. They behave much line alkyl halides and can undergo S_N2 and S_N1 reaction

depending on the conditions.



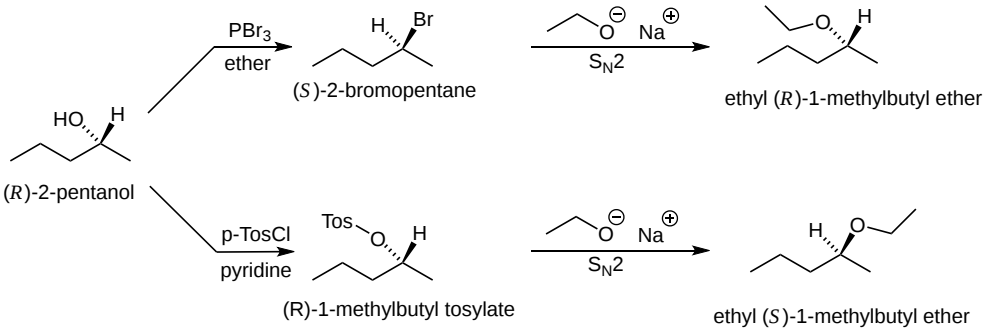
The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* **1986**, *51*, 4768).



Using Sulfonate Esters for Stereochemical Control

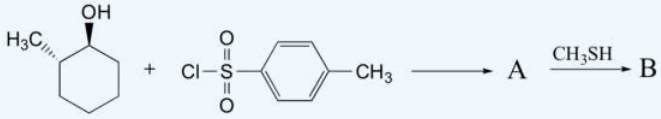
Tosylate and mesylate group's retention of conversion during formation makes them an important source of stereochemical control in organic synthesis. In the conversion of an alcohol to a halide for a subsequent S_N2 substitution there are two inversions of configuration. One during the conversion of the alcohol to a halide and the second during the S_N2 substitution reaction. Overall, these reaction steps produce a product with the same stereochemistry as the alcohol starting material.

When a tosylate or a mesylate are used for a similar conversion there is only one inversion of configuration. During the conversion of an alcohol to a tosylate the configuration of the alcohol strarting material is retained. This means that the tosylate will have the same stereochemical configuration as the alcohol starting material. The subsequent S_N2 reaction with the tosylate causes an inversion of configuration which provides a product of opposite stereochemistry as the alcohol starting material. The figure below outlines the relative stereochemistry of a series of reactions which summarize these points.

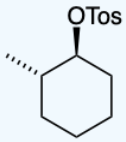


Example 17.6.2

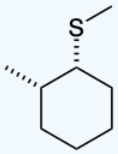
Predict the structures of A and B in the following reaction:



A. The tosylate is formed with retained stereochemistry.

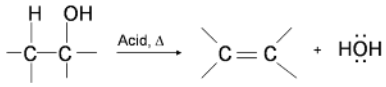


B. The thioether is formed with inverted stereochemistry.



Dehydration of Alcohols to Yield Alkenes

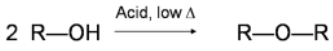
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 1° alcohols: 170° - 180°C
- 2° alcohols: 100°– 140 °C
- 3° alcohols: 25°– 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers (e.g., the Williamson Ether Synthesis).

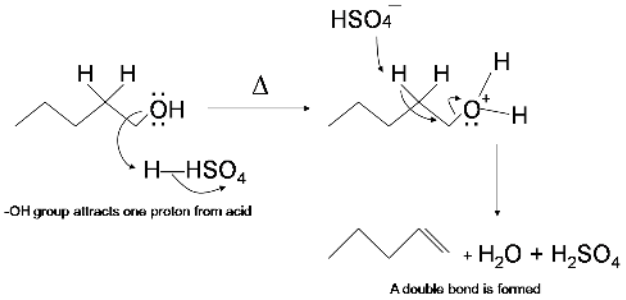


Mechanism for the Dehydration of Alcohol into Alkene

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reaction is ranked as the following

Methanol < primary < secondary < tertiary

Primary alcohol dehydrates through the E2 mechanism. First, the hydoxyl oxygen becomes protonated by reagent acid (sulfuric acid H_2SO_4), forming an alkyloxonium ion leaving group. Next, in a concerted process, then the conjugate base of the reagent acid (HSO_4^-) removes an adjacent hydrogen, the alkyloxonium ion is removed as a leaving group, and alkene double bond is formed. Remember that this reaction follows Zaitsev's rule which states that the most stable alkene will be the major product. In this reaction there is only one possible alkene product.

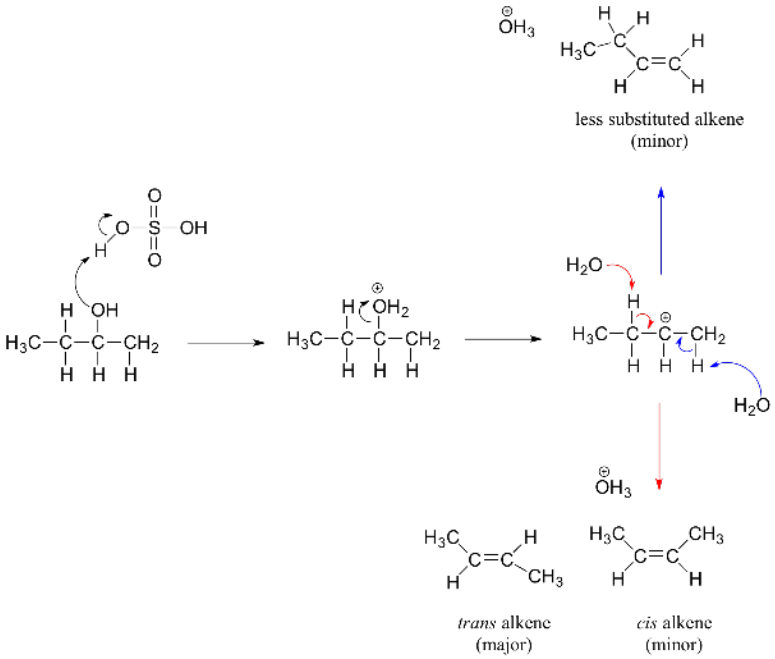


E1 Mechanism for the Dehydration of Alcohols into Alkenes

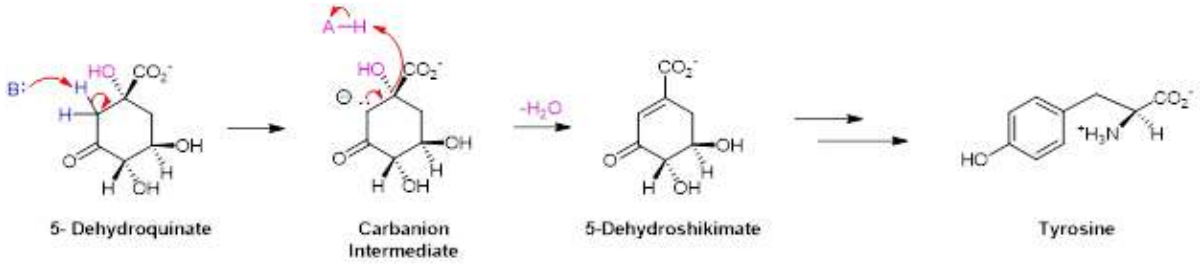
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first to form a carbocation a reaction intermediate. The eliminated water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond.

Notice in the mechanism below that the alkene formed depends on which adjacent proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. This reaction also follows Zaitsev's rule which states that the most stable alkene will be the major product.

As a general rule that more substituted alkenes are more stable than less substituted alkenes. Also, *trans* alkenes are more stable than *cis* alkenes. Therefore, the *trans* isomer of the 2-butene product is expected to be the major product of this reaction.

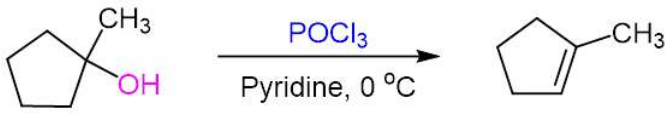


Similar biological dehydrations are fairly common. These reaction usually occur by an E1cB mechanism where the OH leaving group is two carbons away from a carbonyl group. An example is the dehydration of 5-dehydroquinate to form 5-dehydroshikimate as part of aromatic amino acid biosynthesis of tyrosine. Initially a biological deprotonates the carbon adjacent to the carbonyl group. The resulting carbanion intermediate forms a double bond by eliminating an OH group. This OH group is protonated by an acid and form water.



Conversion of Alcohols into Alkenes Using $POCl_3$

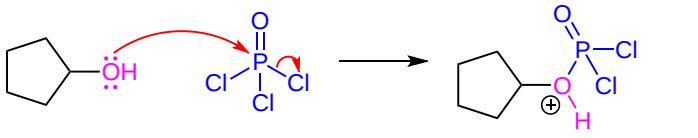
The E2 elimination of 2º and 3º-alcohols under mild, basic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. Pryidine is typically used as the reaction solvent and acts as the base which removes an adjacent proton in the E2 mechanism.



Mechanism

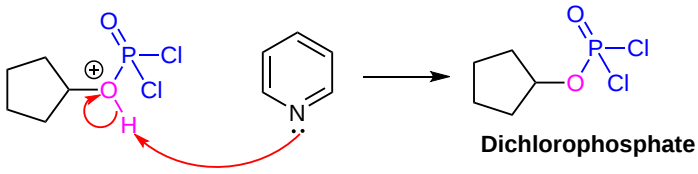
The reaction starts with the reactant alcohol undergoing a substitution reaction with $POCl_3$ to form a dichlorophospate intermediate. Next pyridine removes an adjacent proton and the dichlorophospate group is eliminated as a leaving group to form a double bond by an E2 mechanism.

1) Formation of a dichlorphosphonium intermediate.



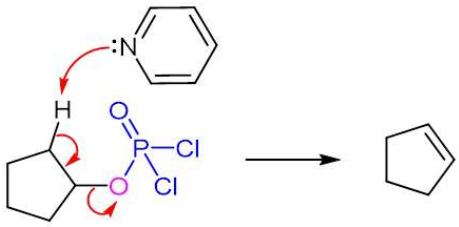
Dichlorophosphonium

2) Deprotonation of the dichlorophosphonium intermediate to form a dichlorophosphate.



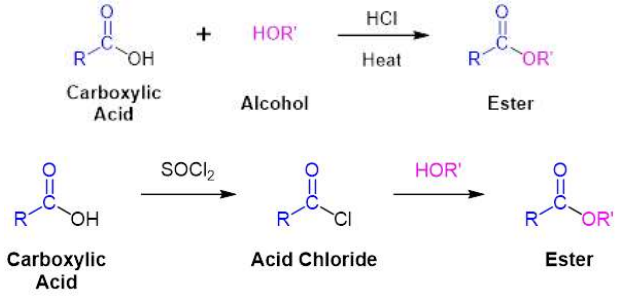
Dichlorophosphate

2) E2 elimination



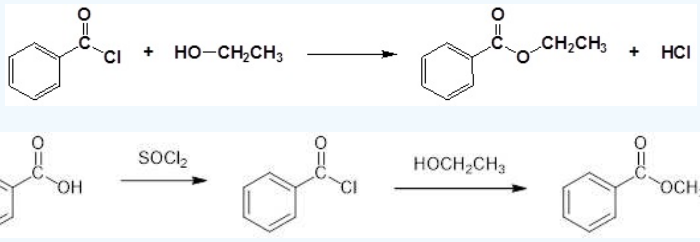
Conversion of Alcohols into Esters

Alcohols can be converted into esters through reaction with carboxylic acids using a strong acid as a catalyst. Often this transformation is performed by increasing the reactivity of the carboxylic acid by first converting it into a carboxylic acid chloride functional group by reacting with thionyl chloride ($SOCl_2$). The acid chloride can then be reacted with an alcohol to create an ester. These reactions will be discussed in greater detail in **Chapter 21**.

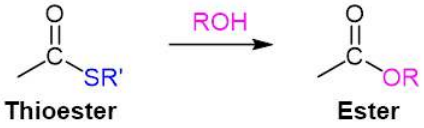


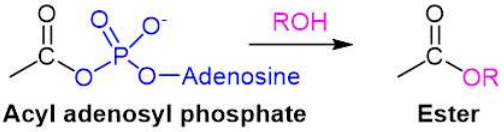
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Example 17.6.3



In biological systems, ester formation occurs through a similar process except thioester or acyl adenosyl phosphates are used instead of carboxylic acid chlorides. These reaction will be discussed in more detail in **Chapter 21**.





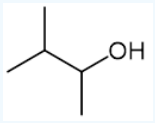
Exercises

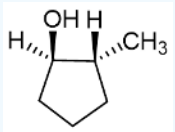
Exercise 3.1.7.1

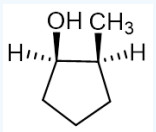
1) Draw the expected product of the reaction of cylohexanol with the following reagents.

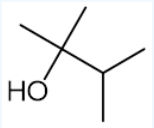
(a) $SOCl_2$ (b) PBr_3

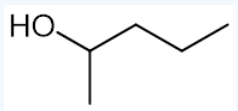
2) Draw the expected product of the treatment of the following compounds with $OPCl_3$ in pyridine.

a) 

b) 

c) 

d) 

e) 

Answer

1) a) Chlorocyclohexane b) Bromocyclohexane

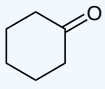
2) a) 2-Methyl-2-butene b) 3-Methylcyclopentene c) 1-Methylcyclopentene d) 2,3-Dimethyl-2-butene e) 2-Methyl-2-butene

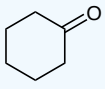
Exercise 3.1.7.2

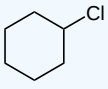
Draw the expected product of the reaction of cylohexanol with the following reagents.

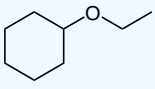
(A) CrO_3, H_2SO_4, H_2O (B) Dess-Martin Periodinane (C) $SOCl_2$ (D) NaH and 1-bromoethane (E) PBr_3

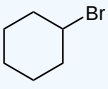
Answer

A) 

B) 

C) 

D) 

E) 

Exercise 3.1.7.3

Starting with cyclohexanol, describe how you would prepare the following?

(A) cyclohexyl acetate (B) 1-allylcyclohexan-1-ol (C) cyclohexene (D) ethoxycyclohexane

Answer

A) This can be seen as a transesterification, acid and some other ester would be needed to form cyclohexylacetate

B) First, oxidize the alcohol to a ketone, take for example Dess-Martin Periodinane, then use an allyl grignard to form 1-allylcyclohexan-1-ol

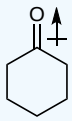
C) Alcohols can dehydrate to form alkenes under acidic conditions, so using anhydrous acid and heat would yield cyclohexene

D) The alcohol can also be a nucleophile, perform a halogen substitution, using 1-X ethane, to yield ethoxycyclohexane

Exercise 3.1.7.4

In cyclohexanone, a ketone, indicate the polarity of the bond between oxygen and carbon.

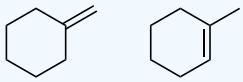
Answer



Oxygen is more electronegative than carbon creating the polar bond. This is the basis for the carbon's electrophilicity.

Exercise 3.1.7.5

In the dehydration of 1-methylcyclohexanol, which product is favored?

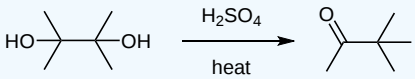


Answer

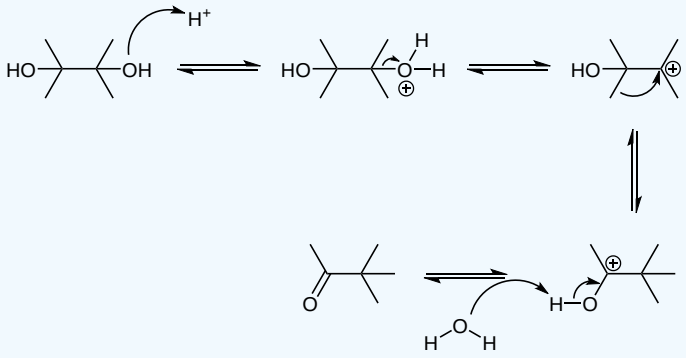
The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.

Exercise 3.1.7.6

In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint: a rearrangement occurs.)

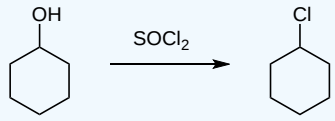


Answer

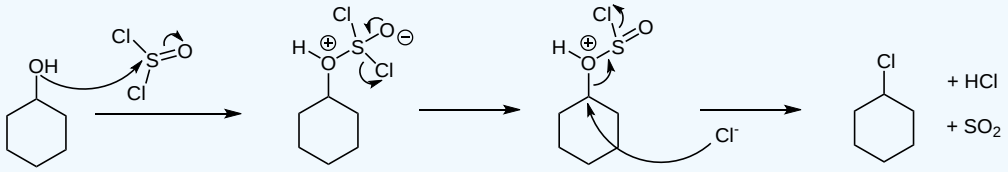


Exercise 3.1.7.7

Draw the mechanism of the reaction of thinoylchloride with cyclohexanol, given below.

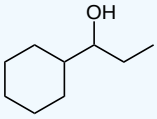


Answer



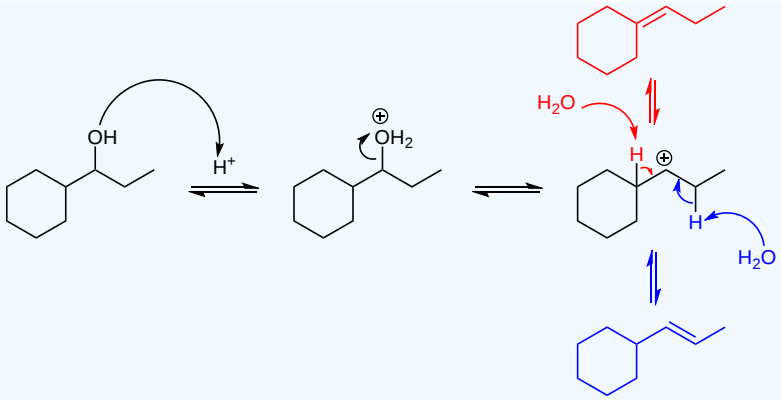
Exercise 3.1.7.8

Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected major product.

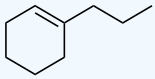


Answer

The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

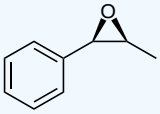


Note the secondary carbocation adjacent a tertiary carbon center, if there were a hydride transfer (rearrangement) to form a tertiary carbocation the following would be the major product. The minor product being the same product as the one formed from the red arrows.



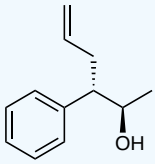
Exercise 3.1.7.9

The following epoxide can be transformed into an alcohol using a grignard reagent, take for example allylmagnesium chloride. Draw the product of the treatment of this epoxide with this grignard after being worked up with H_2O. Note the stereochemistry and also remember that benzyllic carbons are good S_N2 electrophiles.



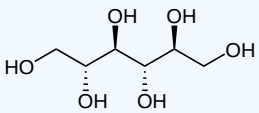
Answer

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Exercise 3.1.7.10

As seen in the previous example, there are many examples of chiral compounds containing alcohols. One common example of these are sugars, is the given the following sugar, allitol, also chiral?



Answer

This compound actually has a plane of symmetry, the plane parallel to the carbon chain/backbone. So, it is not chiral, also called a meso compound.

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3.1.8: Oxidation of Alcohols

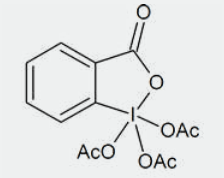
Objectives

After completing this section, you should be able to

1. write an equation to represent the oxidation of an alcohol.
2. identify the reagents that may be used to oxidize a given alcohol.
3. identify the specific reagent that is used to oxidize primary alcohols to aldehydes rather than to carboxylic acids.
4. identify the product formed from the oxidation of a given alcohol with a specified oxidizing agent.
5. identify the alcohol needed to prepare a given aldehyde, ketone or carboxylic acid by simple oxidation.
6. write a mechanism for the oxidation of an alcohol using a chromium(VI) reagent.

Study Notes

The reading mentions that pyridinium chlorochromate (PCC) is a milder version of chromic acid that is suitable for converting a primary alcohol into an aldehyde without oxidizing it all the way to a carboxylic acid. This reagent is being replaced in laboratories by **Dess-Martin periodinane (DMP)**, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983.



Dess–Martin periodinane (DMP)

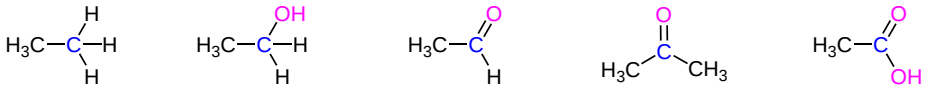
Oxidation States of Carbon

The general idea of oxidation and reduction reactions learned in general chemistry is that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. In order, to keep track of electrons in organic molecules a oxidation state formalism is used. Oxidation states to not represent the actual charge but it will allow the number of electrons being gained or lost by a particular atom during a reaction.

To calculate the oxidation state of a carbon atom the following rules are used:

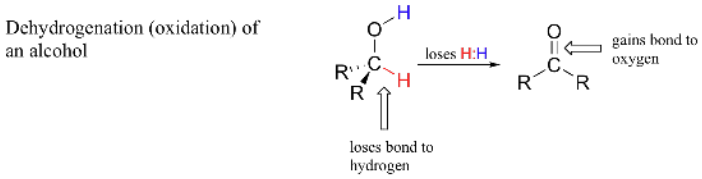
1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative, such as nitrogen, oxygen, sulfur, or a halogen.

When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized.



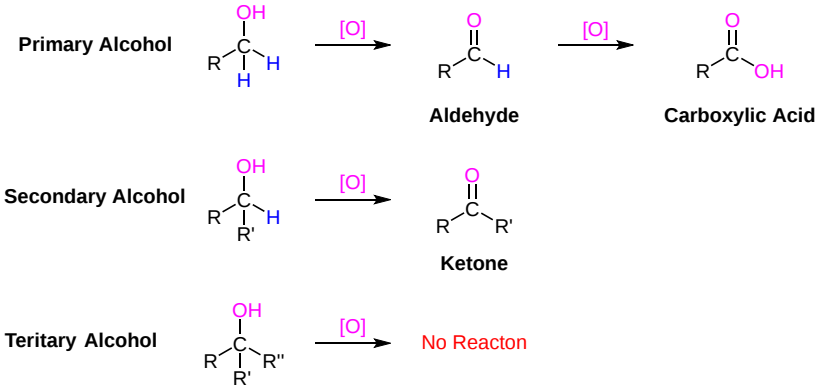
For this section, a simpler way to consider this process is to say that when a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a oxygen it has been oxidized. A very commonly example is the oxidation of an alcohol to a

ketone or aldehyde. Notice that during this process the carbon atom loses a hydrogen and gains a bond to oxygen.



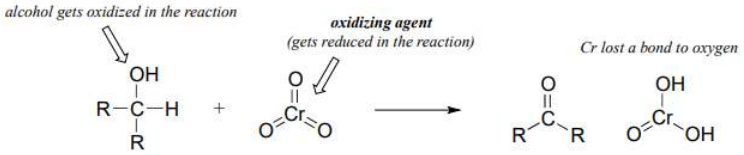
Oxidation of Alcohols

On of the most important reactions of alcohols is their oxidation to carbonyl containing compounds such as aldehyde, ketones, and carboxylic acid. Typically primary alcohols, depending on the reagent used, produce aldehydes or carboxylic acids during oxidations. Secondary alcohols are oxidized to produce ketones, and tertiary alcohols are usually not affected by oxidations.



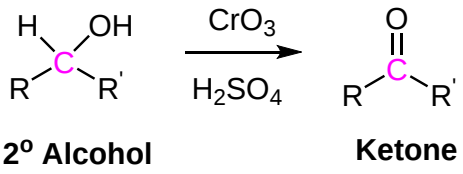
Alcohol Oxidizing Agents

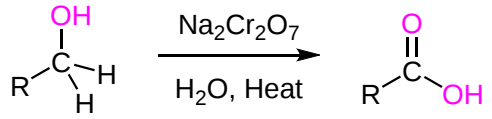
Oxidation and reduction reactions always occurs in tandem: when one compound is oxidized, another compound must be reduced. For an alcohol to be oxidized in a reaction there must also be a compound being reduced. This reduced compound is also called the oxidizing agent. For example, chromium trioxide (CrO_3) is a common oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone. During this reaction CrO_3 is being reduced to form H_2CrO_3. A common method for oxidizing secondary alcohols to ketones uses **chromic acid (H_2CrO_4)** as the oxidizing agent. Chromic acid, also known as **Jones reagent**, is prepared by adding chromium trioxide (CrO_3) to aqueous sulfuric acid.



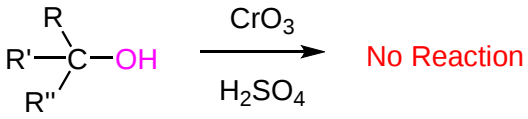
There is a wide selection of oxidizing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. In addition to CrO_3, other commonly used oxidizing agents include potassium permanganate ($KMnO_4$) and sodium dichromate ($Na_2Cr_2O_7$). Any of these reagents can be used to oxidize secondary alcohols to form ketones and primary alcohols to form carboxylic acids. Tertiary alcohols remain unreactive to oxidation.

General Reactions



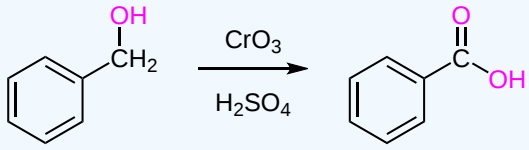


1° Alcohol **Carboyl ic Acid**

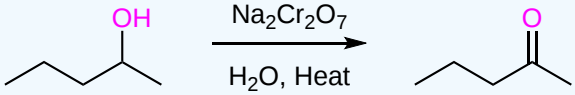


3° Alcohol

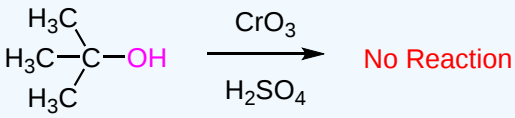
Example 3.1.8.1



Oxidation of Benzyl Alcohol to Benzoic Acid

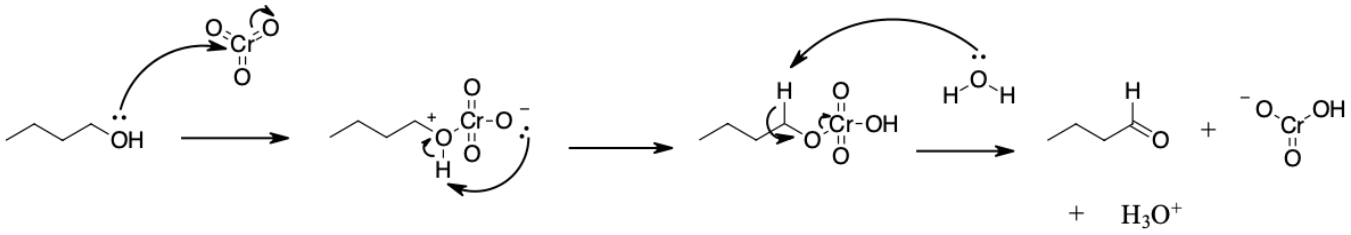


Oxidation of 2-Pentanol to 2-Pentanone



Mechanism

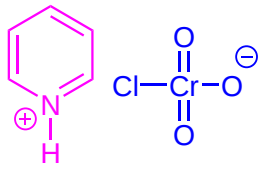
During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double bonds thought the elimination of a halide leaving group, in this case they are use to generate a C=O through the elimination of a reduced metal as a leaving group.



Examples

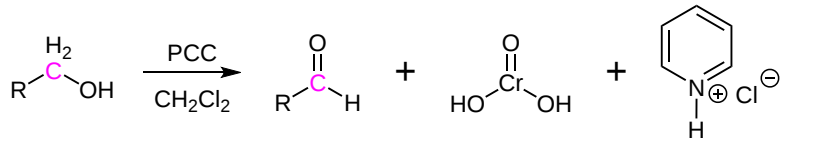
Oxidation of 1° Alcohols with PCC to form Aldehydes

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes 1° alcohols one rung up the oxidation ladder, turning primary alcohols into aldehydes and secondary alcohols into ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Cr(IV) as well as pyridinium chloride are produced as byproducts of this reaction.

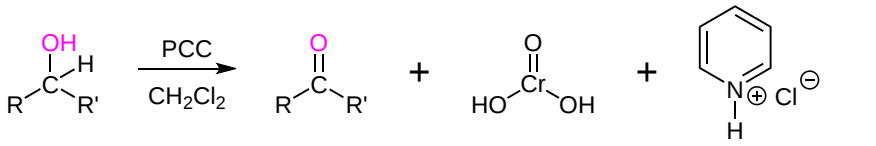


Pyridinium chlorochromate (PCC)

General Reactions

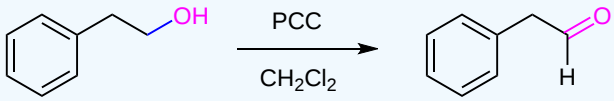


1º Alcohol **Aldehyde** **Cr(IV)** **Pyridinium Chloride**

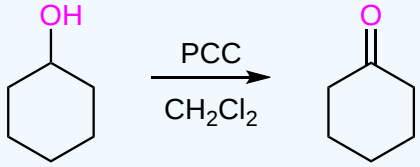


2º Alcohol **Ketone** **Cr(IV)** **Pyridinium Chloride**

? Example 3.1.8.2



Oxidation of 2-Phenylethanol to Phenylacetaldehyde

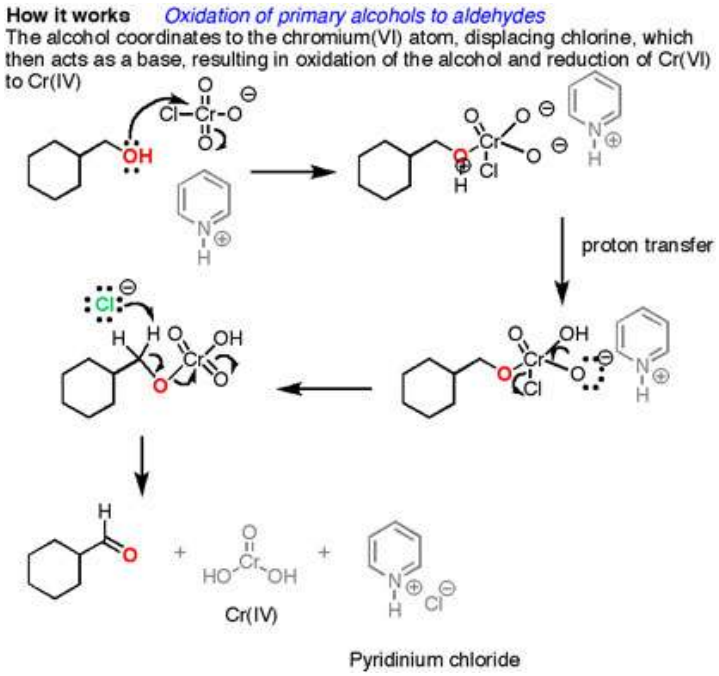


Oxidation of Cyclohexanol to Cyclohexanone

Mechanism

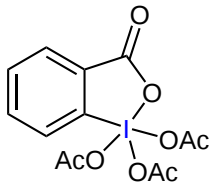
The first step of the mechanism is attack of alcohol oxygen on the chromium atom to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination reaction, to form what is known as a chromate ester.

The C-O double bond is formed when a base removes the proton on the carbon adjacent to the oxygen. It is also possible for pyridine to be used as the base here, although only very low concentrations of the deprotonated form will be present under these acidic conditions. In an E2 reaction, the electrons from the C-H bond move to form the C=O bond, and in the process break the O-Cr bond. During this step Cr(VI) gains two electrons to become Cr(IV) (drawn here as $O{=}Cr(OH)_2$).



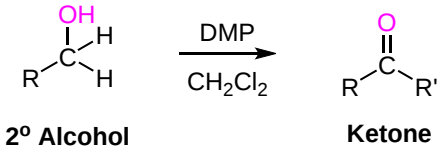
Oxidation of 1° Alcohols with Dess-Martin Periodinane (DMP) to form Aldehydes

PCC is being replaced in laboratories by **Dess-Martin periodinane (DMP)** in dichloromethane solvent, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous conditions (lower reaction temperature and a nonacidic medium). DMP is named after Daniel Dess and James Martin, who developed it in 1983.

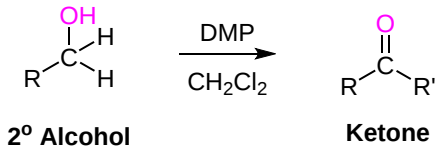


Dess-Martin periodinane (DMP)

General Reactions

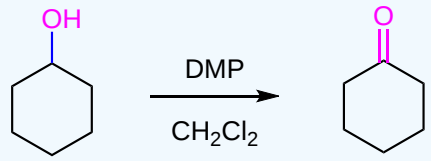


2° Alcohol **Ketone**

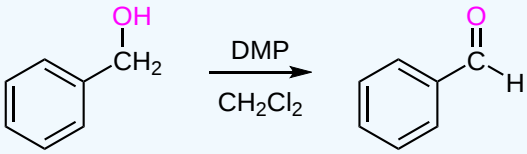


2° Alcohol **Ketone**

Example 3.1.8.3



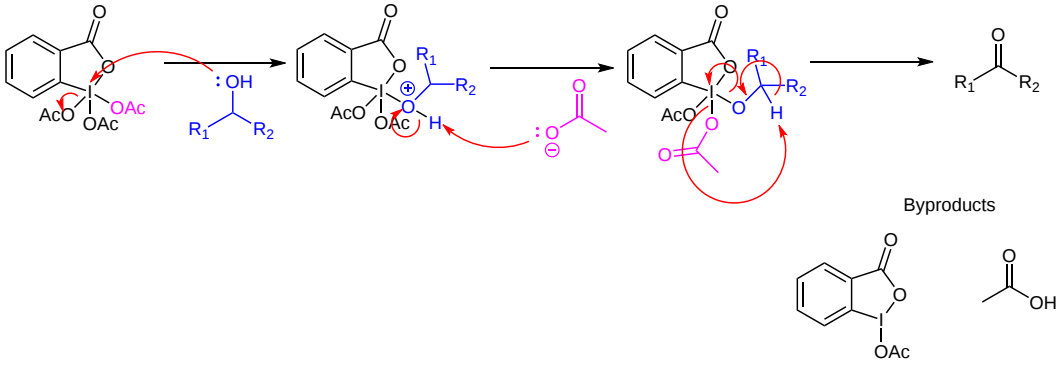
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

Mechanism

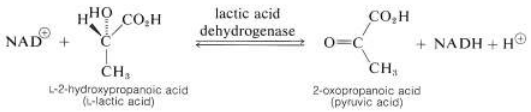
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the C=O bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).

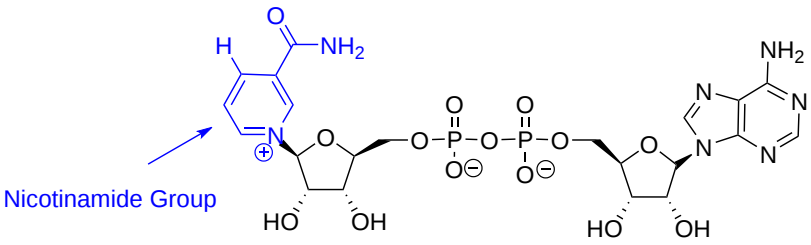


Biological Alcohol Oxidations

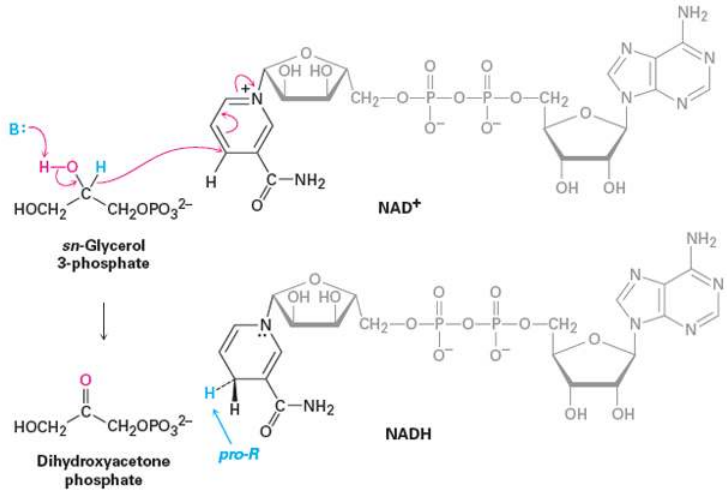
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all require enzymes as catalysts, which for these reactions usually are called *dehydrogenases*. An important group of biological oxidizing agents includes the pyridine nucleotides, of which nicotinamide adenine dinucleotide (NAD^+) is an example. This very complex molecule functions to accept hydride ($H:^-$) or the equivalent ($H^+ + 2e^-$) from the α carbon of an alcohol. The reduced form of NAD^+ is abbreviated as NADH and the $H:^-$ is added at the 4-position of the pyridine ring. It is important to note that the hydride adds exclusively to the *Re* face of the pyridine ring giving NADH a *pro*-R stereochemistry.

An example of the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose is the reduction of 2-oxopropanoic (pyruvic) acid to L-2-hydroxypropanoic (lactic) acid. The reverse process is oxidation of L-lactic acid. The enzyme *lactic acid dehydrogenase* catalyses this reaction, and it functions only with the L-enantiomer of lactic acid. During this reaction a base removes the alcohol hydrogen. The resulting alkoxide ion then forms the C=O bond causing a hydride ion to transfer to NAD^+.



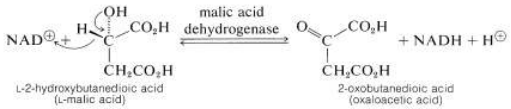


The Structure of NAD+



From an outside source. Convert mechanism to use lactic acid.

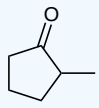
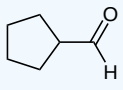
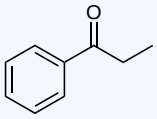
Another example is provided by one of the steps in metabolism by way of the Krebs citric acid cycle, is the oxidation of L-2-hydroxy-butanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:



Exercises

? Exercise 3.1.8.1

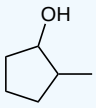
Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

a)  b)  c) 

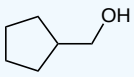
Answer

1)

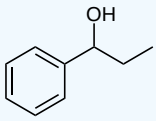
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxyllic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxyllic acid) would work



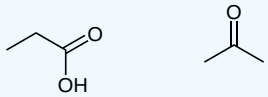
c) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



Exercise 3.1.8.2

Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

Answer



Exercise 3.1.8.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

Answer



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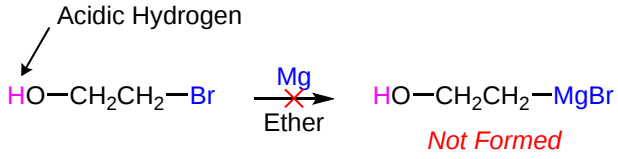
3.1.9: Protection of Alcohols

Objectives

After completing this section, you should be able to

1. explain what is meant by “protecting” a functional group during an organic synthesis.
2. describe one common method for protecting the hydroxy group of an alcohol, and give an example of its use (e.g., in the preparation of a Grignard reagent).

Often during the synthesis of complex molecules one functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.



When situations like this occurs chemists circumvent the problem by changing the interfering functional group into one that does not interfere with the intended reaction. Chemists call this process protection of a functional group. Functional group protection involves three steps:

1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

Protecting Alcohols Through the Formation of Trialkylsilyl Ethers

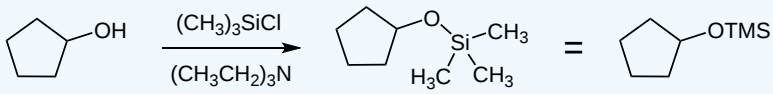
There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkylsilane, Cl-SiR_3 This reactions forms a trialkylsilyl ether, R'O-SiR_3. One of the most common reagents is chlorotrimethylsilane [$(CH_3)_3SiCl$] which is often used in conjunction with a base, such as triethylamine. The base helps to form the alkoxide anion and remove the HCl produced by the reaction. The produced trimethylsilyl ether is commonly abbreviated -OTMS. This silyl ether no longer has the fairly acidic OH proton as the alcohol group has been changed (protected).

General Reaction

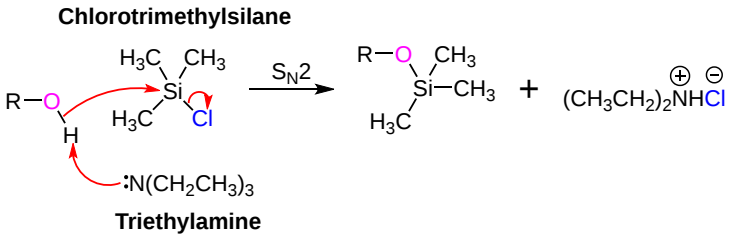


Alcohol **Trimethylsilyl ether (TMS)**

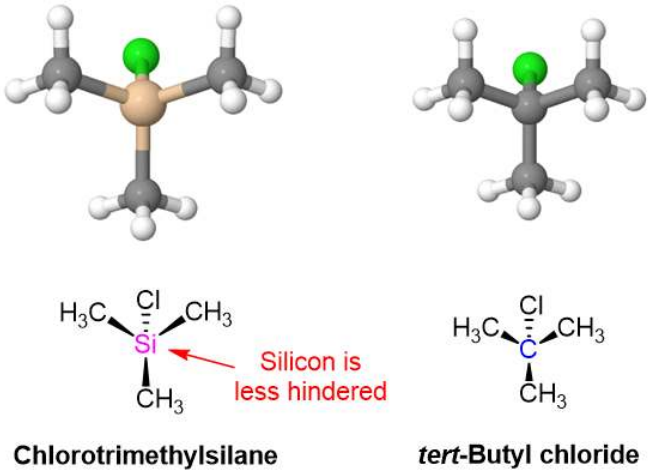
Example 3.1.9.1



Mechanism

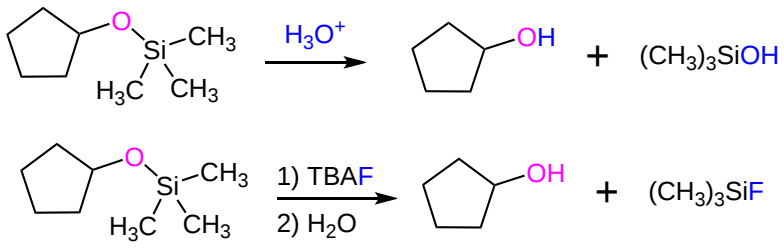


Notice this reaction occurs through an S_N2-like mechanism with the alcohol attacking a trialkyl-substitued silicon atom. Normally, an S_N2 reaction would not be viable for the analogous *tert*-butyl chloride due to the steric hindrance of the tertiary electrophilic carbon. Being a third-row atom, silicon is larger and forms longer bonds that carbon. The Si-C bonds of chlorotrimethylsilane are 195 pm compared to the 154 pm C-C bonds or *tert*-butylchloride. The three methyl groups attached to silicon are more spread out and offer less steric hindrance so the S_N2-like reaction can occur.



Deprotection

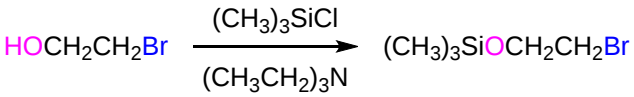
Trimethylsilyl ethers, like most other ethers, are relatively unreactive towards many reagents such as oxidizing agents, reducing agents, or Grignard reagents. However, the TMS ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion (F^-) to regenerate the alcohol. Common sources of the fluoride ion are lithium fluoride (LiF) and tetrabutylammoniumfluoride (TBAF) [$(CH_3CH_2CH_2CH_2)_4NF$]. This step is commonly referred to as a **deprotection**.



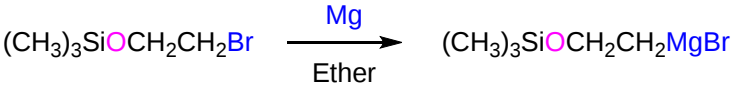
Utilizing a Protecting Group for a Grignard Reaction

The problem posed at the beginning of this section can be solved through the use of a TMS protecting group. Once the alcohol is converted into a TMS ether the acidic hydrogen will no longer be present and a Grignard reagent can be formed.

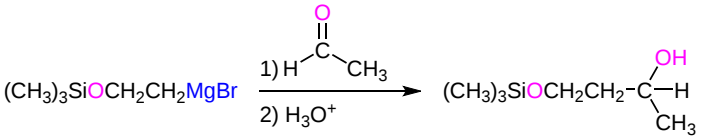
1) Protection of the Alcohol



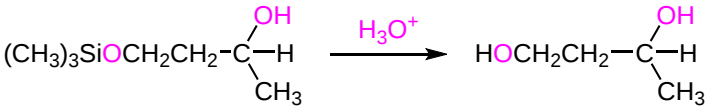
2) Form the Grignard Reagent



3) Perform the Grignard Reaction



4) Deprotection

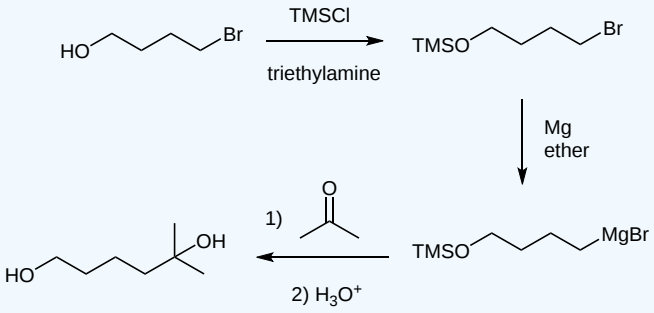


Exercises

? Exercise 3.1.9.1

Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 2-methylhexane-2,6-diol.

Answer



Contributors and Attributions

-
- Layne Morsch (University of Illinois Springfield)
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

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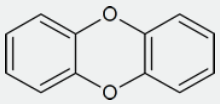
3.1.10: Phenols and Their Uses

Objectives

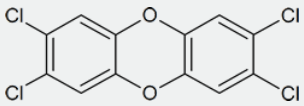
After completing this section, you should be able to describe two methods that can be used to obtain phenol on an industrial scale.

Study Notes

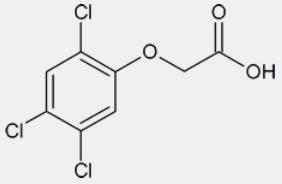
One substance that has become symbolic of the struggle between industrial development and environmental protection is dioxin. The name dioxin is used to refer to a family of compounds having a basic structure in which two benzene rings are joined by two oxygen atoms:

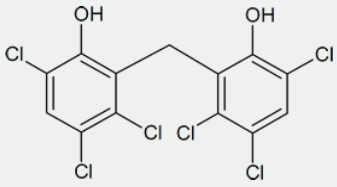


However, media references to dioxin are usually in connection with 2,3,7,8-tetrachlorodibenzo- *p*-dioxin, or TCDD:

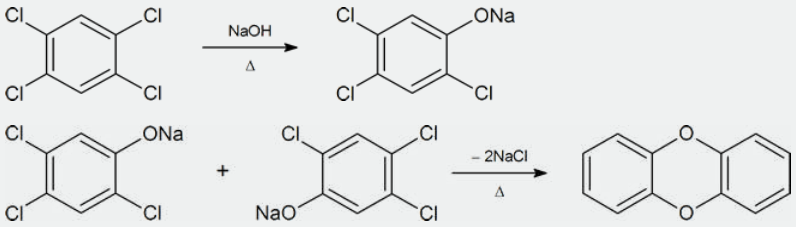


TCDD is a by-product formed in the manufacture of trichlorophenol, an intermediate in the production of the herbicide 2,4,5-T (one of the ingredients of the infamous Agent Orange), in the manufacture of hexachlorophene, by pulp and paper mills that use chlorine to produce white paper, and as a result of the incineration of municipal refuse.





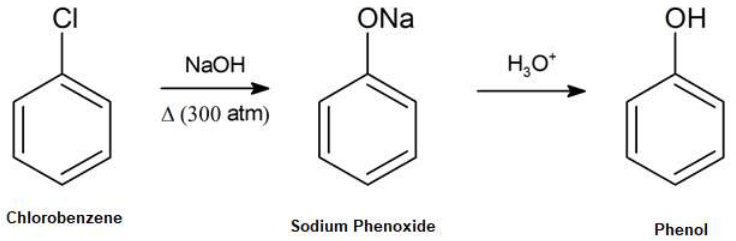
The equation given below shows how 2,3,7,8-tetrachlorodibenzo- *p*-dioxin is formed during the manufacture of 2,4,5-trichlorophenol, an intermediate produced in the synthesis of 2,4,5-T. The process involves the reaction of 1,2,4,5-tetrachlorobenzene with base at a temperature of about 160°C.



The possible hazards presented by dioxin first became apparent in 1957, when some German workers involved in the manufacture of 2,4,5-T developed chloracne—a skin condition resembling acne. The precise toxicological effects of dioxin on humans is open to debate, but as little as 0.6 mg per kg of body weight will kill 50% of guinea pigs injected with TCDD within a specified time.

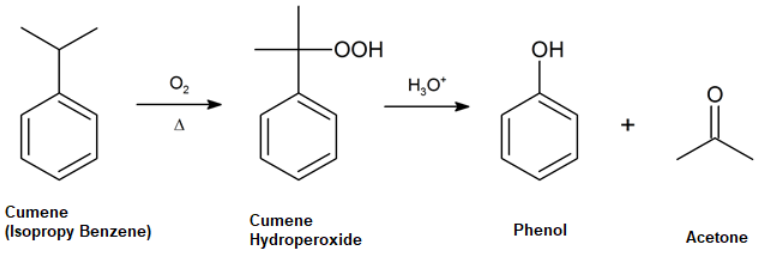
Dow's Process

An early commercial preparation of phenol in the late 19th and early 20th century was by the hydrolysis of chlorobenzene with strong base to produce a sodium phenoxide intermediate, which affords phenol upon acidification.



Cumene Process

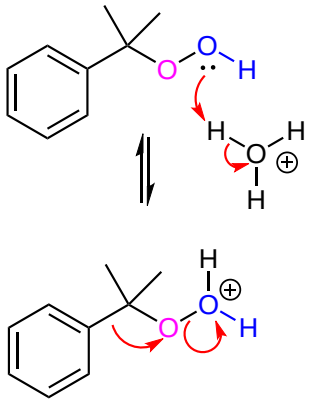
Developed in the 1940s and currently responsible for most industrial phenol production this process involves isopropylbenzene—commonly known as cumene. Treatment of cumene with oxygen in air generates 2-hydroperoxypropan-2-ylbenzene (cumene hydroperoxide) through a radical pathway. When hydrolyzed in acidic medium the peroxide intermediate produces phenol and acetone, which are both valuable chemical products.



Mechanism

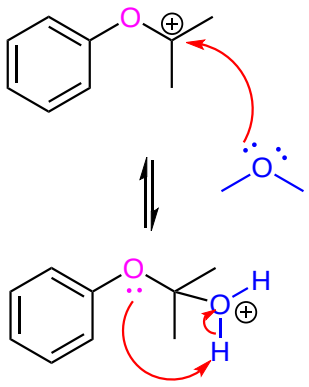
Protonation and water loss

Initially cumene react with oxygen (O_2) to form cumene hydroperoxide. The -OH oxygen of the peroxide is protonated creating a good leaving group. This is following by a rearrangement where the phenyl group shifts form a carbon to an oxygen with the simultaneous loss of water.



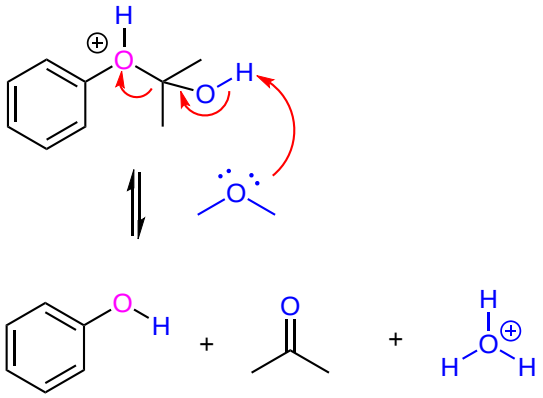
Addition of water and proton transfer

The resulting carbocation intermediate is attacked by a nucleophilic water to form a protonated hemiacetal. A hemiacetal is a compound with an ether group (-OR) and a hydroxide group (-OH) bonded to the same carbon atom. A proton transfer occurs with the oxygen near the ring taking the extra hydrogen.



Elimination

An E2 reaction occurs which forms the C=O bond in the product acetone, and eliminating phenol as the other product.



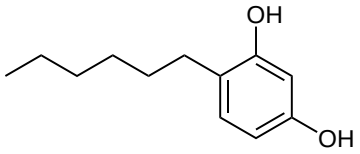
To Your Health: Phenols and Us

Phenols are widely used as antiseptics (substances that kill microorganisms on living tissue) and as disinfectants (substances intended to kill microorganisms on inanimate objects such as furniture or floors). The first widely used antiseptic was phenol. Joseph Lister used it for antiseptic surgery in 1867. Phenol is toxic to humans, however, and can cause severe burns when applied to the skin. In the bloodstream, it is a systemic poison—that is, one that is carried to and affects all parts of the body. Its severe side effects led to searches for safer antiseptics, a number of which have been found.



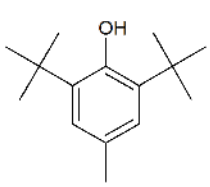
An operation in 1753, painted by Gaspare Traversi, of a surgery before antiseptics were used.

One safer phenolic antiseptic is 4-hexylresorcinol (4-hexyl-1,3-dihydroxybenzene; resorcinol is the common name for 1,3-dihydroxybenzene, and 4-hexylresorcinol has a hexyl group on the fourth carbon atom of the resorcinol ring). It is much more powerful than phenol as a germicide and has fewer undesirable side effects. Indeed, it is safe enough to be used as the active ingredient in some mouthwashes and throat lozenges.

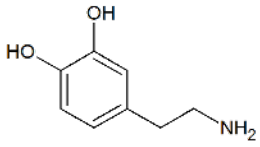


The compound 4-hexylresorcinol is mild enough to be used as the active ingredient in antiseptic preparations for use on the skin.

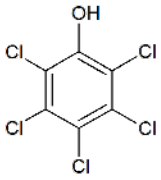
In addition to acting as an antiseptic, phenol is also a useful precursor in many chemical syntheses to produce pharmaceuticals, food preservatives, polymers, resins and adhesives. Phenolics are also present in a number of biological systems and natural products such as neurotransmitters, flavoring agents, and vitamins to name a few.



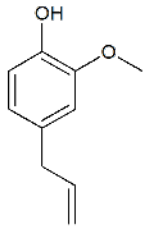
butylated hydroxytoluene
BHT (food preservative)



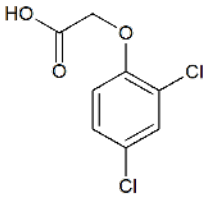
dopamine (neurotransmitter)



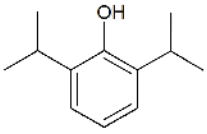
pentachlorophenol (wood preservative)



eugenal (perfume)



2,4-dichlorophenoxyacetic acid
2,4-D (herbicide)



propofol (pharmaceutical)

Bisphenol A

In the United States, single-serve bottled water is the fastest growing beverage of choice. However, drinking tap water creates less pollution and uses less energy and natural resources than transporting and manufacturing plastic water bottles. Unlike soda and other carbonated beverages, there is no deposit on water bottles and therefore fewer are recycled by consumers. Nationally, only 10% of plastic water bottles are recycled creating large quantities of waste. Many water bottles consist of a polycarbonate plastic made with Bisphenol A (BPA).

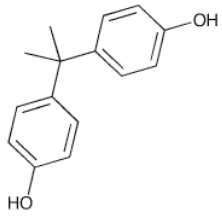


Figure 1: *Bisphenol A*

BPA was first synthesized by Thomas Zincke of the University of Marburg, Germany in 1905. Zincke did not propose uses for BPA however scientists discovered the many uses of BPA in 1953. Polycarbonate plastics became a commonly used commercial product in the 1950's.

BPA was created from a condensation reaction of phenol and acetone with hydrogen chloride, an acid catalyst, and a promoter such as methyl mercaptan. Once formed by this reaction, BPA is washed with water, neutralized with calcium hydroxide and distilled under vacuum. BPA can also be purified further by distillation and extractive crystallisation. Higher purity BPA is used to make polycarbonate plastics while the lower purity BPA is used to make Epoxy Resin. BPA's IUPAC name is 4,4'-dihydroxy-2,2,-diphenylpropane. It's chemical formula is $C_{15}H_{16}O_2$. The production of BPA produces H_2O (see image below) and therefore requires a condensation reaction for production.

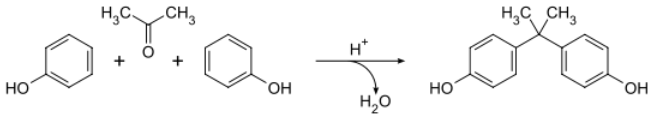


Figure 2 *The production of BPA*

A concern with the use of BPA in water bottles is the potential for leaching into the water which is then consumed. When BPA is present in the human body, it mimics the hormone estrogen and is capable of binding to estrogen receptors. In doing so, it changes the genes in the body that are expressed which triggers changes in hormone concentration, enzyme function and protein synthesis.

Using plastic water bottles that contain BPA is damaging both to the environment and human health. A greener alternative to the use of plastic water bottles is filtered tap water carried in refillable stainless steel containers.

Contributors and Attributions

-
-

- Ed Vitz (Kutztown University), John W. Moore (UW-Madison), Justin Shorb (Hope College), Xavier Prat-Resina (University of Minnesota Rochester), Tim Wendorff, and Adam Hahn.
- Layne Morsch (University of Illinois Springfield)

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3.1.11: Reactions of Phenols

Objectives

After completing this section, you should be able to

1. explain why phenols and phenoxide ions are very reactive towards electrophilic aromatic substitution (see Section 16.4 of the textbook).
2. write an equation to illustrate the oxidation of a phenol or an arylamine to a quinone, and identify the reagents used to oxidize phenols.
3. write an equation to illustrate the reduction of a quinone to a hydroquinone, and identify the reagents used to reduce quinones.
4. describe, briefly, the biological importance of the redox properties of quinones.

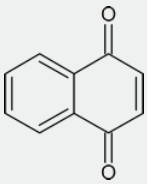
Key Terms

Make certain that you can define, and use in context, the key terms below.

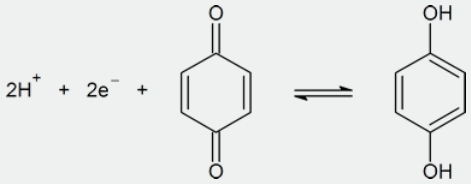
- hydroquinone
- quinone
- ubiquinone

Study Notes

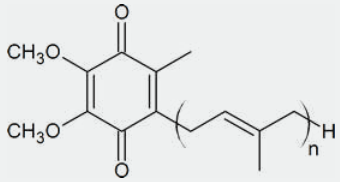
"Quinone" is a term used to describe cyclohexadiendiones in general, and *p*-benzoquinone in particular. In addition to benzene, other aromatic systems also give rise to quinones; for example, 1,4-naphthoquinone



"Hydroquinones" are produced by the reduction of quinones according to the following half-reaction:



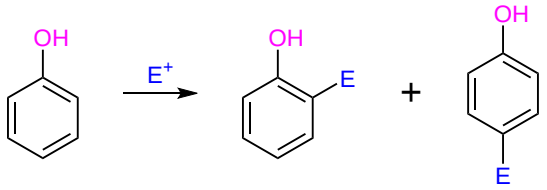
"Ubiquinones" are naturally occurring quinones whose role is to transfer a pair of electrons from one substance to another in enzyme-catalyzed reactions. Ubiquinones are also called coenzymes Q.



Electrophilic Aromatic Substitution Reactions

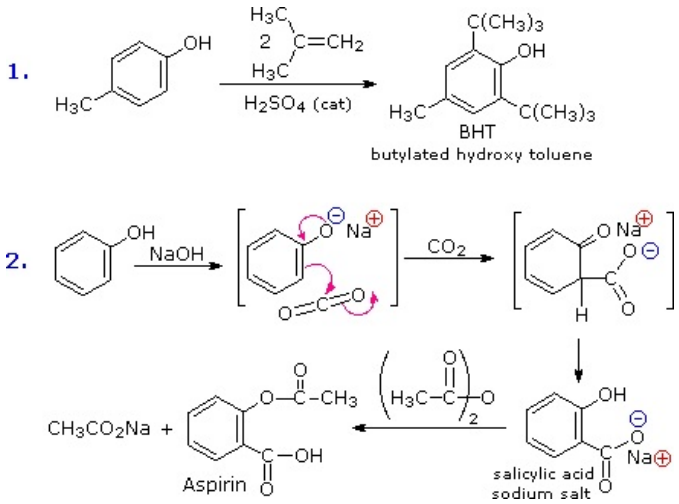
The hydroxyl subsistent of phenol is *ortho* and *para* directing and makes the aromatic ring strongly activated towards electrophilic aromatic substitution reaction (**Section 16-4**). In fact, phenols are strongly activating that often times electrophilic addition is

difficult to limit to a single addition.



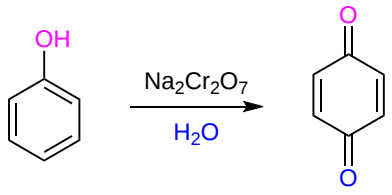
The ease with which the aromatic ring of phenols and phenol ethers undergoes electrophilic substitution is shown in the two examples in the diagram below. The first shows the Friedel-Crafts synthesis of the food preservative BHT from *para*-cresol. In this example, an electrophilic is added to both of the *ortho* positions to the alcohol of *para*-cresol.

The second example is interesting in that it further demonstrates the delocalization of charge that occurs in the phenolate anion. Carbon dioxide is a weak electrophile and normally does not react with aromatic compounds; however, the negative charge concentration on the phenolate ring enables the carboxylation reaction shown in the second step. The sodium salt of salicylic acid is the major product, and the preference for *ortho* substitution may reflect the influence of the sodium cation. This is called the **Kolbe-Schmidt reaction**, and it has served in the preparation of aspirin, as the last step illustrates.



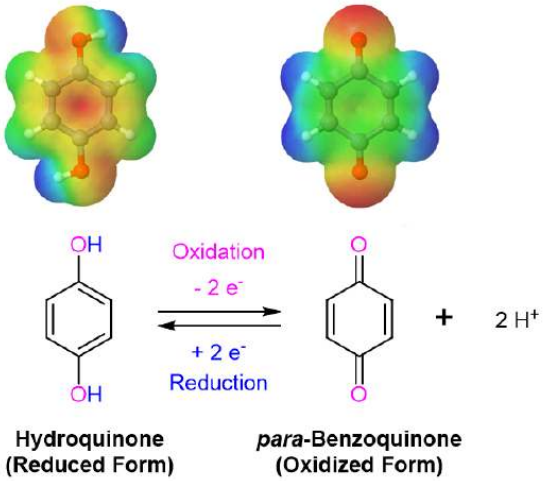
Oxidation of Phenols: Quinones

Phenols are rather easily oxidized despite the absence of a hydrogen atom on the hydroxyl bearing carbon. Among the colored products from the oxidation of phenol by chromic acid is the dicarbonyl compound **para-benzoquinone** (also known as 1,4-benzoquinone).



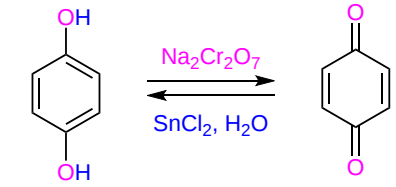
Phenol **para-Benzoquinone**

Quinones are an important class of compounds because of their redox equilibrium with their dihydroxybenzene analogs. The difference in electron density is seen in the electron potential map of hydroquinone and *para*-benzoquinone. The reduced compound, hyrodoquinone, has a greater electron density in the ring seen as a yellow/red color. The oxidized compound, *para*-benzoquinone, has significantly less electron density around the ring shown by the presence of green and blue colors.

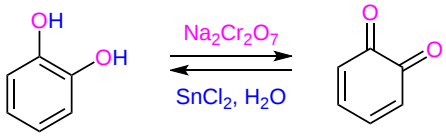


Hydroquinone (Reduced Form) **_para_-Benzoquinone (Oxidized Form)**

Dihydroxybenzenes can easily be oxidzed to the corresponding quinones by a wide variety of oxidizing agents including: sodium dichromate ($Na_2Cr_2O_7$), chromium trioxide (CrO_3), and potassium nitrosodisulfonate [$(KSO_3)_2NO$] called **Fremy's salt**. Likewise, quinone can be easily reduced back to hydroquinones using reagents such as stannous chloride ($SnCl_2$) or sodium borohydride ($NaBH_4$).



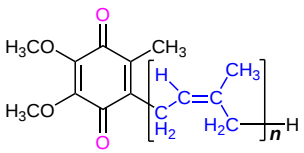
Hydroquinone (1,4-Dihydroxybenzene) **_para_-Benzoquinone**



Catechol (1,2-Dihydroxybenzene) **_ortho_-Benzoquinone**

Ubiquinones

The redox abilities of quinones are utilized as biological oxidizing agents in the mitochondria of cells of aerobic organism. These quinone containing compounds called ubiquinones or coenzymes Q are a coenzyme family that is ubiquitous in all animals and bacteria which is the source of their name.

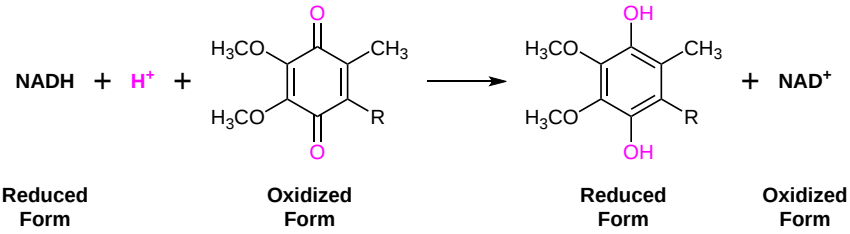


Ubiquinones (n = 1-10)

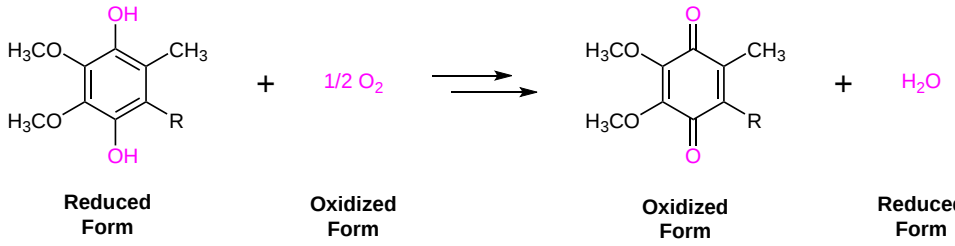
During the production of energy in cells, the redox capabilities of ubiquinones is utilized to mediate the electron-transfer process in which electrons are transferred from the biological reducing agent NADH to molecular oxygen. This process occurs in a series of steps. Initially, a ubiquinone reduced to its corresponding dihydroxy benzene in order to oxidize NADH to NAD^+. Later, the dihydroxy benzene is oxidized back to its ubiquinone form allowing for oxygen (O_2) to be reduced to water. When looking at the

overall process NADH is oxidized to NAD^+ and oxygen is reduced to water. The ubiquinone only acts as an intermediate and is unchanged during this process.

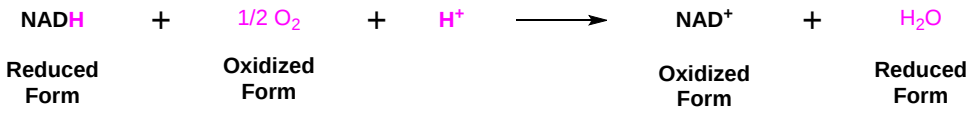
Step 1



Step 2



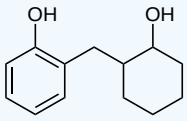
Overall Process



Exercises

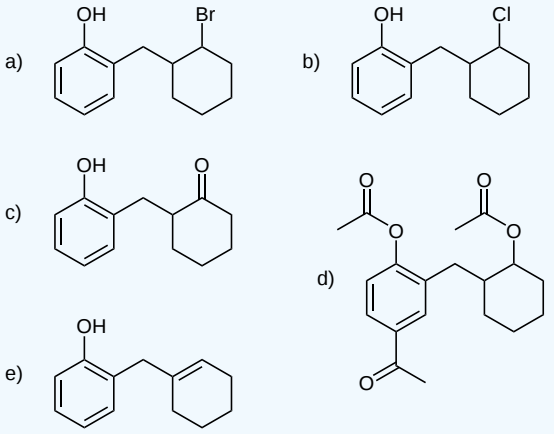
? Exercise 3.1.11.1

Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.



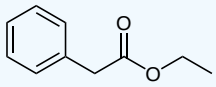
a. 1 equivalent of PBr_3
b. 1 equivalent of $SOCl_2$
c. Dess–Martin periodinane
d. 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst
e. Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

Answer



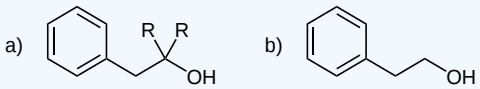
Exercise 3.1.11.2

Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.



a. 2 equivalents of RMgBr and H_3O^+ work-up
b. $LiAlH_4$ and H_3O^+ work-up
c. $NaBH_4$ and H_3O^+ work-up

Answer



Contributors and Attributions

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

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3.1.12: Spectroscopy of Alcohols and Phenols

Objectives

After completing this section, you should be able to

1. identify the two most prominent absorptions seen in the infrared spectra of alcohols and phenols.
2. describe the characteristic feature of the proton NMR spectra of alcohols and phenols.
   a. explain how deuterium oxide (D_2O) can be used to assist in the identification of the signal caused by the presence of the O-H proton in the ^1H NMR spectrum of an alcohol.
   b. predict the general form (i.e., number of peaks, approximate chemical shifts, and splitting pattern) of the proton NMR of a given alcohol or phenol.
3. describe the two most common initial fragmentations in the mass spectra of alcohols.
4. use spectral data (infrared, NMR, mass spectroscopy) to assist in the identification of an unknown alcohol or phenols. You may use tables of characteristic absorptions as an aid to accomplishing this objective.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alpha cleavage
- dehydration

Study Notes

The ^1H NMR chemical shifts for phenols are not particularly distinctive. However, one expects the **—OH** signal to be in the 4–7 ppm range, while the aromatic protons (see Section 15.7) are expected to be found at 7–8 ppm.

In a mass spectrometer, alcohols fragment in two characteristic ways: alpha cleavage and dehydration. From the equation showing H-Y elimination, you can see that the dehydration of an alcohol in a mass spectrometer is essentially the same as the dehydration of an alcohol in a normal chemical reaction. “Alpha cleavage” refers to the breaking of the bond between the oxygen-bearing carbon atom and one of the neighboring carbons.

Infrared Spectroscopy

The IR spectrum of aliphatic alcohols have a distinctive O-H stretch in the range of 3300 to 3400 cm^{-1}. This peak tends to be very strong and very broad. This exact position of the peak is dependent on the amount of hydrogen bonding in the alcohol. In addition alcohol have a strong C-O stretch near 1000 cm^{-1}. In the IR spectra of 1-butanol, show below, the O-H stretch appears at 3300 cm^{-1} and the C-O stretch appears at 1073 cm^{-1}.

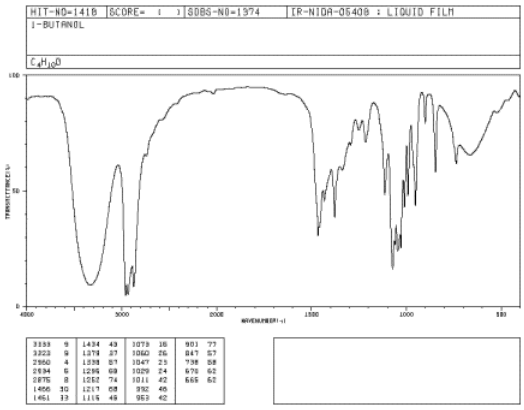
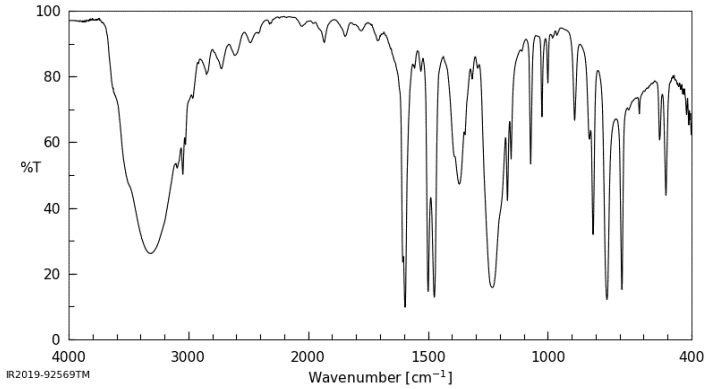


Figure IR8. IR spectrum of 1-butanol. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

Peak shapes are sometimes very useful in recognizing what kind of bond is present. The rounded shape of most O-H stretching modes occurs because of hydrogen bonding between different hydroxy groups. Because protons are shared to varying extent with neighboring oxygens, the covalent O-H bonds in a sample of alcohol all vibrate at slightly different frequencies and show up at slightly different positions in the IR spectrum. Instead of seeing one sharp peak, you see a broad set of multiple overlapping peaks. The broadness of the O-H peak makes it very easy to distinguish in an IR spectrum.

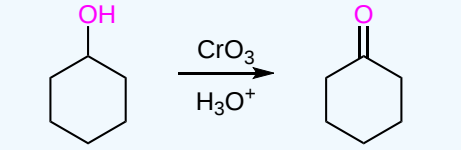
The IR spectrum of phenols the O-H stretch appears at roughly 3500 cm^{-1}. In addition, the IR spectra will show the bands typical for aromatic compounds in the region of 1500-1600 cm^{-1}.



The IR Spectrum of Phenol

? Exercise 3.1.12.1

Assume that you have just converted cyclohexanol into cyclohexanone. How would you use IR spectroscopy to tell if the conversion was successful? What changes would you expect to see between the starting material and the product?



Cyclohexanol **Cyclohexanone**

Answer

The cyclohexanol starting material would have a distinctive O-H stretch between 3300 and 3400 cm^{-1}. If the conversion were successful this peak would not be present in the product. Also, the IR spectrum of the product would have a strong C=O stretch between 1700 and 1800 cm^{-1}.

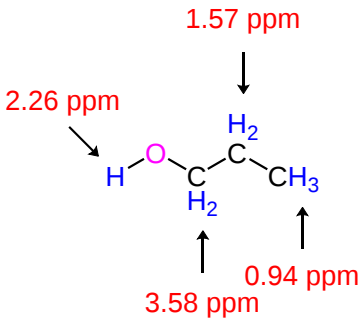
^{1}H Nuclear Magnetic Resonance Spectroscopy

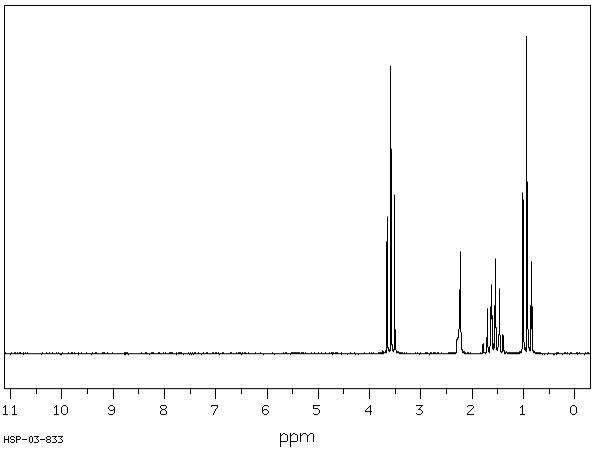
Alcohols

- Protons on carbon adjacent to the alcohol oxygen show up in the region of 3.4-4.5 ppm. The electronegativity of the alcohol oxygen de-shields these protons causing them to appear downfield when compared to alkane protons.
- Protons directly attached to the alcohol oxygen often appear in the region of 2.0 to 2.5 ppm. These peaks tend to appear as short, broad singlets. The position of the -OH peak can vary depending on the conditions, such as the NMR solvent used, the concentration of the alcohol, the purity of the alcohol, temperature, and if any water is present in the sample.

Notice that the alcohol proton is not involved in spin-spin splitting. This is usually true unless the alcohol is exceptionally pure. Most samples of alcohols contain minute amounts of acidic impurities which catalyze the exchange of protons causing the splitting

effects to be removed. This is why alcohol protons typically appears as a singlet in NMR spectrum. The ^1H NMR spectrum of propanol shows the -CH_2- attached to the alcohol as a triplet at 3.58 ppm. This shows that the signal is being split by the adjacent -CH_2- group and not the alcohol -OH. The signal for the proton attached to the oxygen appears as a singlet at 2.26 ppm. If this signal was involved in spin-spin splitting with the adjacent -CH_2- group it would appear as a triplet.

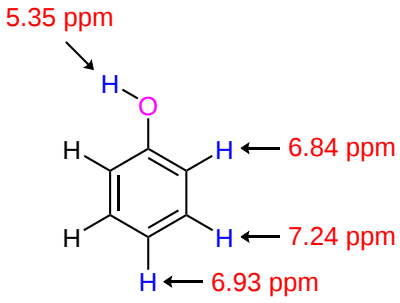


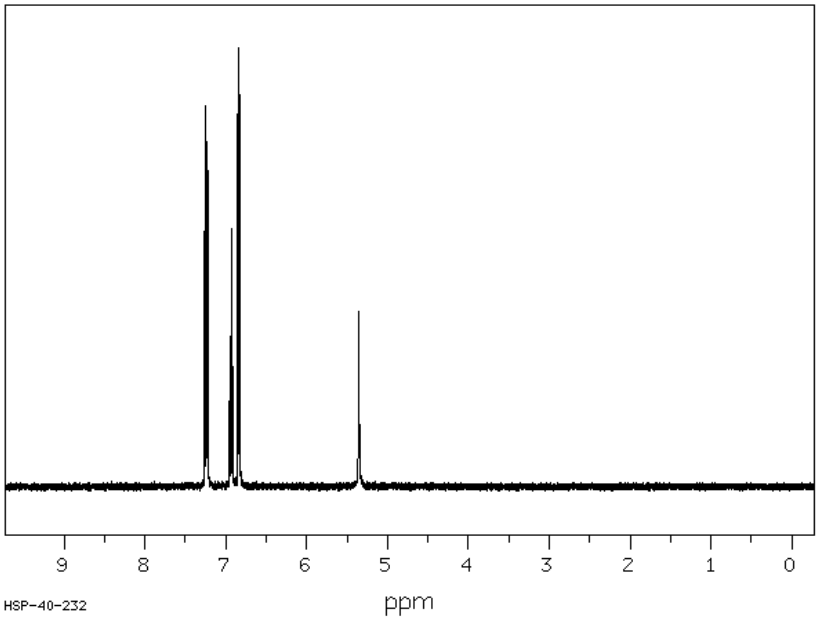


Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017

Phenol

- Protons attached to the aromatic ring in phenols show up near the aromatic region of an NMR spectrum (7-8 ppm). These peaks will have splitting typical for aromatic protons.
- The protons directly attached to the alcohol oxygen of phenols appear in the region of 3 to 8 ppm. These peaks tend to appear as short, broad singlets similarly to other alcohols.

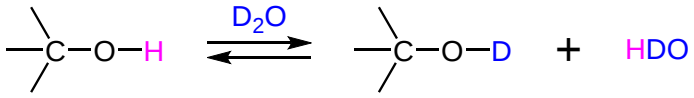




Determining the Position of an -OH Peak in ^{1}H NMR

The position of the -OH absorption for alcohols and phenols can be easily determined through the addition a few drops of deuterium oxide, D_2O to the NMR sample tube.

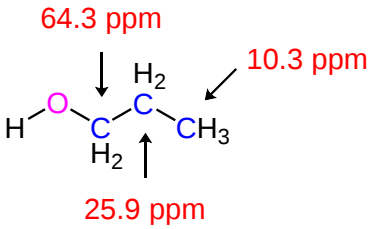
After addition, the OH proton will be rapidly exchanged for a deuterium. Because deuterium atoms do not produce peaks in a typical NMR spectrum the original -OH peak will disappear. This technique is sometimes called a **"D_2O shake"** due to the mixing required after D_2O has been added to the NMR sample tube.

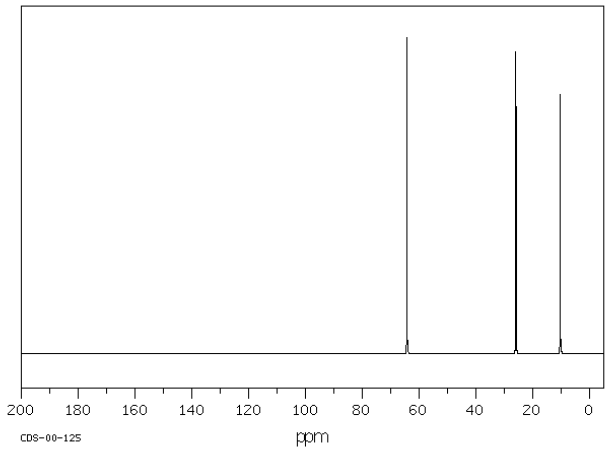


^{13}C Nuclear Magnetic Resonance Spectroscopy

Alcohols

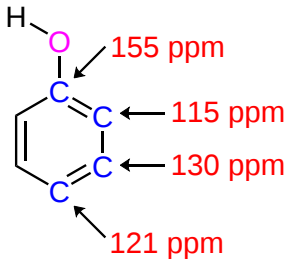
- Carbons adjacent to the alcohol oxygen show up in the distinctive region of 50-65 ppm in ^{13}C NMR spectrum.

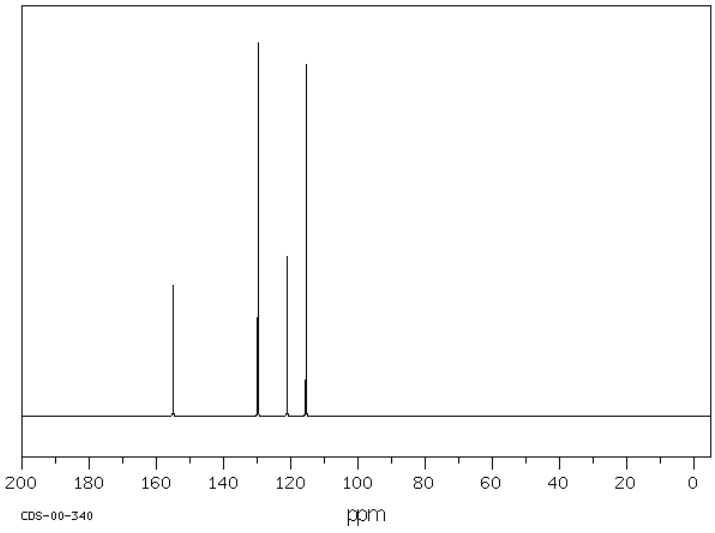




Phenols

- Due to the electronegative oxygen, the aromatic carbon attached to the -OH group is shifted downfield to 155 ppm.
- The other carbons in the phenol ring appear in the region typical for aromatic carbons of 125-150 ppm.





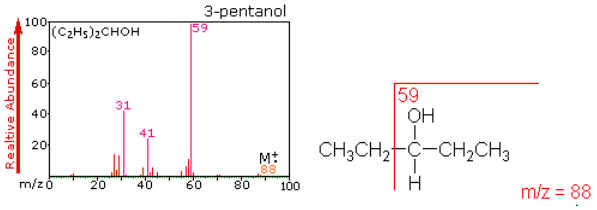
Mass Spectra

Alcohols

An alcohol's molecular ion is small or non-existent. Alpha-cleavage of the C-C bond next to the oxygen usually occurs. A loss of H_2O may occur as in the spectra below.

3-Pentanol ($C_5H_{12}O$) with MW = 88.15

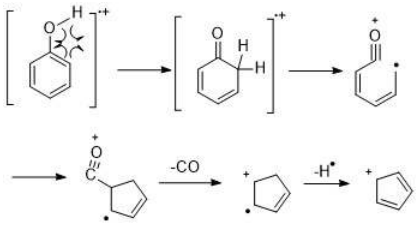
3-Pentanol shows three significant fragment ions. Alpha-fragmentation (loss of an ethyl radical) forms the m/z=59 base peak. Loss of water from this gives a m/z=41 fragment, and loss of ethene from m/z=59 gives a m/z=31 fragment.



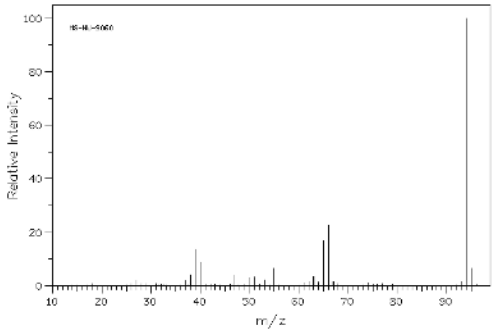
Phenol

Phenol (C_6H_6O) with MW = 94.11

Phenol exhibit a strong molecular ion peak. The presence of an aromatic ring and an OH gives phenol a unique fragmentation pattern. In particular loss of CO (M – 28) and loss of a formyl radical (HCO·, M – 29) are common observed.

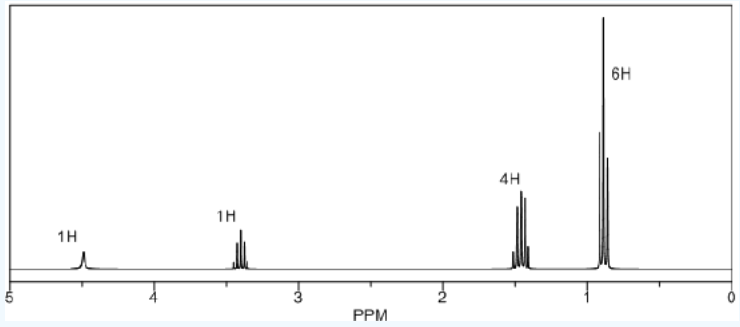


From an outside source



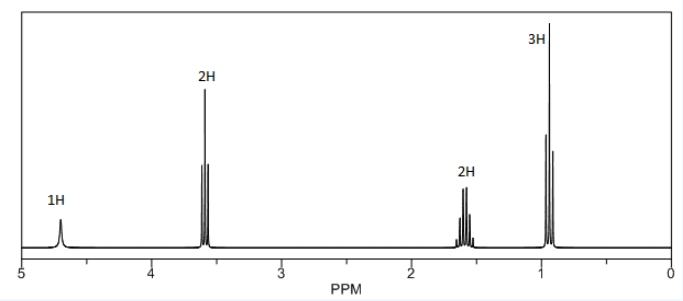
Exercise 3.1.12.1

1) From mass spectroscopy analysis it was determined that a compound has the general formula $C_5H_{12}O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



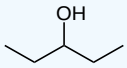
2) How would you expect the NMR spectrum show in question one to change if D_2O was added to the NMR sample tube.

3) From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

1) 3-Pentanol



Exercise 3.1.12.2

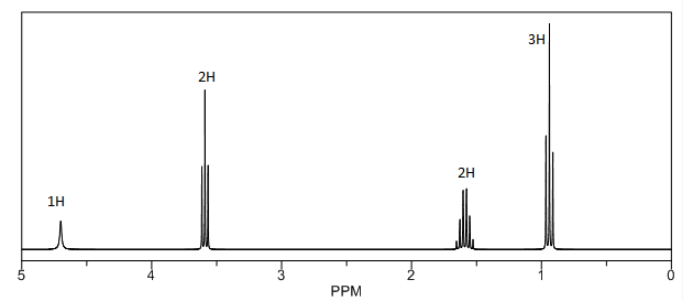
How would you expect the NMR spectrum shown in Exercise 1 to change if D_2O was added to the NMR sample tube.

Answer

The -OH peak at 4.5 ppm would dissappear due to dueterium exchange.

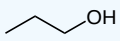
Exercise 3.1.12.3

From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

1-Propanol



Contributors and Attributions

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

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3.1.S: Alcohols and Phenols (Summary)

Concepts & Vocabulary

17.0 Introduction

- Alcohols have hydroxide groups (OH) bonded to an sp^3 carbon.
- Enols have a hydroxide bonded to an sp^2 carbon that is not part of an aromatic ring, a vinyl carbon.
- Phenols have a hydroxide bonded to an sp^2 carbon that is part of an aromatic ring, an aryl carbon.

17.1 Naming Alcohols and Phenols

- Alcohols can be described as methyl, primary, secondary or tertiary, based on the number of alkyl groups attached to the carbon bonded to OH.
- Alcohols are named following IUPAC rules, by dropping the -e of an alkane and replacing with -ol.

17.2 Properties of Alcohols and Phenols

- Alcohols, enols and phenols all have significantly higher boiling points than alkanes, due to hydrogen bonding.
- Small alcohols are soluble in water.
- Alcohols are amphoteric, they act as an acid when reacting with bases and as a base when reacting with acids.
- Phenols are more acidic than alcohols due to resonance delocalization of the negative charge in the phenoxide conjugate base.
- Substituent groups on an aromatic ring that withdraw electron density increase the acidity of phenols, while substituent groups that donate electron density decrease acidity of phenols.

17.3 Preparation of Alcohols: A Review

- Alcohols can be prepared from alkyl halides by reacting with hydroxide.
- Alcohols can be prepared from alkenes by reaction with acid/water or oxymercuration to form the more substituted alcohol.
- Alcohols can be prepared from alkenes by hydroboration/oxidation to form the less substituted alcohol.
- Diols can be prepared from alkenes by first forming an epoxide, then ring opening the epoxide to form an anti-diol.
- Diols can be prepared from alkenes by reacting with osmium tetraoxide, then reducing off the osmium to form syn-diols.

17.4 Alcohols from Carbonyl Compounds: Reduction

- Organic reduction can be defined by increasing the number of bonds to hydrogen.
- Aldehydes and ketones can be reduced to alcohols with several different hydride donor reagents.
- NADH is an example of a biological reducing agent, which donates a hydride to carbonyl groups, reducing them to an alcohol.
- Carboxylic acids and esters can be reduced to alcohols with a strong reducing agent such as lithium aluminum hydride $LiAlH_4$.

17.5 Alcohols from Carbonyl Compounds: Grignard Reaction

- One of the most important organometallic groups of molecules are Grignard reagents, which are alkyl magnesium halides.
- Grignard reagents, like other organometallic compounds, include a nucleophilic alkyl group that can react with many different electrophiles.
- Grignard reagents will add to aldehydes and ketones forming alcohol products.
- Grignard reagents will add twice to ester molecules, forming alcohol products.
- Grignard reagents are strong bases, therefore the will not undergo nucleophilic addition reactions with molecules that have protons that are even slightly acidic such as: alcohols, carboxylic acids, alkynes, and amines or amides that have an N-H bond.

17.6 Reactions of Alcohols

- Alcohols can be converted into alkyl halides directly by reaction with strong hydrogen halides. This works best for 3° alcohols.
- Conversion of 1° and 2° alcohols into alkyl halides commonly use thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3).
- To activate an alcohol in order to make the hydroxide a good leaving group, tosylates (toluenesulfonates) and mesylates (methanesulfonates) can be formed.
- Alcohols can be dehydrated by heating in strong acid solution to form an alkene.
- Alcohols react with acid chlorides to form esters.

17.7 Oxidation of Alcohols

- Primary and secondary alcohols can be oxidized with various chromium reagents, while tertiary alcohols are not.
- Secondary alcohols are oxidized to ketones.
- Primary alcohols are oxidized to carboxylic acids using chromium trioxide or dichromate compounds.
- Primary alcohols can be stopped in their oxidation at aldehydes by reacting with pyridinium chlorochromate or Dess-Martin periodinane.

17.8 Protection of Alcohols

- Protection of a functional group is useful when that functional group may interfere with an intended reaction.
- Protection converts a functional group into a non-interfering derivative molecule through a reaction that can be easily reversed to remove the protecting group.
- Protection consists of a series of reactions that include protect, perform intended reactions, and deprotect.
- Alcohols can be protected as silyl ethers by reacting with chlorotrialkyl silanes.

17.9 Phenols and Their Uses

- Phenols can be prepared from chlorobenzene or isopropylbenzene.
- Phenol and phenol derivatives (such as resorcinol) are used as germicides and antiseptics.
- Bisphenol A (BPA) has controversially been used to create polycarbonate plastics such as water bottles.

17.10 Reactions of Phenols

- Phenols can react with strong electrophiles (such as in Friedel-Crafts reactions).
- Phenols react with strong oxidizing agents including Jones reagent or silver oxide to form quinones.

17.11 Spectroscopy of Alcohols and Phenols

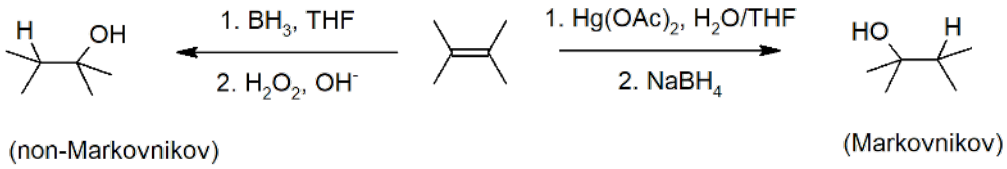
- Alcohols are among the most identifiable functional groups in infrared spectroscopy due to the strong, wide absorbance around 3400 cm^{-1}.
- Alcohol peaks are much more difficult to recognize in ^{1}H NMR, since OH hydrogens are relatively reactive and can exchange with hydrogens from the solvent, they are often weak absorptions without strong, sharp peaks.
- Hydroxide protons are not split in ^{1}H NMR.
- Loss of hydroxide in mass spectroscopy can lead to loss of a fragment with 17 m/z.

Skills to Master

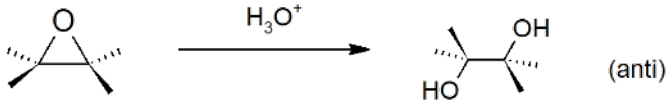
- Skill 17.1 Identify types of alcohols.
- Skill 17.2 Name molecules with hydroxide groups using IUPAC rules.
- Skill 17.3 Describe properties related to intermolecular forces (including hydrogen bonding).
- Skill 17.4 Explain acid-base properties of alcohols and phenols.
- Skill 17.5 Describe how additional functional groups affect the acidity of phenols.
- Skill 17.6 Draw mechanisms to form alcohols from alkyl halides.
- Skill 17.7 Draw mechanisms to form alcohols from alkenes.
- Skill 17.8 Draw mechanisms to form alcohols by reduction reactions.
- Skill 17.9 Draw mechanisms to form alcohols by reaction of carbonyl compounds with Grignard reagents (and other organometallics).
- Skill 17.10 Draw mechanisms for conversion of alcohols to alkyl halides.
- Skill 17.11 Draw mechanisms for conversion of alcohols to tosylates.
- Skill 17.12 Draw mechanisms for dehydration of alcohols to alkenes.
- Skill 17.13 Draw mechanisms for conversion of alcohols to esters.
- Skill 17.14 Draw mechanisms for oxidation of alcohols to aldehydes, ketones, and carboxylic acids.
- Skill 17.15 Write out syntheses that incorporate protection and deprotection of alcohols.
- Skill 17.16 Identify presence of alcohols by IR, NMR and MS.

Summary of Reactions

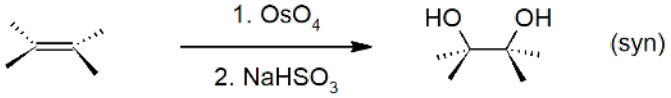
Alcohol Preparation (Hydrolysis)



(non-Markovnikov) (Markovnikov)

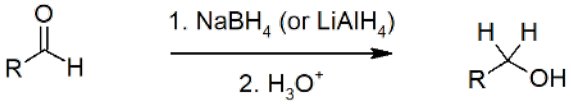


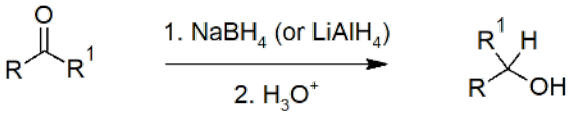
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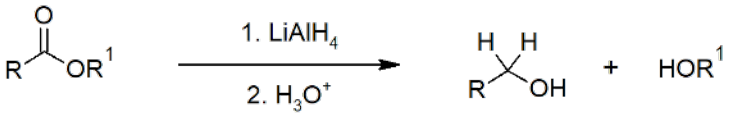


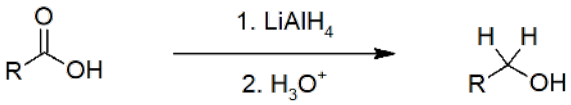
(syn)

Alcohol Preparation (Reducing the Carbonyl)

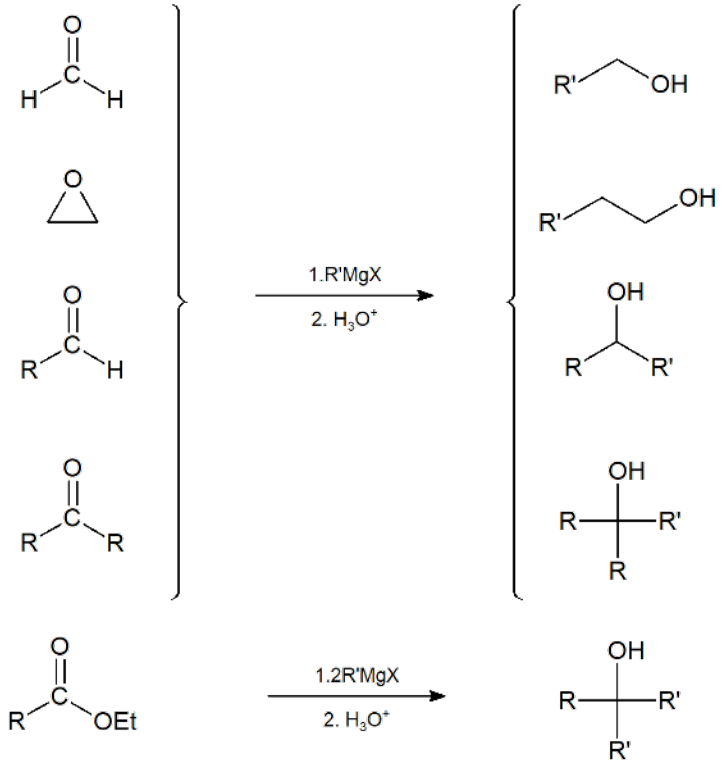




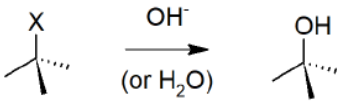




Alcohol Preparation (Grignard Additions)

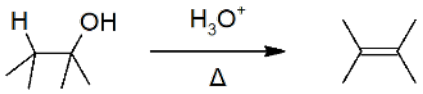


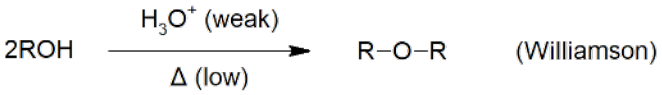
Alcohol Preparation (from Organohalide)

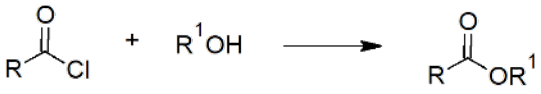


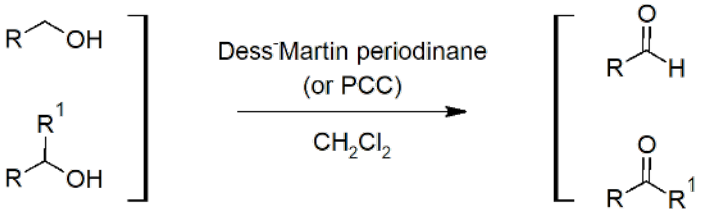
https://chem.libretexts.org/@go/page/413191

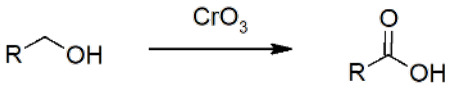
Alcohol Reactions



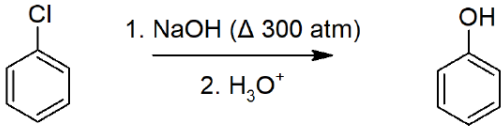


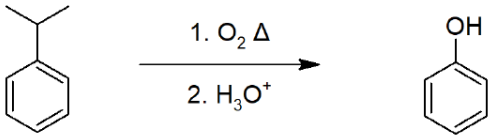






Phenol Preparation





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SECTION OVERVIEW

3.2: Ethers and Epoxides; Thiols and Sulfides

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides (cyclic ethers containing a three-membered ring). We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

3.2.1: Introduction

3.2.2: Names and Properties of Ethers

3.2.3: Preparing Ethers

3.2.4: Reactions of Ethers- Acidic Cleavage

3.2.5: Reactions of Ethers- Claisen Rearrangement

3.2.6: Thiols and Sulfides

Learning Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
- solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
- define, and use in context, the key terms introduced in this chapter.

Contributors and Attributions

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3.2.1: Introduction

Objectives

After completing this section, you should be able to use the terms “ether,” “diethyl ether ” and “ethyl ether ” appropriately in context.

Key Terms

Make certain that you can define, and use in context, the key terms below.

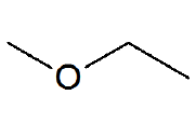
- ether (R–O–R′)
- sulfide (R–S–R′)
- thiol (R–S–H)

Study Notes

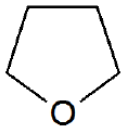
As defined in the textbook, an “ether” is a substance with the general formula (R–O–R′) where R and R′ are alkyl, aryl, vinyl or allyl groups. However, the word “ether” is also commonly used to refer to the specific compound, $CH_3–CH_2–O–CH_2–CH_3$, which is correctly called “diethyl ether.” Further confusion can arise because some chemists refer to “diethyl ether ” as “ethyl ether.” In this course, “ether ” will be used to refer to the class of compounds with the structure (R–O–R′); diethyl ether will refer to the compound, $CH_3–CH_2–O–CH_2–CH_3$; and “ethyl ether ” will not be used.

Ethers and Epoxides

While the general formula for ethers is R-O-R′, keep in mind that there also cyclic ethers like tetrahydrofuran (a common organic solvent) or even epoxides which you first encounter in Section 8.7 in synthesizing diols from alkenes.



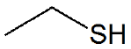
ethyl methyl ether



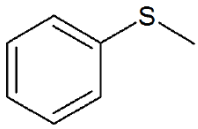
tetrahydrofuran

Thiols and Sulfides

Thiols (thio alcohols or mercaptans) and sulfides (thioethers) are the sulfur analogues of alcohols and ethers and have the general formulas of R-S-H and R-S-R′, respectively.



ethanethiol



methyl phenyl sulfide

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3.2.2: Names and Properties of Ethers

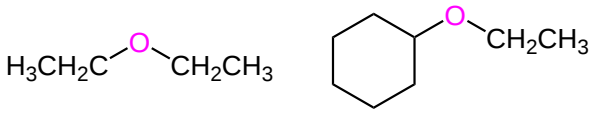
Objectives

After completing this section, you should be able to

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

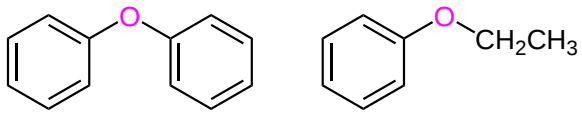
Structure of Ethers

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. These compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



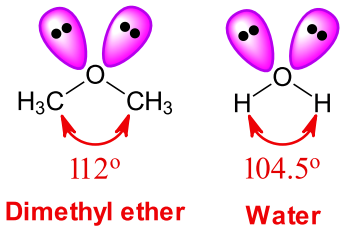
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair electrons on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

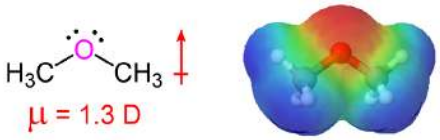


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112° which is larger than the H-O-H bond angle in water (104.5°) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment with the electron density primarily on oxygen (red and orange in the electrostatic potential map).



Comparisons of Physical Properties of Alcohols and Ethers

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass. Despite the presence of a small dipole moment, ethers have boiling points that are about the same as alkanes of comparable molar mass. (Table 18.1.1).

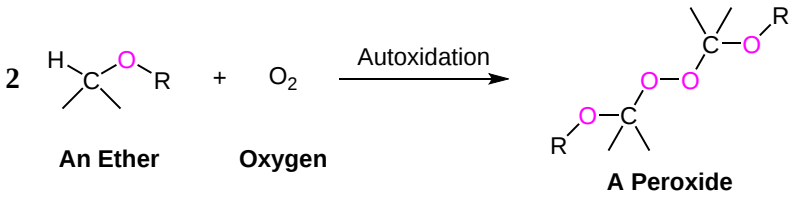
Table 18.1.1 : Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water).

Peroxide Formation

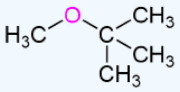
Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.



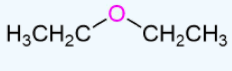
Naming Ethers

When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The common names for alkyl substituents discussed in **Section 3.3** are often used.

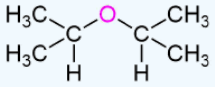
Example 18.1.1



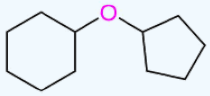
Methyl *tert*-butyl ether



Diethyl ether



Diisopropyl ether



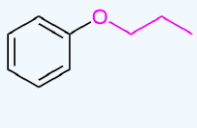
Cyclohexyl cyclopentyl ether

IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent. Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 18.1.2):

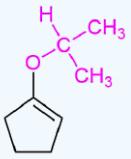
Table 18.1.2 : Common Alkyl and Alkoxy Groups

Alkyl Group	Name		Alkoxy Group	Name
CH_3–	Methyl		CH_3O–	Methoxy
CH_3CH_2–	Ethyl		CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl		$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl		$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl		C_6H_5O–	Phenoxy

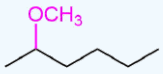
Example 18.1.2



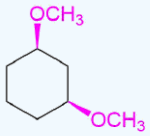
Propoxybenzene



1-**Isopropoxy**cyclopentene



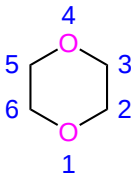
2-**Methoxy**hexane



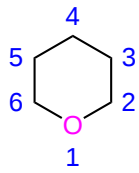
***Cis*-1,3-Dimethoxy**cyclohexane

Cyclic Ethers

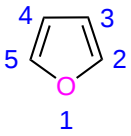
Cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are also found in many biological molecules such as sugars and DNA. The rings are numbered so that an oxygen gets position 1.



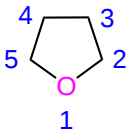
Dioxane



Tetrahydropyran



Furan



Tetrahydrofuran

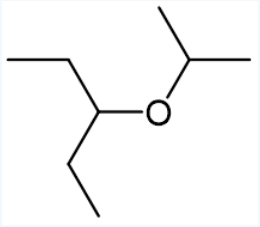
Example 18.1.3



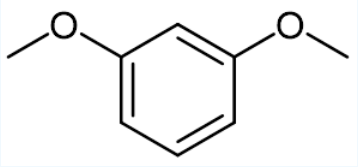
2-Methoxytetrahydrofuran **3-Methyltetrahydropyran**

Exercise 18.1.1

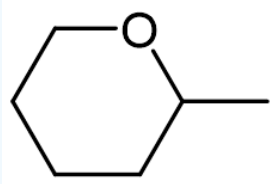
Name the following ethers:



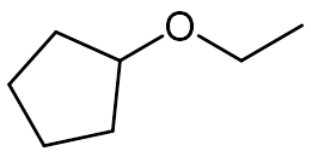
b)



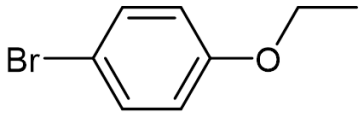
c)



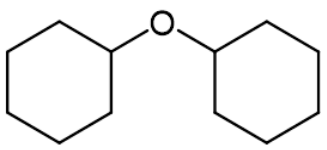
d)



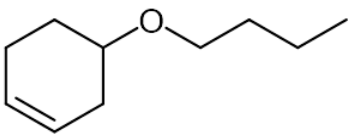
e)



f)



g)



Answers

a) 3-Isopropoxypentane

b) 1,3-Dimethoxybenzene

c) 2-Methyltetrahydropyran

d) Cyclopentyl ethyl ether

e) 4-Bromo-1-ethoxybenzene

f) Dicyclohexyl ether

g) 4-Butoxycyclohexene

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3.2.3: Preparing Ethers

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
    a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
    b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
    c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
    d. write an equation to describe the formation of an alkoxide from an alcohol.
    e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
    a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
    b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
    c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

Study Notes

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.5. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

Description	oxymercuration	alkoxymercuration
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

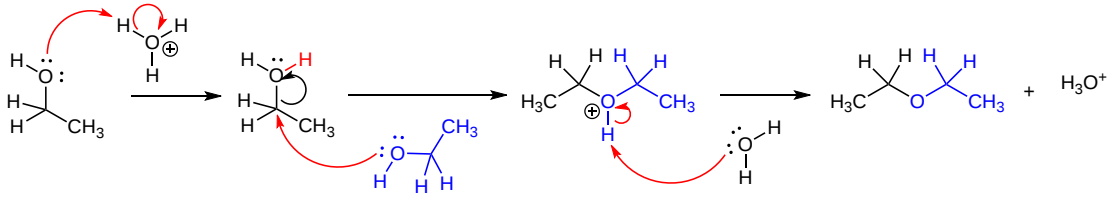
Ether Formation Though Dehydration

Acid-catalyzed dehydration of small 1º-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2º and 3º alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism (**Section 17-6**).

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \qquad (18.2.1)$$

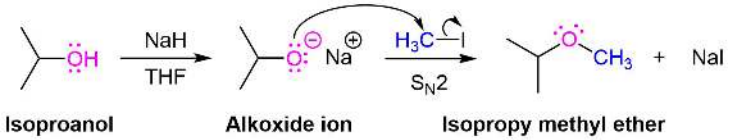
Mechanism

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



Williamson Ether Synthesis

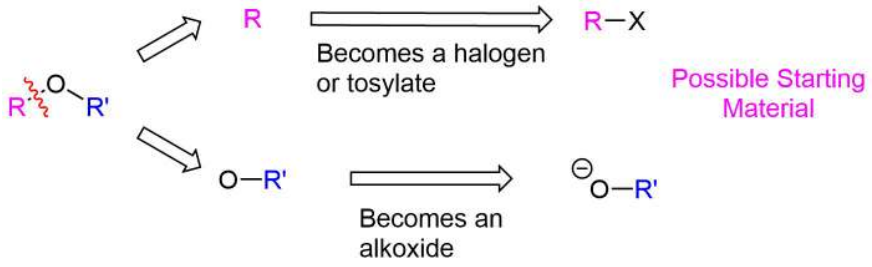
One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed in **Section 17-2**, alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium hydride (NaH). Simple alcohols can be used a solvent during a Williamson ether synthesis and with their alkoxide created through the addition of sodium metal ($Na_{(s)}$).



Planning a Williamson Ether Synthesis

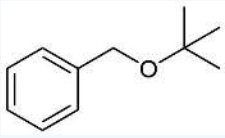
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in **Section 11-3**. Since alkoxide anions are strong bases, utilizing 2º or 3º halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway which utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



? Worked Example 3.2.3.1

How would you prepare the following molecule using a Williamson Ether Synthesis?

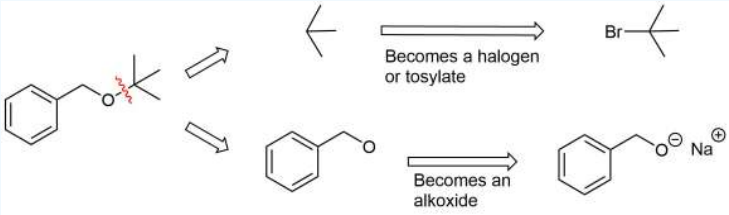


Answer

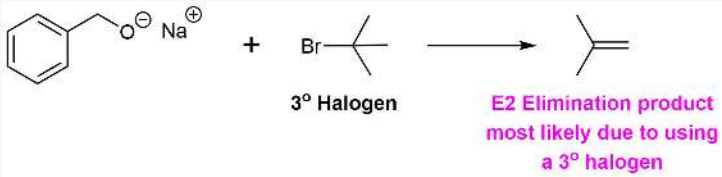
https://chem.libretexts.org/@go/page/413195

Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3° halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3° halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1° halogen as a starting material which is favorable for S_N2 reactions.

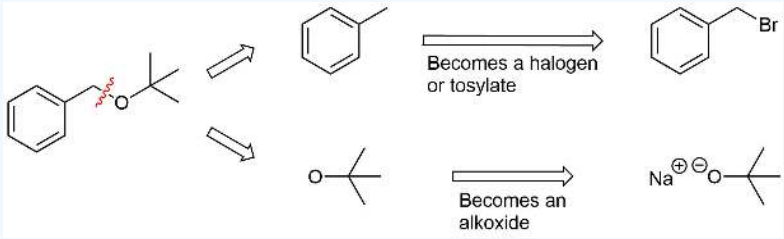
Pathway 1



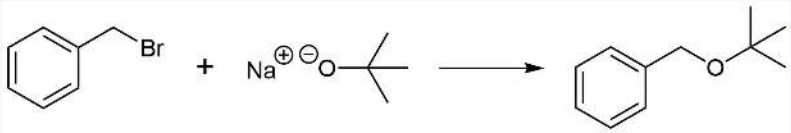
Solution 1



Pathway 2

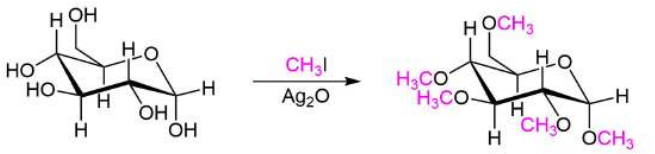


Solution 2



Ether Synthesis Using Silver Oxide

A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particually useful when converting the -OH groups on a sugar into ethers.



α-D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

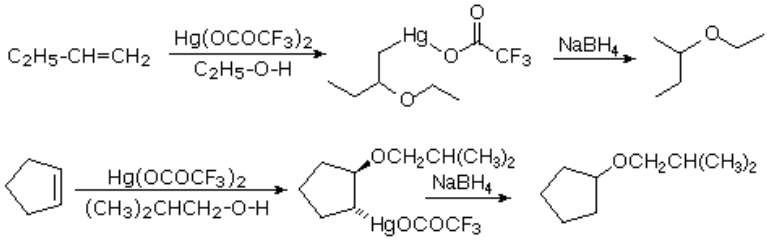
Mechanism

During this reaction a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



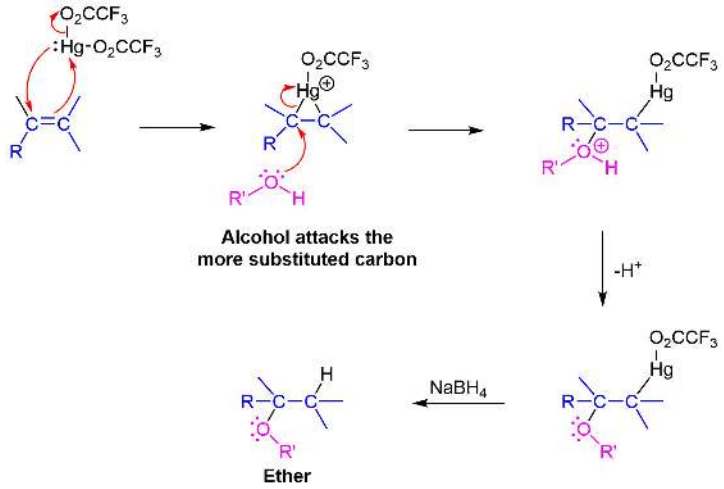
Ether Synthesis Using Alkoxymercuration

Alkoxymercuration, is patterned after the oxymercuration reaction discussed in **Section 8-4**. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1º, 2º, 3º alcohols can be successfully used for this reaction.



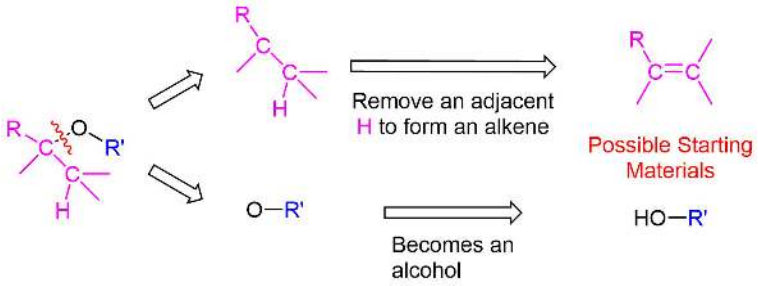
Mechanism

The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally, sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



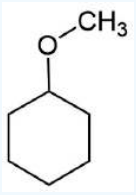
Planning the Synthesis of an Ether using Alkoxymercuration

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



Worked Example 3.2.3.2

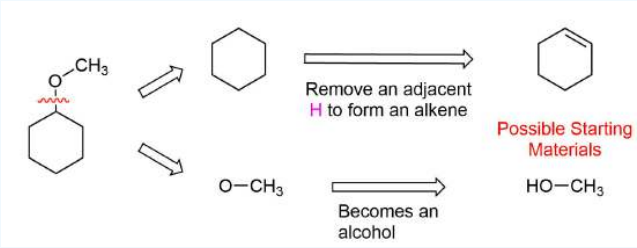
How would you prepare the following molecule using a alkoxymercuration?



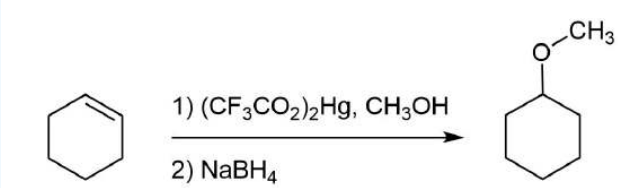
Answer

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

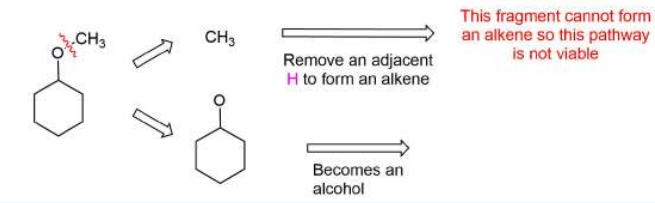
Pathway 1



Solution 1



Pathway 2



Exercise 3.2.3.1

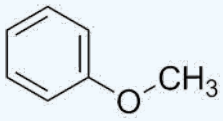
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

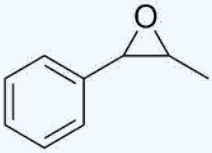
Answer

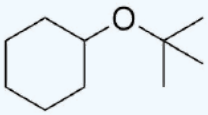
The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

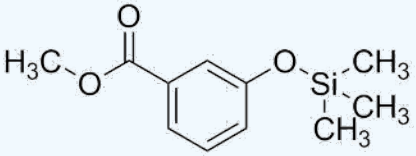
Exercise 3.2.3.2

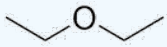
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

(c) 

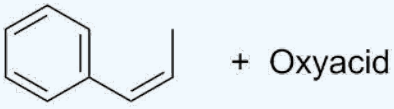
(d) 

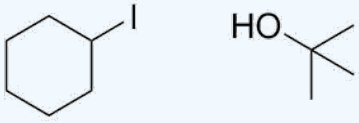
(e) 

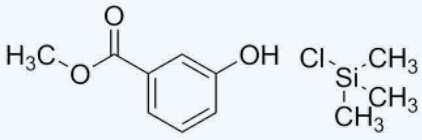
Answer

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

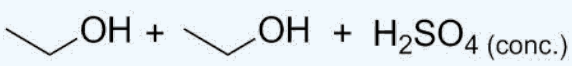
(a) 

(b) 

(c) 

(d) 

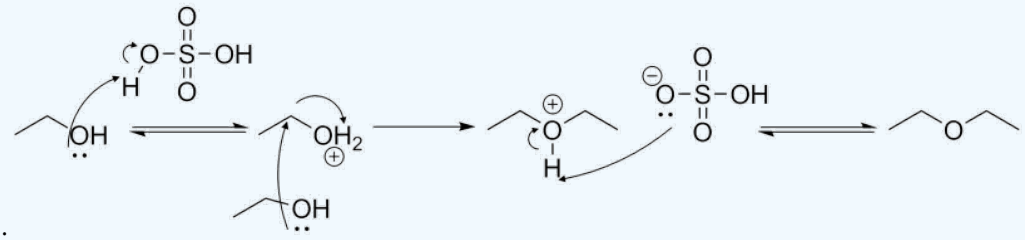
Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 

Exercise 3.2.3.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

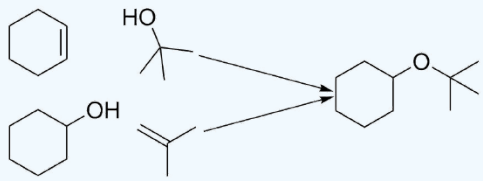
Answer



Exercise 3.2.3.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

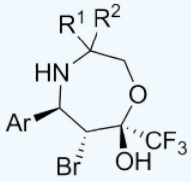
Answer



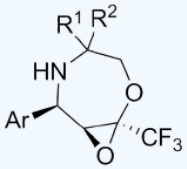
While both are possible, the top route is likely easier because both starting materials are a liquid.

Exercise 3.2.3.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)



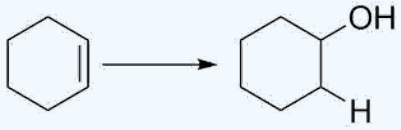
Answer



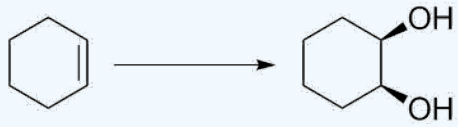
Exercise 3.2.3.6

What reagents would you use to perform the following transformations?

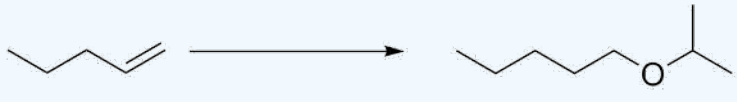
(a)



(b)

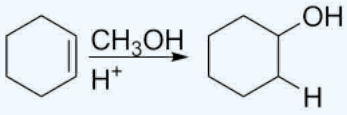


(c)

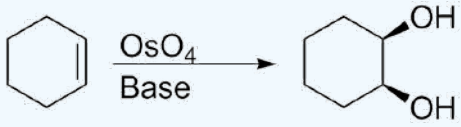


Answer

(a)

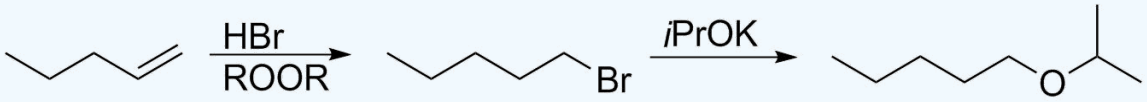


(b)



Note the cis addition

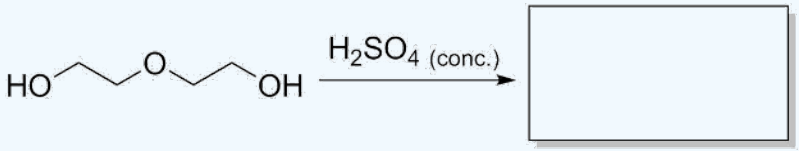
(c)



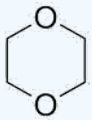
An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

? Exercise 3.2.3.7

Predict the product of the following.



Answer



The result is the production of dioxane, a common solvent.

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3.2.4: Reactions of Ethers- Acidic Cleavage

Objectives

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

Study Notes

There are a number of points in this section that require additional explanations.

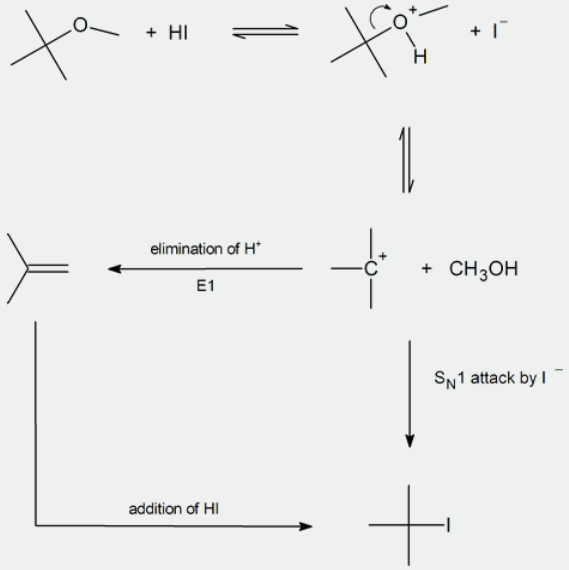
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$$\mathbf{ROH + HI \longrightarrow RI + H_2O}$$

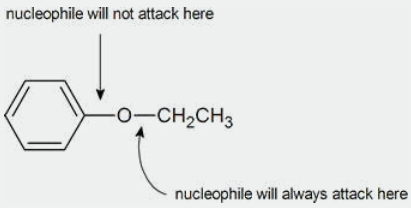
In view of this substitution, some textbooks simplify the overall cleavage process as:

$$\mathbf{R{-}O{-}R' + 2\,HI \longrightarrow RI + R'I + H_2O}$$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:



Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:

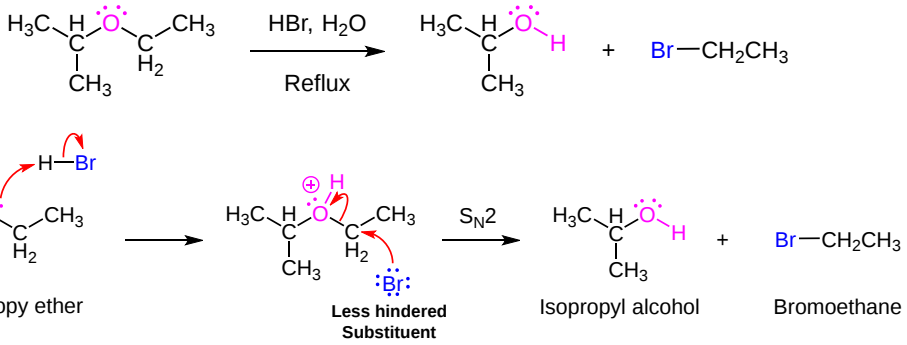


> As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

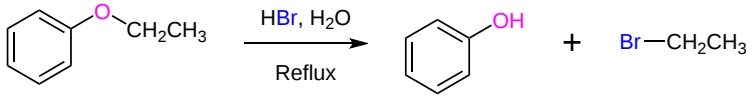
Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving groups which can be eliminated as part of an S_N2, S_N1, or E1 reaction mechanism. The mechanistic pathway is primarily determined by the strong acid used and the type of substituents attached to the ether.

Acidic Cleavage of Ethers

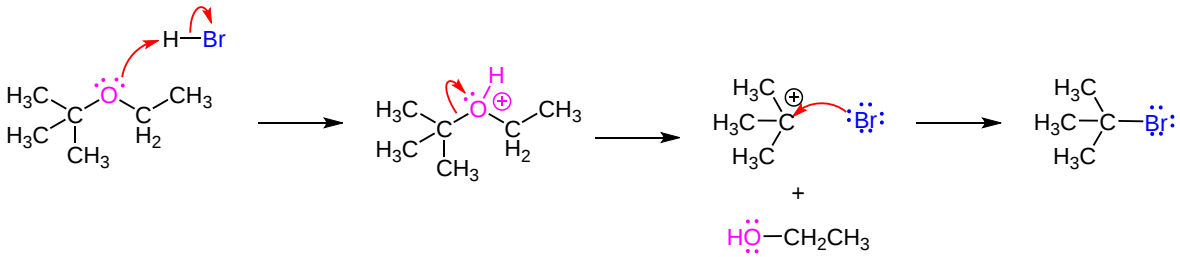
Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, the strong acid protonates the ether oxygen. Then resulting halide conjugate base attacks the protonated ether at the less sterically hindered alkyl substituent forming a halogen product. The ether's more sterically hindered alkyl substituent is ejected as a leaving group and forms an alcohol product. The example below show that when ethyl isopropyl ether is cleaved with hydrobromic acid the products isopropyl alcohol and bromoethane are produced. The bromide nucleophile preferably attacks the ether's ethyl substituent because it is less hindered (1º) than the isopropyl substituent (2º).



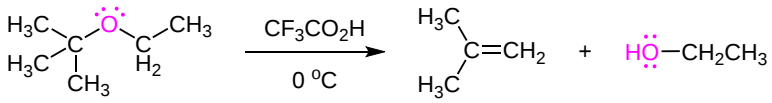
It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.



When using HBr or HI, the acidic cleavage of ethers with tertiary, benzylic, or allylic substituents tend to occur by an S_N1 mechanism. The ability of these substituents to produce relatively stable carbocations promotes the S_N1 mechanism. The change in mechanism causes the tertiary, benzylic, or allyic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

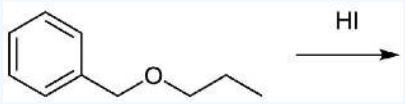


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid (CF_3CO_2H), for the the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1. In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



Worked Example 3.2.4.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

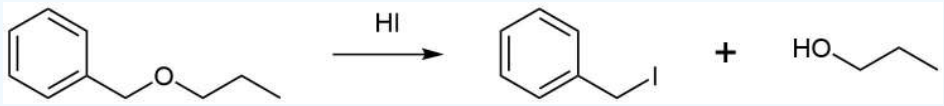
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

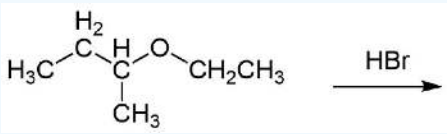
Solution



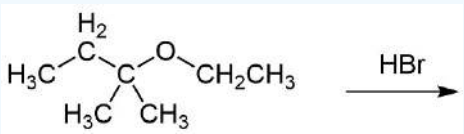
Exercises 3.2.4.1

1) Predict the product of the following reactions:

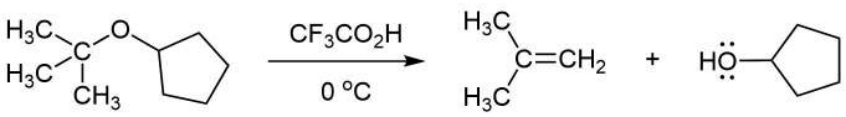
a)



b)



2) Please draw the mechanism for the following reaction:

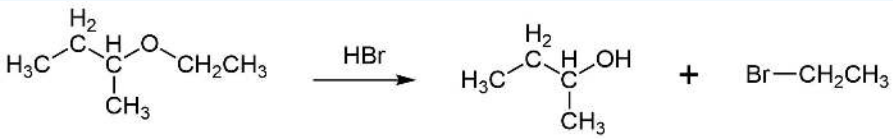


3) Why is HCl less effective at cleaving ethers than HBr or HI?

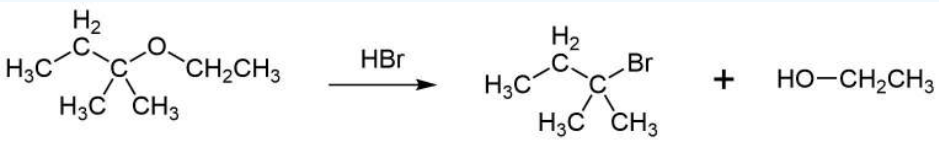
Answer

1)

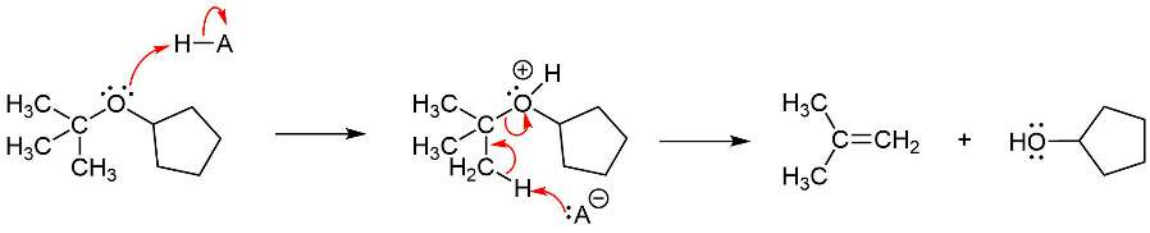
a)



b)



2)



3) HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

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3.2.5: Reactions of Ethers- Claisen Rearrangement

Objectives

After completing this section, you should be able to

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

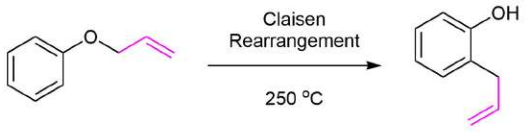
Key Terms

Make certain that you can define, and use in context, the key term below.

- Claisen rearrangement

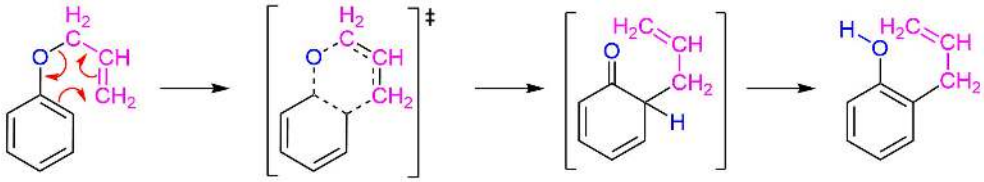
Claisen Rearrangements

The Claisen rearrangement is a key organic reaction that involves the thermal rearrangement of allyl vinyl ethers to form β-aryl allyl ethers. This reaction is specific to ally aryl ethers and allyl vinyl ethers. Heating an allyl aryl ether to 250 ^{o}C causes an intramolecular rearrangement to produce an *o*-allylphenol.



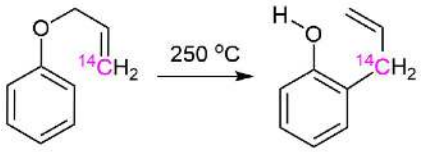
Allyl phenyl ether **o-Allylphenol**

The Claisen rearrangement takes place through a concerted mechanism in which a C-C bond forms between the C3 of the allyl group and the ortho position of the benzene ring at the same time that the C-O bond of the ether breaks. This rearrangement initially produces the non-aromatic 6-allyl-2,4- cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the concerted movement of six bonding electrons in the first step. The presence of six electrons in a ring suggests that the transition state may have aromatic characteristics. The Claisen rearrangement is part of a broader class of reactions called sigmatropic rearrangements which will be discussed in more detail in **Section 30-8**.



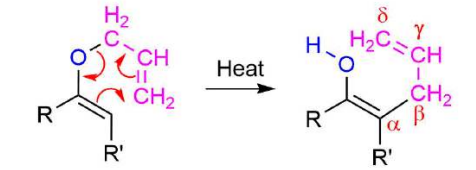
Transition State **Intermediate**

Evidence for this mechanism was provided by performing the rearrangement with allyl group with a ^{14}C label at C3. The product of this reaction was shown to have the ^{14}C labeled carbon exclusively bonded to the ring.

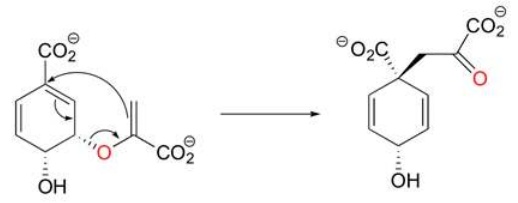


Only Product

Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



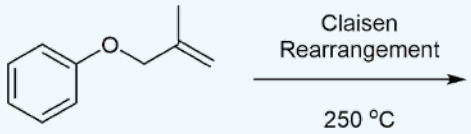
Claisen rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



Exercise 3.2.5.1

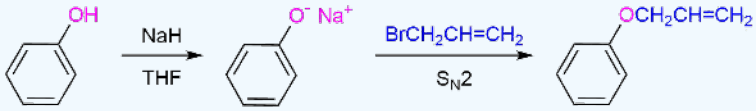
1) Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

2) What would be the expected product of the following Claisen rearrangement?

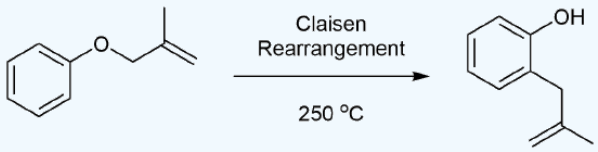


Answer

1)



2)



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3.2.6: Thiols and Sulfides

Objectives

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

Key Terms

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

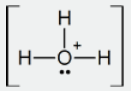
Study Notes

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

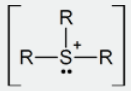
A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



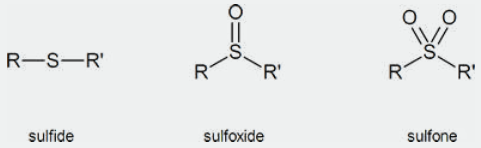
hydronium ion



trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.



sulfide sulfoxide sulfone

Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table **3.2.6.1**: Comparison of compounds containing oxygen and sulfur

Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

Oxidation States of Sulfur Compounds

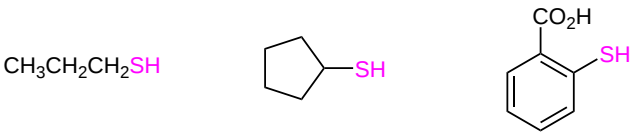
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S–R (R) sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R–O–S(=O)–O–R sulfite esters	SO_3 R–O–S(=O)(=O)–O–R sulfate esters

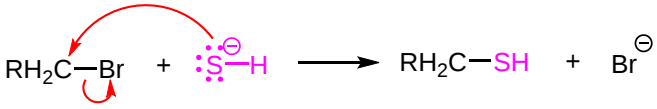
Thiols

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



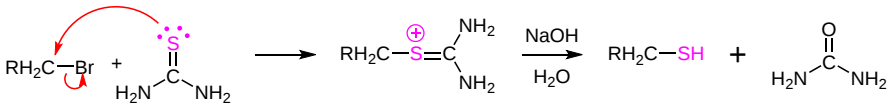
Propanethiol **Cyclopentanethiol** ***o*-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



Hydrosulfide ion **Thiol**

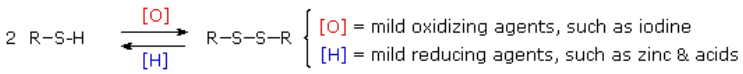
One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



Thiourea **Thiol** **Urea**

Disulfides

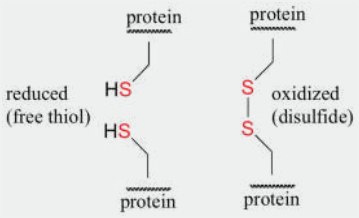
Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.



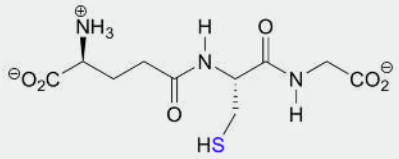
Thiol **Disulfide**

Disulfide bridges in proteins

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

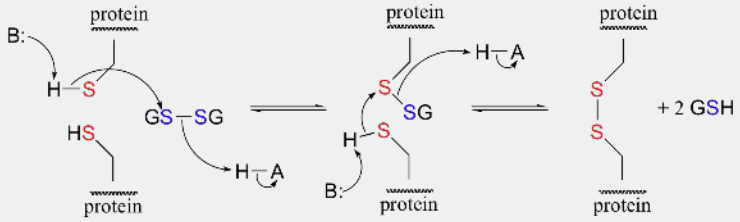


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Sulfides

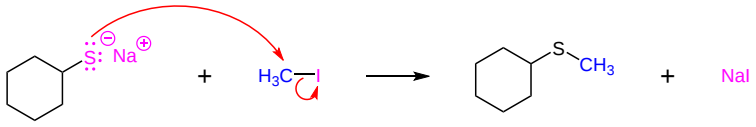
Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

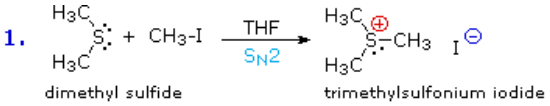
Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 18-2**)



Cyclohexanethiolate **Cyclohexyl methyl sulfide**

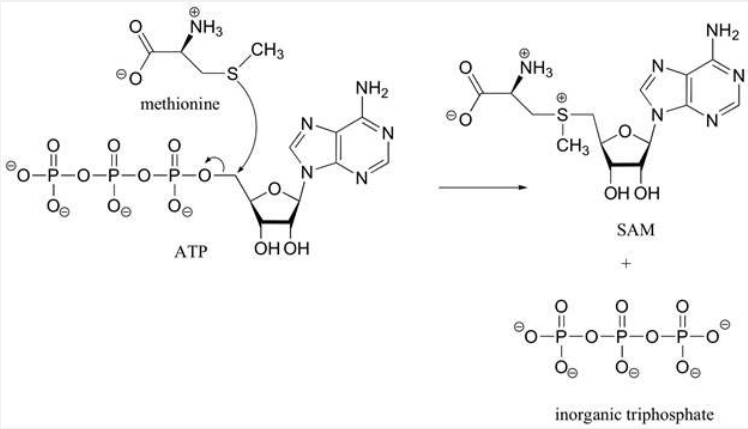
The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary

alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3º-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

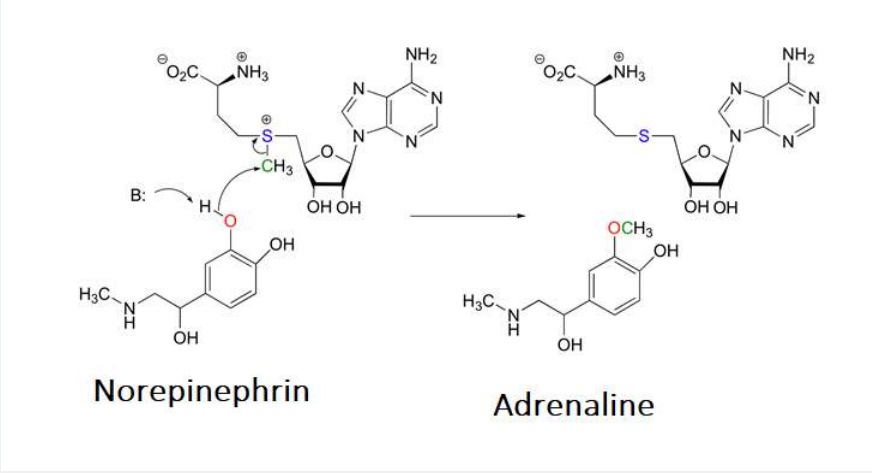


Biological Sulfonium Ion Formation

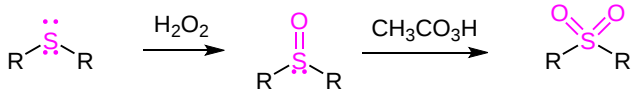
In biological systems the sulfonium ion, *S*-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.

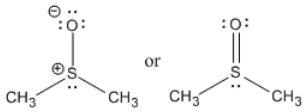


Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



Sulfide **Sulfoxide** **Sulfone**

A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.

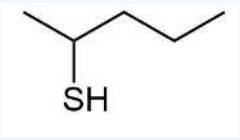


DMSO is a very polar, aprotic solvent

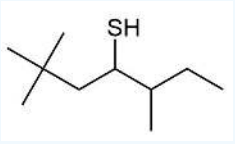
? Exercise 3.2.6.1

Give IUPAC names the following compounds:

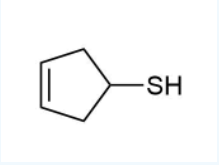
a)



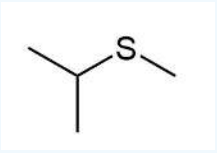
b)



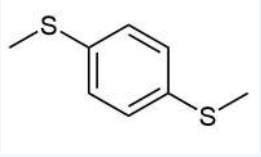
c)



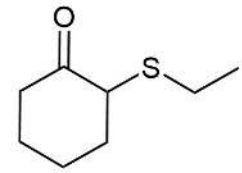
d)



e)



f)



Answer

a) 2-Pentanethiol

b) 2,2,5-Trimethyl-4-heptanethiol

c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide

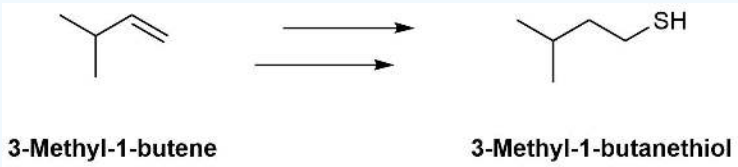
e) *p*-Di(methylthio)benzene

f) 2-(Ethylthio)cyclohexanone

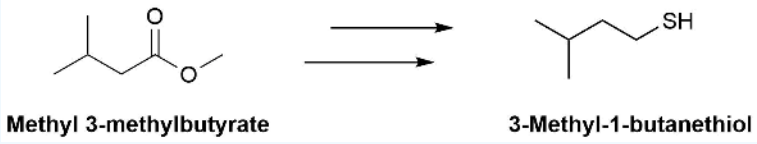
Exercise 3.2.6.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



b)



Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

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SECTION OVERVIEW

3.3: Amines and Heterocycles

Learning Objectives

When you have completed Chapter 24, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

3.3.1: Naming Amines

3.3.2: Structure and Properties of Amines

3.3.3: Synthesis of Amines

3.3.4: Reactions of Amines

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3.3.1: Naming Amines

Objectives

After completing this section, you should be able to

1. classify a given amine as being primary, secondary or tertiary.
2. explain, briefly, the difference in meaning of the terms primary, secondary and tertiary when they are applied to the structures of amines and alcohols.
3. determine whether a given structure represents a quaternary ammonium cation.
4. provide an acceptable IUPAC name for an amine, given its Kekulé, condensed or shorthand structure.
5. draw the structure of an amine, given its IUPAC name.
6. give the name and structure of one typical heterocyclic amine (e.g., pyridine).

Key Terms

Make certain that you can define, and use in context, the key terms below.

- amine
- primary amine
- secondary amine
- quaternary ammonium cation
- tertiary amine

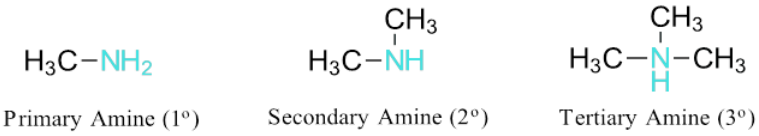
Study Notes

You should recognize that heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are very common in organic chemistry. Be prepared to meet such compounds throughout this, and subsequent chapters, but do not try to memorize all of the names and structures givenin the reading. You should, however, commit the structures of pyridine and pyrrole to memory.

Classification of Amines

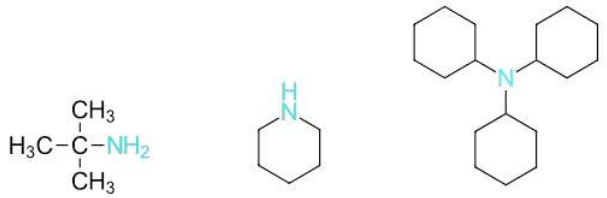
Amines are made up of an sp^3 hybridized nitrogen and are either alkyl substituted (alkylamines) or aryl substituted (arylamines).

Amines are classified as primary, secondary, or tertiary based on the number or organic substituents directly attached to the nitrogen. An amine attached to one substituent is primary (1°), two substituents is secondary (2°), and three substituents is tertiary (3°).



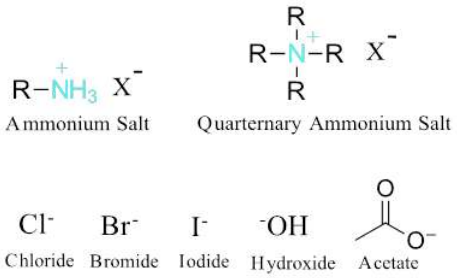
Primary Amine (1°) Secondary Amine (2°) Tertiary Amine (3°)

Example



Primary Amine (1°) Secondary Amine (2°) Tertiary Amine (3°)

Amines attached to 4 substituents and at least one substituent is a hydrogen are called ammonium salts. Amines attached to 4 alkyl substituents are called quaternary ammonium salts. The nitrogen in ammonium salts lacks lone pair electrons and carries a formal positive charge. Ammonium salts are also require a negatively charged counter-ion which can vary in composition.

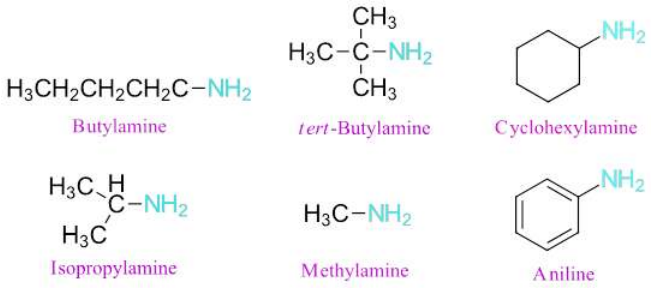


Common Counterions of Ammonium Salts

Nomenclature of Amines

Nomenclature of Primary Amines

Primary amines are named in two main ways using the IUPAC system. They can either be named as alkylamines or as alkanamines. Most 1° amines which are attached to linear alkanes, cycloalkanes, and alkyl groups with common names (Section 3.3), tend to be named as alkylamines. The alkyl groups is named as a substituent (**prefix + yl**) then the suffix -amine is added. Many amines have common names that are used by IUPAC, for example the primary arylamine ($C_6H_5NH_2$) is called aniline.

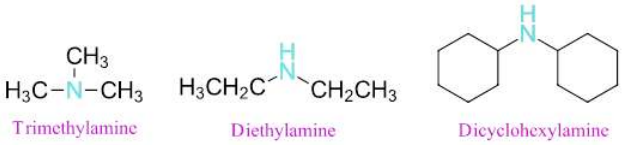


Other primary amines tend to be named as alkanamines. The alkyl group is named as an alkane (**prefix+ane**) and –e ending is replaced with the suffix **-amine**. The –e ending is not removed for diamines.



Nomenclature of Symmetrical Secondary and Tertiary Amines

Symmetrical 2° and 3° amines (where all substituents are identical) are named as alkylamines and the prefix di- or tri -added to indicate the number of substituents.



Nomenclature of Unsymmetrical Secondary and Tertiary Amines

Unsymmetrical 2° and 3° amines are named with the largest chain being the base chain (**prefix+yl+amine**). The other alkyl groups are named as N-substituents. This notation is used to indicate that the substituent is attached to the amine nitrogen and not an alkyl carbon.

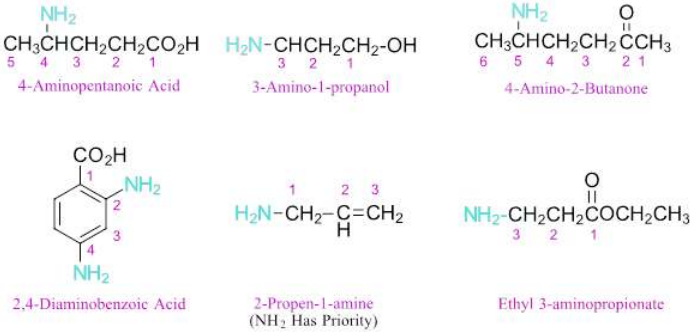


Nomenclature of Ammonium Salts

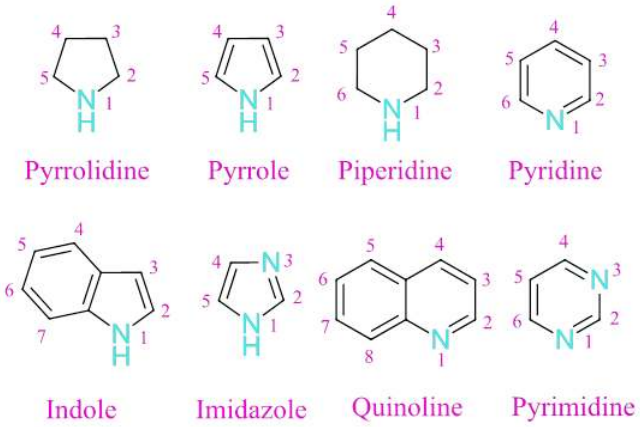
Ammonium salts and quaternary ammonium salts are named using the same rules as 2° and 3° amines except the –amine suffix is replaces with -ammonium + the name of the counter ion. The counter ion name is separated with a space.



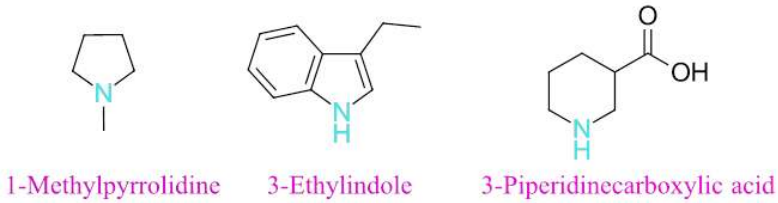
Amines have one of the lower functional group priorities in the IUPAC nomenclature system. When present in a compound with a functional group of higher priority, the amine group is named as a substituent called **"amino."**



Heterocyclic amine have one or more nitrogens as part of the ring and can be aliphatic or aromatic. Most heterocyclic amine ring systems have a common name and are numbered such that a nitrogen always gets position 1. An amine attached to a heterocyclic ring is named as an amino substituent.



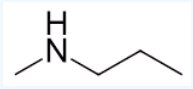
Example



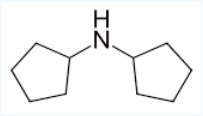
Exercises 3.3.1.1

Name the following compounds:

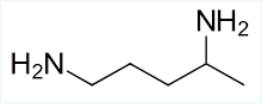
a)



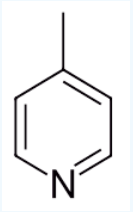
b)



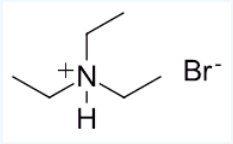
c)



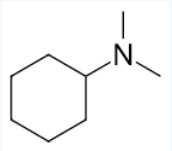
d)



e)



f)



Answers

a. N-Methylpropylamine
b. Dicyclopentylamine
c. 1,4-Pentanediamine
d. 4-Methylpyridine
e. Triethylammonium Bromide
f. N,N-Dimethylcyclohexylamine

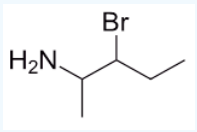
Exercise 3.3.1.1

Draw the structures corresponding to the following names:

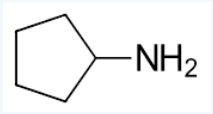
a. 3-Bromo-pentan-2-amine
b. Cyclopentanamine
c. *Trans*-3-ethylcyclohexanamine
d. *Sec*-butyl-*tert*-butyl amine
e. N,N-Dimethyl-3-pentanamine
f. 4-Methyl-2-hexanamine
g. 6-Bromo-4-amino-2-heptanol3)

Answer

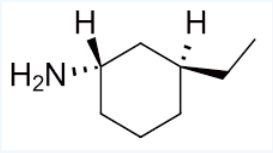
a)



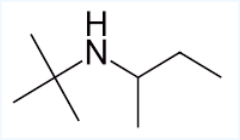
b)



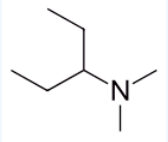
c)



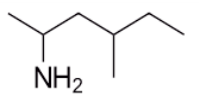
d)



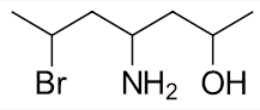
e)



f)



g)



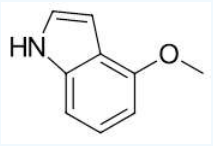
Exercise 3.3.1.3

Draw the structures of the following heterocyclic compounds:

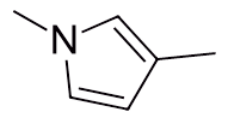
a. 4-Methoxyindole
b. 1,4-Dimethylpyrrole
c. 3-(N,N-Dimethylamino)pyridine
d. 2-Aminopyrimidine

Answer

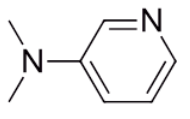
a)



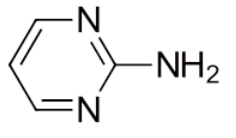
b)



c)



d)



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3.3.2: Structure and Properties of Amines

Objectives

After completing this section, you should be able to

1. describe the geometry and bonding of simple amines.
2. explain why most chiral amines cannot be resolved into their two enantiomers.

Key Terms

Make certain that you can define, and use in context, the key term below.

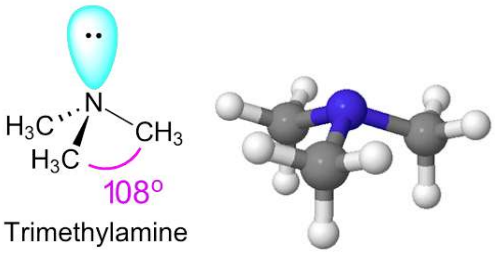
- pyramidal inversion

Study Notes

Molecular models may help you to understand pyramidal inversion.

Bonding, Shape, and Hybridization of Amines

The nitrogen atom in most amines is sp^3 hybridized. Three of the sp^3 hybrid orbitals form sigma bonds with the fourth orbital carrying the lone pair electrons. Single-bonded nitrogen is trigonal pyramidal in shape, with the non-bonding lone electron pair pointing to the unoccupied corner of a tetrahedron. Due to crowding by the lone pair electrons, the C-N-C bond angle between alkyl substituents on an amine is roughly 108° which is slightly less than the 109.5^o bond angle for a perfect tetrahedral geometry.

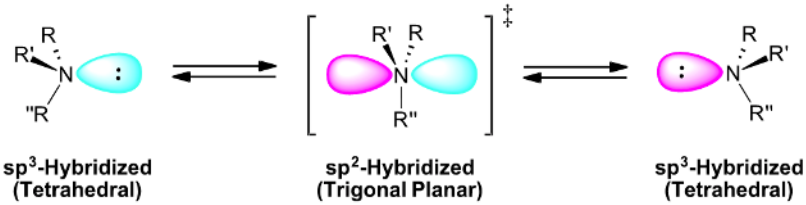


Trimethylamine

The C-N bonds (147 pm) of non-conjugated amines is shorter than C-C bond (154 pm) in alkanes, and longer than the C-O bond (143 pm) present in alcohols. This difference in bond length is expected given that the relative atom sizes are C > O > N.

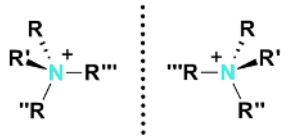
Chirality of Amines

Due to their tetrahedral configuration, amines with three different substituents are chiral. The R and S enantiomeric forms of a chiral amine cannot be resolved due to their rapid interconversion by a process called pyramidal or nitrogen inversion. During the inversion, the sp^3 hybridized amine momentarily rehybridizes to a sp^2 hybridized, trigonal planar, transition state where the lone pair electrons occupy a p orbital. The nitrogen then returns to a tetrahedral sp^3 hybridization causing the lone pair electrons to return to a sp^3 orbital on the opposite side of the nitrogen. During this process substituents invert to form the enantiomer. The thermodynamic barrier for this inversion (~25 kJ/mol) is low enough to allow rapid inversion at room temperature, leading to a mixture of interconverting R and S configurations. At room temperature a nitrogen atom exists as a racemic mixture of R and S configurations at equilibrium.



sp^3-Hybridized (Tetrahedral) **sp^2-Hybridized (Trigonal Planar)** **sp^3-Hybridized (Tetrahedral)**

Quarternary amines lack lone pair electrons and therefore do not undergo pyramidal inversions. Quarternary amines with four different substituents are chiral and are readily resolved into separate enantiomers.

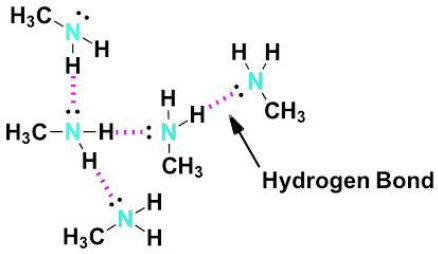


Enantiomers of a Chiral Quarternary Amine

Boiling Point and Water Solubility

Methyl, dimethyl, trimethyl, and ethyl amines are gases under standard conditions. Most common alkyl amines are liquids, and high molecular weight amines are, quite naturally, solids at standard temperatures.

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1º-amines is roughly half the increase observed for equivalent alcohols.



A Representation of the Hydrogen Bonding in Methyamine

Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point ºC	-88.6º	65º	-6.0º	-42º	78.5º	16.6º

The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher than isomeric 3º-amines (no hydrogen bonding). Indeed, 3º-amines have boiling points similar to equivalent sized ethers; and in all but the smallest compounds, corresponding ethers, 3º-amines and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 ºC.

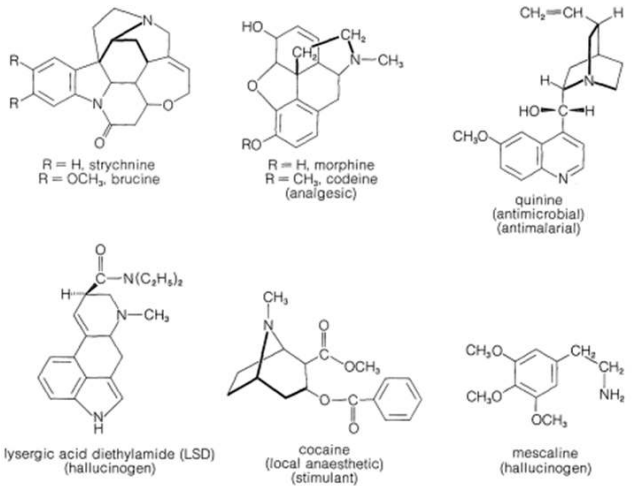
Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$
Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point ºC	-0.5º	97º	48º	37º	-12º	82º	34º	3º

Most aliphatic amines display some solubility in water, reflecting their ability to form hydrogen bonds. Solubility decreases proportionally with the increase in the number of carbon atoms in the molecule – especially when the carbon atom number is greater than six. Aliphatic amines also display significant solubility in organic solvents, especially in polar organic solvents.

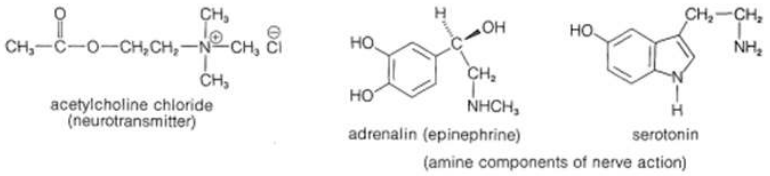
The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. The basicity of amines allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

Naturally Occurring Amines

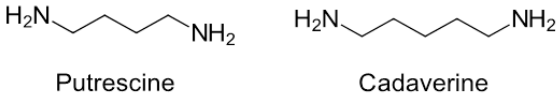
A large and widespread class of naturally occurring amines is known as alkaloids. The structures of the plant alkaloids are extraordinarily complex, yet they are related to the simple amines in being weak nitrogen bases. In fact, the first investigator to isolate an alkaloid in pure form was F. W. A. Sertürner who, in 1816, described morphine as basic, salt-forming, and ammonia-like. He used the term "organic alkali" from which is derived the name alkaloid. Alkaloids include compounds that may be classified as antimicrobial (quinine), as analgesics (morphine, codeine), as hallucinogens (mescaline, LSD), and as topical anesthetics (cocaine).



Certain amines and ammonium compounds play key roles in the function of the central nervous system as neurotransmitters and the balance of amines in the brain is critical for normal brain functioning. The amines acetylcholine chloride, adrenalin, and serotonin play important roles in nerve function in the human body.



Most amines have “interesting” odors. The simple ones smell very much like ammonia. Higher aliphatic amines smell like decaying meat. The stench of rotting meat is due in part to two diamines: putrescine and cadaverine. They are made during the decarboxylation of the amino acids, ornithine and lysine, by bacteria.



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3.3.3: Synthesis of Amines

Objectives

After completing this section, you should be able to

1. write equations to illustrate the synthesis of amines by
   a. reduction of nitriles or amides and nitro compounds.
   b. reactions involving alkyl groups:
      i. S_N2 reactions of alkyl halides, ammonia and other amines.
      ii. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
      iii. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
   c. reductive amination of aldehydes or ketones.
   d. Hofmann or Curtius rearrangements.
2. write detailed mechanisms for each of the steps involved in the synthetic routes outlined in Objective 1.
3. identify the product or products formed when
   a. a given nitrile or amide is reduced using lithium aluminum hydride.
   b. a given alkyl halide is reacted with ammonia or an alkylamine.
   c. a given alkyl halide is reacted with azide ion and the resulting product is reduced.
   d. a given alkyl halide is reacted with potassium phthalimide and the resulting product is hydrolyzed.
   e. a given aldehyde or ketone is reacted with ammonia or an amine in the presence of nickel catalyst.
   f. a given amide is treated with halogen and base.
   g. a given acyl azide is heated and then hydrolyzed.
4. identify the starting material, the other reagents, or both, needed to synthesize a given amine by any of the routes listed in Objective 1.
5. write a general equation to illustrate the preparation of an arylamine by the reduction of a nitro compound, and balance such an equation.
6. identify the product formed from the reduction of a given aromatic nitro compound.
7. identify the organic compound, the inorganic reagents, or both, needed to prepare a given arylamine.

Key Terms

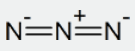
Make certain that you can define, and use in context, the key terms below.

- azide synthesis
- Curtius rearrangement
- Hofmann rearrangement
- Gabriel synthesis
- imide
- reductive amination

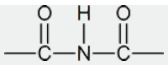
Study Notes

You may wish to review the mechanism of S_N2 reactions which is discussed in some detail in Sections 11.2 and 11.3.

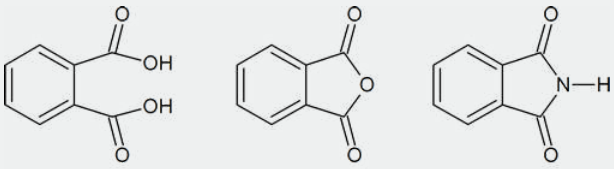
Azide synthesis is the first method on the table of synthesis of primary amines. The Lewis structure of the azide ion, N_3^-, is as shown below.



An “imide” is a compound in which an N$\ce{-}$H group is attached to two carbonyl groups; that is,



You should note the commonly used trivial names of the following compounds.



The phthalimide alkylation mentioned in the reading is also known as the Gabriel synthesis.

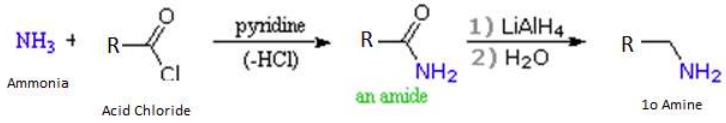
If necessary, review the reduction of nitriles (Section 20.7) and the reduction of amides (Section 21.7).

Before you read the section on reductive amination you may wish to remind yourself of the structure of an imine (see Section 19.8).

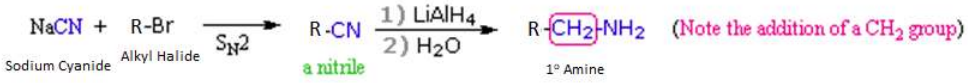
The Hofmann rearrangement is usually called the Hofmann degradation. In a true rearrangement reaction, no atoms are lost or gained; however, in this particular reaction one atom of carbon and one atom of oxygen are lost from the amide starting material, thus the term “rearrangement” is not really appropriate. There is a rearrangement step in the overall degradation process, however: this is the step in which the alkyl group of the acyl nitrene migrates from carbon to nitrogen to produce an isocyanate.

Reduction of Nitriles, Amides, and Nitro Compounds

Acid chlorides react with ammonia to give amides, by an addition-elimination path, and these are reduced to amines by $LiAlH_4$ (**Section 21-7**).

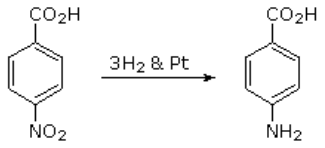


Alkyl halides can be converted to primary amines through a two-step process. First an S_N2 reaction with a cyanide anion converts the alkyl halide into a nitrile. Then the nitrile is reduced to a primary amine by $LiAlH_4$ (**Section 20-7**). During this reaction sequence an additional carbon atom is added.

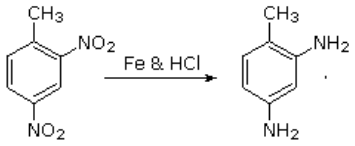


Arylamines are typically prepared by the reduction of a nitro group on an aromatic ring. Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + platinum catalyst), and zinc, iron, or tin(II) chloride in dilute mineral acid. The procedures described above are sufficient for most cases. Catalytic hydrogenation can be problematic because it is known to reduce other functional groups such as alkenes, alkynes, and some carbonyl groups.

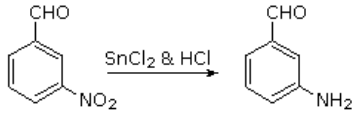
Nitro Group Reduction



p-Nitrobenzoic acid p-Aminobenzoic acid



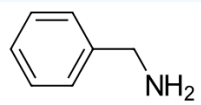
2,4-Dinitrotoluene 2,4-Toluenediamine



p-Nitrobenzaldehyde p-Aminobenzaldehyde

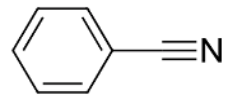
? Exercise 3.3.3.1

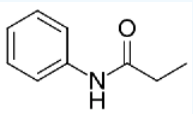
Propose structures of the starting materials needed to make the the following amines using the reduction of a nitrile or an amide:

a. $CH_3CH_2CH_2CH_2NH_2$
b. $(CH_3CH_2)_2NH$
c. 

d. N-Propylaniline

Answer

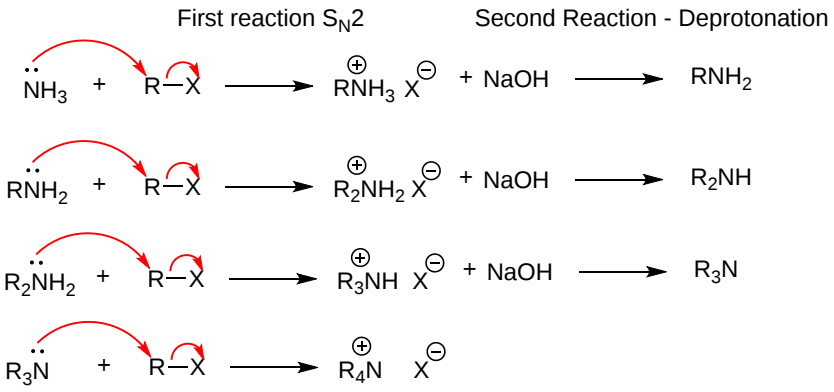
a. $CH_3CH_2CH_2CONH_2$
b. $CH_3CONHCH_2CH_3$
c. 

d. 

S_N2 Reactions of Alkyl Halides

Because they posses lone pair electrons, ammonia and amines are considered good nucleophiles. Ammonia and amines can by alkylated by an S_N2 reaction with alkyl halides. The product of the reaction is an ammonium salt where the negative counter-ion is

the halogen of the alkyl halide. When the alkylated products are 1°, 2°, and 3° amines, they can be deprotonated with NaOH to produce the neutral amine. When a 3° amine is alkylated, a quaternary ammonium salt is produced.



Alkylation is an efficient method for the synthesis of 3° and 4° amines. However, when 1° and 2° amines are alkylated a mixture of products is typically produced. When ammonia is reacted with an alkylhalide an monoalkylammonium salt is formed.

$$RX + NH_3 \rightarrow RNH_3^+ + X^-$$

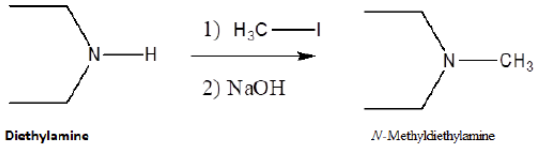
It is possible for any remaining ammonia present in the reaction to deprotonate the ammonium salt to produce the neutral monoalkyl amine.

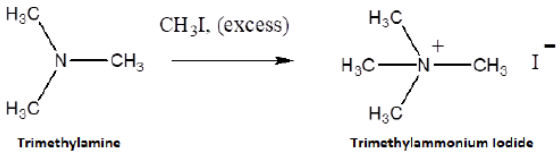
$$RNH_3^+ + NH_3 \rightarrow RNH_2 + NH_4^+$$

The monoalkyl amine is then free to react with a second alkyl halide creating a dialkylammonium salt. This process can be repeated to to eventually to create a tetralkylammonium salt. Typically when a alkyl halide is reacted with ammonia, a mixture of mostly 1° and 2° amines, with trace amounts of 3° amines and 4° ammonium salts, is produced.

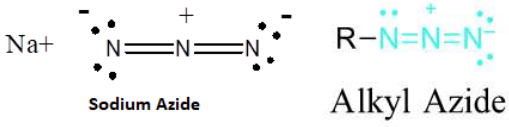
$$RNH_2 + RX \rightarrow R_2NH_2^+ + X^-$$

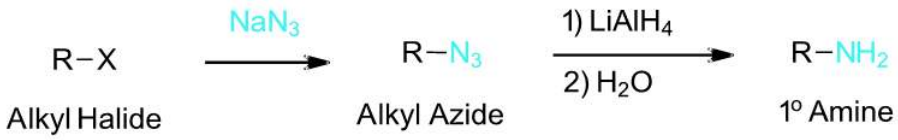
Example



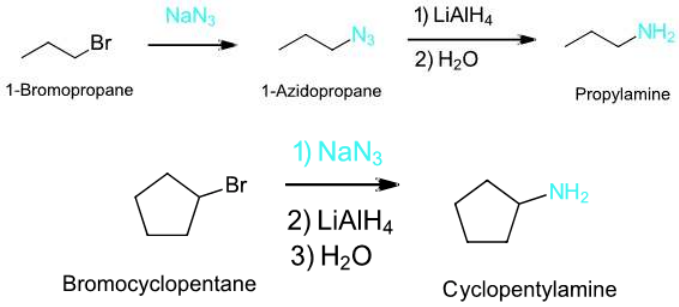


To synthesize a 1° or 2° amine, specific reactions are usually employed. A more efficient method starts with an S_N2 reaction between a 1° or 2° alkyl halide and the nucleophilic azide anion (N_3^-) to produce an alkyl azide. The alkyl azide is not nucleophilic so it cannot react with additional alkyl halide to produce overalkylation. Alkyl azide is then reduced with $LiAlH_4$ to produce a 1° amine.



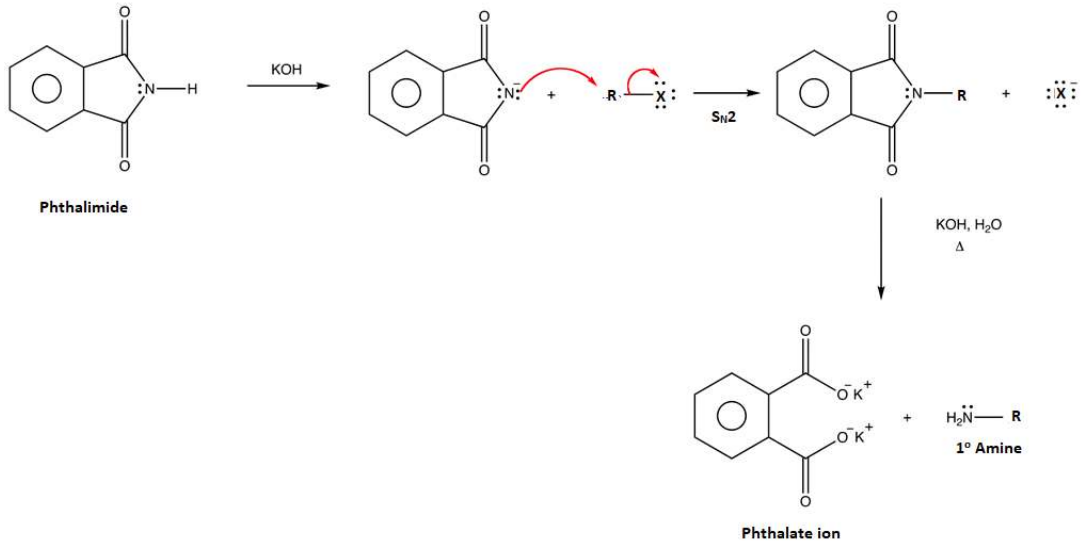


Example

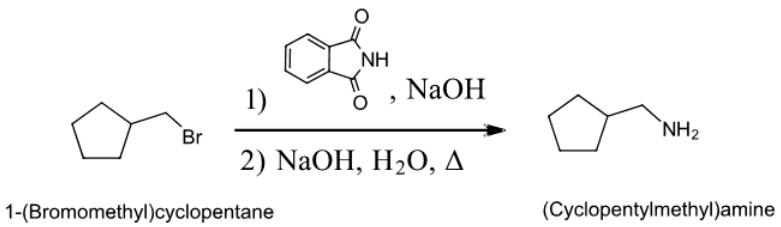


Gabriel Amine Synthesis

Another common method for the synthesis of 1º amines is called the **Gabriel amine synthesis**. This reaction starts with the deprotonation of phthalimide by a hydroxide base such as potassium hydroxide (KOH). The N-H hydrogen of an imide functional group is acidic because its conjugate base is resonance stabilized by two carbonyl groups. The phthalimide anion is nucleophilic and easily alkylated through an S_N2 reaction with an alkyl halide. The resulting N-alkylated phthalimide then undergoes base hydrolysis to produce a 1º amine product. The mechanism for the base promoted hydrolysis of the N-alkylated phthalimide is analogous to the hydrolysis of an amide (Section 21-7).



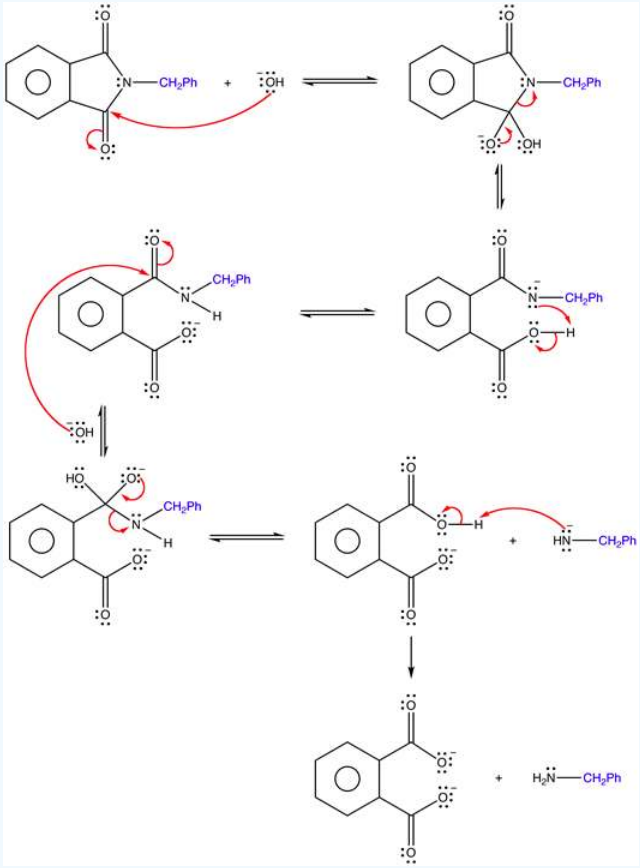
Example



Exercises 3.3.3.1

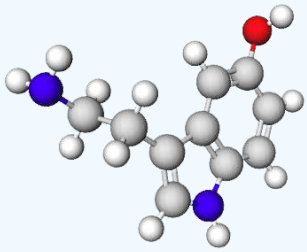
Write the mechanism for the base promoted hydrolysis of an N-alkyl phthalimide to create a 1° amine and the phthalate ion.2)

Answers



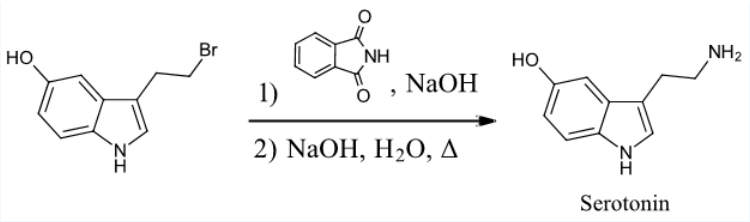
Exercise 3.3.3.2: Serotonin

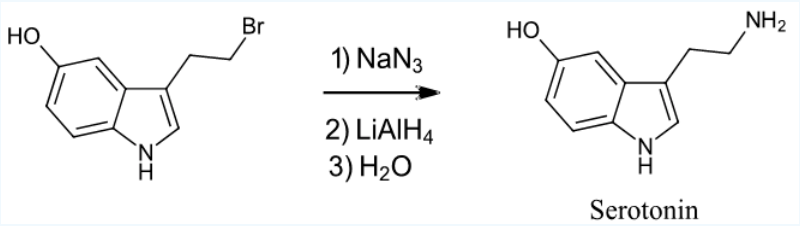
Starting with any alkyl halide, show two methods to synthesize the neurotransmitter serotonin.



Answer

https://chem.libretexts.org/@go/page/413202

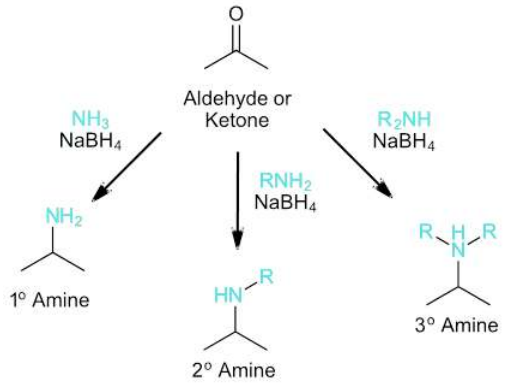




Reductive Amination

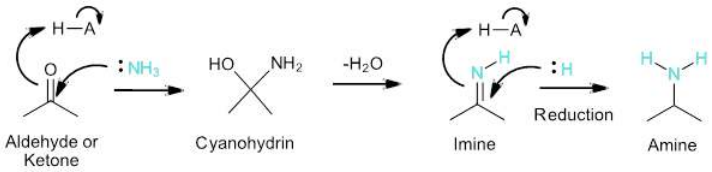
Aldehydes and ketones can be converted into 1°, 2° and 3° amines using **reductive amination**. The reaction takes place in two parts. The first step is the nucleophiic addition of ammonia, a 1° amine, or a 2° amine to a carbonyl group to form an imine (**Section 19-8**). The second step is the reduction of the imine to an amine using a hydride reducing agent. Some common reducing agents used for this reaction are: sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$), $NaBH(OAc)_3$, or hydrogen gas (H_2) over a nickel catalyst.

General Reaction

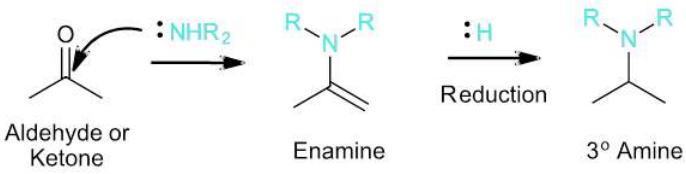


Mechanism

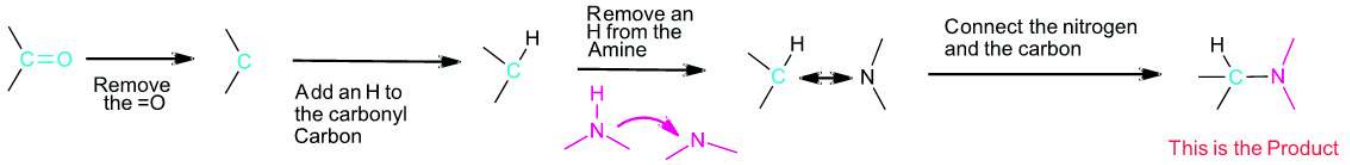
Reductive amination starts with the nucleophilic addition of ammonia or a 1° amine to an aldehyde or ketone forms a cyanohydrin intermediate. Subsequent dehydration forms an imine intermediate (Section 19-8). The imine undergoes hydride reduction in a similar fashion as C=O carbonyl bonds are reduced to an alcohol.



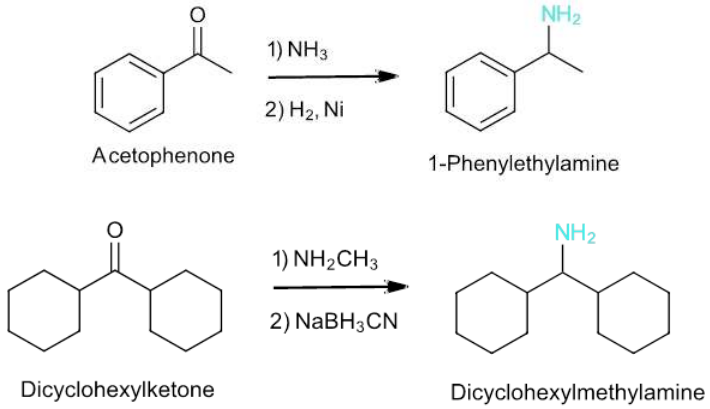
When a 2° amine is used for reductive amination, an enamine intermediate is formed which then undergoes hydride reduction to form a 3° amine.



Predicting the Products of a Reductive Amination



Examples



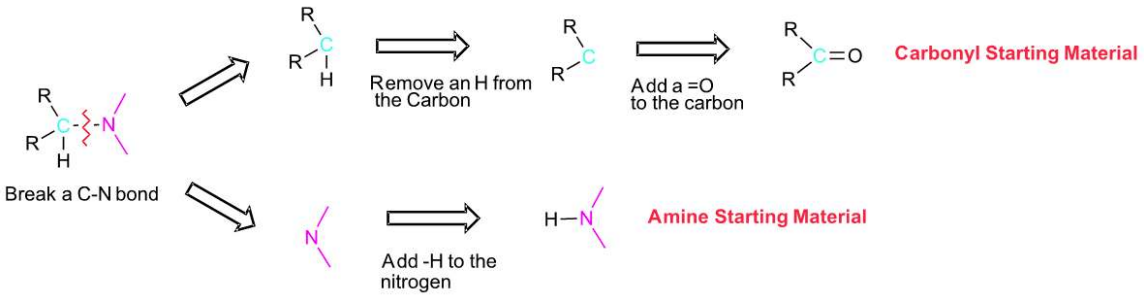
Biological Reductive Aminations

Reductive amination is used in the biosynthesis of the amino acid proline. The enzyme pyrroline-5-carboxylate synthase **(P5CS)** catalyzes glutamate undergoing an intramolecular imine formation to produce 1-pyrrolinium 5-carboxylate. Then the enzyme pyrroline-5-carboxylate reductase **(PYCR)** catalyzed the nucleophilic hydride reduction of the C=N bond to produce proline. The biological hydride reducing agent for this sequence is reduced nicotinamide adenine dinucleotide **(NADH).**



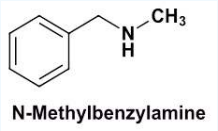
Planning a Synthesis using a Reductive Amination

If you are trying to develop a synthesis of an amine molecule, the key bond break is a C-N bond in the target molecule. There may be multiple C-N bonds present, so each should be broken separately to produce a possible set of starting materials. Because the amine is commonly used in excess during a reductive animation, the pathway which provides the simplest amine starting material is preferred. The carbon from the broken C-N bond goes on to become a carbonyl starting material. The nitrogen gains a hydrogen to become the amine starting material.



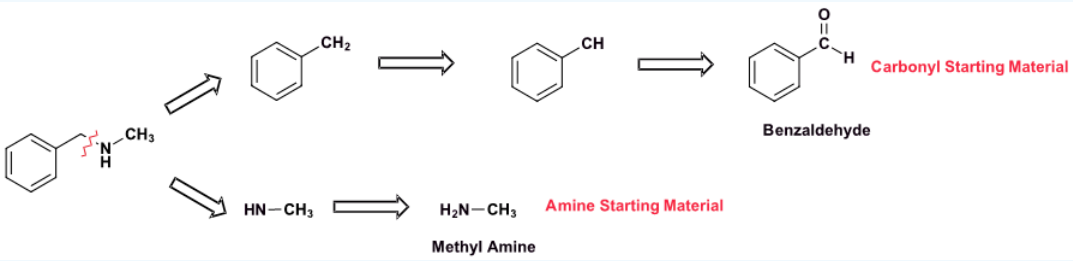
Worked Exercise 3.3.3.1

Show how N-methylbenzylamine can be synthesized using a reductive amination. If more than one pathway is possible, draw them both and determine which one would be preferred.

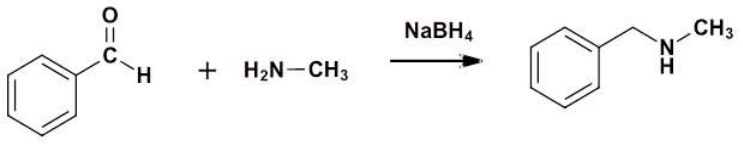


Answer

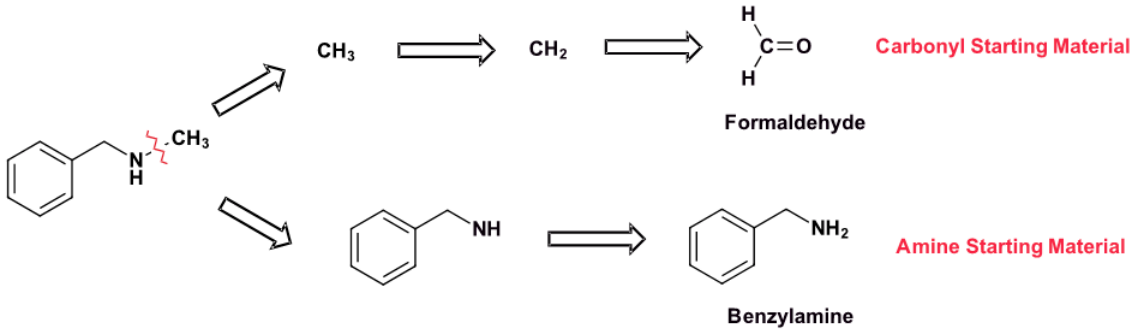
Pathway 1



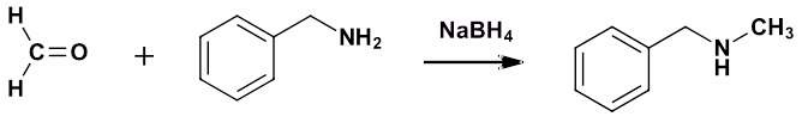
Solution 1



Pathway 2



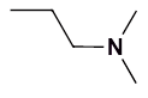
Solution 2

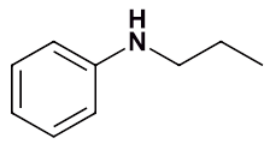


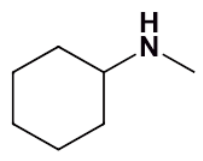
Because N-methylbenzylamine has two C-N bonds there are two possible synthesis pathways. Pathway 1 is most likely preferred because it uses the simplest amine starting material, methyl amine.

? Exercise 3.3.3.1

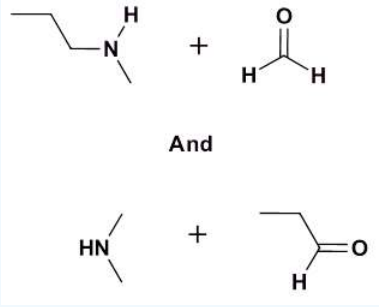
Provide starting materials which could be used to prepare the following compounds using a reductive amination. Show all possible pathways.

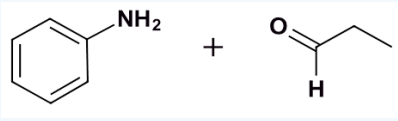
a. 

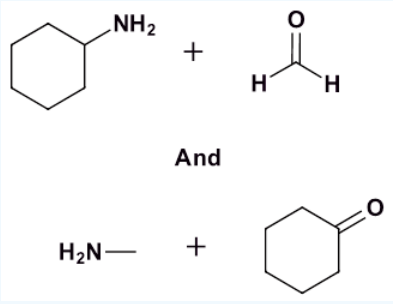
b. 

c. 

Answers

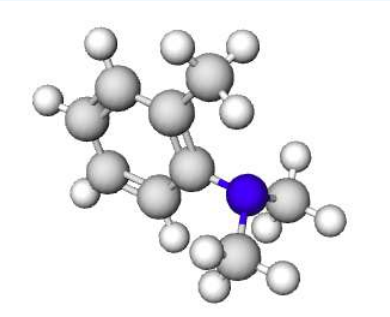
a. 

b. 

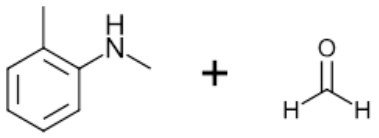
c. 

? Exercise 3.3.3.4

Identify the starting materials which could provide the following molecule using a reductive amination.



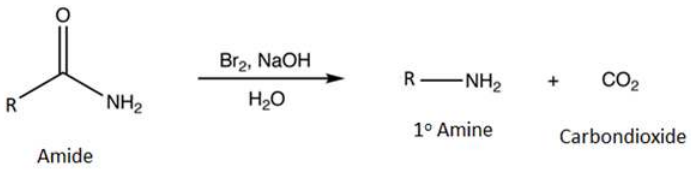
Answer



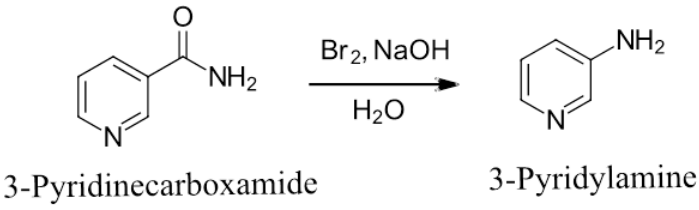
Hofmann Rearrangement

The Hofmann rearrangement occurs when a 1° amide is reacted with bromine (Br_2) and a base. The products are a 1° amine with one less carbon and carbon dioxide (CO_2).

General Reaction

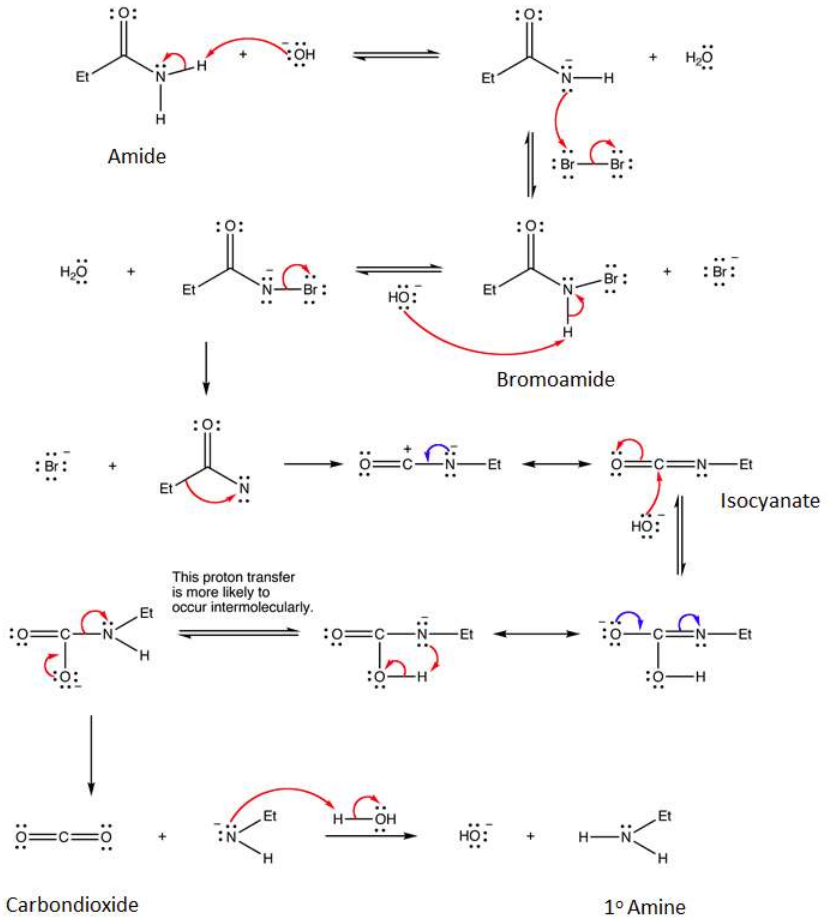


Example



Mechanism

The mechanism for the Hofmann rearrangement is quite complex. The mechanism starts with the deprontation of the primary amide by a base. The nitrogen is brominated during an S_N2 reaction with Br_2 to produce an N-bromoamide. Bromide is eliminated as a leaving group to produce a electron deficient nitrene-like nitrogen. Electrons from the adjacent C-C bond migrate to the nitrogen as part of a rearrangment to finally produce an isocyanate. The carbon in the isocyante is electrophilic and reacts with a nucleophilic hydroxide to create a C-O bond. After movement of electrons through resonance and a proton transfer a carbamate intermediate is formed. The carbamate decomposes to create an amide anion and a stable CO_2 molecule. Finally, water protonates the amide anion to produce a 1° amine.

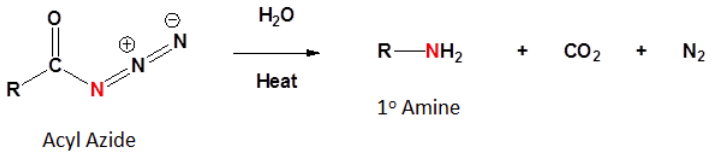


Curtius Rearrangement

The Curtius Rearrangement is another method used to synthesize a 1° amine.

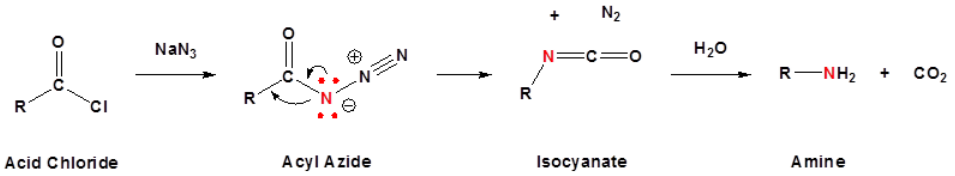
General Reaction

The Curtius rearrangement involves an acyl azide reacting with water and heat to produce a 1° amine along with CO_2 and N_2. The acyl azide is usually made by a nucleophilic substitution of an acid chloride with sodium azide (NaN_3)

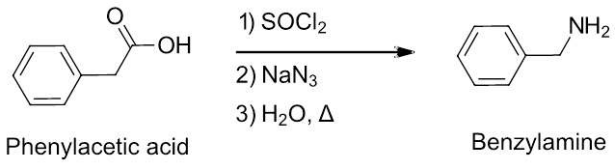


Mechanism

The mechanism of the Curtius rearrangement is quite similar to the Hoffman rearrangement. The loss of N_2 as a leaving group creates an electron deficient nitrogen. The adjacent -R group migrates to form an isocyanate. Reaction of the isocyanate forms a carbamate which decomposes to form a 1° amine and CO_2.

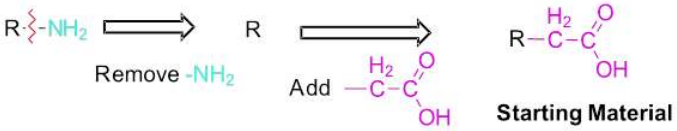


Example



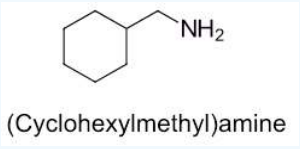
Planning a Synthesis using a Hoffman or Curtius Rearrangement

Because the amide and the acyl azide required for these rearrangements both are best made from an acid chloride, synthesis of amines using these reaction are best started from the corresponding carboxylic acid. For retrosynthetic analysis starting from the desired amine product - the key break is the C-NH_2 bond. The amine is removed and replaced with a -CH_2CO_2H fragment to provide the required carboxylic acid starting material.



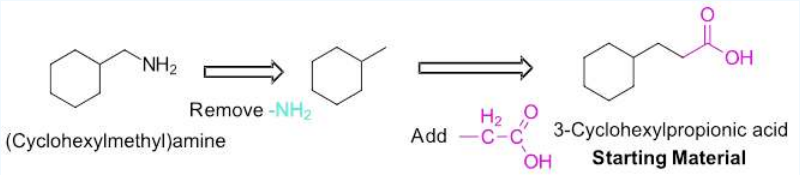
? Worked Example 3.3.3.1

Show how the following molecule could be prepared from a carboxylic acid starting material using both the Hoffman and Curtius rearrangements.



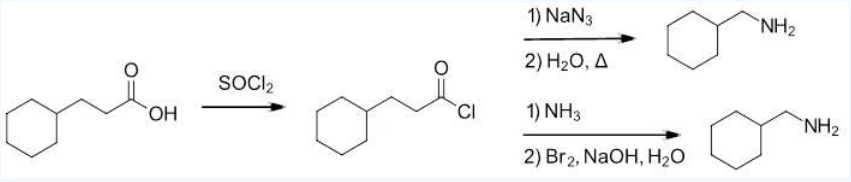
Answer

First determine the structure of the carboxylic acid starting material. This will be the starting material for both rearrangements. In the first step, convert the carboxylic acid into an acid halide using thionyl chloride ($SOCl_2$). Then use the required conditions for each rearrangement.



Solution

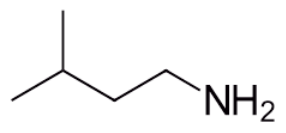
The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



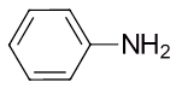
Exercises 3.3.3.1

1) Using a carboxylic acid starting material explain how to prepare the following molecules using both the Hoffman and Curtius rearrangements.

a)



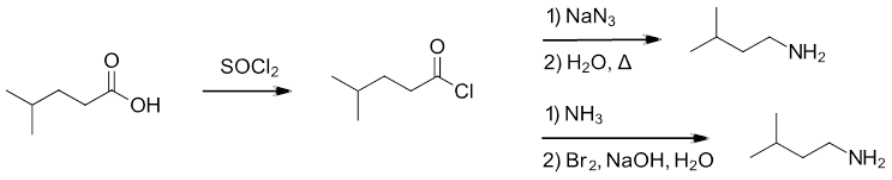
b)



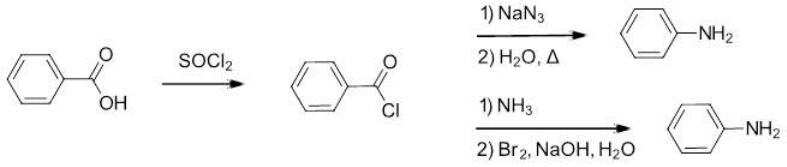
Answers

1)

a) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



b) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



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3.3.4: Reactions of Amines

Objectives

After completing this section, you should be able to

1. write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
2. identify the product formed when a given amine reacts with a given acid chloride.
3. identify the amine, the acid chloride, or both, needed to synthesize a given amide.
4. write a reaction sequence to illustrate the overall conversion of an amine to an alkene via a Hofmann elimination.
5. identify the alkene most likely to be formed when a given quaternary ammonium salt is heated with moist silver oxide (or silver hydroxide).
6. deduce the structure of an unknown quaternary ammonium salt, given the identity of the alkene or alkenes produced when the salt is heated with moist silver oxide.

Key Terms

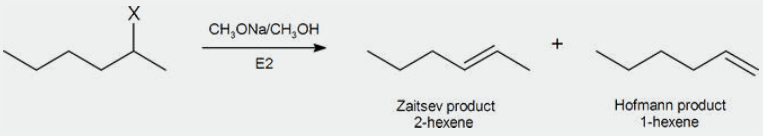
Make certain that you can define, and use in context, the key term below.

- Hofmann elimination

Study Notes

The alkylation and acylation of amines have been dealt with in previous sections: alkylation in Section 24.6 and acylation in Sections 21.4 and 21.5. Review these sections if necessary.

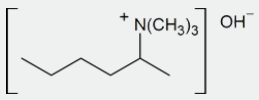
One explanation is given for Hofmann elimination further on in this reading. Another argument, based on the consideration of the structures of the possible transition states, has been suggested by Joseph Bunnett and is widely accepted. We can begin to understand Bunnett's reasoning by considering the elimination products formed from by the dehydrohalogenation of a number of substituted hexanes in the reaction



The table below describes the proportion of each product you would expect when X in the above reaction represents a given halogen.

X	% 2-hexene	% hexene
I	81	19
Br	72	28
Cl	67	33
F	30	70

As we descend this table, the electron-withdrawing ability of X increases, and the percentage of Hofmann product also increases. Given that the $(CH_3)_3N^+$ group is strongly electron-withdrawing, it is quite consistent for a compound of the type



to give 96% Hofmann product and 4% Zaitsev product in an E2 elimination reaction. But why does the proportion of Hofmann product increase as the electron-withdrawing ability of X increases? Bunnett suggests that the transition state in an E2 process can vary from being “carbocation-like” on one hand to “carbanion-like” on the other.

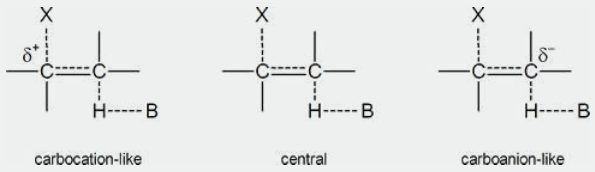
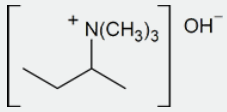


Figure 24.1 Various transition states for an E2 elimination reaction

In a carbocation-like transition state, the C-X bond is broken to a greater extent than the C-H bond; in the central transition state both, the C-X bond and the C-H bond are broken to an equal extent; and in the carbanion-like transition state, the C-H bond is broken to a greater extent than the C-X bond. In the latter case, a partial negative charge will develop on the carbon atom to which the hydrogen is attached, hence the term “carbanion-like.” As we already know, any species or transition state bearing a full or partial negative charge is stabilized by the presence of electron-withdrawing groups and destabilized by the presence of electron-releasing groups.

Let us now consider the two possible transition states for an E2 elimination of $(CH_3)_3NH^+$ from a quaternary ammonium hydroxide,



One transition state leads to Zaitsev elimination, the other to Hofmann elimination.

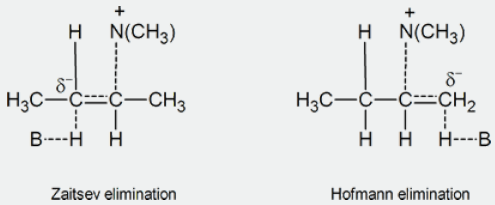
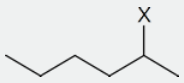


Figure 24.2 Possible carbanion-like transition states

In the transition state leading to the Zaitsev product, the carbon atom carrying the partial negative charge is bonded to an electron-releasing methyl group. This is clearly a less favourable situation than the one that exists in the transition state leading to Hofmann elimination, where there are no electron-releasing groups attached to the carbon atom bearing the partial negative charge. Bunnett’s argument is that carbanion-like transition states are much more likely when the atom or group X in a compound such as



is strongly electron withdrawing, because the \(\ce{C-X}\) bond becomes stronger as the electron-withdrawing ability of X increases.

Thus, as we go along the series X = I, Br, Cl, F, $(CH_3)_3N^+$, the electron-withdrawing ability of X increases, the C-X bond becomes more difficult to break, the transition state becomes more carbanion-like in character, and Hofmann elimination becomes more pronounced.

Alkylation of Amines

It is instructive to examine these nitrogen substitution reactions using the common alkyl halide class of electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1°-amine, presumably by an S_N2 mechanism. The hydrogen bromide produced in the reaction combines with some of the excess ammonia, giving ammonium bromide as a by-product. Water does not normally react with 1°-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

$$2\,RCH_2Br + NH_3(\text{large excess}) \longrightarrow RCH_2NH_2 + NH_4{}^{(+)}Br^{(-)}$$

It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a byproduct, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.

$$2\,RNH_2 + C_2H_5Br \longrightarrow RNHC_2H_5 + RNH_3{}^{(+)}Br^{(-)} \rightleftharpoons RNH_2C_2H_5{}^{(+)}Br^{(-)} + RNH_2$$

Unfortunately, the direct alkylation of 1º or 2º-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3º-amines may be alkylated to form quaternary (4º) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base (N,N-diisopropylethylamine) may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3º-amine (Hünig's base) from being methylated.

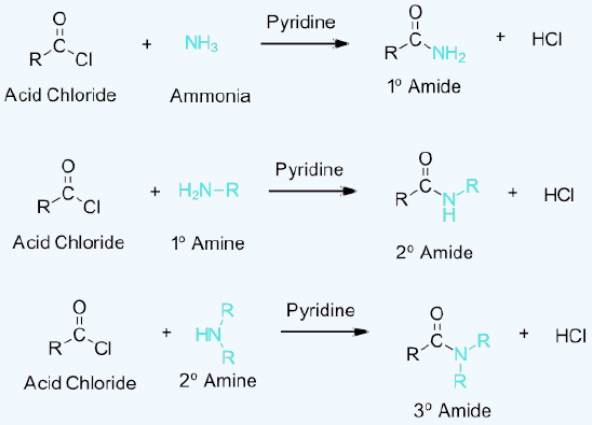
$$C_6H_5NH_2 + 3\,CH_3I + \text{Hünig's base} \longrightarrow C_6H_5N(CH_3)_3{}^{(+)}I^{(-)} + \text{HI salt of Hünig's base}$$

Acylation of Amines

Ammonia, 1º amines, and 2º amines react rapidly with acid chlorides or acid anhydrides to form 1º, 2º, and 3º amides respectively **(Sections 21-4 and 21.5)**. These reactions typically take place rapidly at room temperature and provide high reaction yields.

The reaction is commonly run with a base, such as NaOH or pyridine, to neutralize the HCl produced. Over-acylation does not occur because the lone pair electrons on the amide nitrogen are conjugated with the carbonyl making it less nucleophilic than an amine starting material.

Example 24.7.1

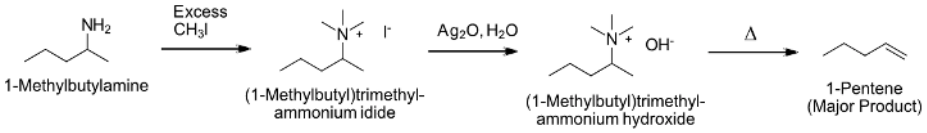


Hofmann Elimination

Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. As noted earlier, 1º and 2º-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a leaving group. In this context we note that the acidity of the potential ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. However, amines can be turned into a good leaving group by alkylation with an alkyl halide to form a quarternary ammonium salt. Upon elimination the quarternary ammonium salt produces a stable 3º amine as a leaving group.

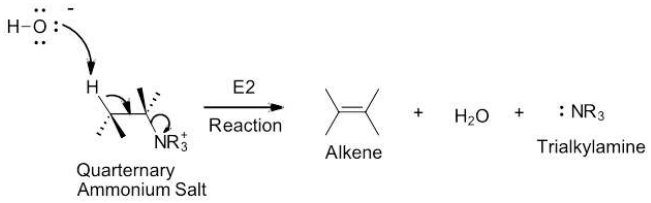
Elimination reactions of 4º-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4º-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 ºC) to affect the E2-like elimination of a 3º-amine. For an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, which is similar to elimination reactions of alkyl halides. Simple amines are easily converted to the necessary 4º-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction).

General Reaction



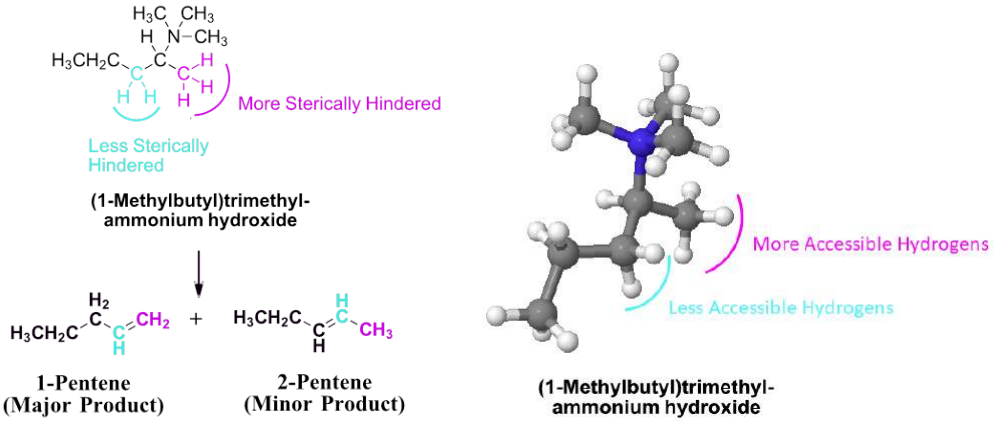
Mechanism

During the Hofmann elimination, the hydroxide counter ion acts as a base to remove a beta-hydrogen and cause an E2 elimination to form an alkene. A trialkyl amine is eliminated as a leaving group during this reaction.

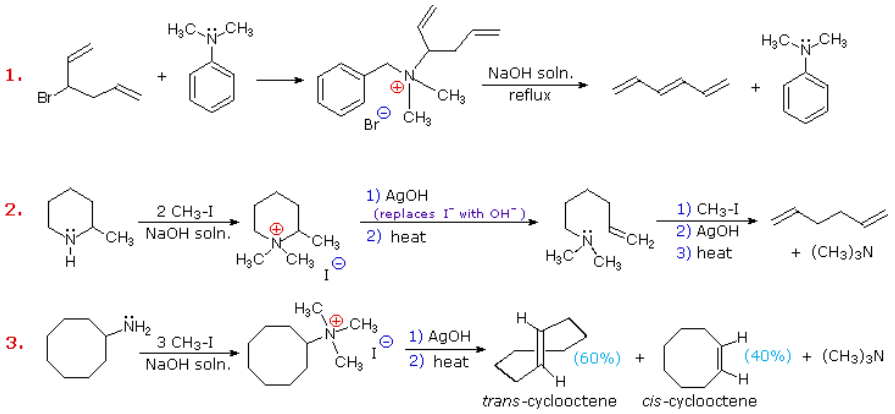


When predicting the products of an E2 elimination, the more substituted alkene is expected to be the preferred product based on Zaitsev's rule. The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**. To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state.

The reason for the difference in products in a Hofmann elimination is most likely due to steric hindrance of the base. The large size of of the quaternary ammonium group forces the base to remove a hydrogen from the least sterically hindered position. This correspondingly leads to the alkene with the least number of substituents to be preferred.



Examples

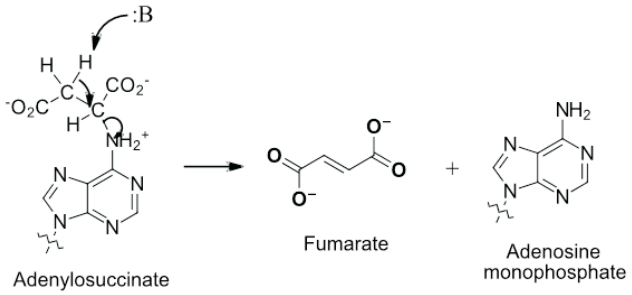


Example #1 is interesting in two respects. First, it generates a 4º-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.

Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to remove the nitrogen from the remaining molecular framework.

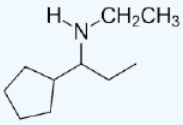
Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

Eliminations analogous to the Hofmann elimination are often seen in biological systems. In these cases, ammonium ions (protonated amines) are used instead of quaternary ammonium salts. An example is seen in the biosynthesis of nucleic acids where a biological base causes a Hofmann-like elimination of protonated adenylosuccinate to produce the alkene containing fumarate and adenosine monophosphate.



? Worked Exercise 3.3.4.1

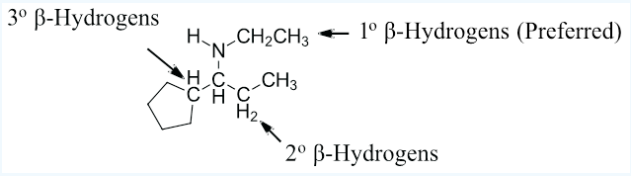
Predict the preferred product of a Hofmann elimination with the following molecule.



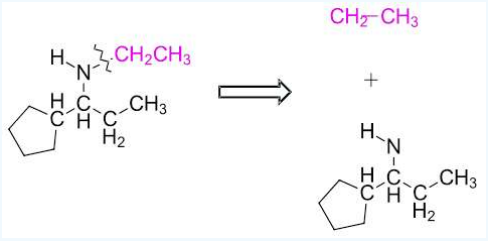
Answer

Predicting the product of a Hofmann elimination can be difficult so it is best done stepwise.

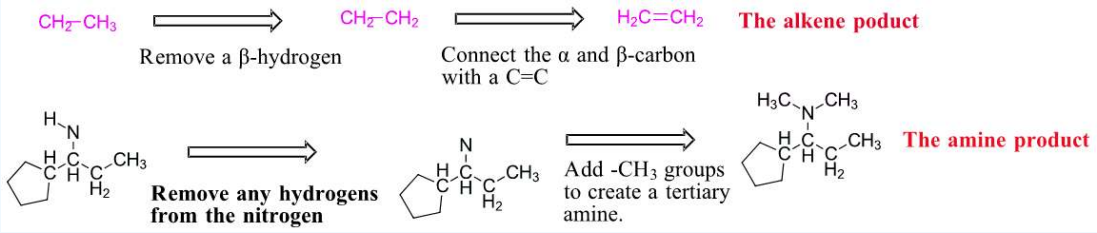
Step 1: Find the least sterically hindered beta hydrogens. Beta hydrogens are on the second carbon away from the nitrogen. The order of preferred hydrogens are $1^o > 2^o > 3^o$. If the molecule is presented as a line structure it is usually beneficial to convert to a condensed structure first.



Step 2: Break the C-N bond of the alkyl group which contains the preferred hydrogens. This will form two fragments.



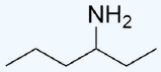
Step 3: Remove one of the original beta hydrogens in the alkyl fragment then draw a C=C between the alpha and beta carbon. This produces the alkene product of the Hofmann elimination. Sometimes the amine fragment of a Hofmann elimination is of interest. Remember that prior to elimination the amine is exhaustively alkylated with CH_3I. This means any hydrogens attached to amine will starting material will be removed and the amine product will have enough methyl (-CH_3) groups added to become a tertiary amine. In this case two methyl groups are added to the nitrogen. The end result are the two products of a Hofmann elimination.



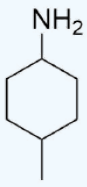
? Exercise 3.3.4.1

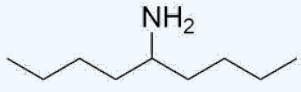
Draw the product for a Hofmann elimination for each of the following molecules.

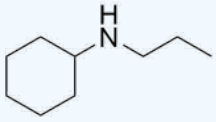
a.



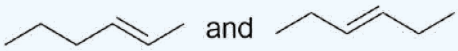
b.

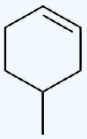


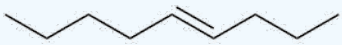
c. 

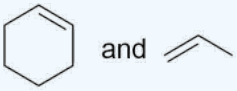
d. 

Answer

a. 

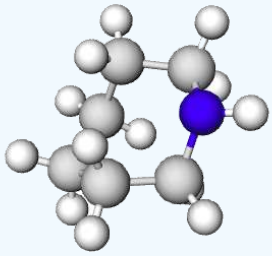
b. 

c. 

d. 

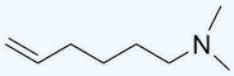
Exercise 3.3.4.2

Draw the product of a Hofmann elimination for the following molecule.



Azepane

Answer



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CHAPTER OVERVIEW

4: Carbonyls

4.1: Aldehydes and Ketones- Nucleophilic Addition Reactions

4.1.1: Chapter Objectives and Preview of Carbonyl Chemistry

4.1.2: Naming Aldehydes and Ketones

4.1.3: Preparing Aldehydes and Ketones

4.1.4: Oxidation of Aldehydes and Ketones

4.1.5: Nucleophilic Addition Reactions of Aldehydes and Ketones

4.1.6: Nucleophilic Addition of Water- Hydration

4.2: Carboxylic Acids

4.2.1: Chapter Objectives and Introduction to Carboxylic Acids

4.2.2: Naming Carboxylic Acids and Nitriles

4.2.3: Structure and Properties of Carboxylic Acids

4.2.4: Reactions of Carboxylic Acids - An Overview

4.2.5: Chemistry of Esters

4.2.6: Chemistry of Amides

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SECTION OVERVIEW

4.1: Aldehydes and Ketones- Nucleophilic Addition Reactions

4.1.1: Chapter Objectives and Preview of Carbonyl Chemistry

4.1.2: Naming Aldehydes and Ketones

4.1.3: Preparing Aldehydes and Ketones

4.1.4: Oxidation of Aldehydes and Ketones

4.1.5: Nucleophilic Addition Reactions of Aldehydes and Ketones

4.1.6: Nucleophilic Addition of Water- Hydration

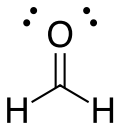
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4.1.1: Chapter Objectives and Preview of Carbonyl Chemistry

Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis in which you may have to use any of the reactions discussed in this chapter together with any number of reactions from previous chapters.
- solve “road-map” problems that require a knowledge of the chemistry of aldehydes and ketones.
- use evidence from any combination of infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy and chemical reactions to determine the structure of an unknown aldehyde or ketone.
- define, and use in context, the key terms introduced in this chapter.

In 1969 the molecule formaldehyde was discovered to be the first polyatomic organic molecule present in interstellar space by the National Radio Astronomy Observatory. The reactivity of formaldehyde gives it a wide variety of uses from embalming fluid to finger nail polish. Formaldehyde contain a C=O bond called a carbonyl, which is fundamental to study of organic chemistry. In this chapter we will begin a multi-chapter discussion on the chemistry of the carbonyl bond starting with aldehyde and ketone functional groups.



formaldehyde

In Chapter 19, we make a comprehensive study of the chemistry of aldehydes and ketones. Aldehydes and ketones are discussed together because their chemistry is very similar. However, as you work through the chapter, be sure to look for specific instances where the chemistry of these two classes of compounds differs.

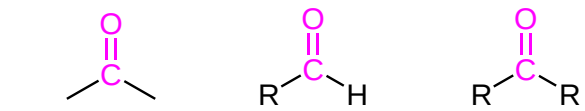
As usual, we begin the chapter with a discussion of nomenclature. This introduction is followed by descriptions of the methods used to prepare aldehydes and ketones in the laboratory. You will notice that a number of these reactions have already appeared in previous units. Note that an important difference between aldehydes and ketones is the resistance of ketones to oxidation.

A large part of this chapter is concerned with the addition of various nucleophiles to the carbonyl group of aldehydes and ketones. In particular, we discuss the addition of a variety of nitrogen-containing compounds, alcohols and phosphorus ylides. Many of these reactions are important to chemists concerned primarily with the synthesis of new organic compounds.

We also describe the Cannizzaro reaction and conjugate addition to α, β-unsaturated carbonyl compounds. We mention the occurrence of nucleophilic addition reactions in biological systems, and conclude the unit with a look at the use of spectroscopic techniques in the analysis of aldehydes and ketones.

Preview of Carbonyl Chemistry

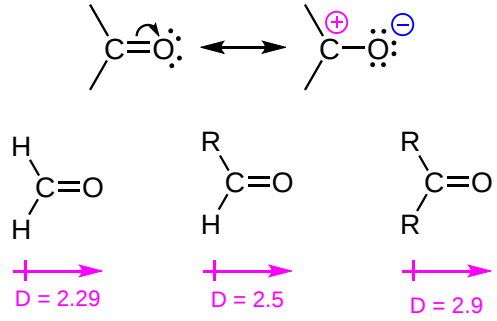
Aldehydes and ketones are organic compounds which incorporate a carbonyl functional group, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an aldehyde. If both are carbons, the compound is a ketone.



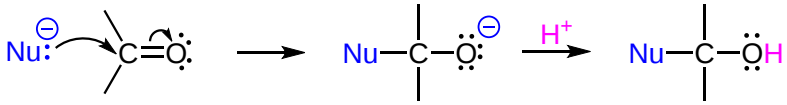
Carbonyl Group Aldehyde Ketone

Because of the greater electronegativity of oxygen, the carbonyl group is polar, and aldehydes and ketones have larger molecular dipole moments (D) than do alkenes. The resonance structures below illustrate this polarity, and the relative dipole moments of

formaldehyde, other aldehydes and ketones.



This polarity causes the carbonyl carbon to be partially positive (electrophillic) and the oxygen partially negative (nucleophillic). The C=O bond is prone to nucleophillic attack because or carbon's positive charge and oxygen's negative charge. In general, nucleophiles attack the electrophilic carbon and become a part of the structure while the oxygen is protonated forming a hydroxyl group.



Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain an aldehyde or ketone functional group are shown in the following two figures. The compounds in the **figure 1** are found chiefly in plants or microorganisms and those in the **figure 2** have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author’s favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-heptanone provides part of the sharp scent from blue cheese and (R)-muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, cortisone.

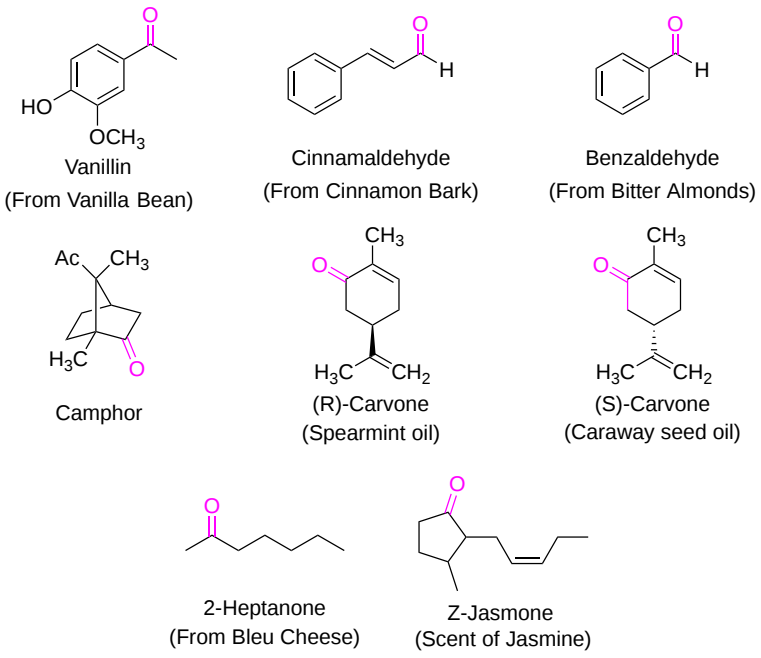


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

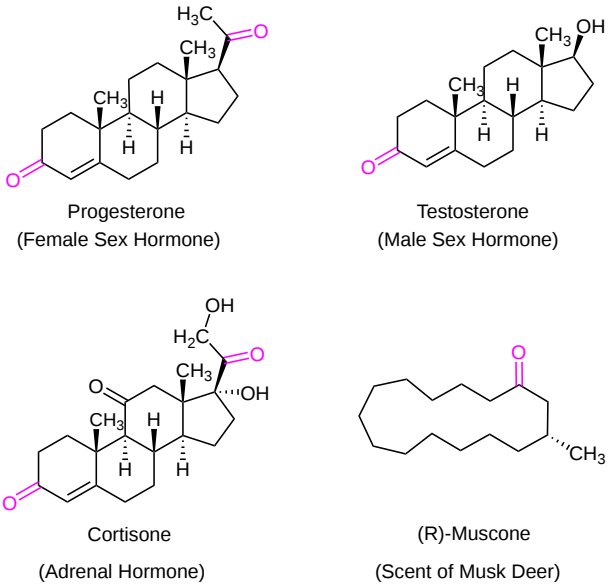


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

Contributors and Attributions

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-
- Layne Morsch (University of Illinois Springfield)

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4.1.2: Naming Aldehydes and Ketones

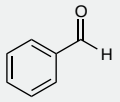
Objectives

After completing this section, you should be able to

- provide the IUPAC name of an aldehyde or ketone, given its Kekulé, condensed, or skeletal structure.
- draw the structure of an aldehyde or ketone, given its IUPAC name.
- draw the structure of the following aldehydes and ketones, given their common names: formaldehyde, acetaldehyde, benzaldehyde, acetone, acetophenone, benzophenone.

Study Notes

We will only use those common names listed under Objective 3, above. We will use systematic names in all other cases. For example, the systematic name of the compound shown below is benzenecarbaldehyde, but it has the common name of benzaldehyde.



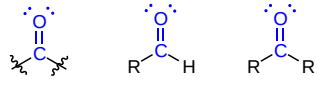
benenecarbaldehyde
(benzaldehyde)

When naming unsaturated aldehydes and ketones, you must give the carbonyl group "priority" over the double bond when you are deciding which end of the carbon chain to begin numbering The carbonyl-carbon of an aldehyde will always be at the end of the carbon chain in an acyclic compound; and therefore numbering always starts at this carbon. It is for this reason, too, that the number "1" is not required when naming a compound such as 2-ethyl-4-methylpentanal.

The most potent and varied odors are aldehydes. Ketones are widely used as industrial solvents. Aldehydes and ketones contain the carbonyl group. Aldehydes are considered the most important functional group. They are often called the formyl or methanoyl group. Aldehydes derive their name from the *dehyd*ration of *al*cohols. Aldehydes contain the carbonyl group bonded to at least one hydrogen atom. Ketones contain the carbonyl group bonded to two carbon atoms.

Introduction to Naming Carbonyls

Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.

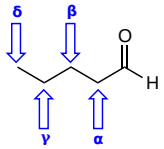


carbonyl group | aldehyde | ketone

Naming Aldehydes

The IUPAC system of nomenclature assigns a characteristic suffix ***-al*** to aldehydes. For example, $H_2C{=}O$ is methan**al**, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name. There are several simple carbonyl containing compounds which have common names which are retained by IUPAC.

Also, there is a common method for naming aldehydes and ketones. For aldehydes common parent chain names, similar to those used for carboxylic acids, are used and the suffix ***–aldehyde*** is added to the end. In common names of aldehydes, carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



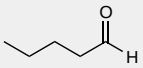
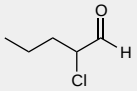
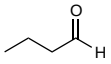
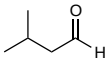
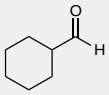
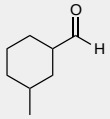
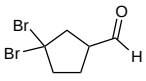
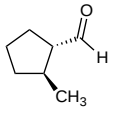
If the aldehyde group (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this group will get the #1 location number in naming the ring.

Summary of Aldehyde Nomenclature rules

1. Aldehydes take their name from their parent alkane chains. The ***-e*** is removed from the end and is replaced with ***-al***.
2. The aldehyde funtional group is given the #1 numbering location and this number is not included in the name.
3. For the common name of aldehydes start with the common parent chain name and add the suffix ***-aldehyde***. Substituent positions are shown with Greek letters.
4. When the -CHO functional group is attached to a ring the suffix ***-carbaldehyde*** is added, and the carbon attached to that group is C1.

Example 4.1.2.1

The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

 methanal (formaldehyde)	 ethanal (acetaldehyde)
 pentanal (valeraldehyde)	 2-chloropentanal (α-chlorovaleraldehyde)
 butanal (butyraldehyde)	 3-methylbutanal (isovaleraldehyde)
 cyclohexanecarbaldehyde	 3-methylcyclohexanecarbaldehyde
 3,3-dibromocyclopentanecarbaldehyde	 *trans*-2-methylcyclopentanecarbaldehyde

Naming Ketones

The IUPAC system of nomenclature assigns a characteristic suffix of **-one** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple ketones, such as propanone and phenylethanone do not require a locator number, since there is only one possible site for a ketone carbonyl function

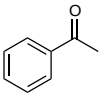
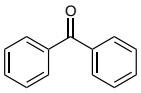
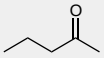
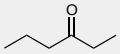
The common names for ketones are formed by naming both alkyl groups attached to the carbonyl then adding the suffix **-ketone**. The attached alkyl groups are arranged in the name alphabetically.

Summary of Ketone Nomenclature rules

1. Ketones take their name from their parent alkane chains. The ending ***-e*** is removed and replaced with ***-one***.
2. The common name for ketones are simply the **substituent groups listed alphabetically + *ketone*.**
3. Some simple ketones are known by their common names. Such as *propanone* which is commonly referred to as *acetone*.

Example 4.1.2.2

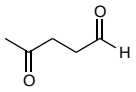
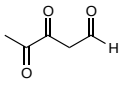
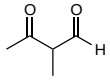
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.

 propanone (acetone)	 acetophenone (methyl phenyl ketone)	 benzophenone (diphenyl ketone)
 2-pentanone (methyl propyl ketone)	 3-methyl-2-butanone (methyl isopropyl ketone)	 3-hexanone (ethyl propyl ketone)

Naming Aldehydes and Ketones in the Same Molecule

As with many molecules with two or more functional groups, one is given priority while the other is named as a substituent. Because aldehydes have a higher priority than ketones, molecules which contain both functional groups are named as aldehydes and the ketone is named as an **"oxo"** substituent. It is not necessary to give the aldehyde functional group a location number, however, it is usually necessary to give a location number to the ketone.

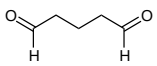
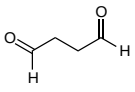
Example 4.1.2.3

 4-oxopentanal	 3,4-dioxopentanal	 2-methyl-3-oxobutanal

Naming Dialdehydes and Diketones

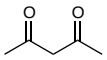
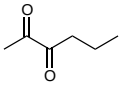
For dialdehydes the location numbers for both carbonyls are omitted because the aldehyde functional groups are expected to occupy the ends of the parent chain. The ending **–dial** is added to the end of the parent chain name.

Example 4.1.2.4

 pentanedial	 butanedial

For diketones both carbonyls require a location number. The ending **-dione** is added to the end of the parent chain.

Example 4.1.2.5

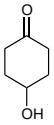
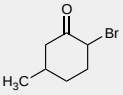
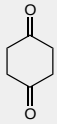
 2,4-pentanedione	 2,3-hexanedione

Naming Cyclic Ketones and Diketones

In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before the parent chain name to indicate that it is in a ring. As with other ketones the **–e** ending is replaced with the **–one** to indicate the presence of a ketone.

With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

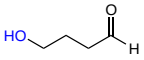
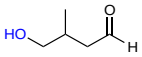
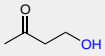
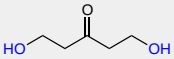
Example 4.1.2.6

 cyclopentanone	 2-bromocyclopentanone	 4-hydroxycyclohexanone
 2-bromo-5-methylcyclohexanone	 1,4-cyclohexanedione	 1,2-cyclopentanedione

Naming Carbonyls and Hydroxyls in the Same Molecule

When an aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

Example 4.1.2.7

 4-hydroxybutanal	 4-hydroxy-3-methylbutanal
 4-hydroxy-2-butanone	 1,5-dihydroxy-3-pentanone

Naming Carbonyls and Alkenes in the Same Molecule

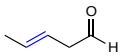
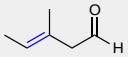
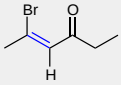
When an aldehyde or ketone is present in a molecule which also contains an alkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

When carbonyls are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

Example 4.1.2.8

 4-penten-2-one	 *trans*-3-pentenal
 (*E*)-3-methyl-3-pentenal	 (*Z*)-5-bromo-4-hexen-3-one

Aldehydes and Ketones as Fragments

- **Alkanoyl** is the common name of the R-C=O fragment, though the older naming, *acyl*, is still widely used.
- **Formyl** is the common name of the H-C=O fragment.
- **Acetyl** is the common name of the CH_3-C=O- fragment.

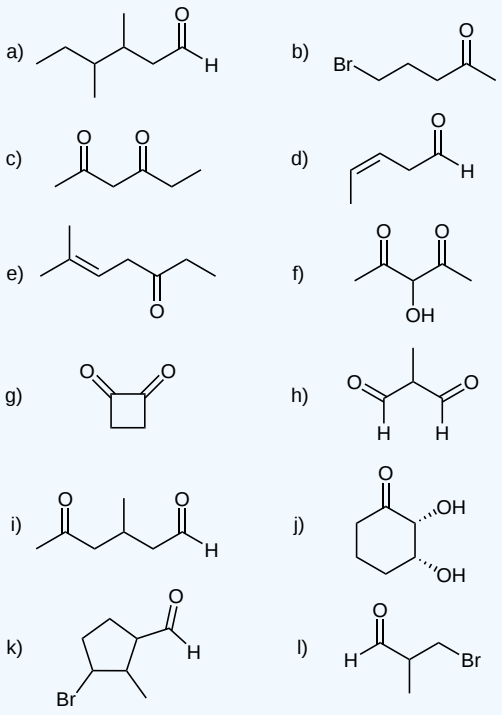
Example 4.1.2.9

 acetyl chloride	 acetylaldehyde	 formyl fluoride

Exercises

Exercise 4.1.2.1

Give the IUPAC name for each compound:



Answer

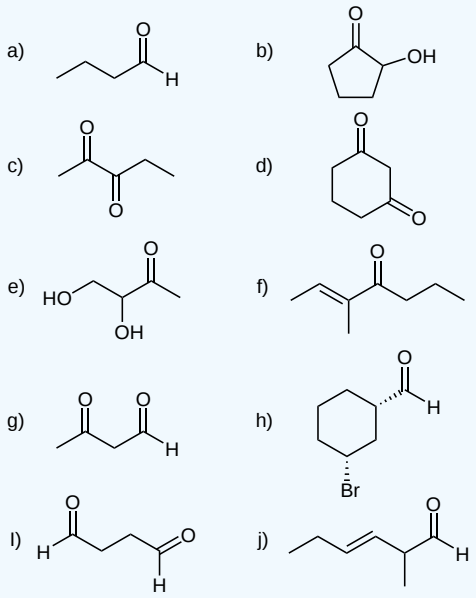
a. 3,4-dimethylhexanal
b. 5-bromo-2-pentanone
c. 2,4-hexanedione
d. *cis*-3-pentenal
e. 6-methyl-5-hepten-3-one
f. 3-hydroxy-2,4-pentanedione
g. 1,2-cyclobutanedione
h. 2-methyl-propanedial
i. 3-methyl-5-oxo-hexanal
j. *cis*-2,3-dihydroxycyclohexanone
k. 3-bromo-2-methylcyclopentanecarboaldehyde
l. 3-bromo-2-methylpropanal

? Exercise 4.1.2.2

Give the structure corresponding to each IUPAC name:

a. butanal
b. 2-hydroxycyclopentanone
c. 2,3-pentanedione
d. 1,3-cyclohexanedione
e. 3,4-dihydoxy-2-butanone
f. 3-methyl-2-hepten-4-one
g. 3-oxobutanal
h. *cis*-3-bromocyclohexanecarboaldehyde
i. butanedial
j. *trans*-2-methyl-3-hexenal

Answer



References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.
2. Zumdahl, Steven S., and Susan A. Zumdahl. Chemistry. 6th ed. Boston: Houghton Mifflin College Division, 2002.

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4.1.3: Preparing Aldehydes and Ketones

Objectives

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
   a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
   b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
   c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
   a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
   b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
   c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

Study Notes

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.5.

The "new" method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.9, which you might now wish to review.

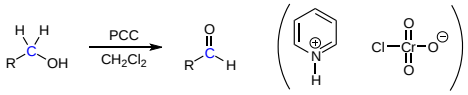
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

Formation of Aldehydes

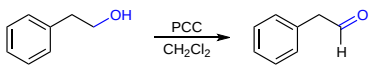
Oxidation of 1º Alcohols to form Aldehydes (Section 17.7)

PCC

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes alcohols one rung up the oxidation ladder, from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids.

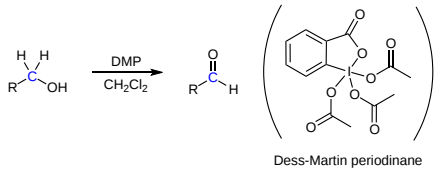


Example oxidation of a primary alcohol to an aldehyde

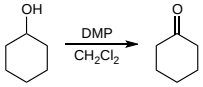


Dess-Martin Periodinane (DMP)

PCC is being replaced in laboratories by Dess-Martin periodinane (DMP), which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983. Similar to PCC, it oxidizes primary alcohols to aldehydes without continuing the oxidation to a carboxylic acid. It can also be used to oxidize secondary alcohols to ketones.

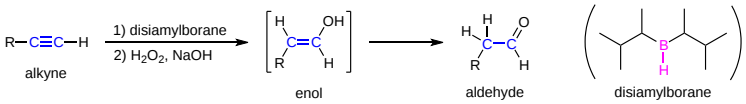


Example oxidation of an alcohol to a ketone using DMP

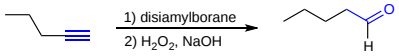


Hydration of an Alkynes to form Aldehydes (Section 9.5)

Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. This can be accomplished by hydroboration-oxidation reactions.

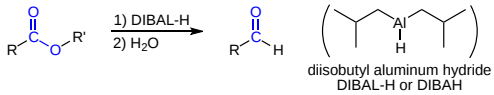


Example reaction of a terminal alkyne with disiamylborane followed by oxidation with hydrogen peroxide and hydroxide converting 1-pentyne to pentanal.



Hydride Reduction of Esters to form Aldehydes (Section 21.8)

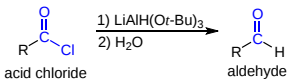
Various hydride sources allow for the partial reduction of some carboxylic acid derivatives to form aldehydes. These reactions are usually carried out at low temperatures (-78 ^oC) to prevent over reaction with the aldehyde product.



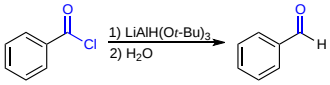
DIBAL-H reduction of methyl benzoate to benzaldehyde

Hydride Reduction of Acid Chlorides to form Aldehydes (Sections 21.6)

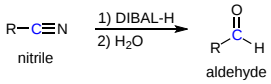
Reduction of acid chlorides to aldehydes requires hydride reagents with reduced reactivity as lithium aluminum hydride will continue reducing to the primary alcohol.



Example reduction of an acid halide to form an aldehyde



Hydride Reduction of a Nitrile to form Aldehydes

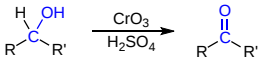


nitrile aldehyde

Formation of Ketones

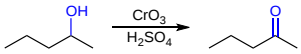
Oxidation of 2° Alcohols to form Ketones (Section 17.7)

Oxidation of 2° alcohols to form ketones typically uses Jones reagent (CrO_3 in H_2SO_4) but many other oxidizing agents can be used.



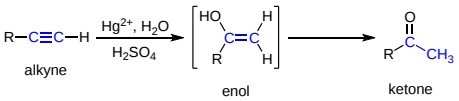
2° alcohol ketone

Example oxidation of a secondary alcohol to a ketone



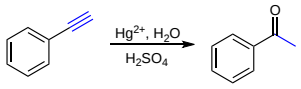
Hydration of Alkynes to form Ketones (Section 9.4)

The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.



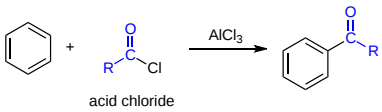
alkyne enol ketone

Example reaction of an alkyne with Hg^{2+}, H_2O, and H_2SO_4 to give a ketone



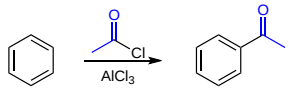
Friedel-Crafts Acylation to form a Ketone (Section 16.3)

Aromatic ketones can synthesized through Friedel–Crafts acylation of an aromatic ring with an acid chloride. Aluminum chloride ($AlCl_3$) is used as a Lewis acid catalyst.



acid chloride

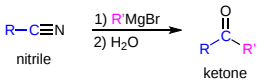
Example of Friedel-Crafts acylation to form a ketone from benzene.



benzene methyl phenyl ketone

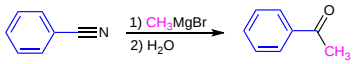
Reaction of Grignard reagents with nitriles to form ketones (Section 20.7)

Grignard reagents can attack the electophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.



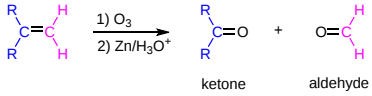
nitrile ketone

Example of Grignard addition to a nitrile to give a ketone.

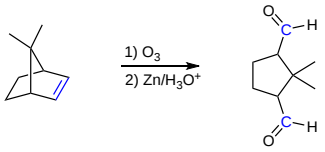


Alkenes can be Cleaved using Ozone (O_3) to form Aldehydes and/or Ketones (Section 8.8)

Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen.

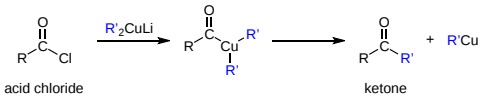


Example ozonolysis of an alkene to form aldehydes.

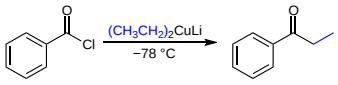


Organocuprate Reagents Convert Acid Chlorides to Ketones (Section 21.4)

An important reaction exhibited by lithium alkylcopper reagents (Gilman Reagents), is the nucleophilic addition to acid chlorides. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference is exploited to allow for a single nucleophilic addition to form a ketone.



Example of organocuprate addition to an acid chloride to generate a ketone.



? Exercise 4.1.3.1

What reagents would be required to prepare hexanal from the following starting materials?

a. $CH_3CH_2CH_2CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$
c. $CH_3CH_2CH_2CH_2CO_2CH_3$
d. $CH_3CH_2CH_2CH{=}CH_2$

Answer

a. Dess–Martin periodinane or PCC in CH_2Cl_2
b. 1. O_3, 2. Zn/H_3O^+
c. 1. DIBAH 2. H_2O
d. 1. BH_3 2. $H_2O_2/NaOH$; 2. Dess–Martin periodinane or PCC

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4.1.4: Oxidation of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

- write an equation for the oxidation of an aldehyde using
  - CrO_3/sulphuric acid.
  - Tollens reagent.
- explain the difference in structure which makes aldehydes susceptible to oxidation and ketones difficult to oxidize.
- identify the carboxylic acid produced when a given aldehyde is oxidized.
- identify the aldehyde, the oxidizing agent, or both, needed to prepare a given carboxylic acid.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Tollens reagent

Study Notes

An important difference between aldehydes and ketones is the ease with which the latter can be oxidized. Tollen's reagent is a classical organic laboratory technique to test for the presence of an aldehyde. The reagent consists of silver(I) ions dissolved in dilute ammonia. When the aldehyde is oxidized, the silver(I) ions are reduced to silver metal. When the reaction is carried out in a test-tube, the metallic silver is deposited on the walls of the tube, giving it a mirrorlike appearance. This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

Why do aldehydes and ketones behave differently?

Aldehydes have a proton attached to the carbonyl carbon which can be abstracted, allowing them to be easily oxidized to form carboxylic acids. The lack of this hydrogen, makes ketones generally inert to these oxidation conditions. Nevertheless, ketones can be oxidized but only under extreme conditions.

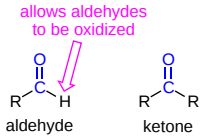
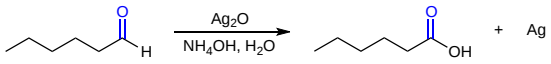


Figure 4.1.4.1: This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

A significant distinction between aldehydes and ketones lies in their susceptibility to oxidation, with aldehydes being more easily oxidized than ketones. One of the classic methods for identifying aldehydes in the laboratory is through the use of **Tollen's reagent** which consists of silver(I) ions dissolved in dilute ammonia. When an aldehyde is present, it undergoes oxidation, causing the silver(I) ions to be reduced to metallic silver. This reduction results in the deposition of silver on the surface of the test tube, forming a reflective, mirror-like coating. This reaction is commonly referred to as the "silver mirror test," and it serves as a reliable way to distinguish aldehydes from ketones. Ketones, in contrast, do not react with Tollen's reagent, making this test specific for aldehydes.



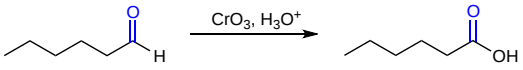
Figure 4.1.4.2: Tollens test for Aldehyde. The left side is positive (silver mirror) and the right side is negative.



Oxidation of hexanal to form hexanoic acid using Tollens Reagent

Oxidation of Aldehydes

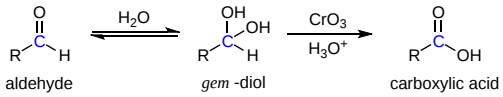
There are a wide variety of reagents which can cause the oxidation of aldehydes to carboxylic acids. The most common reagent for this conversion is CrO_3 in aqueous acid also called **Jones Reagent**. This reaction generally gives good yields at room temperature.



Example of the oxidation of hexanal to form hexanoic acid using Jones Reagent

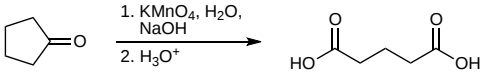
Mechanism

The oxidation of aldehydes occur through the reversible nucleophilic addition of water to the carbonyl to form a gem-diol functional group. This addition reaction is discussed in greater detail in Section 19.5. One of the OH groups of the *gem*-diol is oxidized to create a carbonyl (C=O) thereby forming a carboxylic acid.



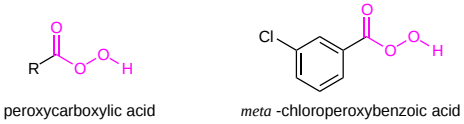
Oxidation of Ketones and Baeyer-Villiger Oxidation

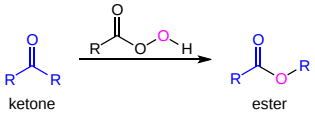
Because ketones do not have hydrogen atom attached to their carbonyl, they are resistant to oxidation. Only very strong oxidizing agents such as potassium manganate(VII) (potassium permanganate) solution oxidize ketones. However, this type of powerful oxidation occurs with cleavage, breaking carbon-carbon bonds and forming two carboxylic acids. Because of this destructive nature this reaction is rarely used.



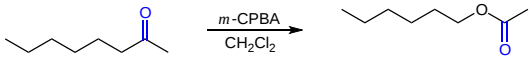
Oxidation of cyclopentanone to form pentanedioic acid

Peroxycarboxylic acids, such as **meta-chloroperoxybenzoic acid (mCPBA)**, are capable of oxidizing ketones to esters in a reaction known as the **Baeyer-Villiger oxidation**. Baeyer-Villiger oxidation has considerable synthetic utility because ketones normally are difficult to oxidize without degrading the structure to smaller fragments.

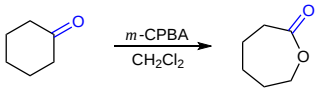




Baeyer-Villiger oxidations can be used with both straight chain ketones and cyclic ketones as shown in the following examples.



Baeyer-Villiger Oxidation of 2-octanone to form hexyl ethanoate

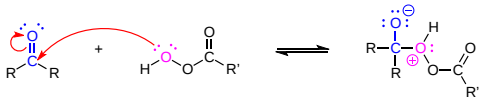


Baeyer-Villiger Oxidation of cyclohexanone to 6-hexanolactone

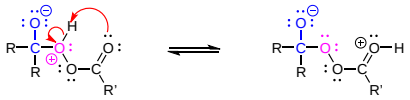
Mechanism

The mechanism of the Baeyer-Villiger oxidation has been studied extensively and is of interest because it involves a rearrangement step in which a substituent group (R) moves from a carbon to an oxygen. In the first step, one oxygen from the peroxy carboxylic acid adds to the carbonyl group of the ketone. The adduct has multiple oxygen atoms on which protons can reside. An intramolecular proton transfer followed by protonation allows for generation of the Criegee intermediate. Migration of an alkyl group and elimination of a carboxylic acid, R^1CO_2H, then occur in the fourth step. This generates a protonated form of the ester product, which is deprotonated in the final step of the mechanism.

Step 1: Nucleophilic attack on the carbonyl



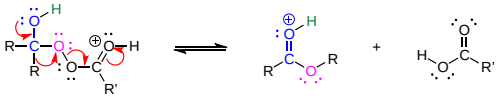
Step 2: Intramolecular Proton Transfer



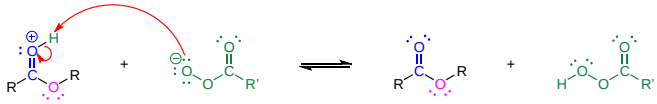
Step 3: Protonation of the alkoxide



Step 4: Migration of an Alkyl Group



Step 5: Deprotonation



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4.1.5: Nucleophilic Addition Reactions of Aldehydes and Ketones

Objectives

After completing this section, you should be able to

- give a general description of the nucleophilic addition reactions of aldehydes and ketones, identifying the two possible courses (or variations) that such reactions can take after the initial attack by the nucleophile.
- explain why, in general, aldehydes undergo nucleophilic addition reactions more readily than do ketones, and determine which of two given aldehydes or ketones will react most readily in such reactions.

Key Terms

Make certain that you can define, and use in context, the key term below.

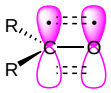
- nucleophilic addition reaction

Study Notes

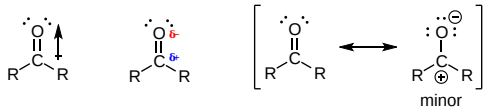
We have already discussed electrophilic addition reactions at some length; in this section nucleophilic addition reactions will be presented. Nucleophilic addition reactions involve the initial attack of a nucleophile on the slightly positive carbon center of the carbonyl group.

Introduction

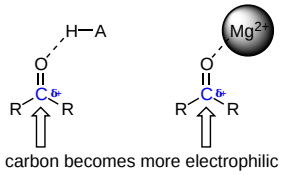
Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming three sigma bonds by overlapping with orbitals from the R groups (carbons or hydrogens) and an sp^2 hybrid orbital from oxygen. Due to the sp^2 orbitals, these three bonds adopt trigonal planar geometry seen in carbonyls. The carbonyl carbon's remaining unhybridized 2p orbital is perpendicular to this plane, and forms a ‘side-by-side’ pi bond by overlapping with a 2p orbital from the carbonyl oxygen.



The carbon-oxygen double bond is polar since oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow (pointing toward the more electronegative atom), or by showing the oxygen as holding a partial negative charge and the carbonyl carbon with a partial positive charge. A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pi bond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.



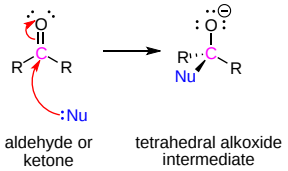
The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond’s polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen. The same effect can also be achieved if a Lewis acid, such as a magnesium ion (Mg^{2+}), is located near the carbonyl oxygen.



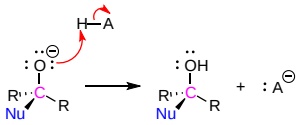
Nucleophilic Addition to a Carbonyl

Most important reactions involving carbonyl groups characteristically have a nucleophilic addition as part of their mechanism. The generic mechanism for the nucleophilic addition of a negatively charged nucleophile to a carbonyl is shown below.

In the first step of the nucleophilc addition mechanism, the nucleophile forms a bond with the the electrophilic C=O carbon atom. This causes the rehybridization of the carbonyl carbon from sp^2 to sp^3. These reactions differ from nucleophilic substitution reactions since neither aldehydes nor ketones have a leaving group. Instead electrons in the pi bond are pushed up to the electronegative oxygen atom forming a tetrahedral alkoxide intermediate.

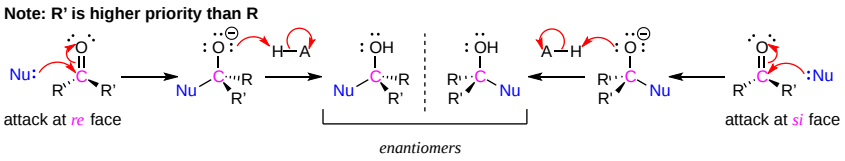


In the second step of the mechanism, the alkoxide is protonated by the addition of an acid to form an alcohol.



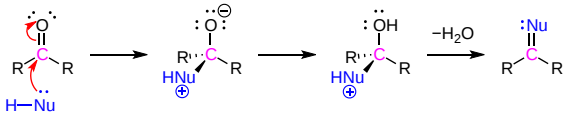
Stereochemistry of Nucleophilic Addition to a Carbonyl

When the two groups adjacent to a carbonyl are not the same, we can distinguish between the **re** and **si** 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.



Nucleophilic Addition of a Neutral Nucleophile

Neutral nucleophiles can also undergo nucleophilic addition to carbonyls. The mechanism is slightly different than with a negatively charged nucleophile. The presence of an additional hydrogen atom in the nucleophile allows for the the carbonyl oxygen to be completely removed as water and a C=Nu bond to be formed.



Relative Reactivity of Aldehydes and Ketones to Nucleophilic Addition

In general, aldehydes are more reactive than ketones because they have a greater polarization of the carbonyl bond. The primary carbocation formed in the polarizing resonance structure of an aldehyde (shown below) is less stable and therefore more reactive than the secondary carbocation formed in a similar resonance structure formed by a ketone. The stability difference in these resonance structures is due to the extra alkyl group present in the ketone. Alky groups stabilize carbocations through induction as discussed in Section 7.11.

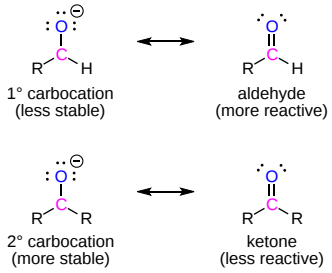


Figure **4.1.5.1**). The carbonyl carbon of formaldehyde is more positive (more blue) and therefore more reactive towards nucleophlic addition than the carbonyl carbon in acetone which is less positive (more green). As discussed above, electron-attracting groups can further increase its positive character of a carbonyl carbon and thereby facilitate nucleophilic addition.

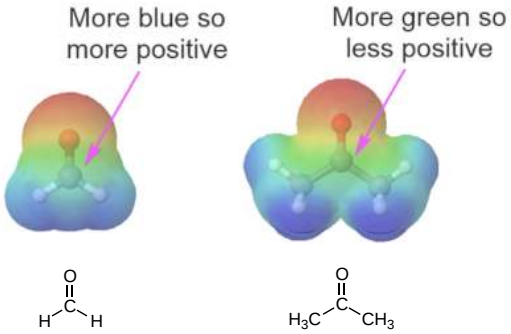


Figure **4.1.5.1**: The Electrostatic Potential Map of Formaldehyde (Left) and Acetone (Right)

Another reason aldehydes tend to me more reactive to nucleophilic addition than ketones is steric hindrance. Ketones have two alkyl groups attached to their carbonyl carbon while aldehydes only have one. This means nucleophiles have a less sterically hindered path when attacking the carbonyl carbon of an aldehyde. Also, the transition state of the rate determining step for formation of the tetrahedral intermediate is less sterically crowded, lower in energy, and more kinetically favorable for an aldehyde than a ketone. The difference in sterics in the carbonyl carbon of an aldehyde and a ketone is easily seen when comparing the space filling models of acetaldehyde and acetone (Figure **4.1.5.2**).

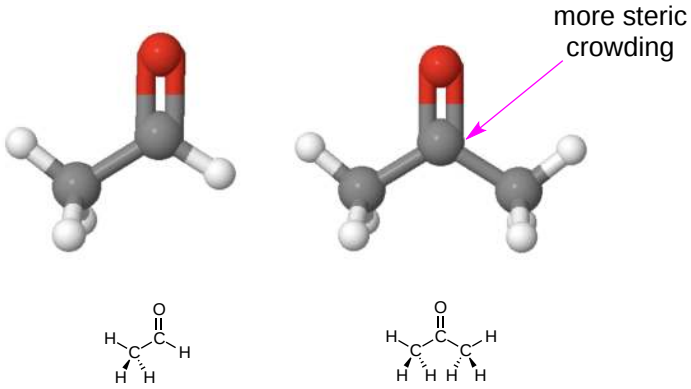
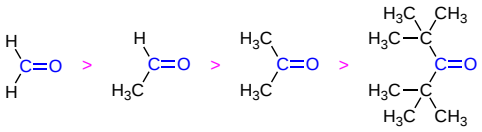


Figure **4.1.5.2**: The Relative Steric Crowding of Acetaldehyde (Left) and Acetone (Right)

In fact, reactivity of a carbonyl toward nucleophilic addition decreases with increasing bulkiness of carbonyl substituents, as seen in the following series.

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? Exercise 4.1.5.1

Benzaldehyde is less reactive to nucleophilic addition reactions than aliphatic aldehydes. Explain.

Answer

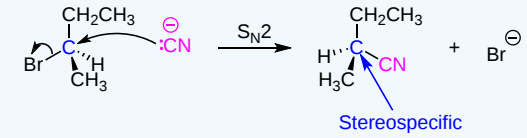
Aromatic rings act as an electron-donating group due to resonance effect. Electron donating groups make the carbonyl group in benzaldehyde less electrophilic.

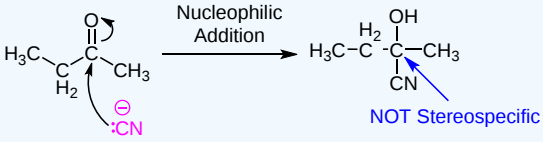
? Exercise 4.1.5.2

Compare the mechanisms of an S_N2 reaction between 2-bromobutane and cyanide and the tetrahedral complex formation between 2-butanone and cyanide.

Answer

In the S_N2 reaction the cyanide nucleophilic must undergo back side attack. This causes an inversion of stereochemistry and creates a product which is stereospecific. The carbonyl used in the nucleophilic addition is trigonal planar. This means the cyanide nucleophile can attack from either plane. This tends to create a racemic mixture of enantiomers.





4.1.5: Nucleophilic Addition Reactions of Aldehydes and Ketones is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Dietmar Kennepohl.

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4.1.6: Nucleophilic Addition of Water- Hydration

Objectives

After completing this section, you should be able to

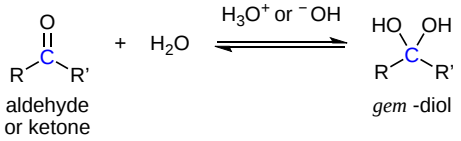
- write the step-wise mechanism for the base-catalyzed hydration of an aldehyde or ketone.
- write the step-wise mechanism for the acid-catalyzed hydration of an aldehyde or ketone.

Key Terms

Make certain that you can define, and use in context, the key term below.

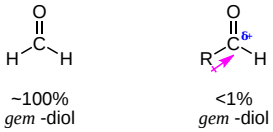
- geminal (gem) diol

It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol, *gem*-diol, or 1,1-diol). The term hydrate implies the addition of water. The word germinal or abbreviation gem comes from the Latin word for twin, *geminus*.



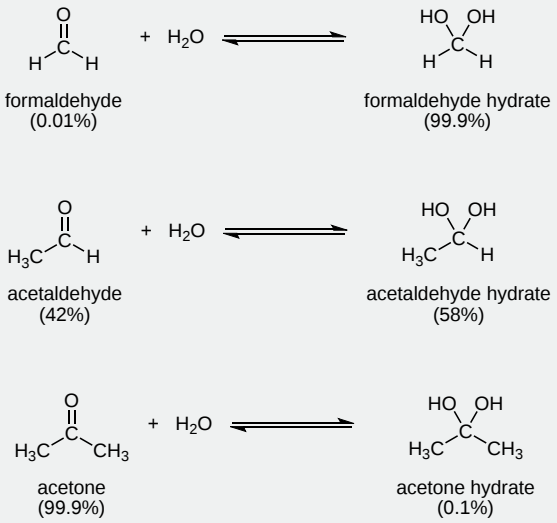
Factors Affecting the Hydrate Equilibrium

The equilibrium for hydrate formation depends both on steric and electrical factors of the carbonyl as discussed in the previous section. In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the small size of the hydrogen substituents relative to aldehydes and ketones favor hydrate formation. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. The addition of electron donating alkyl groups stabilized the partial positive charge on the carbonyl carbon and decreases the amount of *gem*-diol product at equilibrium. Because of this ketones tend to form less than 1% of the hydrate at equilibrium.

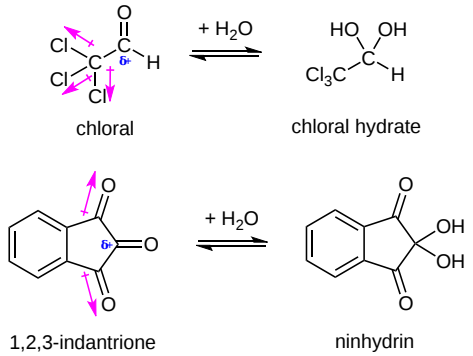


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Equilibrium Distribution of Common Aldehydes and Ketones with their Hydrate Forms

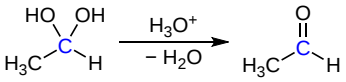


Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable hydrates. Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to reveal fingerprints.



Reversibility of Hydrate Formation

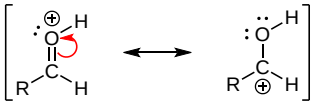
Isolation of hydrates is difficult because the reaction is reversible. Removal of water from the hydrate can cause the conversion of a gem-diol back to the corresponding carbonyl.



Acid or Base Catalyzed Hydrate Formation

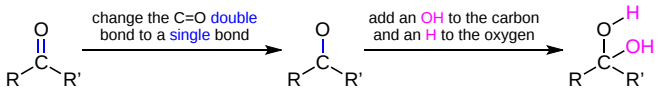
The nucleophilic addition of water to a carbonyl to form a hydrate is usually slow under neutral condition (pH = 7). The rate can be significantly increased through the addition of an acid or base as a catalyst.

The addition of an acid or base changes the mechanism and promote the nucleophilic addition of water to a carbonyl to form a hydrate. Basic conditions speed up the reaction because hydroxide is a better nucleophile than water. Acidic conditions speed up the reaction because the carbonyl becomes protonated. Protonation increases the polarity of the carbonyl bond which increase the partial positive charge on the carbon making it more electrophilic.

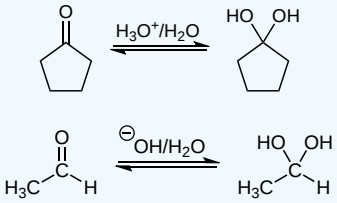


Predicting the Product of a Hydration

Overall, the C=O of the carbonyl in the starting material is removed and replaced by two single bonds both of which are attached to the original carbonyl carbon. Both of these single bonds are attached to OH groups in the product.



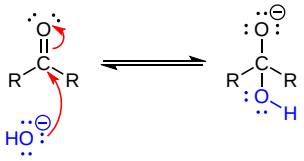
Example 4.1.6.1



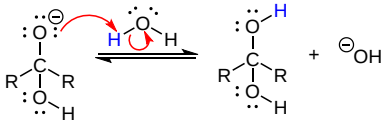
Mechanism of Acid or Base Catalyzed Hydrate Formation

Hydrate Formation under Basic conditions

Step 1: Basic conditions means there is a significant amount of hydroxide present. Hydroxide is a better nucleophile than water which speeds up the reaction. The negatively charged hydroxide forms a single bond with the electrophilic carbonyl carbon. This pushes the two electrons of the pi bond onto the electronegative oxygen forming an alkoxide ion intermediate.

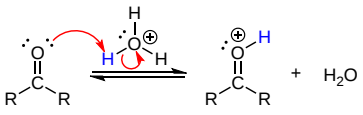


Step 2: Water acts as an acid and protonates the alkoxide ion to form a neutral hydrate while also regenerating hydroxide. The fact that hydroxide is not being used during the reaction is consistent with it acting as a catalyst.



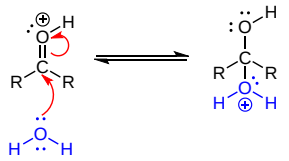
Hydrate Formation under Acidic conditions

Step 1: Acidic conditions means there is a significant amount of hydronium present. Hydronium protonates the carbonyl oxygen thereby making the carbonyl carbon more electrophilic. After protonation the oxygen becomes positively charged.

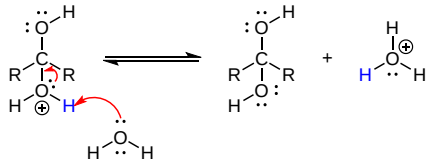


Step 2: Under acidic conditions the most nucleophilic species is water. Water forms a single bond with the electrophilic carbon. This pushes the two electrons in the carbonyl pi bond onto the electronegative oxygen. The oxygen from the carbonyl becomes

neutral while the oxygen from the water nucleophile become positively charged.

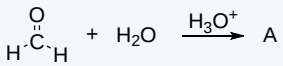


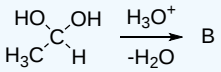
Step 3: Water acts as a base and deprotonates the intermediate to produce the neutrally charged hydrate while regenerating hydronium. The fact that hydronium is not being used during the reaction is consistent with it acting as a catalyst.

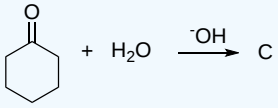


Exercise 4.1.6.1

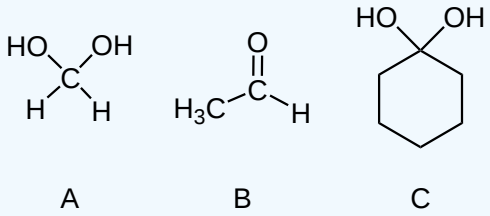
Draw the expected products of the following reactions.







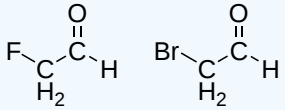
Answer



A B C

Exercise 4.1.6.2

Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

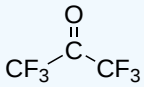


Answer

The compound on the left would. Fluorine is more electronegative than bromine and would remove more electron density from the carbonyl carbon. This would destabilize the carbonyl allowing for more gem-diol to form.

Exercise 4.1.6.3

Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

Although ketones tend to not form gem-diols, this compound exists almost entirely in the gem-diol form when placed in water. Ketones tend to not form gem-diols because of the stabilizing effect of the electron donating alkyl group. However, in this case the electron donating effects of the alkyl group is dominated by the presence of six highly electronegative fluorines turning these into electron withdrawing groups.

4.1.6: Nucleophilic Addition of Water- Hydration is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer & Dietmar Kennepohl.

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SECTION OVERVIEW

4.2: Carboxylic Acids

This chapter presents a straightforward discussion of the chemistry of carboxylic acids (formerly called “fatty acids”) and nitriles. As usual, we begin with a description of how the compounds are named. We then consider the subtleties of their structure, and how these structural features influence physical properties, such as boiling point. We place considerable emphasis on the dissociation of carboxylic acids and the effect of substituents on acid strength.

We have already encountered a number of methods of preparing carboxylic acids. We shall review these methods, and learn about two additional procedures. The only reactions of carboxylic acids that we study in detail in this chapter are reduction and decarboxylation, although two other common reactions of carboxylic acids, alpha substitution and nucleophilic acyl substitution, will be described in later chapters.

We will then look at the formation of nitriles and their chemical reactivity; and our discussion of carboxylic acid and nitrile chemistry concludes with a look at the infrared and NMR spectra of these compounds, with emphasis on the characterization of carboxylic acids.

4.2.1: Chapter Objectives and Introduction to Carboxylic Acids

4.2.2: Naming Carboxylic Acids and Nitriles

4.2.3: Structure and Properties of Carboxylic Acids

4.2.4: Reactions of Carboxylic Acids - An Overview

4.2.5: Chemistry of Esters

4.2.6: Chemistry of Amides

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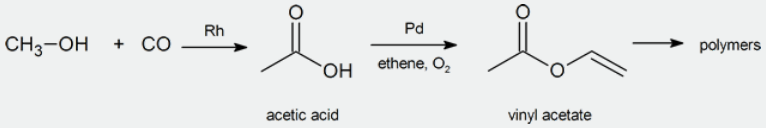
4.2.1: Chapter Objectives and Introduction to Carboxylic Acids

Objectives

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
- solve road-map problems which require a knowledge of the chemistry of carboxylic acids.
- define, and use in context, the key terms introduced in this chapter.

Study Notes

The global demand for acetic acid is about 6.5 million tonnes per year. A common industrial preparation of acetic acid is the catalytic oxidation of methanol with carbon monoxide. Much of the acetic acid produced is converted to vinyl acetate polymer and used in adhesives and paints.

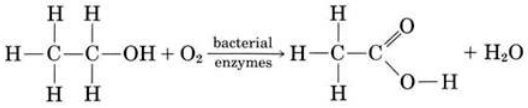


acetic acid vinyl acetate

Not only are carboxylic acids valuable, but they and their derivatives are useful starting materials for many synthetic products. Finally, carboxylic acids and their derivatives are also found in a variety of natural systems and important biological pathways.

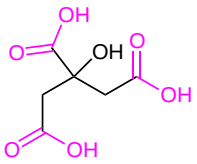
Carboxylic Acids

Carboxylic acids have been known throughout human history. Prehistoric people likely made acetic acid when their fermentation reactions went awry and produced vinegar instead of wine. The Sumerians (2900–1800 BCE) used vinegar as a condiment, a preservative, an antibiotic, and a detergent. Vinegar contains 4 to 5 percent acetic acid. Acetic acid gives vinegar its sour taste and pungent odor and can do the same thing to wine. Acetic acid, CH_3COOH, is an example of the class of compounds called **carboxylic acids**, each of which contains one or more carboxyl groups, COOH. The general formula of a carboxylic acid is RCOOH.



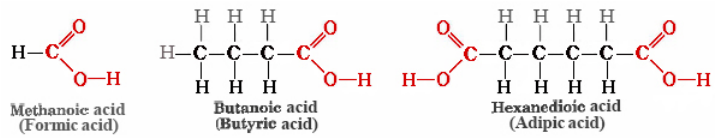
Ethanol **Ethanoic Acid (Acetic Acid)**

Citric acid was discovered by an Islamic alchemist, Jabir Ibn Hayyan (also known as Geber), in the 8th century, and crystalline citric acid was first isolated from lemon juice in 1784 by the Swedish chemist Carl Wilhelm Scheele. Medieval scholars in Europe were aware that the crisp, tart flavor of citrus fruits is caused by citric acid.



Citric acid

Naturalists of the 17th century knew that the sting of a red ant's bite was due to an organic acid that the ant injected into the wound. Formic acid (the name comes from Latin word *formica* meaning "ant") is present in ants and bees and is responsible for the burning pain of their bites and stings. Butyric acid, a component of rancid butter and Limburger cheese, has a vile odor. Adipic acid is an example of a dicarboxylic acid—it has two functional groups—and is used to make nylon



Naturally Occurring Carboxylic Acids

Carboxylic acids are widespread in nature, often combined with other functional groups. Simple alkyl carboxylic acids, composed of four to ten carbon atoms, are liquids or low melting solids having very unpleasant odors. The **fatty acids** are important components of the biomolecules known as lipids, especially fats and oils. As shown in the following table, these long-chain carboxylic acids are usually referred to by their common names, which in most cases reflect their sources. A mnemonic phrase for the C_{10} to C_{20} natural fatty acids capric, lauric, myristic, palmitic, stearic and arachidic is: "**C**urly, **L**arry & **M**oe **P**erform **S**illy **A**ntics" (note that the names of the three stooges are in alphabetical order).

Table 17.4.1: Common Saturated Fatty Acids

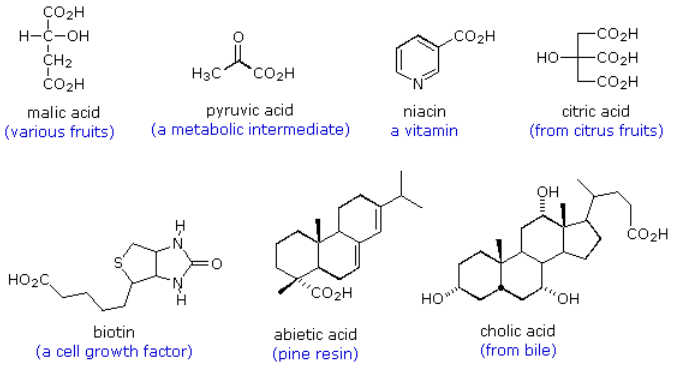
Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC

Interestingly, the molecules of most natural fatty acids have an *even number of carbon atoms*. Since nature makes these long-chain acids by linking together acetate units, it is not surprising that the carbon atoms composing the natural products are multiples of two. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. All the double bonds in the unsaturated compounds listed on the table have *cis* (or Z) stereochemistry.

Table 17.4.2: Common Unsaturated Fatty Acids

Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The following formulas are examples of other naturally occurring carboxylic acids. The molecular structures range from simple to complex, often incorporate a variety of other functional groups, and many are chiral.



Naturally occurring carboxylic acids

Carboxylic Acid Derivatives

Other functional group combinations with the carbonyl group can be prepared from carboxylic acids, and are usually treated as related derivatives. The chemistry behind the conversion of carboxylic acids to carboxylic acid derivatives will be discussed in then next chapter. Five common classes of these **carboxylic acid derivatives** are listed in the following table. Although nitriles do not have a carbonyl group, they are included here because the functional carbon atoms all have the same oxidation state. The top row shows the general formula for each class, and the bottom row gives a specific example of each. As in the case of amines, amides are classified as 1º, 2º or 3º, depending on the number of alkyl groups bonded to the nitrogen.

acyl halide	anhydride	ester	amide	nitrile
X = F, Cl, Br or I			R′ = H or alkyl	
propanoyl chloride	acetic anhydride	ethyl acetate	formamide	acetonitrile

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4.2.2: Naming Carboxylic Acids and Nitriles

Objectives

After completing this section, you should be able to

1. write the IUPAC name of a carboxylic acid, given its Kekulé, condensed or shorthand structure.
2. draw the condensed or shorthand structure of a carboxylic acid, given its IUPAC name.
3. draw the structure of the following carboxylic acids, given their trivial names: formic acid and acetic acid.
4. provide an acceptable name for a nitrile of given structure.
5. draw the condensed or shorthand structure of a nitrile, give either its trivial or IUPAC name.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- carboxylic acid
- nitrile

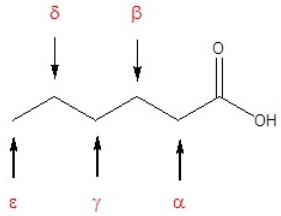
Study Notes

You need not memorize all the trivial names listed in the table, just remember the two names identified in Objective 3, above.

Carboxylic Acids, RCO_2H

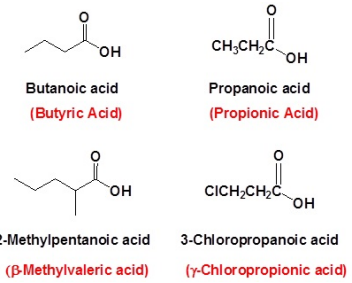
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-oic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of carboxylic acids, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

Example (Common Names Are in Red)



Naming carboxyl groups added to a ring

When a carboxyl group is added to a ring, the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.

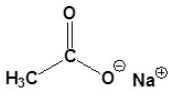


The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid (C_6H_5COOH).

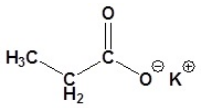


Naming carboxylates

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the carboxylic acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



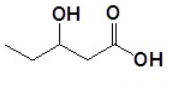
Sodium ethanoate
(Sodium Acetate)



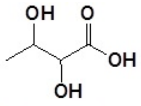
Potassium Propanoate
(Potassium propionate)

Naming carboxylic acids which contain other functional groups

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups, the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

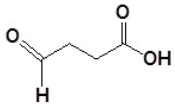


3-Hydroxypentanoic acid

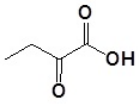


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups, the carbonyl is named as an "Oxo" substituent.

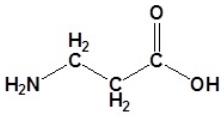


4-Oxobutanoic acid

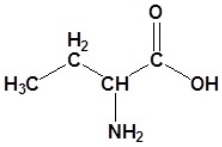


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group, the amine is named as an "amino" substituent.



3-Aminopropanoic acid

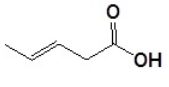


2-Aminobutanoic acid

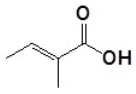
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that *cis/tran* or E/Z nomenclature for the alkene needs to be included if necessary.



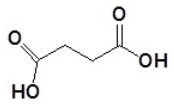
Trans-3-pentenoic acid



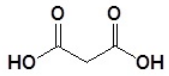
(E)-2-Methyl-2-butenoic acid

Naming dicarboxylic acids

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain name.



Butanedioic acid

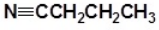


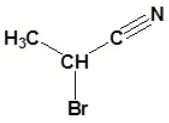
Propanedioic acid

Naming Nitriles, R−C≡N

A **nitrile** is any organic compound with a −C≡N functional group. In literature the prefix **cyano-** is used interchangeably with the term nitrile to refer to the functional group. Nitriles used to be known as cyanides; the smallest organic nitrile is ethanenitrile, CH_3CN, (old name: methyl cyanide or acetonitrile).

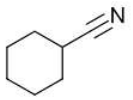
Open chain nitriles are named with the word **-nitrile** after the name of the parent alkane name. Remmber to include the carbon atom of the nitrile as part of the parent chain. For example, CH_3CN has two carbons including the nitrile carbon, therefore it is ethanenitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.



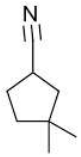


Butane nitrile 2-Bromopropane nitrile

When a nitrile is the highest priority functional group attached to a cycloalkane, the name of the parent cycloalkane is followed by the word **-carbonitrile**. The ring carbon attached to the nitrile is numbered C1 and the nitrile is not given a number in the name.

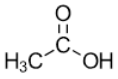


Cyclohexanecarbonitrile

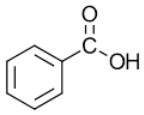


3,3-Dimethylcyclopentanecarbonitrile

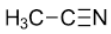
Nitriles are often named based off the common name of the corresponding carboxylic acid. This is done by replacing the -ic acid or -oic acid ending with **-onitrile**. In these cases the nitrile carbon is numbered C1 but the nitrile itself is not given a number in the name.



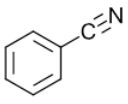
Acetic Acid



Benzoic Acid

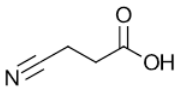


Acetonitrile



Benzonitrile

In the case of molecules containing a carboxylic acid and nitrile functional group, the nitrile is named as a "cyano" substituent. Note! The carbon in the nitrile is not counted as part of the parent chain when named as a cyano substituent.



3-Cyanopropanoic Acid

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4.2.3: Structure and Properties of Carboxylic Acids

Objectives

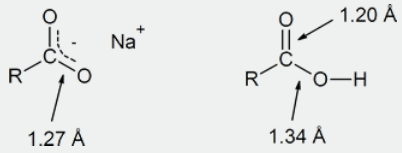
After completing this section, you should be able to

1. describe the geometry and electronic structure of a simple carboxylic acid; for example, acetic acid.
2. describe the hydrogen bonding that occurs between carboxylic acid molecules, and hence account for the relatively high boiling points of these compounds.
3. write an expression for the dissociation constant of a given carboxylic acid, and use it to calculate dissociation constants, percentage dissociation, etc.
4. identify carboxylic acids as being weaker acids than mineral acids, such as hydrochloric acid, but stronger acids than alcohols.
5. use the concept of resonance to explain why carboxylic acids are stronger acids than alcohols.
6. draw an orbital picture of a carboxylate anion to show the equivalence of the two oxygen atoms.
7. explain why the two carbon-oxygen bond lengths are identical in sodium carboxylate, but different in carboxylic acid.
8. write an equation for the reaction of a carboxylic acid with a base, such as sodium hydroxide.

Study Notes

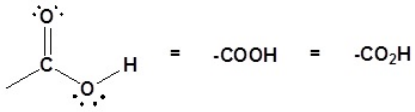
You might wish to review Sections 2.7, “Acids and Bases: The Brønsted-Lowry Definition” and 6.7, “Describing a Reaction: Equilibria, Rates, and Energy Changes” in conjunction with this section.

In the reading, the discussion of the role of resonance in the acidity of a carboxylic acid explains that the two carbon-oxygen bonds in the delocalized carboxylate anion are identical (both 1.27 Å). However, in the structure of a carboxylic acid the **C–O** bond (1.20 Å) is shorter than the **C–OH** bond (1.34 Å).



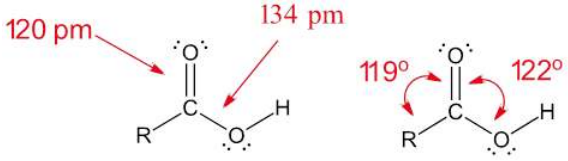
Structure of the carboxyl acid group

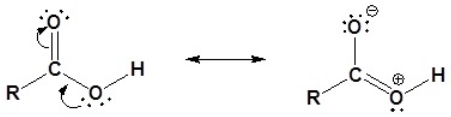
Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



Carboxyl Group

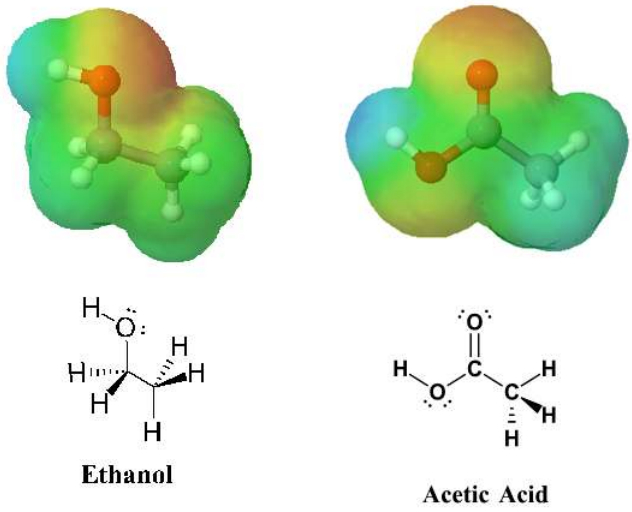
The carbon and oxygen in the carbonyl are both sp^2 hybridized which gives a carboxylic acid a trigonal planar shape (around the carbonyl carbon) making the bond angles roughly 120°. A resonance structure exists where one of the lone pairs of the hydroxyl oxygen (OH) is conjugated with the pi bond system of the carbonyl group. The conjugation can be represented by the resonance structure shown below which holds all the atoms in the carboxylic acid in a co-planar arrangement.





Major Contributor Minor Contributor

The effects of conjugation in a carboxylic acid can be seen when comparing the electrostatic potential maps of ethanol and acetic acid. Conjugation creates a greater polarization in the O-H bond in acetic acid, as shown by its darker blue color, which subsequently leads to a greater acidity in carboxylic acids.



Ethanol Acetic Acid

Acidity of Carboxylic Acids

Carboxylic acids are named such because they tend to be more acidic than other functional groups in organic chemistry. In dilute aqueous solutions, they act as Brønsted–Lowry acids and partially dissociate to produce the corresponding carboxylate ion and hydronium (H_3O^+).



Carboxylic acid Carboxylate ion

The extent of this dissociation is described by the K_a value of the carboxylic acid. In a 0.1 M solution of acetic acid ($K_a = 1.75 \times 10^{-5}$ @ 25 °C) only about 0.1% of the molecules are dissociated.

$$\begin{aligned} K_{eq} &= K_a \\ &= \frac{[\mathrm{RCOO^-}][\mathrm{H_3O^+}]}{[\mathrm{RCOOH}]} \\ &= 1.75 \times 10^{-5} \end{aligned}$$

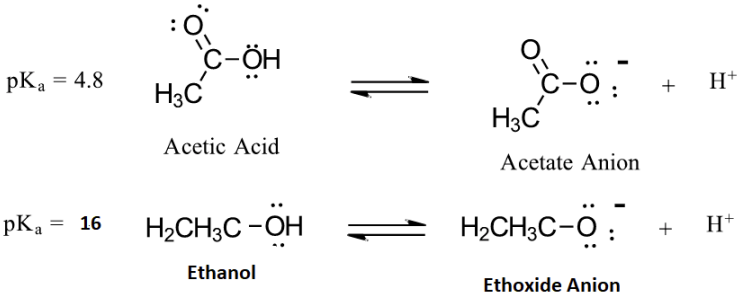
with $pK_a = -\log K_a$.

The pK_a's of some typical carboxylic acids are listed in Table 4.2.3.1. The factors which affect the acidity of different carboxylic acids will be discussed in the next section of this text.

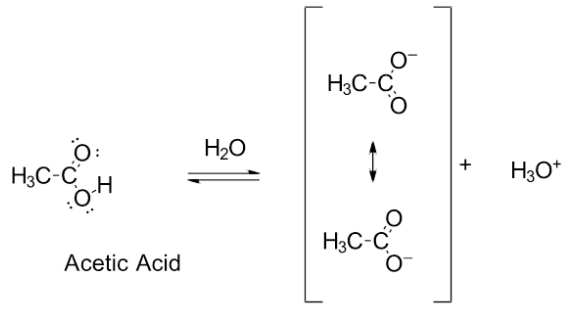
Table 4.2.3.1: Acidity of example carboxylic acids

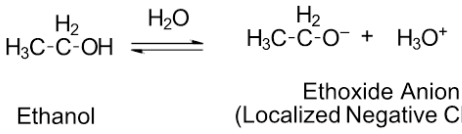
Compound	K_a	pK_a
F_3CCO_2H	0.59	0.23
Cl_3CCO_2H	0.22	0.66
$p\text{-}O_2NC_6H_4CO_2H$	3.39×10^{-4}	3.47
HCO_2H	1.78×10^{-4}	3.75
$C_6H_5CO_2H$	6.31×10^{-5}	4.20
$p\text{-}CH_3OC_6H_4CO_2H$	3.55×10^{-5}	4.45
CH_3CO_2H	1.75×10^{-5}	4.76
$CH_3CH_2CH_2CO_2H$	1.51×10^{-5}	4.82

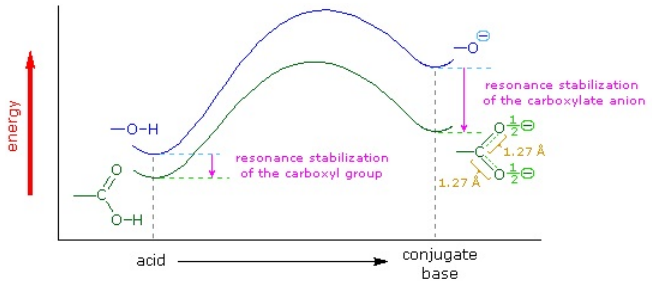
The acidity of carboxylic acids comes about, in part, due to resonance stabilization of the carboxylate conjugate base. A classic example compares the relative acidity of ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups. Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are very different (acetic acid is more than 10^{11} times more acidic than ethanol). In both species, the negative charge on the conjugate base is held by an oxygen so electronegativity does not explain the difference in acidity.



For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy allowing for the the negative charge on the acetate ion to be equally shared between two oxygens. In the ethoxide anion, by contrast, the negative charge is 'locked' on the single oxygen. This stabilization leads to a marked increase in stability of the acetate anion, as illustrated by the energy diagram shown below. The increased stabilization of the acetate anion conjugate base promotes the acidity of acetic acid.

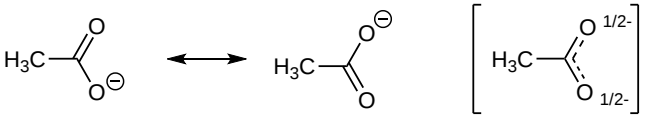






The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 11 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so this represents a difference of over 10^{11} between the acidity constants for the two molecules). The acetate anion is that much more stable than the ethoxide anion, all due to the effects of resonance delocalization.

X-ray crystallographic studies provide experimental evidence of the acetate anion resonance hybrid. Both C-O bonds in acetate are 126 pm which is roughly the average of C=O double bond (123 pm) and the C-O single bond (132 pm) of acetic acid. Both of the C-O bonds in the acetate anion are considered to have a bond order of 1 1/2. The negative charge is equally spread between the two oxygens giving them each a charge of -1/2.



Resonance structures and resonance hybrid of acetate ion.

Physical Properties of Some Carboxylic Acids

Carboxylic acids tend to have higher boiling points when compared to ethers, alcohols, aldehydes, or ketones with a similar molecular weight. For example acetic acid and ethanol have boiling points of 117.9 ^oC and 78.3 ^oC respectively despite the fact that they both contain two carbons. Because carboxylic acids and alcohols both contain an O-H bond they are strongly associated by a hydrogen-bonding intermolecular force. The difference is that for carboxylic acids, two molecules of a carboxylic acid form two hydrogen bonds with each other to create a cyclic dimer (pair of molecules). Two alcohol molecules can only form one hydrogen bond between each other. Thus, carboxylic acids have stronger intermolecular forces and higher boiling points than their corresponding alcohols.

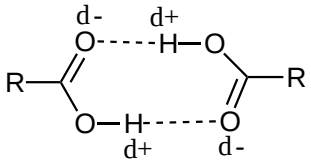
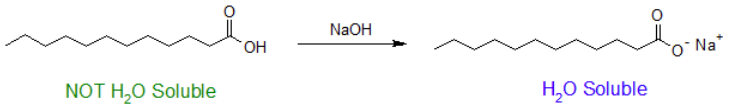


Table **4.2.3.2**: Intermolecular hydrogen bonding in carboxylic acids.

Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

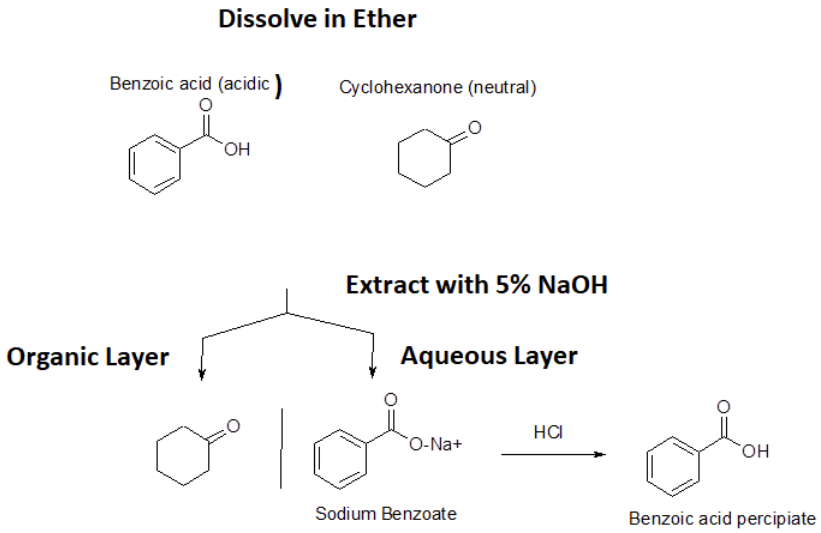
Water Solubility of Carboxylic Acids

The ability to form hydrogen bonds gives carboxylic acids with low molecular weights some measure of solubility in water. Carboxylic acids with six or more carbons tend to only be slightly soluble in water. However, conversion to the corresponding carboxylate anion tends to immensely increase water solubility due to the creation of an ion-dipole intermolecular force. Typically a strong base is used to deprotonate a carboxylic acid and drive this reaction to completion as shown below.



NOT H_2O Soluble H_2O Soluble

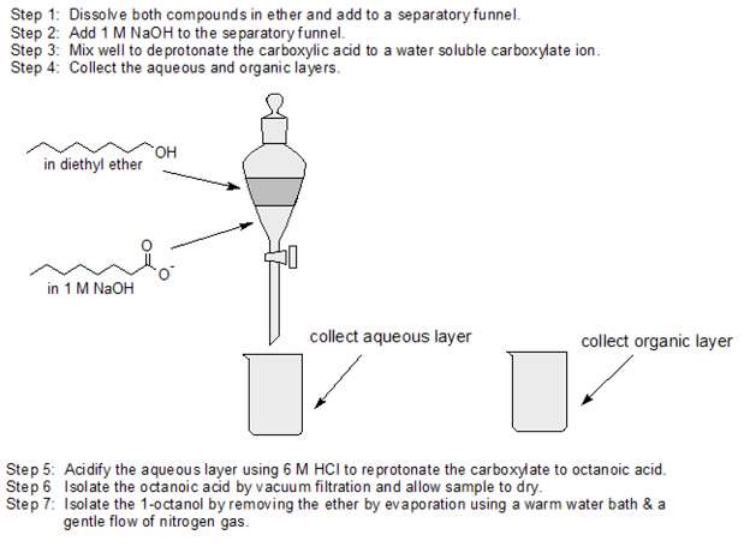
This property of carboxylic acids allows many carboxylic acids to be purified by a technique called acid/base extraction. The figure below shows how a carboxylic acid (benzoic acid) can easily be separated from non-acidic water insoluble compounds (cyclohexanone) using an acid/base extraction. First, the two compounds are dissolved in an organic solvent immiscible with water (ether). Then a basic aqueous solution (5% NaOH) is added and two liquid layers are formed. As the layers are mixed, benzoic acid reacts with the basic solution to become sodium benzoate. Because sodium benzoate is soluble in water it is extracted into the aqueous layer while the non-acidic cyclohexanone remains in the organic layer. The two layers can be separated using a separatory funnel effectually removing the cyclohexanone. The aqueous layer can then be acidified with a strong acid causing sodium benzoate to become protonated, reforming benzoic acid. Because benzoic acid is insoluble in water it will form a precipitate which can easily be filtered off.



Exercise 4.2.3.1

Use acid-base chemistry and differences in water solubility to separate 1-octanol from octanoic acid using the following solutions: 1 M NaOH, ether, and 6 M HCl and any lab equipment.

Answer



Exercise 4.2.3.2

What percentage of propanoic acid (CH_3CH_2COOH) is dissociated into its conjugate base in a 0.20 M aqueous solution? K_a = 1.32 x 10^{-5}

Answer

From the acid equilibrium expression we get that:

$[CH_3CH_2COO^-][H_3O^+]/[CH_3CH_2COOH] = K_a = 1.32 \times 10^{-5}$

$[X][X]/[0.20\ M - X] = 1.32 \times 10^{-5}$

Assume X is small compared to 0.20 M

$[X]^2/[0.20\ M] = 1.32 \times 10^{-5}$

$X = [CH_3CH_2COO^-] = 1.62 \times 10^{-3}\ M$

$[CH_3CH_2COO^-] / [CH_3CH_2COOH]\ X\ 100 = \%Disassociation$

$1.62 \times 10^{-3}\ M / 0.20\ M\ X\ 100 =$ **0.812%**

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4.2.4: Reactions of Carboxylic Acids - An Overview

Objectives

After completing this section, you should be able to identify the four types of reaction which a carboxylic acid can undergo.

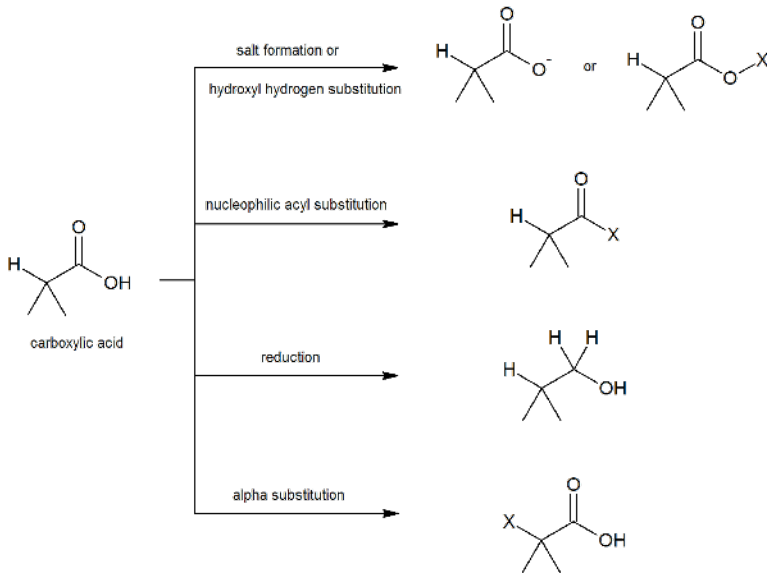
Study Notes

You may wish to review Section 17.4 which discusses reduction of carbonyl compounds to form alcohols and Sections 20.2–20.4 which highlights the acidity of carboxylic acids, which is important to salt formation and substitution of the hydroxyl hydrogen. Nucleophilic acyl substitution (Chapter 21) and alpha substitutions (Chapter 22) are discussed later in more detail.

Four Categories of Carboxylic Acid Reactions

Carboxylic acid reactions are typically classified into four major categories:

1. As carboxylic acids are easily deprotonated, they readily form a carboxylate salt which can then potentially be reacted with an electrophile to complete a substitution of the hydroxyl hydrogen.
2. Nucleophilic acyl substitution reactions allow substitution of the hydroxyl group which leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). We will see these reactions in more detail in Chapter 21.
3. Like other carbonyl compounds, carboxylic acids can be reduced by reagents such as $LiAlH_4$.
4. While the proton on the carbon alpha to the carbonyl group is not as acidic as the hydroxyl hydrogen, it can be removed leading to substitution at the alpha position. The scheme summarizes some of the general reactions that carboxylic acids undergo.

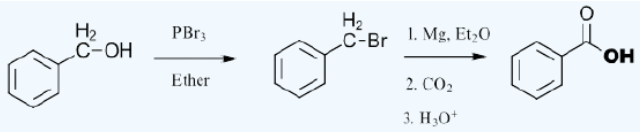


Exercise 4.2.4.1

Show how the following transformation can be performed. Multiple steps may be required.

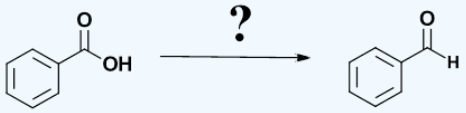


Answer

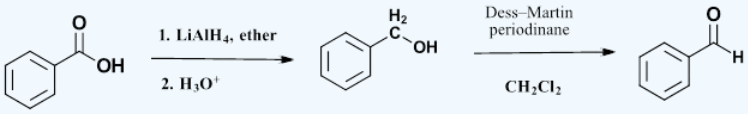


? Exercise 4.2.4.2

Show how the following transformation can be performed. Multiple steps may be required.



Answer



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4.2.5: Chemistry of Esters

Objectives

After completing this section, you should be able to

1. discuss the wide occurrence of esters in nature, and their important commercial uses, giving one example of an ester linkage in nature, and one example of a commercially important ester.
2. write an equation to describe the hydrolysis of an ester under acidic or basic conditions.
3. identify the products formed from the hydrolysis of an given ester.
4. identify the reagents that can be used to bring about ester hydrolysis.
5. identify the structure of an unknown ester, given the products of its hydrolysis.
6. write the mechanism of alkaline ester hydrolysis.
7. write the mechanism of acidic ester hydrolysis.
8. write an equation to describe the reduction of an ester with lithium aluminum hydride.
9. identify the product formed from the reduction of a given ester (or lactone) with lithium aluminum hydride.
10. identify the ester, the reagents, or both, that should be used to prepare a given primary alcohol.
11. write a detailed mechanism for the reduction of an ester by lithium aluminum hydride.
12. identify diisobutylaluminum hydride as a reagent for reducing an ester to an aldehyde, and write an equation for such a reaction.
13. write an equation to describe the reaction of an ester with a Grignard reagent.
14. identify the product formed from the reaction of a given ester with a given Grignard reagent.
15. identify the ester, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
16. write a detailed mechanism for the reaction of an ester with a Grignard reagent.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- lactone
- saponification

Study Notes

Many esters have characteristic aromas and flavours. Some examples are listed below.

Basic structure:

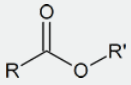
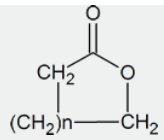


Table 21.1 Structures and characteristic odours of selected esters

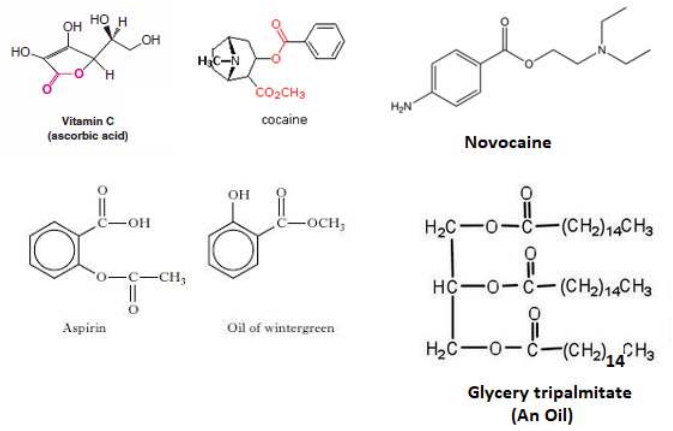
IUPAC name	R	R′	Aroma
octyl ethanoate	CH_3	$CH_3(CH_2)_6CH_2$	orange
propyl ethanoate	CH_3	$CH_3CH_2\ CH_2$	pear
2-methylpropyl propanoate	CH_3CH_2	$(CH_3)_2CHCH_2$	rum
methyl butanoate	$CH_3CH_2CH_2$	CH_3	apple
ethyl butanoate	$CH_3CH_2CH_2$	CH_3CH_2	pineapple

A “lactone” is a cyclic ester and has the general structure

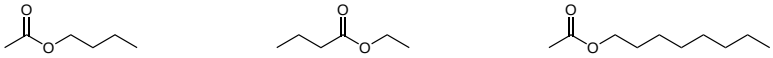


By recognizing that the steps in the acidic hydrolysis of an ester are exactly the same as those in a Fischer esterification (but in the reverse order!), you can again minimize the amount of memorization that you must undertake. The details of both mechanisms can be deduced from the knowledge that both reactions are acid-catalyzed nucleophilic acyl substitutions.

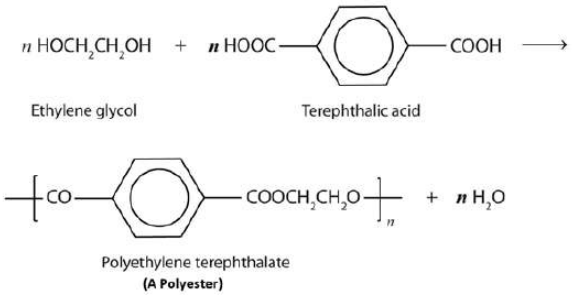
Esters are present in a many biologically important molecules, which have a wide range of effects including fats, waxes, Vitamin C, Cocaine, Novacaine, oil of wintergreen, and aspirin.



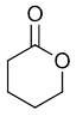
Esters compounds are often the source of the pleasant aromas of many fruits.



Esters are also present in a number of important commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers. PET is used to make bottles for water and other beverages. It is also formed into films called Mylar which is used in balloons. Synthetic arteries can be made from PET, polytetrafluoroethylene (PTFE), and other polymers.



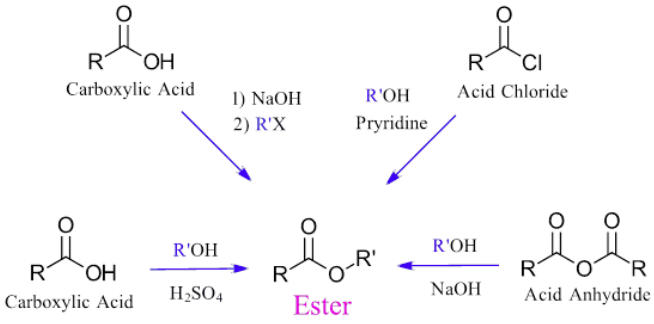
Lactones, cyclic esters, have similar reactivity as acyclic esters.



Lactone
(Cyclic Ester)

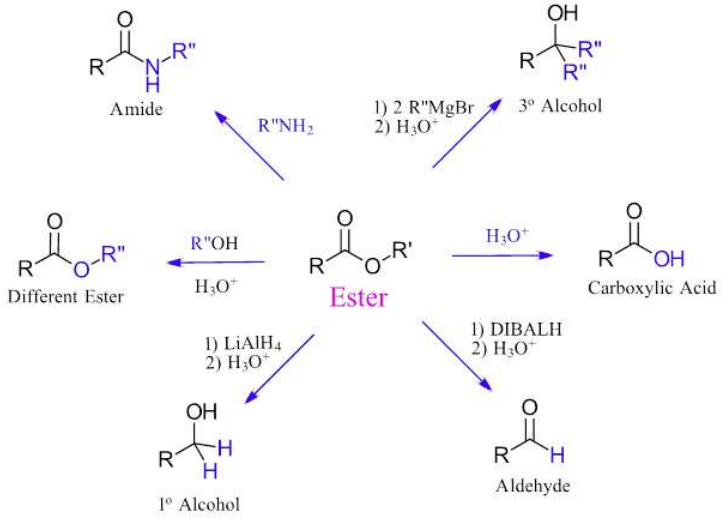
Preparation of Esters

The most versatile method for the preparations of esters is the nucleophilic acyl substitution of of an acid chloride with an alcohol. Acid ahydrides and carboxylic acids can also react with alcohols to form esters but both reactions are limited to formation of simple esters. Esters can also be formed by deprotonating a carboxylic acid to form a carboxylate and then reacting it with a primary alkyl halide using an S_N2 reaction.



Reactions of Esters

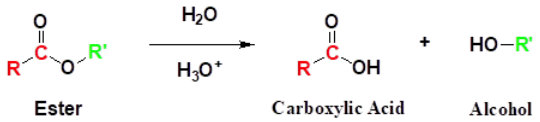
Esters are one of the more useful functional groups. Their low reactivity makes the easy to work with and they are stable enough to be used as a solvent in organic reactions (ex. ethyl acetate). Esters are still reactive enough to undergo hydrolysis to form carboxylic acids, alcoholysis, to form different esters, and aminolysis to form amides. Also, they can react with Grignard reagents to form 3º alcohols and hydride reagents to form 1º alcohols or aldehydes.



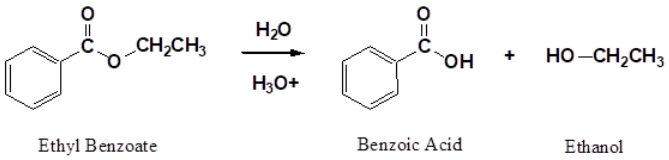
Conversion of Esters to Carboxylic Acids: Hydrolysis

Esters can be cleaved back into a carboxylic acid and an alcohol through reaction with water and a catalytic amount of strong acid. This reaction represents the reverse of the acid catalyzed esterification of a carboxylic acid and an alcohol discussed in Section 21.3. Both the ester formation and cleavage reactions are part of an equilibrium which can be manipulated using Le Chatelier's principle. For ester hydrolysis, the equilibrium is shifted toward carboxylic acid formation by using a large excess of water in the reaction.

General Reaction



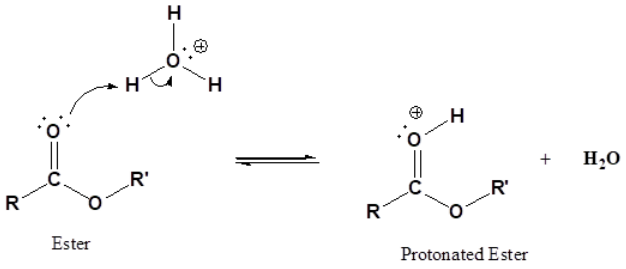
Example



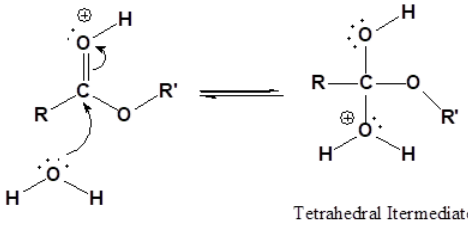
Mechanism

Acid catalysis is required during ester hydrolysis due to water being a weak nucleophile. Protonation of the ester carbonyl increases the partial positive charge on the carbonyl carbon increasing its electrophilicity. After protonation, water adds to the carbonyl carbon causing the formation of a tetrahedral alkoxide intermediate. Then a proton transfers to the –OR group, increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an alcohol (HOR) as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, water acts as a base, removing a hydrogen, to form a carboxylic acid and regenerating the acid catalyst.

1) Protonation of the carbonyl



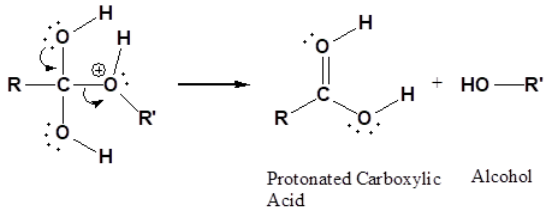
2) Nucleophilic attack by water



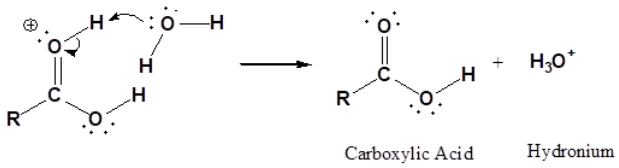
3) Proton transfer



4) Leaving group removal

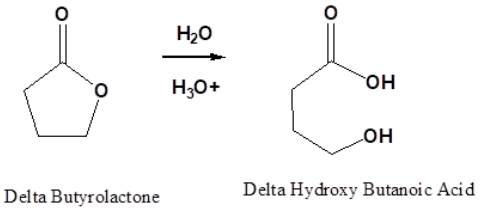


5) Deprotonation



Hydrolysis of Lactones

Lactones (Cyclic esters) undergo typical reactions of esters including hydrolysis. Hydrolysis of the lactone under acidic conditions creates a hydroxyacid.

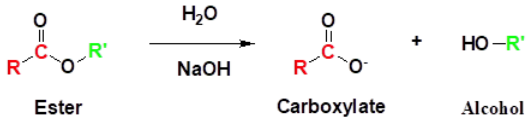


Conversion of Esters to Carboxylic Acids: Saponification

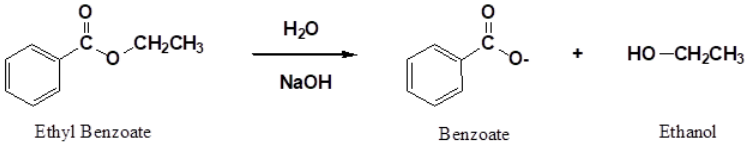
Esters can also be cleaved into a carboxylate and an alcohol through reaction with water and a base. The reaction is commonly called a saponification from the Latin sapo which means soap. This name comes from the fact that soap used to me made by the ester hydrolysis of fats.

Saponification reaction utilize a better nucleophile (hydroxide) and are typically faster than an acid catalyzed hydrolysis. The carboxylation ions produced by saponification are negatively charged and very unreactive toward further nucleophilic substitution which makes the reaction irreversible.

General Reaction



Example

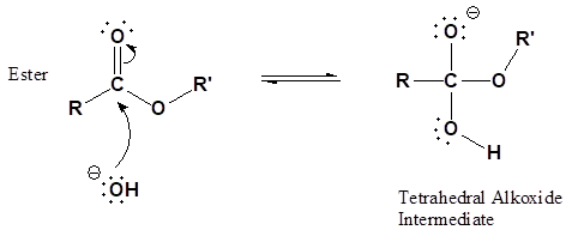


Mechanism

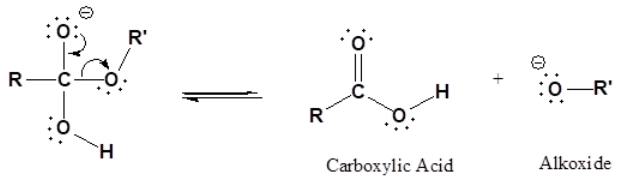
The base-promoted hydrolysis of an ester follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of ester saponification begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon to give a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an alkoxide (-OR) leaving group yielding a carboxylic acid. The alkoxide base deprotonates the carboxylic acid to for a carboxylate salt and an alcohol as products.

The last deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the saponification towards completion. Because the carboxylic acid is no longer part of the equilibrium the reaction is effectively irreversible.

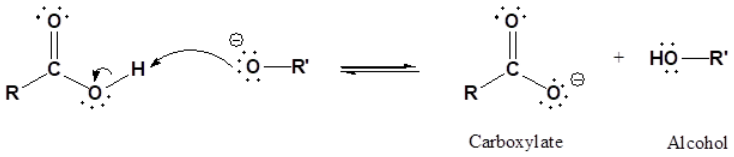
1) Nucleophilic attack by hydroxide



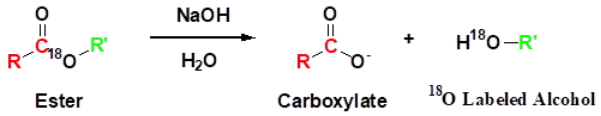
2) Leaving group removal



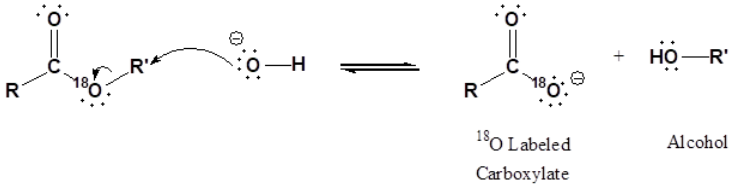
3) Deprotonation



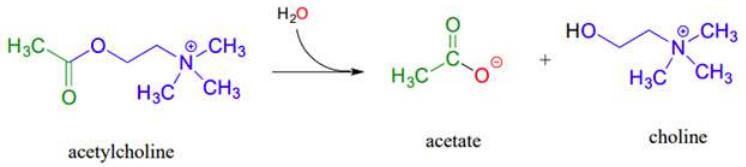
This mechanism is supported by experiments performed using isotopically labeled esters. When the ether-type oxygen of the ester was labeled with ^{18}O, the labeled oxygen showed up in the alcohol product after hydrolysis.



An alternative mechanism would be if the hydroxide participated in an S_N2 reaction to create the carboxylate product. If this were to happen the alcohol reaction product would not contain the labeled oxygen.



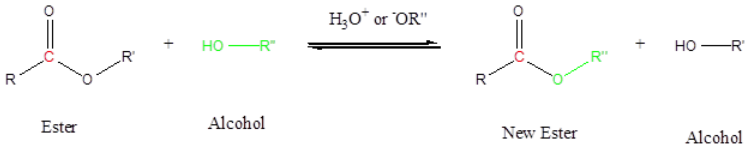
Ester saponification in biological systems, called hydrolytic acyl substitution reactions, are common. In particular, acetylcholinesterase, an enzyme present in the synapse, catalyzes hydrolysis of the ester group in acetylcholine which is a neurotransmitter that triggers muscle contraction. Like many other hydrolytic enzymes, the acetylcholinesterase reaction proceeds in two phases: first, a covalent enzyme-substrate intermediate is formed when the acyl group of acetylcholine is transferred to an active-site serine on the enzyme (a transesterification reaction). A water nucleophile then attacks this ester, driving off acetate and completing the hydrolysis



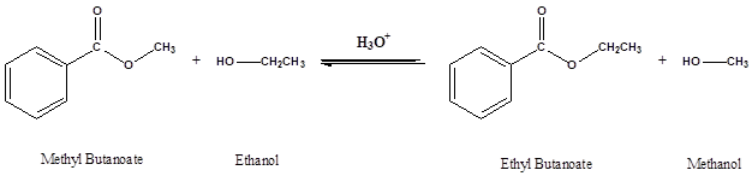
Conversion of Esters to Different Esters: Transesterification

Transesterification is a reaction where an ester is converted to a different ester through reaction with an alcohol. Because there is typically very little difference in stability between both esters, the equilibrium constant of this reaction is usually near one. Using a large excess of the reactant alcohol or removing the alcohol side-product can push the reaction equilibrium towards the products by Le Chatelier's principal. Transesterifications also shows that great care should be taken when an ester containing compound is used in a reaction involving an alcohol.

General Reaction



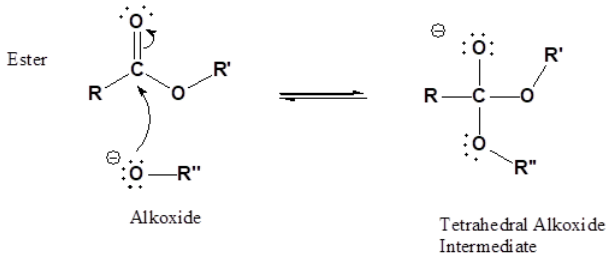
Example



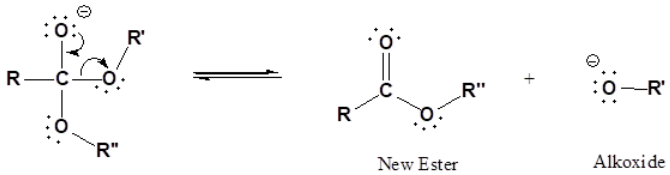
Mechanism in Basic Conditions

The reaction follows the basic mechanism of a nucleophilic acyl substitution. The alkoxide leaving group of the ester is replace by an incoming alkoxide nucleophile creating a different ester.

1) Nucleophilic attack by an alkoxide



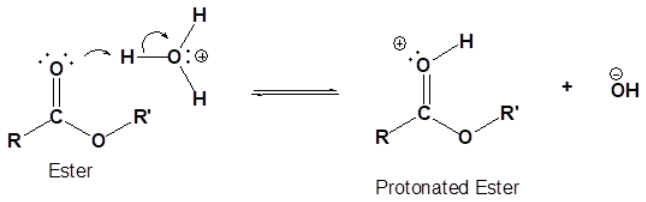
2) Leaving group removal



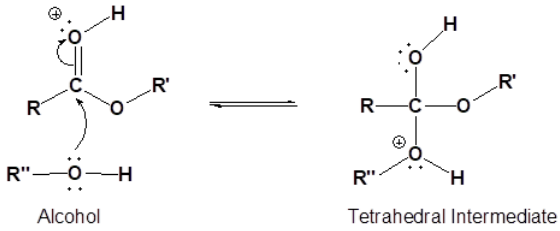
Mechanism in Acidic Conditions

Protonation allows the alcohol reactant to add to the ester carbonyl. Proton transfer to the ester's alkoxy group increases it ability to act as a leaving group. Reforming the C=O carbonyl bond removes the leaving group and subsequent deprotonation by water forms the ester product.

1) Protonation of the carbonyl



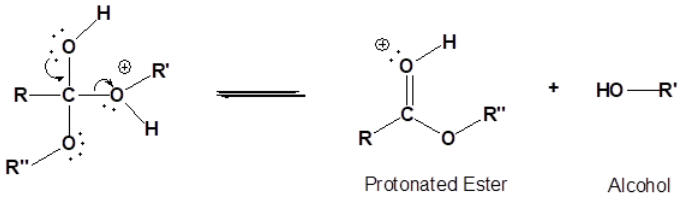
2) Nucleophilic attack on the carbonyl



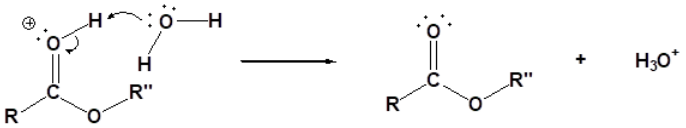
3) Proton transfer



4) Removal of the leaving group

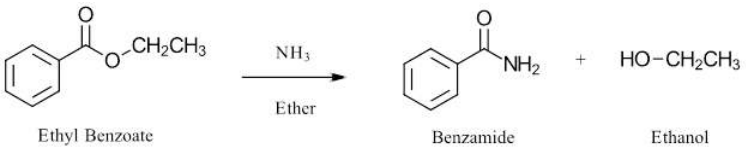


5) Deprotonation



Conversion of Ester to Amides: Aminolysis

It is possible to convert esters to amides through direct reaction with ammonia or amines. However, these reactions are not commonly used because the formation of an amide using an acid chloride is a much simpler reaction.

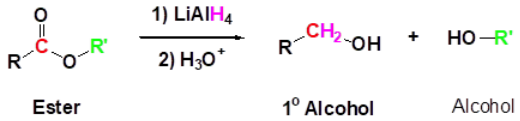


Conversion of Esters to 1° Alcohols: Hydride Reduction

Esters can undergo hydride reduction with $LiAlH_4$ to form two alcohols. The alcohol derived from the acyl group of the ester will be 1° and is typically considered the main product of the reaction. The other alcohol is derived from the ester's alkoxy group and is typically considered a side-product of the reaction. Note! Sodium borohydride ($NaBH_4$) is not a reactive enough hydride agent to

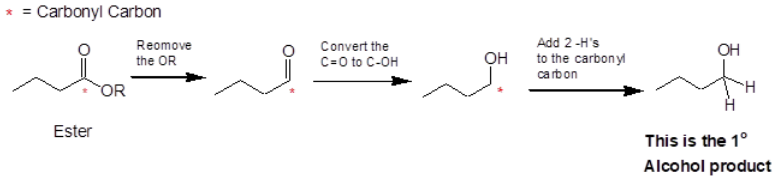
reduce esters or carboxylic acids. In fact, $NaBH_4$ can selectively reduce aldehydes and ketones in the presence of ester functional groups.

General Reaction

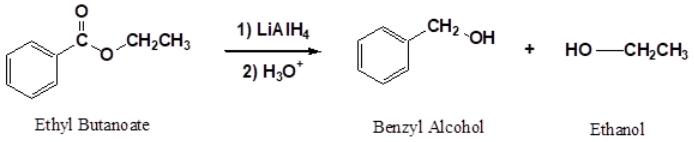


Predicting the Products of a Hydride Reduction

There are three major changes in bonding during this reaction: 1) The –OR leaving group is removed from the ester. 2) The C=O carbonyl bond is converted to a C-O-H, an alcohol. 3) Two C-H bonds are formed as two of the hydride nucleophiles are added to the original carbonyl carbon of the ester.



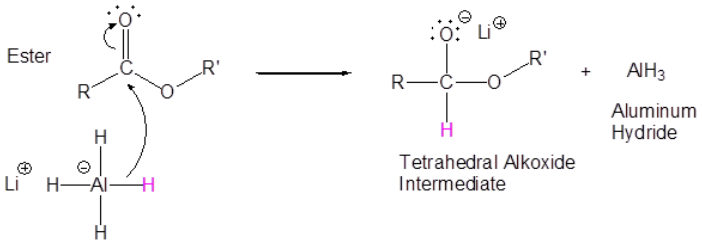
Example



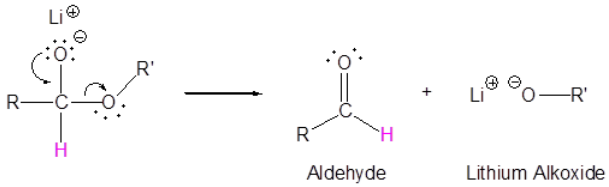
Mechanism

The mechanisms for the hydride reduction of esters is analogous to the hydride reduction of carboxylic acids. Nucleophilic acyl substitution replaces the –OR leaving group in ester with a hydride nucleophile to form an aldehyde intermediate. Because aldehydes are more reactive than esters, they rapidly undergo a second nucleophilic hydride addition to form a tetrahedral alkoxide intermediate. An acid work-up protonates the alkoxide to create a 1° alcohol.

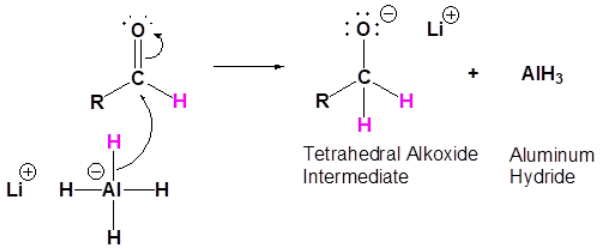
1) Nucleophilic attack by the hydride



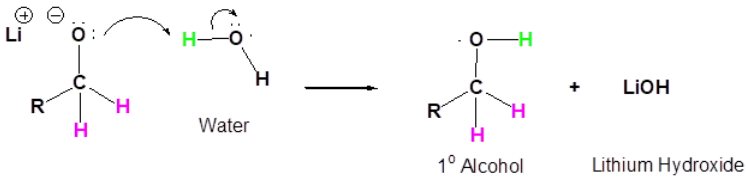
2) Leaving Group Removal



3) Nucleopilic attack by the hydride anion



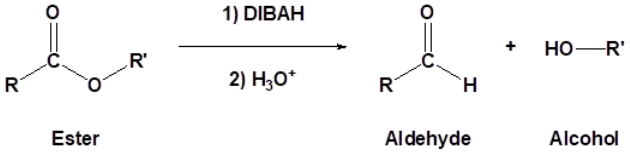
4) The alkoxide is protonated



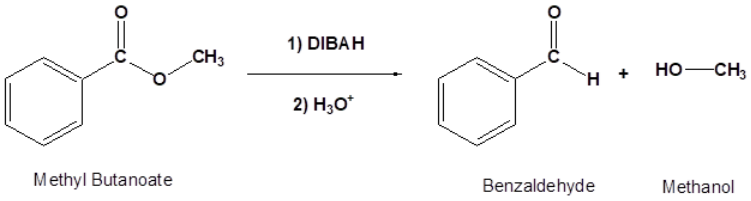
Conversion of Esters to Aldehydes: Hydride Reduction

Much like acid chlorides, esters can be converted to aldehydes using the weaker reducing reagent diisobutylaluminum hydride (DIBALH). As shown above, an aldehyde intermediate is produced after an ester undergoes nucleophilic acyl substitution with a hydride. When DIBALH is used as the hydride source, the aldehyde does not react further and is isolated as the product of the reaction. The reaction is usually carried out at -78 ^{o}C to help isolate the aldehyde product.

General Reaction



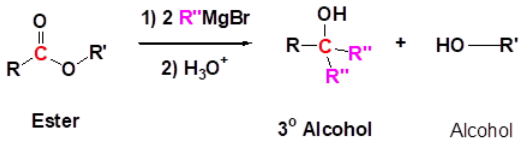
Example



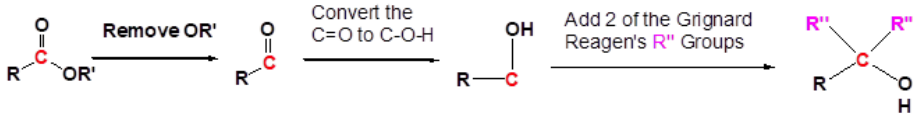
Conversion of Esters to 3° Alcohols: Grignard Reagents

Addition of Grignard reagents converts esters to two alcohols, one 3° alcohols (main product) and one 1° alcohol (considered a side product). The Grignard reagent adds to the ester twice, once during a nucleophilic acyl substitution to form a ketone intermediate then again during a nucleophilic addition to form the 3° alcohol product. Overall, during this reaction two C-C bonds are formed on the ester's original carbonyl carbon.

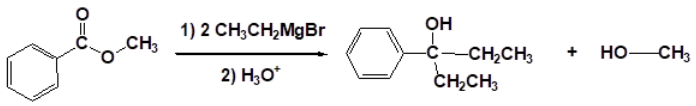
General Reaction



Predicting the Products of a Grignard Reaction



Example

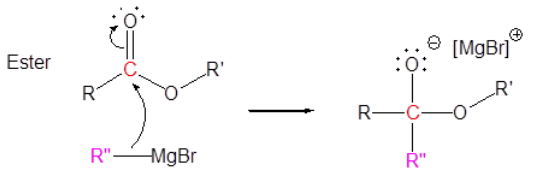


Methyl Benzoate | 3-Phenyl-3-Pentanol | Methanol

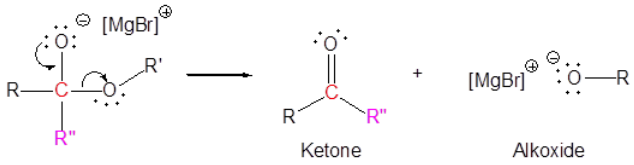
Mechanism

In the first two steps of the mechanism, the OR leaving group from the ester is replaced by the R group from the Grignard reagent through a nucleophilic acyl substitution. This forms a ketone intermediate which is not isolated because ketones, which are more reactive than esters, rapidly undergo nucleophilic addition with a second equivalent of the Grignard reagent to form an alkoxide intermediate. An acid work-up protonates the alkoxide to form the 3º alcohol product.

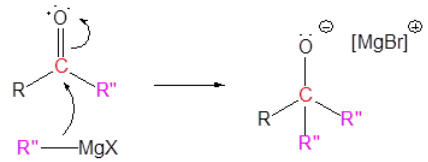
1) Nucleophilic Attack



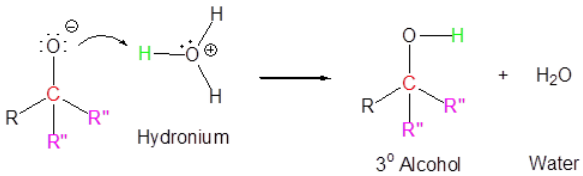
2) Leaving group removal



3) Nucleophilic attack

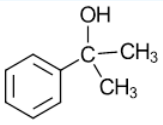


4) Protonation



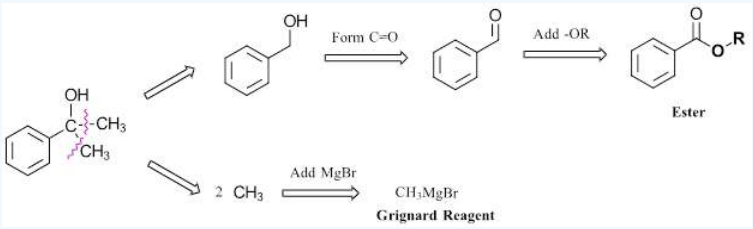
Example 4.2.5.1

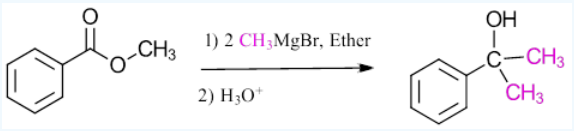
How could the following molecule be made using a Grignard reagent and an ester?



Solution

The key bond breaks for this example are two C-C sigma bonds between the carbonyl carbon and two alpha carbons. Reactions with esters involve a double addition of the Grignard reagent so the fragments removed must be the same. In this example, the C-C bonds involving the two methyl groups are broken. Breaking these bonds separate the target molecule into the required starting materials. The fragment which contains the alcohol carbon forms a C=O carbonyl bond and gains an –OR to become an ester. The R group of the ester is largely unimportant to the overall reaction and is typically a methyl or ethyl group. The alkyl fragments gain MgBr to form a Grignard reagent. Remember that the Grignard reagent only contains one alkyl fragment.

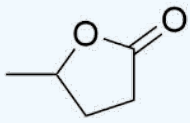




Exercises 4.2.5.1

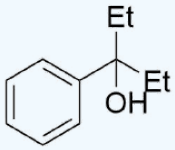
1) Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

2) Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.

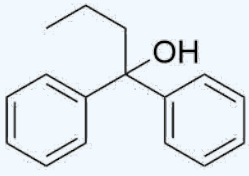


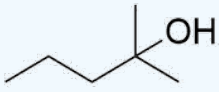
3) How might you Prepare the following molecules from esters and Grignard reagents?

(a)



(b)

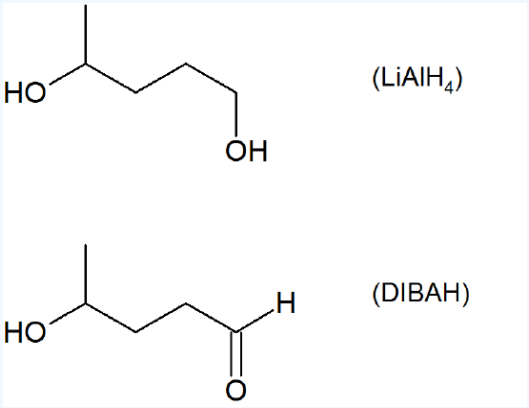


(c) 

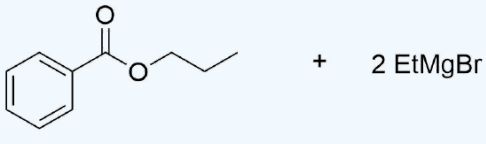
Answers

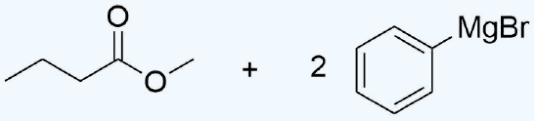
1) The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

2)



3)

(a) 

(b) 

(c)

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4.2.6: Chemistry of Amides

Objectives

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

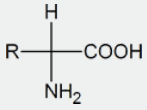
Key Terms

Make certain that you can define, and use in context, the key term below.

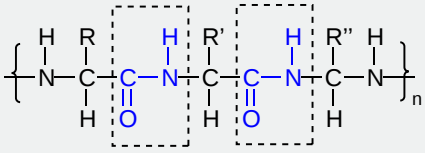
- lactam

Study Notes

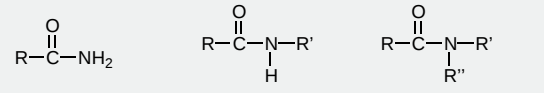
When we talk about amino acids, we are generally referring to α-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:



Notice that such compounds contain a chiral carbon atom (unless R = H, which is glycine). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in *N*-substituted primary amides.

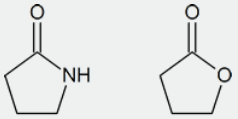


peptide (amide) links



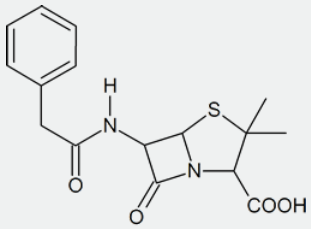
primary amide | *N*—substituted primary amide | *N*, *N*—disubstituted primary amide

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:



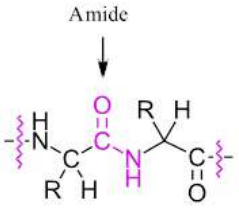
a lactam | a lactone

Among the most important molecules that contain lactam rings are the penicillins:



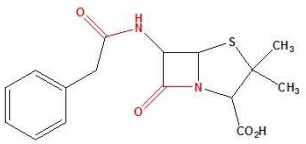
penicillin G (benzylpenicillin)

The amide functional group is extremely important for biological molecules because amides make up the backbone of proteins. Proteins are actually polymers of amino acids, linked by amide groups known as peptide bonds. Proteins (polymers of ~40 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. The individual amino acids within a peptide or protein are called **amino acid residues**.

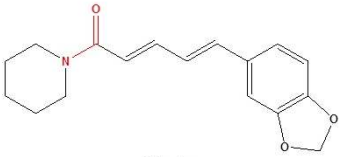


Protein Backbone

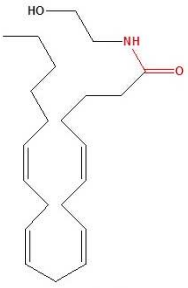
Compounds containing amides have a wide range of biological activity and include penicillin G an antibiotic, piperine which is responsible for the pungent flavor of black pepper, and anandamide which provides some of the pleasurable sensations gained from eating chocolate.



Penicillin G
(An Antibiotic)



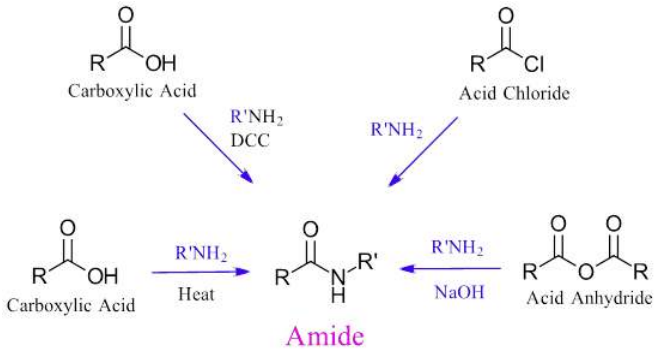
Piperine
(From Black Pepper)



Anandamide
(From Chocolate)

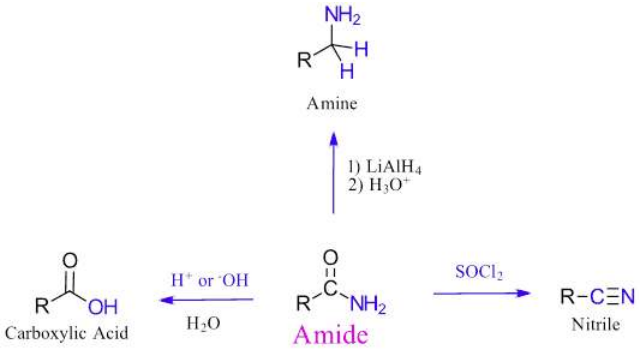
Preparation of Amides

Amides are most commonly prepared though the reaction of an acid chloride with ammonia, a 1º amine, or 2º amine. In an analogous reaction, an amide can be prepared through the reaction of a carboxylic acid and an amine using a coupling agent such as DCC. Simple amides can be prepared by reacting an acid anhydride with an amine. Lastly, amides can be formed through the direct reaction of a carboxylic acid and an amine. However, this reaction is rarely used because the conditions are relatively severe.



Reactions of Amides

Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group. Despite this, amides can react with water under acidic or basic conditions to create a carboxylic acid through nucleophilic acyl substitution. Reaction of primary amides with thionyl chloride ($SOCl_2$) creates nitriles. Hydride reduction using $LiAlH_4$ causes the carbonyl oxygen of the amide to eliminate as a leaving group creating the corresponding amine.



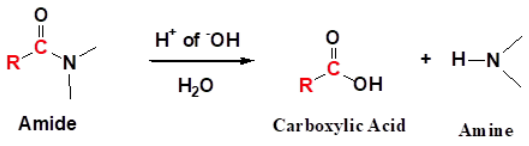
Lactams, cyclic amides, are affected by these reactions in the same fashion as acyclic amides.



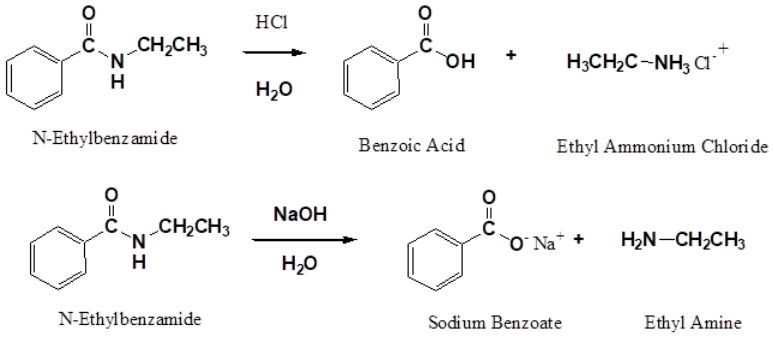
Conversion of Amides to Carboxylic Acids: Hydrolysis

Amides can be hydrolyzed into a carboxylic acid and ammonia or an amine by heating in an acidic or basic aqueous solution. In both cases, acid-base reactions occurring with the products make the overall reaction irreversible. Under acidic conditions the amine produced by the reaction is protonated to form a non-nucleophilic ammonium compound. Under basic conditions the carboxylic acid produced by the reaction is deprotonated to a non-electrophilic carboxylate.

General Reaction



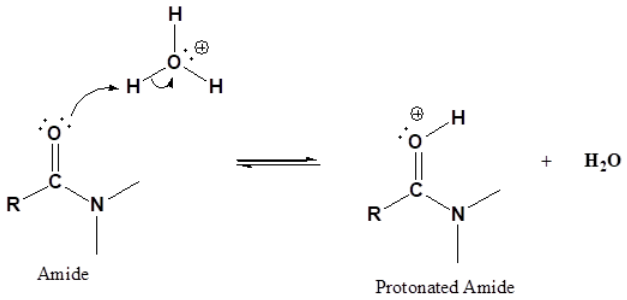
Examples



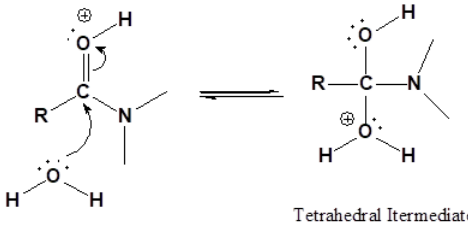
Mechanism Under Acidic Conditions

Protonation of the amide increases the electrophilicity of the carbonyl carbon allowing water to add causing formation of a tetrahedral oxonium intermediate. Next a proton is transferred to the amide nitrogen giving it a positive charge and increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an amine as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, the produced amine acts as a base, removing a hydrogen, to form a carboxylic acid and an ammonium compound. This final deprotonation step essentially removes the amine from the equilibrium which drives the reaction towards completion. Since the amine is no longer part of the equilibrium, the reaction is effectively irreversible.

1) Protonation of the carbonyl



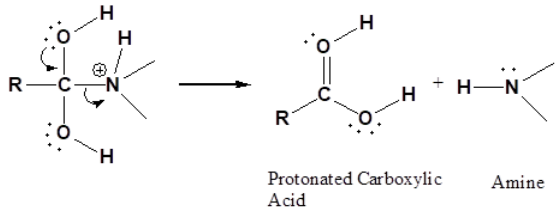
2) Nucleophilic attack by water



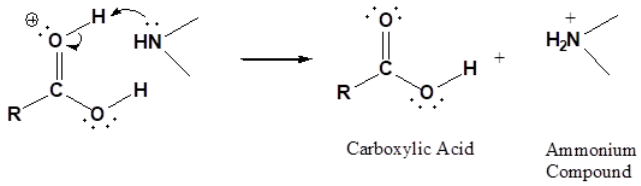
3) Proton transfer



4) Leaving group removal



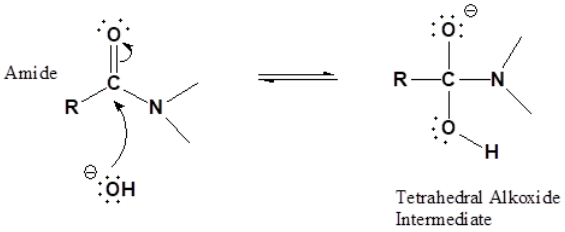
5) Deprotonation



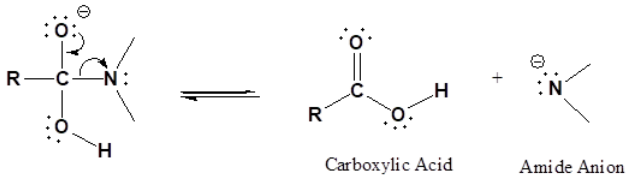
Mechanism Under Basic Conditions

The base-promoted hydrolysis of an amide follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of basic amide hydrolysis begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon creating a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an amide ion (-NHR) leaving group (note this is a different use of the word amide meaning an amine anion), forming a carboxylic acid. In the last step, the amide ion deprotonates the carboxylic acid to form a carboxylate salt and an amine as products. This final deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the reaction towards completion. Since the carboxylic acid is no longer part of the equilibrium, the reaction is effectively irreversible.

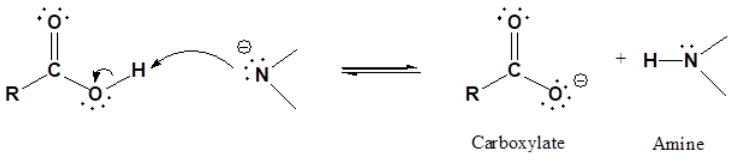
1) Nucleophilic attack by hydroxide



2) Leaving group removal



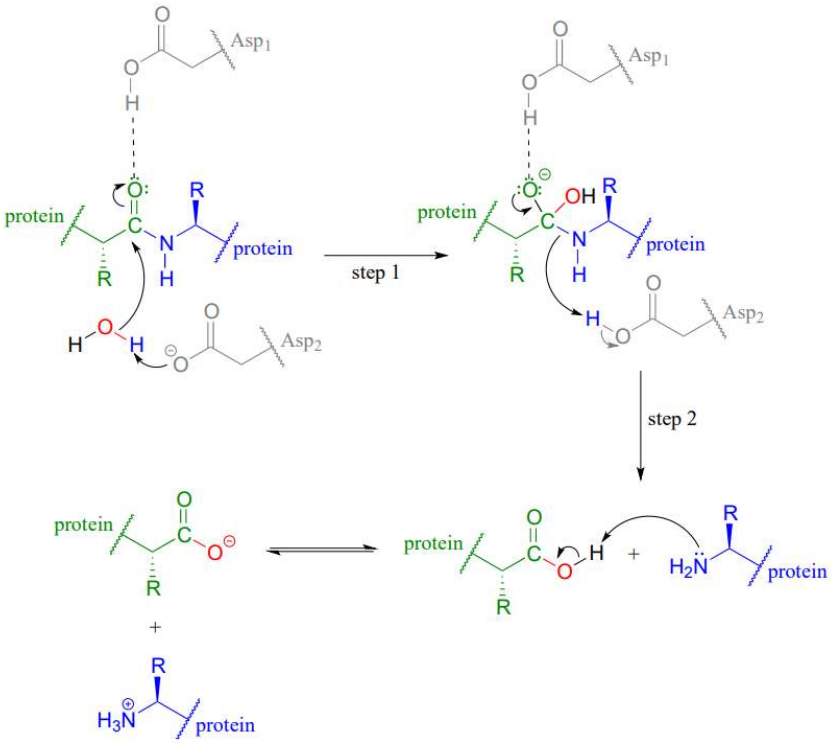
3) Deprotonation



Hydrolysis of Proteins

Hydrolysis of amide bonds is the first step in the metabolism of dietary proteins. Protein hydrolysis is catalyzed by protease enzymes (abbreviated Asp_1 and Asp_2 in the figure below). The mechanisms starts with the nucleophilic acyl substitution by water

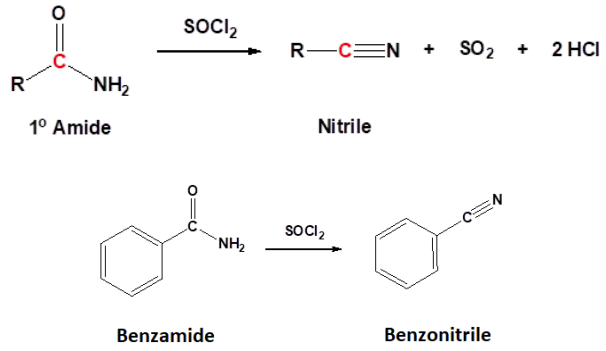
while breaking the amide C-N bond. This produces a protein fragment with an amine and another with a carboxylic acid. The amine fragment will deprotonate the carboxylic acid forming the carboxylate and ammonium fragments.



Conversion of 1° Amides to Nitriles: Dehydration

1° Amides can be converted into a nitrile through reaction with thionyl chloride ($SOCl_2$). Sulfurdioxide (SO_2) and hydrochloric acid are produced as byproducts.

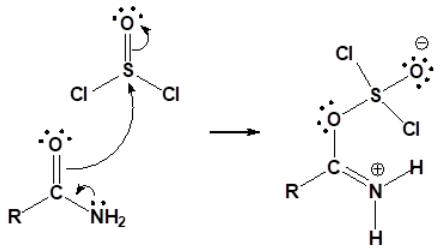
General Reaction



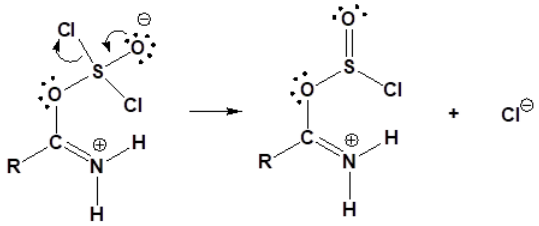
Mechanism for the Conversion of a 1° Amide to a Nitrile

During the first step of the mechanism, the amide acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Removal of a chloride anion as a leaving group allows the sulfoxide S=O bond to reform creating a protonated imine chlorosulfite. Deprotonation forms an imine chlorosulfite intermediate. A second deprotonation eliminates the chlorosulfite leaving group as sulfur dioxide and a chloride anion and forms the C-N triple bond of the nitrile product.

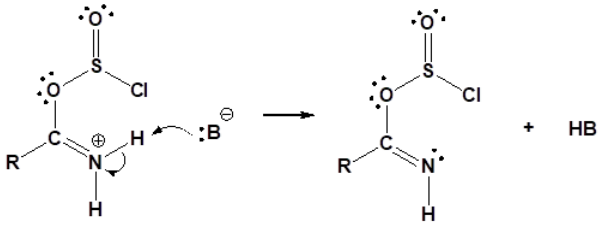
1) Nucleophilic attach on thionyl chloride



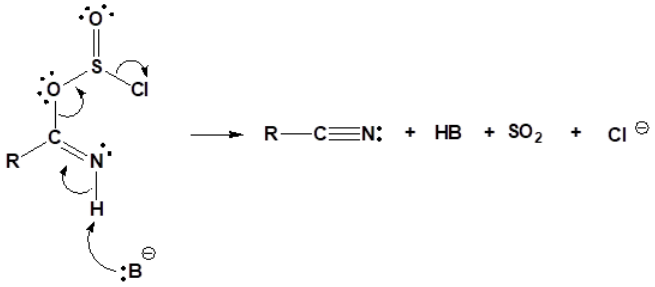
2) Leaving group removal



3) Deprotonation



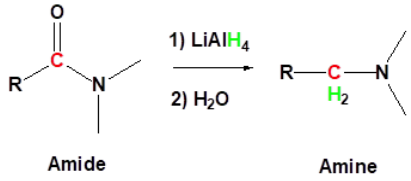
4) Leaving group removal



Conversion of Amides to 1º, 2º or 3º Amines: Hydride Reduction

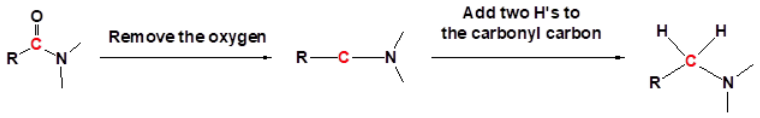
Amides are reduced to amines by treatment with $LiAlH_4$, and this has proven to be one of the most general methods for preparing all classes of amines (1º, 2º & 3º). Due to the nitrogen in the Y group of amides, the outcome of $LiAlH_4$ reductions is distinctly different than for esters since amide anions are poorer leaving groups than alkoxide anions. Furthermore, oxygen forms especially strong bonds to aluminum. During this reaction the carbonyl oxygen of the amide is removed as a leaving group and not the nitrogen containing Y group. Removal of the leaving group allows for a formation of a C=N iminium bond which can accept a second addition of a hydride nucleophile to form the amine.

General Reaction

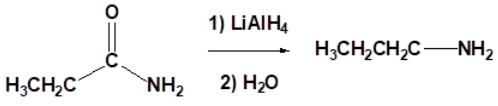


Predicting the Products of a Hydride Reduction

There are two major changes in bonding during this reaction: 1) The C=O carbonyl is removed from the starting material 2) Two hydride nucleophiles are added to what was the carbonyl carbon of the amide.

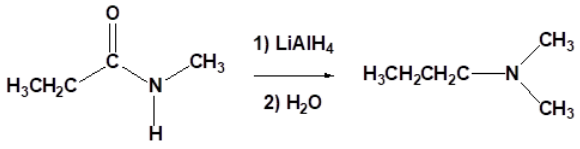


Example

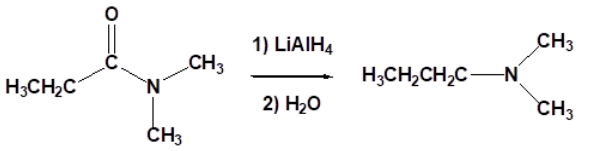


Propanamide — Propyl Amine

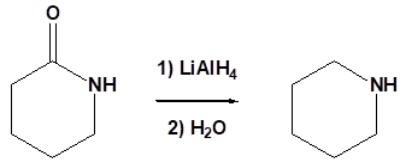
Alkyl groups attached to the nitrogen do not affect the reaction.



N-Methylpropanamide — N-Methylpropylamine



N,N-Dimethylpropanamide — N,N-Dimethylpropylamine

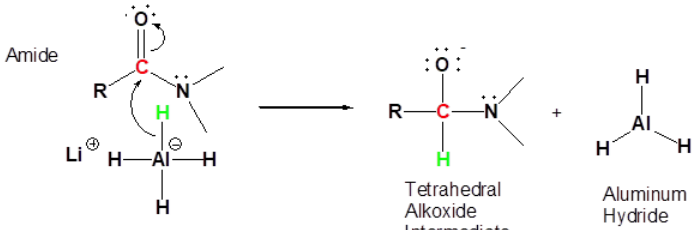


δ-Valerolactam — Piperidine

Mechanism for the Hydride Reduction of an Amide to Form an Amine

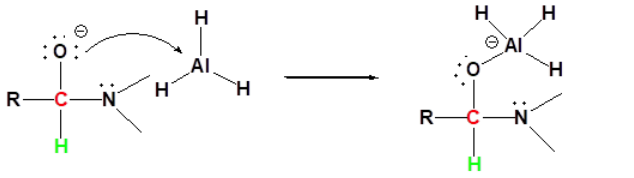
Addition of a hydride nucleophile to the carbonyl carbon of the amide produces a tetrahedral alkoxide intermediate. A Lewis acid-base interaction occurs between the alkoxide (Lewis Base) and AlH_3 (Lewis acid) forming a complex with an O-Al bond. The nitrogen lone pair forms a double bond with the previous carbonyl carbon ejecting a metal oxide species (e.g. $[H3Al–O]^{2–}$) as a leaving group, and while forming an iminium double bond. Addition of a second equivalent of hydride nucleophile to the iminium carbon produces an amine.

1) Nucleophilic attack by the hydride

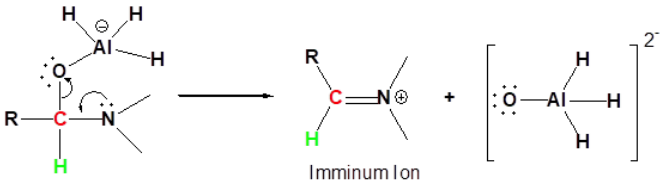


Lithium Aluminum Hydride — Tetrahedral Alkoxide Intermediate — Aluminum Hydride

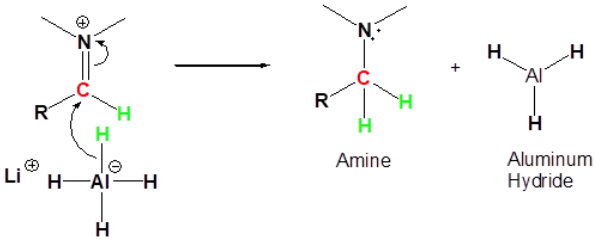
2) Complex formation



3) Leaving group removal

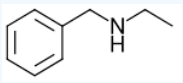


4) Nucleophilic attach by the hydride



Example 4.2.6.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



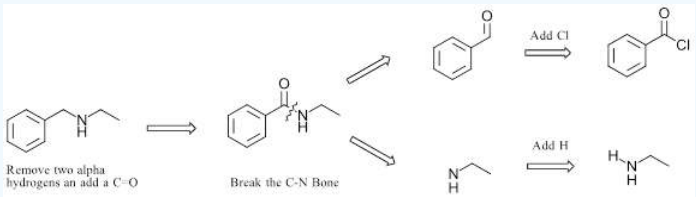
Answer

One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

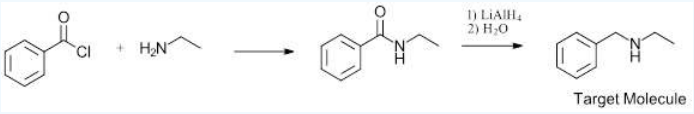
In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1° amine. In the forward reaction pathway, the acid chloride and the 1° amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

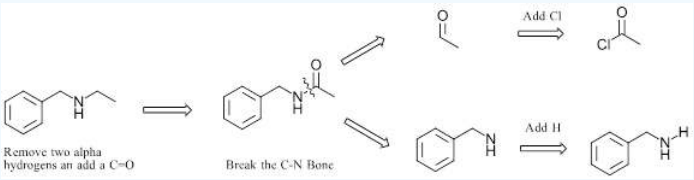
Pathway 1



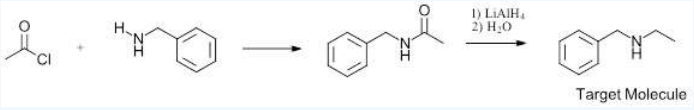
Solution 1



Pathway 2



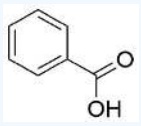
Solution 2



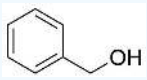
Exercise 4.2.6.1

1) How would you prepare the following compounds from N-Propypl benzamide?

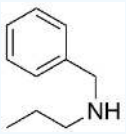
(a)



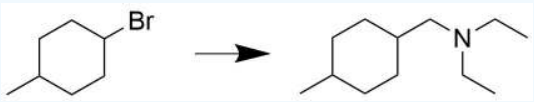
(b)



(c)



2) Propose a synthesis pathway for the following conversion:



Answer

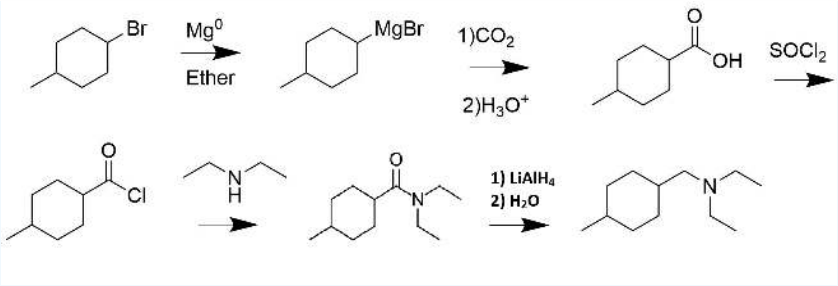
1) (a) NaOH, H_2O

(b) NaOH, H_2O, then $LiAlH_4$

(c) $LiAlH_4$

2)

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CHAPTER OVERVIEW

5: Biomolecules

5.1: Biomolecules- Carbohydrates

5.1.1: Introduction

5.1.2: Classification of Carbohydrates

5.1.3: Depicting Carbohydrate Stereochemistry - Fischer Projections

5.1.4: D, L Sugars

5.1.5: Configurations of Aldoses

5.1.6: Cyclic Structures of Monosaccharides - Anomers

5.1.7: Reactions of Monosaccharides

5.1.8: The Eight Essential Monosaccharides

5.1.9: Disaccharides

5.1.10: Polysaccharides and Their Synthesis

5.1.11: Other Important Carbohydrates

5.1.12: Cell-Surface Carbohydrates and Influenza Viruses

5.1.S: Biomolecules- Carbohydrates (Summary)

5.2: Biomolecules- Amino Acids, Peptides, and Proteins

5.2.1: Introduction

5.2.2: Structures of Amino Acids

5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points

5.2.4: Synthesis of Amino Acids

5.2.5: Peptides and Proteins

5.2.6: Amino Acid Analysis of Peptides

5.2.7: The Edman Degradation

5.2.8: Peptide Synthesis

5.2.9: The Merrifield Solid-Phase Technique

5.2.10: Protein Structure

5.2.11: Enzymes and Coenzymes

5.2.12: How do Enzymes Work? Citrate Synthase

5.3: Biomolecules - Lipids

5.3.1: Introduction to Lipids

5.3.2: Waxes, Fats, and Oils

5.3.3: Soap

5.3.4: Phospholipids

5.3.5: Prostaglandins and Other Eicosanoids

5.3.6: Terpenoids

5.3.7: Steroids

5.3.8: Biosynthesis of Steroids

5.3.S: Biomolecules - Lipids (Summary)

5.4: Biomolecules - Nucleic Acids

5.4.1: Nucleotides and Nucleic Acids

5.4.2: Base Pairing in DNA - The Watson-Crick Model
5.4.3: Replication of DNA
5.4.4: Transcription of DNA
5.4.5: Translation of RNA - Protein Biosynthesis
5.4.6: DNA Sequencing
5.4.7: DNA Synthesis
5.4.8: The Polymerase Chain Reaction

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SECTION OVERVIEW

5.1: Biomolecules- Carbohydrates

This chapter is designed to provide you with an overview of the biologically important group of compounds known as carbohydrates. Many of the compounds you will encounter while studying this chapter may appear to have very complex structures, but much of their chemistry can be readily understood in terms of the concepts and reactions discussed in earlier chapters of the course.

The chapter begins with an explanation of the classification schemes used to simplify the study of carbohydrates. We make extensive use of Fischer projection formulas throughout the chapter. We place considerable emphasis on gaining an appreciation of the configurations of carbohydrates, particularly of the aldoses. We describe the disadvantages of representing monosaccharides by open-chain structures, and at this point, introduce you to cyclic representations—called Haworth projections—of these substances. We describe the mutarotation of glucose, explaining it in terms of the existence of anomers. We then examine some reactions of monosaccharides, including the formation of ethers and esters, the formation of glycosides, and reduction and oxidation. We discuss the structures of some common disaccharides and polysaccharides, and conclude the chapter with a brief explanation of the role played by carbohydrates in cell recognition.

5.1.1: Introduction

5.1.2: Classification of Carbohydrates

5.1.3: Depicting Carbohydrate Stereochemistry - Fischer Projections

5.1.4: D, L Sugars

5.1.5: Configurations of Aldoses

5.1.6: Cyclic Structures of Monosaccharides - Anomers

5.1.7: Reactions of Monosaccharides

5.1.8: The Eight Essential Monosaccharides

5.1.9: Disaccharides

5.1.10: Polysaccharides and Their Synthesis

5.1.11: Other Important Carbohydrates

5.1.12: Cell-Surface Carbohydrates and Influenza Viruses

5.1.S: Biomolecules- Carbohydrates (Summary)

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5.1.1: Introduction

Objectives

After completing this section, you should be able to

1. identify carbohydrates (sugars) as being polyhydroxylated aldehydes and ketones.
2. describe, briefly, the process of photosynthesis, and identify the role played by carbohydrates as an energy source for living organisms.

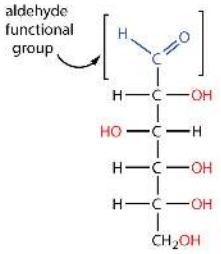
Key Terms

Make certain that you can define, and use in context, the key term below.

- carbohydrate

Introduction

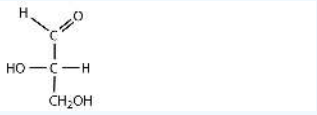
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. The term *carbohydrate* had its origin in a misinterpretation of the molecular formulas of many of these substances. For example, because its formula is $C_6H_{12}O_6$, glucose was once thought to be a "carbon hydrate" with the structure $C_6 \cdot 6H_2O$.

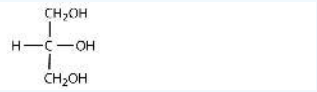
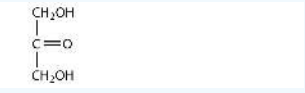
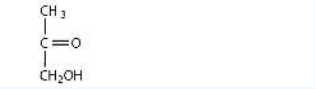


Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

Example 1

Which compounds would be classified as carbohydrates?

a. 

- 
- 
- 

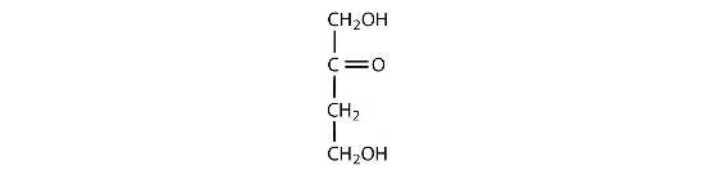
Solution

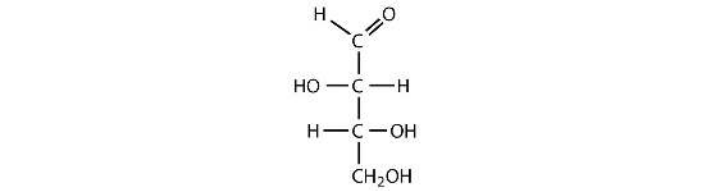
a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.

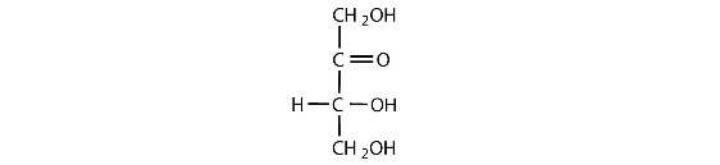
c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.
d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

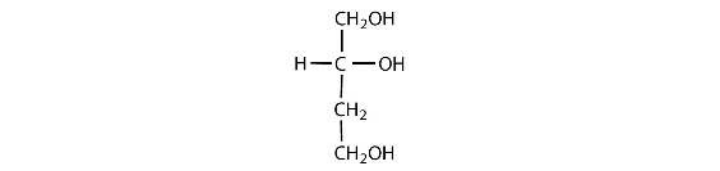
? Exercise 1

Which compounds would be classified as carbohydrates?

1. 

- 

- 

- 

Green plants are capable of synthesizing glucose ($C_6H_{12}O_6$) from carbon dioxide (CO_2) and water (H_2O) by using solar energy in the process known as photosynthesis:

$$6\,CO_2 + 6\,H_2O + 2870\,kJ \longrightarrow C_6H_{12}O_6 + 6\,O_2$$

(The 2870 kJ comes from solar energy.) Plants can use the glucose for energy or convert it to larger carbohydrates, such as starch or cellulose. Starch provides energy for later use, perhaps as nourishment for a plant's seeds, while cellulose is the structural material of plants. We can gather and eat the parts of a plant that store energy—seeds, roots, tubers, and fruits—and use some of that energy ourselves. Carbohydrates are also needed for the synthesis of nucleic acids and many proteins and lipids.

Animals, including humans, cannot synthesize carbohydrates from carbon dioxide and water and are therefore dependent on the plant kingdom to provide these vital compounds. We use carbohydrates not only for food (about 60%–65% by mass of the average diet) but also for clothing (cotton, linen, rayon), shelter (wood), fuel (wood), and paper (wood).

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5.1.2: Classification of Carbohydrates

Objectives

After completing this section, you should be able to

1. classify a specific carbohydrate as being a monosaccharide, disaccharide, trisaccharide, etc., given the structure of the carbohydrate or sufficient information about its structure.
2. classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.

Key Terms

Make certain that you can define, and use in context, the key terms below.

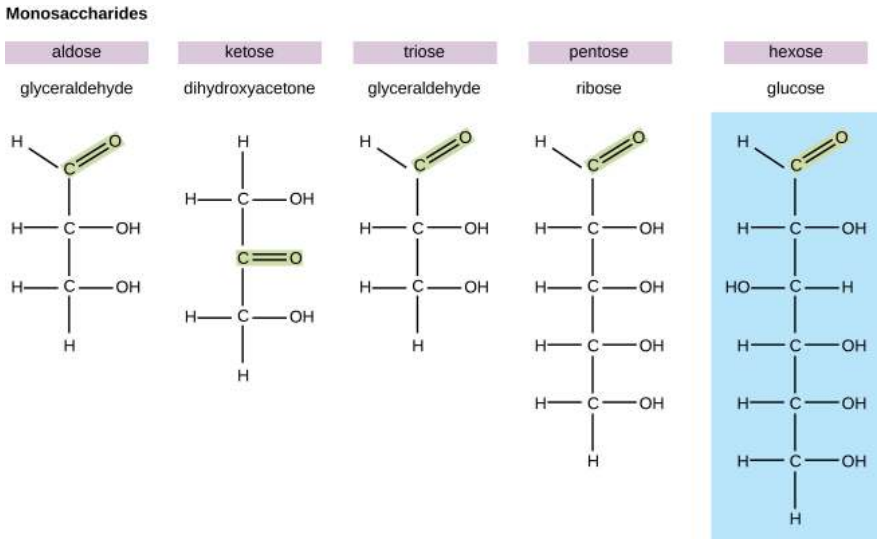
- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

What Are Carbohydrates?

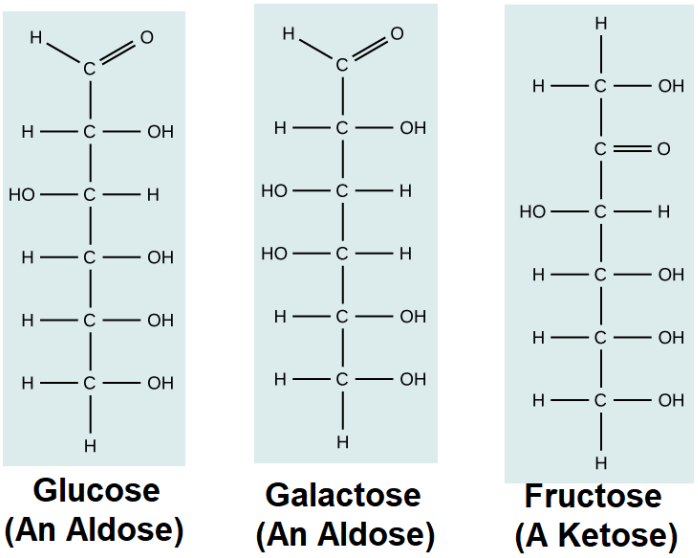
The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as "hydrated" carbon atom chains in which water molecules attach to each carbon atom, leading to the term "carbohydrates." Although all carbohydrates contain carbon, hydrogen, and oxygen, there are some that also contain nitrogen, phosphorus, and/or sulfur. Carbohydrates have myriad different functions. They are abundant in terrestrial ecosystems, many forms of which we use as food sources. These molecules are also vital parts of macromolecular structures that store and transmit genetic information (i.e., DNA and RNA). They are the basis of biological polymers that impart strength to various structural components of organisms (e.g., cellulose and chitin), and they are the primary source of energy storage in the form of starch and glycogen.

Monosaccharides

In biochemistry, carbohydrates are often called saccharides, from the Greek *sakcharon*, meaning sugar, although not all the saccharides are sweet. The simplest carbohydrates are called monosaccharides, or simple sugars. They are the building blocks (monomers) for the synthesis of polymers or complex carbohydrates, as will be discussed further in this section. Monosaccharides are classified based on the number of carbons in the molecule. General categories are identified using a prefix that indicates the number of carbons and the suffix *–ose*, which indicates a saccharide; for example, triose (three carbons), tetrose (four carbons), pentose (five carbons), and hexose (six carbons). The hexose D-glucose is the most abundant monosaccharide in nature. Other very common and abundant hexose monosaccharides are galactose, used to make the disaccharide milk sugar lactose, and the fruit sugar fructose.



A second comparison can be made when looking at glucose, galactose, and **fructose**. All three are hexoses; however, there is a major structural difference between glucose and galactose versus fructose: the carbon that contains the **carbonyl** (C=O). In glucose and galactose, the carbonyl group is on the C_1 carbon, forming an **aldehyde** group. In fructose, the carbonyl group is on the C_2 carbon, forming a **ketone** group. The former sugars are called **aldoses** based on the aldehyde group that is formed; the latter is designated as a **ketose** based on the ketone group. Again, this difference gives fructose different chemical and structural properties from those of the related aldoses, glucose, and galactose, even though fructose, glucose, and galactose all have the same chemical composition: $C_6H_{12}O_6$.



Complex Carbohydrates

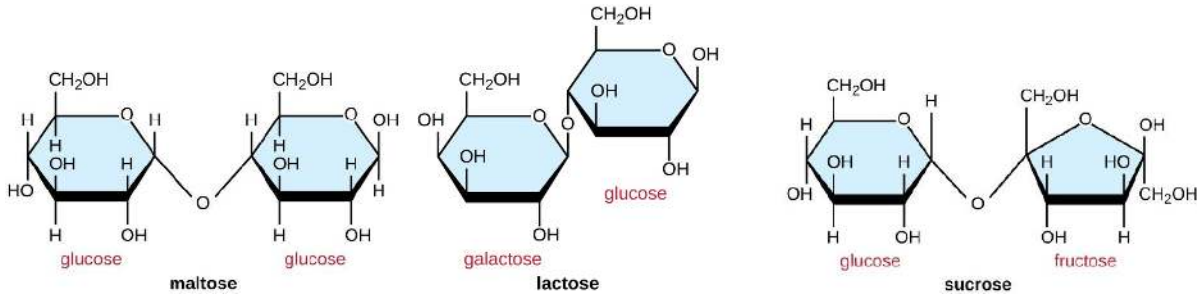
The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

Disaccharides

Two monosaccharide molecules may chemically bond to form a disaccharide. The name given to the covalent bond between the two monosaccharides is a glycosidic bond. Glycosidic bonds form between hydroxyl groups of the **two saccharide molecules**, an example of the dehydration synthesis described later in this chapter.

$$\text{monosaccharide-OH} + \text{HO-monosaccharide} \rightarrow \underbrace{\text{monosaccharide-O-monosaccharide}}_{\text{disaccharide}}$$

Common disaccharides are the grain sugar maltose, made of two glucose molecules; the milk sugar lactose, made of one galactose and one glucose molecule; and the table sugar sucrose, made of one glucose and one fructose molecule.

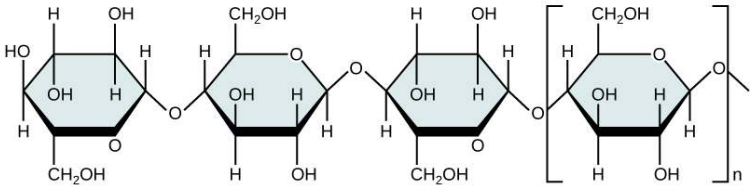


Polysaccharides

Polysaccharides, also called glycans, are large polymers composed of hundreds of monosaccharide monomers. Unlike mono- and disaccharides, polysaccharides are not sweet and, in general, they are not soluble in water. Like disaccharides, the monomeric units of polysaccharides are linked together by glycosidic bonds.

Polysaccharides are very diverse in their structure. Three of the most biologically important polysaccharides—starch, glycogen, and cellulose—are all composed of repetitive glucose units, although they differ in their structure. **Cellulose** consists of a linear chain of glucose molecules and is a common structural component of cell walls in plants and other organisms. **Glycogen** and **starch** are branched polymers; glycogen is the primary energy-storage molecule in animals and bacteria, whereas plants primarily store energy in starch. The orientation of the glycosidic linkages in these three polymers is different as well and, as a consequence, linear and branched macromolecules have different properties.

Cellulose structure

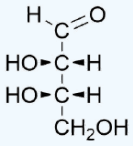


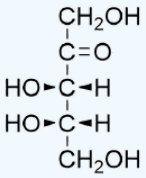
Summary

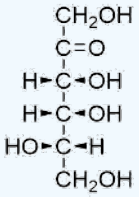
Complexity		**Simple Carbohydrates** monosaccharides		**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides	
Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.
C=O Function			**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.		

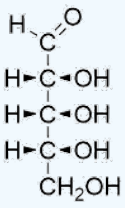
Exercise 5.1.2.1

Classify each of the following sugars.

a. 

b. 

c. 

d. 

Answer

a. Aldoterose
b. Ketopentose
c. Ketohexose
d. Aldopentose

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5.1.3: Depicting Carbohydrate Stereochemistry - Fischer Projections

Objectives

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge and dash structure or a molecular model.
2. draw the wedge and dash structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge and dash structure.

Key Terms

Make certain that you can define, and use in context, the key term below.

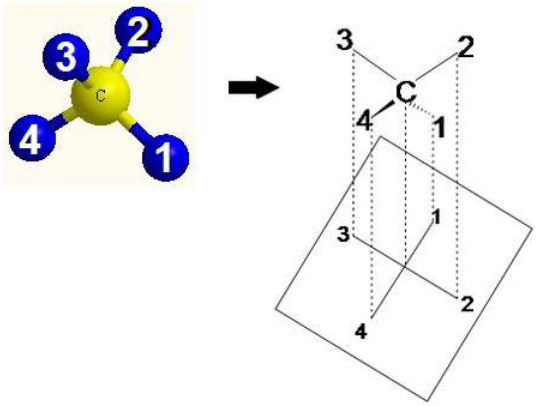
- Fischer projection

Study Notes

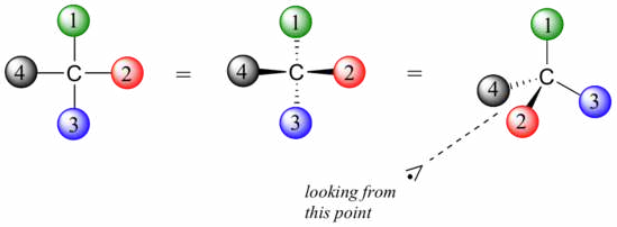
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

Drawing Representations of 3D Structures

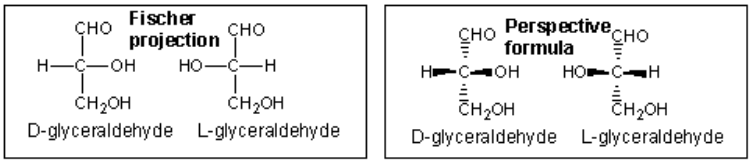
The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and dash notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. Fischer Projections allow us to represent 3D molecular structures in a 2D environment without changing their properties and/or structural integrity.



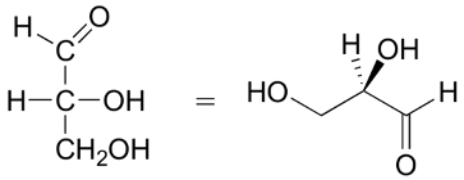
Fisher projections show sugars in their open chain form. In a Fischer projection, the carbon atoms of a sugar molecule are connected vertically by solid lines, while carbon-oxygen and carbon-hydrogen bonds are shown horizontally. Stereochemical information is conveyed by a simple rule: vertical bonds point into the plane of the page, while horizontal bonds point out of the page.



Sugars can be drawn in the straight chain form as either Fisher projections or perspective structural formulas. When drawing Fischer projections, the aldehyde group is written at the top, and the H and OH groups that are attached to each chiral carbon are written to the right or left. The arrangement of the atoms distinguishes one stereoisomer from the other.

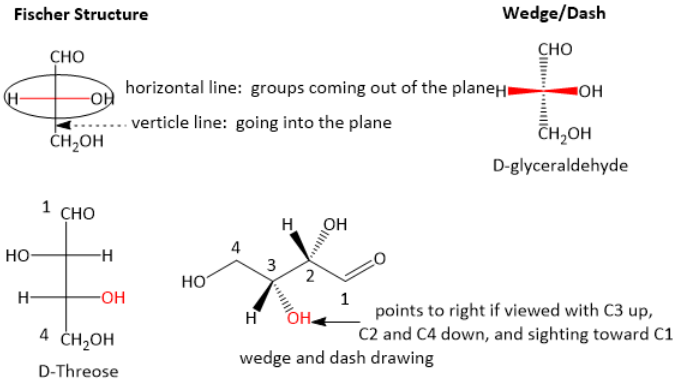


Below are two different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):

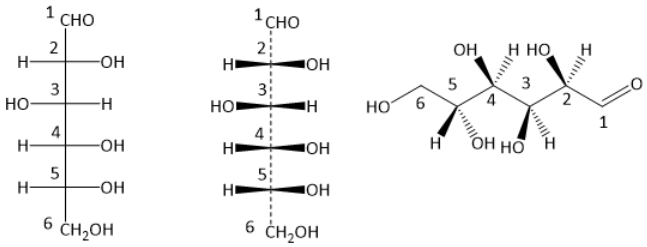


(R)-glyceraldehyde
(D-glyceraldehyde)

In the Fisher projection, the vertical bonds point down into the plane of the paper. That's easy to visualize for 3C molecules. but more complicated for bigger molecules. For those draw a wedge and dash line drawing of the molecule. When determining the orientation of the hydroxides on each C, orient the wedge and dash drawing in your mind so that the C atoms adjacent to the one of interest are pointing down. Sighting towards the carbonyl C, if the OH is pointing to the right in the Fisher project, it should be pointing to the right in the wedge and dash drawing, as shown below for D-erthyrose and D-glucose.

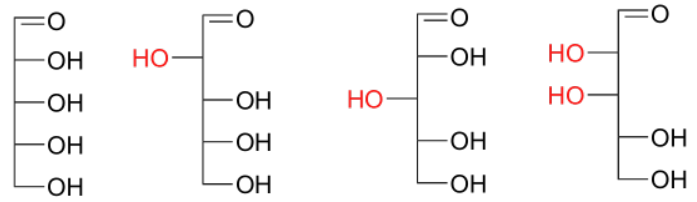


Below are three representations of the open chain form of D-glucose: in the conventional Fischer projection, a wedge/dash version of a Fischer projection, and finally in the 'zigzag' style that is preferred by many organic chemists.



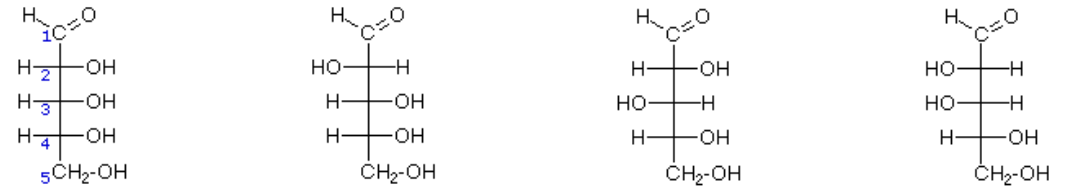
D-Glucose

Fischer projections are useful when looking at many different diastereomeric sugar structures, because the eye can quickly pick out stereochemical differences according to whether a hydroxyl group is on the left or right side of the structure.



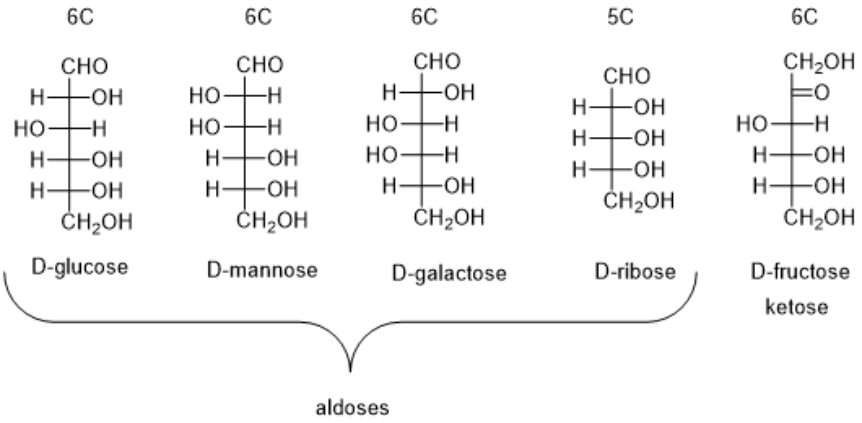
The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses (aldo- since the oxidized carbon is an aldehyde and -pentose since the molecules contain 5 carbons). Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



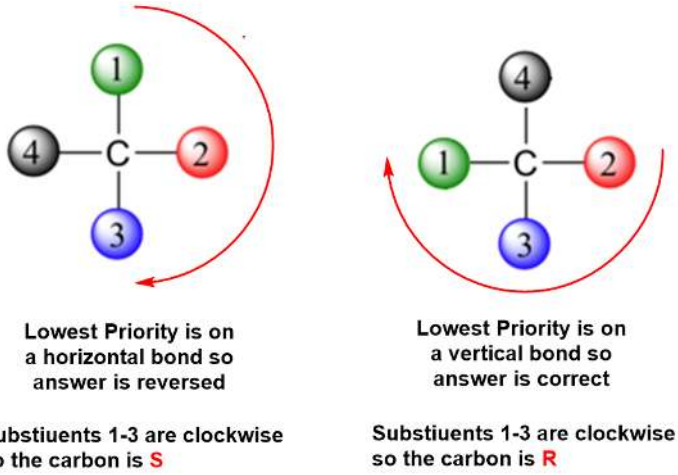
The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

The Fisher structures of the most common monosaccharides (other than glyceraldehyde and dihydroxyacetone), which you will encounter most frequently are shown below.



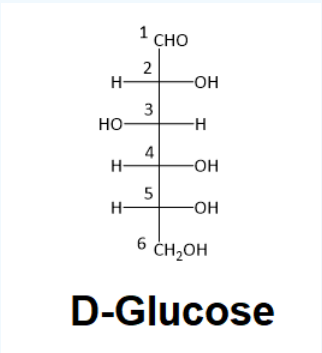
Determining R and S in Fischer Projections

Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.



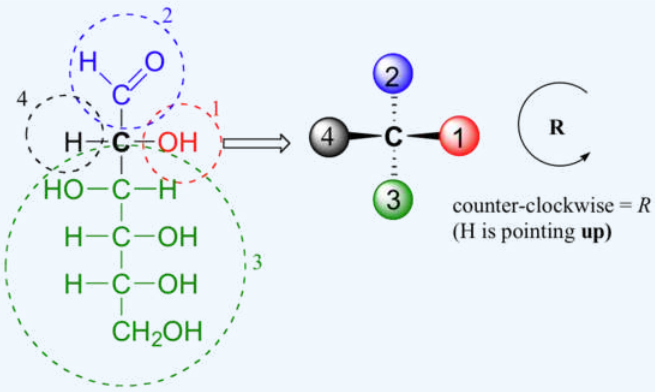
Worked Example 5.1.3.1

Determine if carbon #2 in D-glucose is R or S.



Answer

When deciding whether a stereocenter in a Fischer projection is *R* or *S*, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means *S*. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.



How to make Fischer Projections

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

Exercise 5.1.3.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.

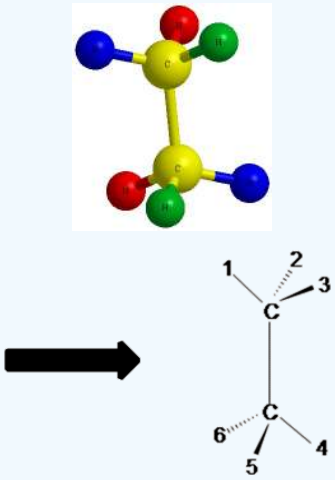


Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a “flat” Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the

ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

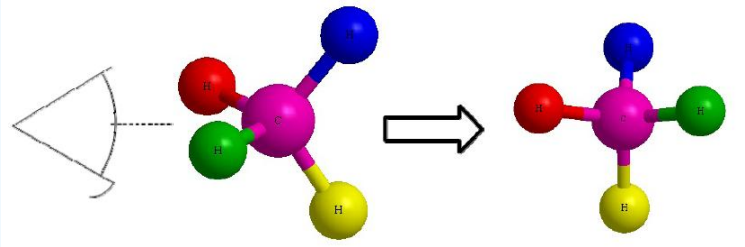
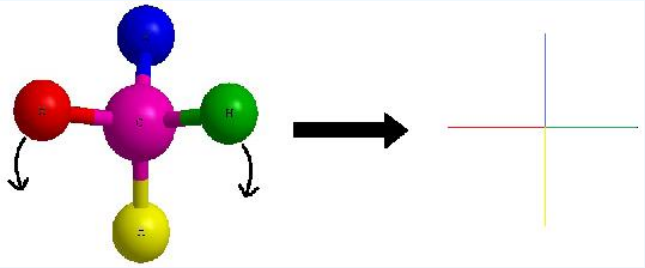


Figure D

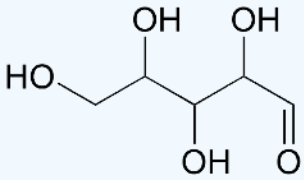
Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.



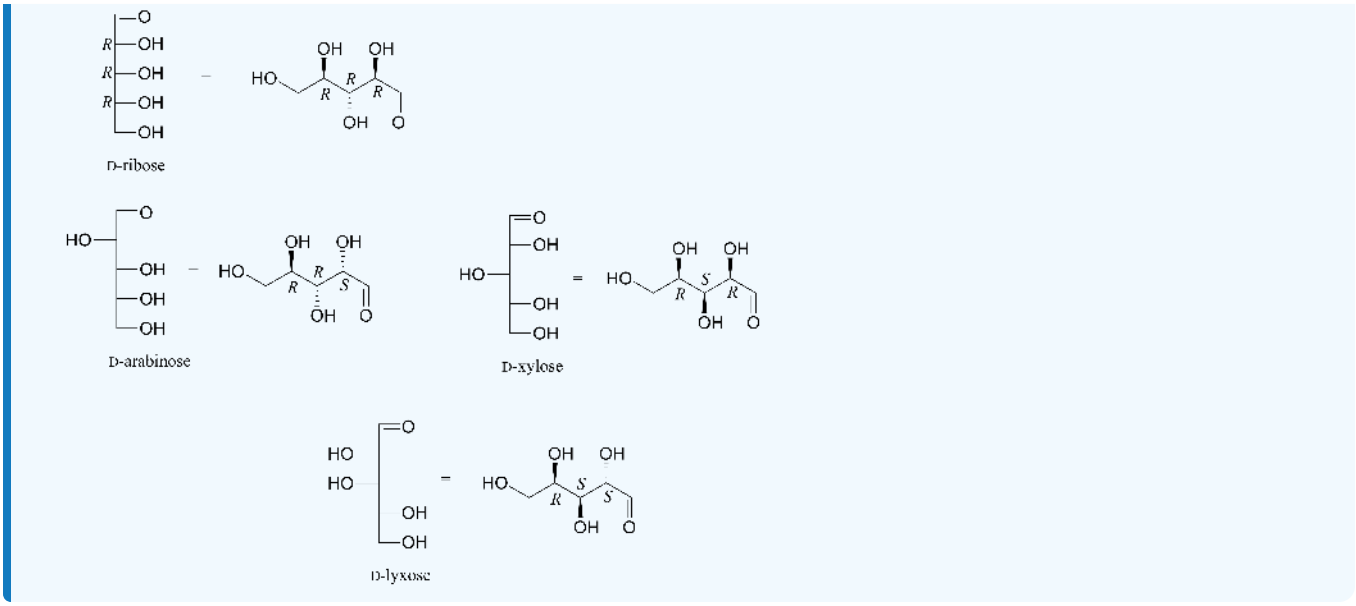
As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

? Exercise 5.1.3.1

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or *S*.



Answer



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5.1.4: D, L Sugars

Objectives

After completing this section, you should be able to

1. identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
2. identify the limitations of the D, L system of nomenclature for carbohydrates.
3. assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
4. draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
5. construct a molecular model of a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.

Key Terms

Make certain that you can define, and use in context, the key terms below.

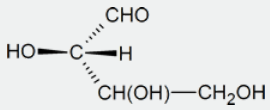
- D sugar
- L sugar

Study Notes

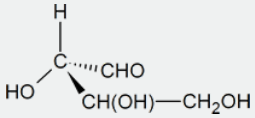
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

How would you set about the task of deciding whether each chiral carbon has an *R* or an *S* configuration? True, you could use molecular models, but suppose that a model set had not been available—what would you have done then?

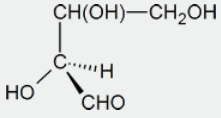
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the page. Thus, the configuration around carbon atom 2 in structure a can be represented as follows:



In your mind, you should be able to imagine how this molecule would look if it was rotated so that the bonds that are shown as coming out of the page are now in the plane of the page. [One possible way of doing this is to try and imagine how the molecule would look if it was viewed from a point at the bottom of the page.] What you should see in your mind is a representation similar to the one drawn below.



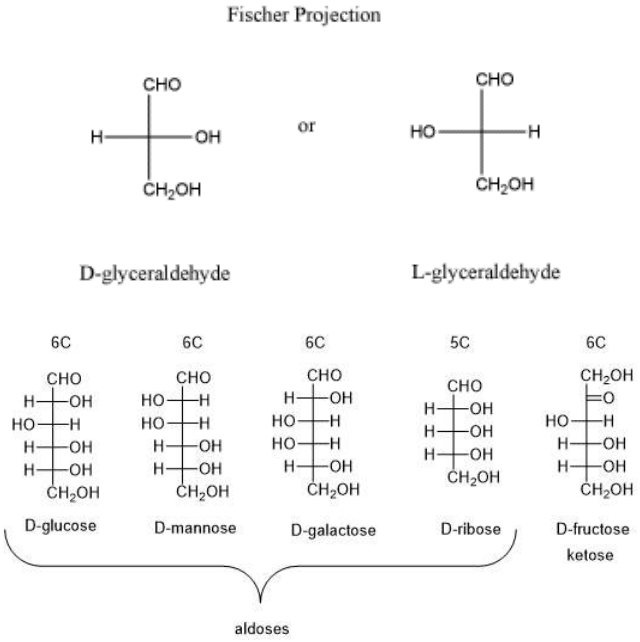
To determine whether the configuration about the central carbon atom is *R* or *S*, we must rotate the molecule so that the group with the lowest priority (H), is directed away from the viewer. This effect can be achieved by keeping the hydroxyl group in its present position and moving each of the other three groups one position clockwise.



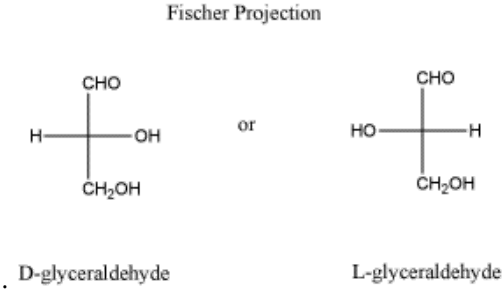
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

D and L Labeling of Monosaccharide Stereochemistry

Glyceraldehyde, the simplest possible aldose, is made up of three carbons and only one these is chiral. Glyceraldehyde has two stereoisomers, an R/S pair of enantiomers. Before the R,S system for designating chiral configuration was adopted by organic chemists (R)-glyceraldehyde was called D-glyceraldehyde (Latin for right: dexter) and (S)-glyceraldehdye was called L-glyceraldehyde (Latin for left:laevus). D- and L-glyceraldehyde were then used to provide reference points for designating and drawing all other monosaccharides. Sugars whose Fischer projections have the same configuration at the chiral carbon furthest from the carbonyl group as D-glyceraldehyde are designated as **D sugars**; those with the same configuration as L-glyceraldehyde are designated as **L sugars**. D and L designations of sugars are based on the position of the hydroxyl on the chiral carbon farthest from the carbonyl group in the Fischer projection of the molecule. All D-sugars have the –OH on the right side and L-sugars have the –OH on the left side.



D-sugars predominate in nature, though L-forms of some sugars, such as fucose, do exist. The D and L designation is a bit more complicated than it would appear on the surface. The confusion about D and L arises because the L sugars of a given name (glucose, for example) are mirror images of the D sugars of the same name. This concept is most easily seen with glyceraldehyde. In the same way D- and L- glyceraldehyde represent two enantiomers, the D- and L- forms larger monosaccharides are enantiomers of one another. The figure below shows the structure of D- and L- glucose. Notice that D-glucose is not converted into L-glucose simply by flipping the configuration of the fifth carbon in the molecule. Rather all of the arrangement around all of the chiral centers (horizontal lines) in the Fischer project of D-glucose need to be opposite to make L-glucose.



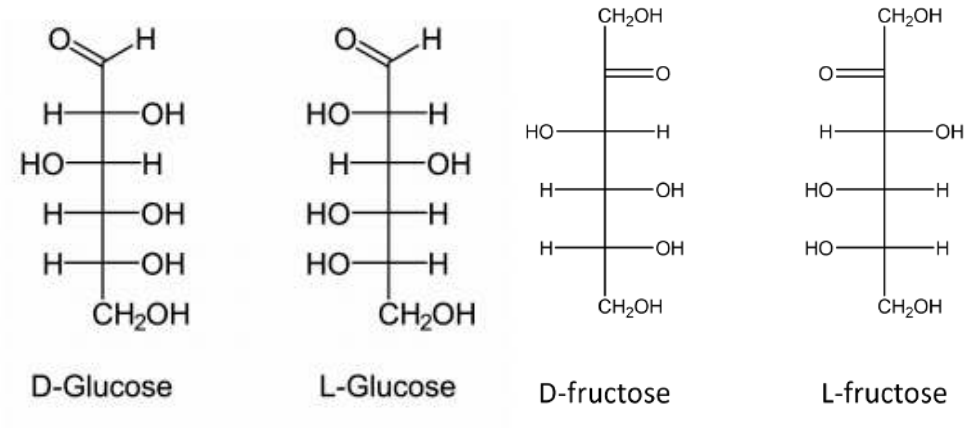


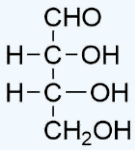
Figure 6. Fischer projections of enantiomers of glucose (left) and fructose (right).

It is important to recognize that the sign of a compound's specific rotation of plane polarized light (+)/(−) does not correlate with its configuration (D or L). The D/L labeling does not indicate which enantiomer is (+)/(−). Rather, it says that the compound's stereochemistry is related to that of the D or L enantiomer of glyceraldehyde. It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

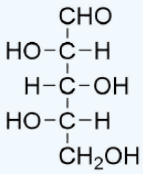
? Exercise 5.1.4.1

In the following Fischer projections, assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

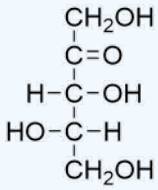
a)



b)



c)



Answer

a) From top to bottom, 2R, 3R, and it is a D sugar.

b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

c) From to to bottom, 3R, 4S, and it is an L sugar.

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5.1.5: Configurations of Aldoses

Objectives

After completing this section, you should be able to

1. draw the structures of all possible aldotetroses, aldopentoses, and aldohexoses, without necessarily being able to assign names to the individual compounds.
2. draw the Fischer projection of D-glyceraldehyde, D-ribose and D-glucose from memory.

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (D)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red.

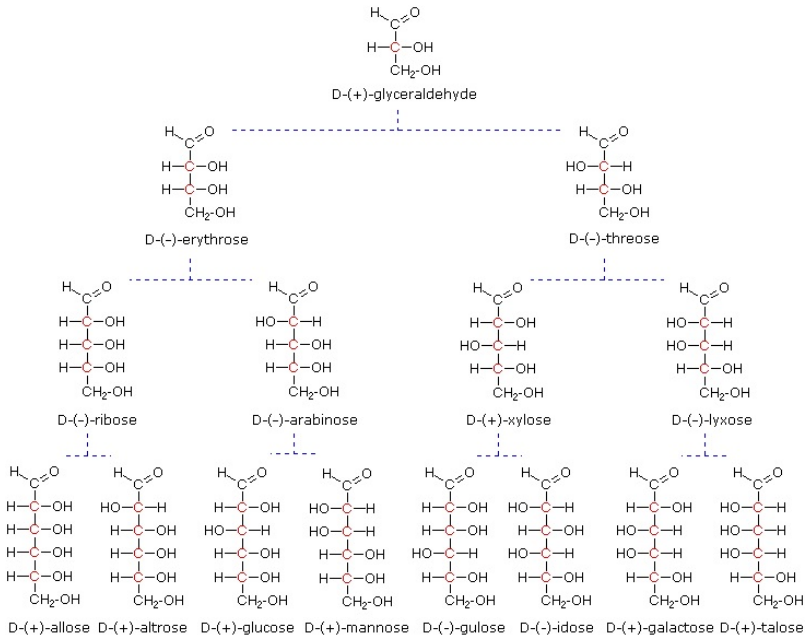
Aldotrioses: 3 carbon sugars with one chiral center. Aldotrioses have two (2^1) possible stereoisomers. A pair of enantiomers called D-gylceraldehyde and L-glyceraldehyde.

Aldotetroses: 4 carbon sugars with two chiral centers. Aldotetroses have four (2^2) possible stereoisomers. Two pairs of D/L enantiomers called erythrose and threose.

Aldopentoses: 5 carbon sugars with three chiral centers. Aldopentoses have eight (2^3) possible stereoisomers. Four pairs of D/L enantiomers called ribose, arabinose, xylose, and lyxose.

Aldohexoses: 6 carbon sugars with four chiral centers. Aldohexoses have sixteen (2^4) possible stereoisomers. five pairs of D/L enantiomers called allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.

Below are the Fischer projects 3-6 carbon aldoses. Starting with the three carbon aldose D-glyceraldehyde, each additional carbon adds a new chiral center and doubles the number of possible stereoisomers of the D-aldoses. Remember that only D-aldoses are represented below. Each D-aldose has an L-aldose enantiomer which is not shown. The L-aldose versions can be draw by inverting all of the chiral centers in the D-aldose's Fischer projection as discussed in the previous section.

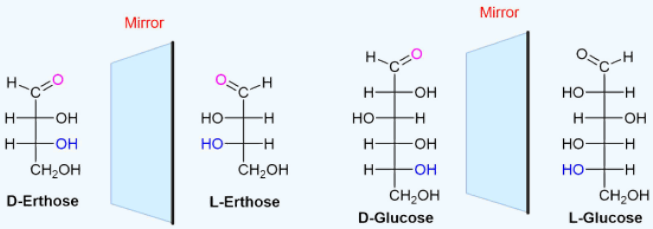


Worked Example 5.1.5.1

Draw the Fisher projection of L-erythrose and L-Glucose

Solution

Use the Fischer projection provided above and reverse all of the chiral centers to provide the L-sugar. Note that in both cases the D sugars have the OH going to the right on the chiral center furthest away from the carbonyl. The L-sugars have the OH going to the left.



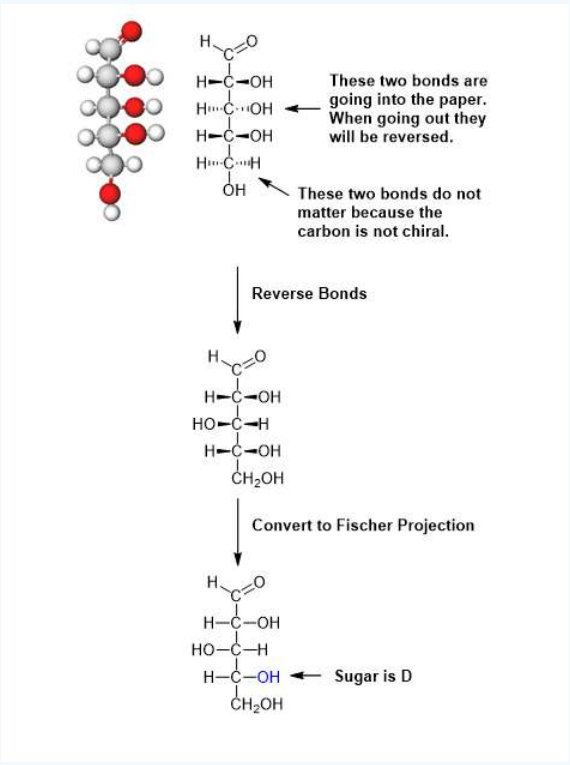
Worked Example 5.1.5.2

Please draw the Fischer projection fo the following aldopentose and determine if the sugars is D or L.

GLmol

Solution

First, rotate the model so that the carbonyl is at the top. This is requirement of a Fischer projection. Next rotate the model so that the H and OH of the chiral carbon just below the carbonyl are facing towards you. In this orientation, a dash/wedge model will have every other set of bonds going into the plane of the page. This is not the correct orientation of a Fischer project so they must be modified. The H and OH bonds need to be coming out of the plane of the page in a Fisher projects. When converting bonds from going into the page to going out of the page the orientation of the H and OH are reversed. Remember that the last -CH_2OH of a sugar is achiral so the orientation does not need to be shown. Once the bonds are oriented correctly the wedge bonds can be converted to those of a Fischer projection.



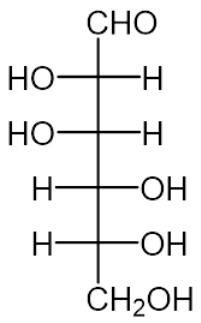
? Exercise 5.1.5.1

For the following model of a sugar, please draw its Fischer projection and name it.

GLmol

Answer

D-Mannose



? Exercise 5.1.5.2

How many heptose stereoisomers would there expected to be? How many would be D-Sugars?

Answer

There would be $2^5 = 32$ heptose stereoisomers. Half of these would be D-sugars or 16.

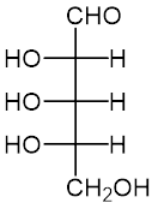
? Exercise 5.1.5.3

Draw the Fischer projection of the following sugars.

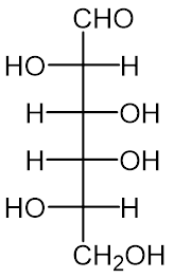
a. L-Ribose
b. L-Galactose
c. L-Talose

Answer

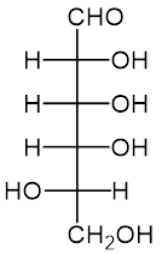
a)



b)



c)



5.1.5: Configurations of Aldoses is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, William Reusch, & William Reusch.

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5.1.6: Cyclic Structures of Monosaccharides - Anomers

Objectives

After completing this section, you should be able to

1. determine whether a given monosaccharide will exist as a pyranose or furanose.
2. draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
3. draw the Fischer projection of a monosaccharide, given its cyclic pyranose form.
4. draw, from memory, the cyclic pyranose form of D-glucose.
5. determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
6. describe the phenomenon known as mutarotation.
7. explain, through the use of chemical equations, exactly what happens at the molecular level during the mutarotation process.

Key Terms

Make certain that you can define, and use in context, the key terms below.

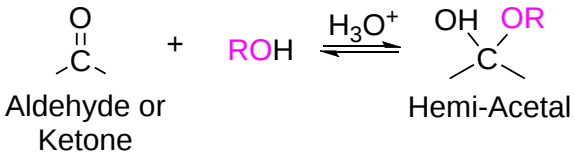
- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

Study Notes

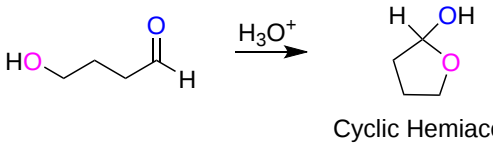
If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

Cyclic Monosaccharides

In Section 19-10 it was discussed that the reaction of one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (*hemi*, Greek, half).



Molecules which have both an alcohol and a carbonyl can undergo an intramolecular version of the same reaction forming a cyclic hemiacetal.



Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed furanose (five-membered) or pyranose (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown below.

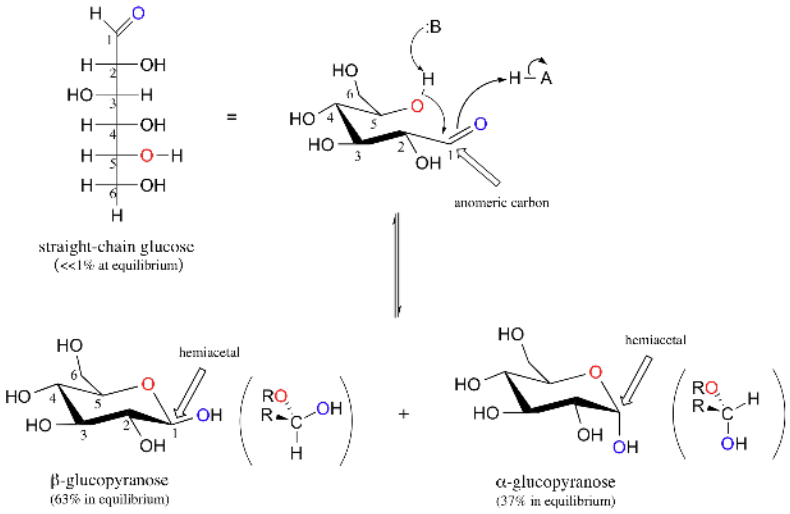


Furan (5-membered ring) and pyran (6-membered ring) structures

Unlike most of the biochemical reactions you will see in this text, sugar cyclization reactions are not catalyzed by enzymes: they occur spontaneously and reversibly in aqueous solution. Sugars are often shown in their open-chain form, however, in aqueous solution, glucose, fructose, and other sugars of five or six carbons rapidly interconvert between straight-chain and cyclic forms. For most five- and six-carbon sugars, the cyclic forms predominate in equilibrium since they are more stable. The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.

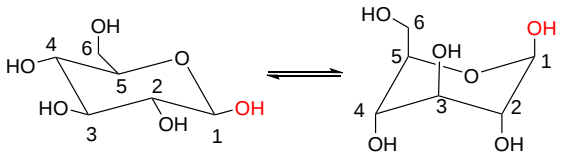
Aldohexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. At equilibrium less than 1% of glucose is in an open chain form with the rest being almost exclusively in its cyclic pyranose form. The pyranose ring is formed by attack of the hydroxyl on carbon 5 of glucose to the aldehyde carbon (carbon #1, also called the anomeric carbon in carbohydrate terminology). The cyclic form of glucose is called glucopyranose. Notice that for glucose and other aldohexoses the hydroxyl that forms the cyclic hemiacetal is also the one that determines the D/L designation of a sugar.

Pyranose rings are often drawn in a chair conformation like cyclohexane rings (**Section 4-6)** with substituents being either an axial or equatorial position. Pyranose rings are even capable of undergoing a ring flip to change between chair conformations. By convention the ring oxygen is placed to the right and to the rear of the structure (top right of the drawing). Groups which go to the right in a Fischer projection will be orientend 'down' of the pyranose ring while groups to the left are oriented 'up' in the chair structure. Also, the terminal -CH_2OH group is oriented up on the pyranose ring for D-sugars and down for L-Sugars.



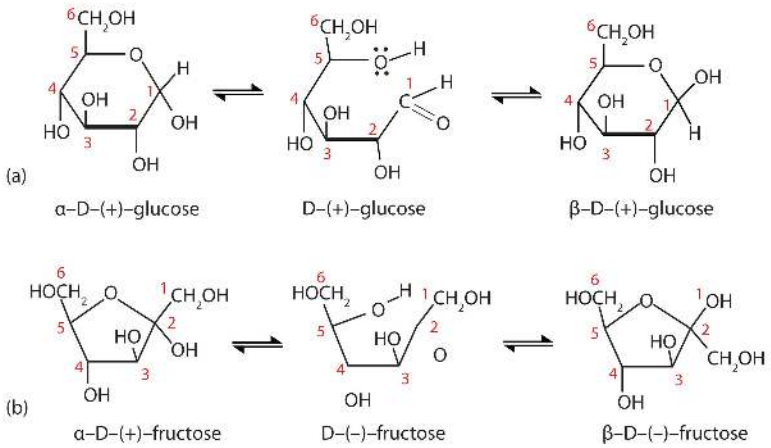
When D-glucose cyclizes it forms a 37/63 mixture of the alpha and beta anomer respectively. The beta anomer is preferred because β-D-glucopyranose is the only aldohexose which can be drawn with all its bulky substituents (-OH and -CH_2OH) in equatorial positions, making it the most stable of the eight D-aldohexoses, which probably accounts for its widespread prevalence in nature.

Conformational Isomers

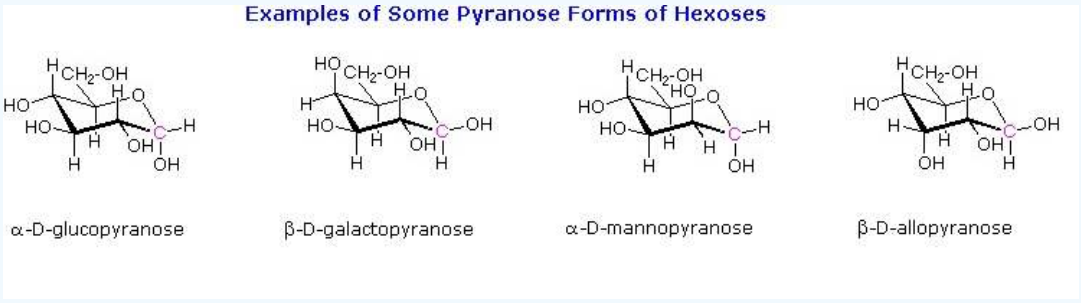


b-D-glucopyranose

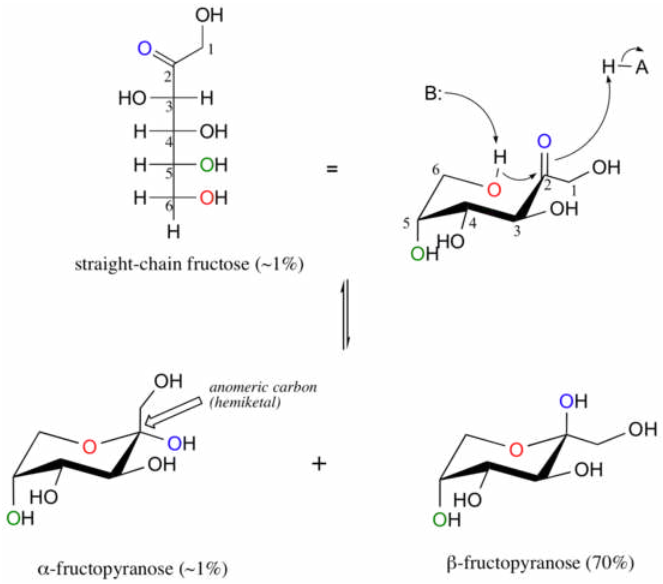
It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium. You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then re-close to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change"). At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.



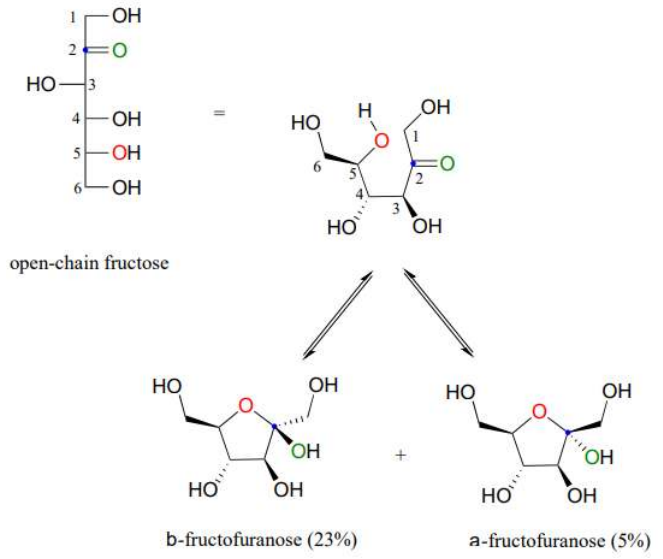
? Example 5.1.6.1



Fructose in aqueous solution forms a six-membered cyclic hemiketal called fructopyranose when the hydroxyl oxygen on carbon #6 attacks the ketone carbon (carbon #2, the anomeric carbon in fructose).



In this case, the β anomer is heavily favored in equilibrium by a ratio of 70:1, because in the minor α anomer the bulkier -CH_2OH group occupies an axial position. Notice in the above figure that the percentages of α and β anomers present at equilibrium do not add up to 100%. Fructose also exists in solution as a five-membered cyclic hemiketal, referred to in carbohydrate nomenclature as fructofuranose. In the formation of fructofuranose from open-chain fructose, the hydroxyl group on the fifth carbon attacks the ketone.



In aqueous solution, then, fructose exists as an equilibrium mixture of 70% β-fructopyranose, 23% β-fructofuranose, and smaller percentages of the open chain and cyclic α-anomers. The β-pyranose form of fructose is one of the sweetest compounds known, and is the main component of high-fructose corn syrup. The β-furanose form is much less sweet.

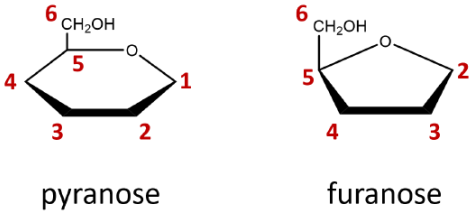
Although we have been looking at specific examples for glucose and fructose, other five- and six-carbon monosaccharides also exist in solution as equilibrium mixtures of open chains and cyclic hemiacetals and hemiketals. Shorter monosaccharides are unlikely to undergo analogous ring-forming reactions, however, due to the inherent instability of three and four-membered rings.

Drawing Cyclic Structures of Monosaccharides

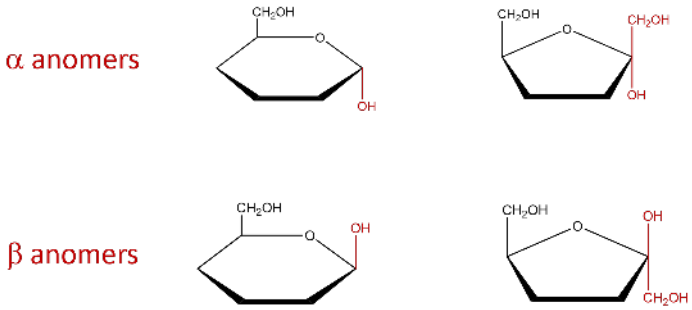
The cyclic forms of sugars are commonly depicted as **Haworth projections**. This convention, first suggested by the English chemist Walter N. Haworth, shows molecules drawn as planar rings with darkened edges representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the *right* in a Fischer projection appears *below (bottom face)* the plane of the ring in a Haworth projection, and any group written to the *left* in a Fischer projection appears *above* (top face) the plane in a Haworth projection.

Figure: Conversion of the Fischer projection of D-glucose to the Haworth projection of ß-D-glucose.

1. When converting a Fischer projection (line) to a Haworth projection, you must first identify the type of monosaccharide involved. If the carbohydrate represents an aldohexose, the **pyranose** ring is typically used. A pyranose is a cyclic structure that contains five carbon atoms and an oxygen. If the carbohydrate represents a ketohexose, the **furanose** ring is typically used. The furanose ring contains four carbon atoms and an oxygen.

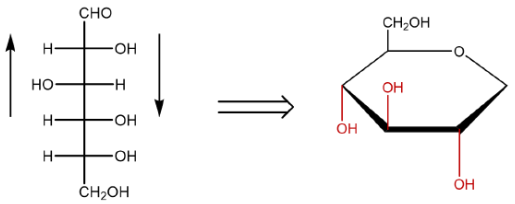


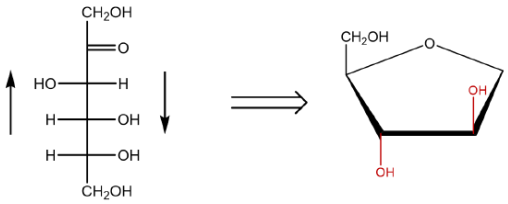
2. Indicate the arrangement of the hydroxyl group attached to the anomeric carbon to identify the sugar as an alpha or beta anomer. The α and β anomers are determined with respect to carbon 6. If the molecule represents a D-sugar, carbon 6 will be above the plane of the ring (top face) and form an L-sugar, carbon 6 will be below the plane of the ring (ring). The α anomer occurs when the OH on the anomeric carbon is trans to carbon 6 and the β anomer occurs when the OH on the anomeric carbon is cis to carbon 6. If the cyclic structure contains a furanose, since carbon 1 is not included within the ring, that carbon group would be arranged in the opposite direction of the OH group.



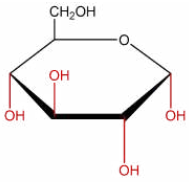
3. The remaining chiral centers (carbons 2, 3 and 4 of the pyranose or carbons 3 and 4 of the furanose) are arranged based on the directions of the hydroxyl from the Fischer projection structures. Groups to the left of the Fischer projection would point up (top face), while groups to the right would point down (bottom face).

https://chem.libretexts.org/@go/page/413250

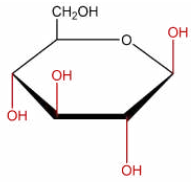




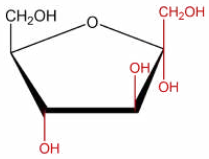
Since the Fischer Projection of any given carbohydrate is always the same, the Haworth Projection is essentially always the same. The only differences between the Haworth Projection of the alpha or beta form of a single carbohydrate, is how the OH (and carbon 1 if furanose ring) is arranged around the anomeric carbon to determine whether the molecule is alpha or beta.



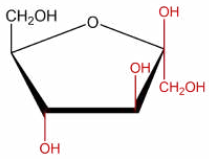
α-D-glucose
(or α-D-glucopyranose)



β-D-glucose
(or β-D-glucopyranose)



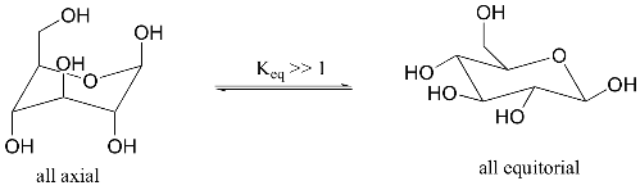
α-D-fructose
(or α-D-fructofuranose)



β-D-fructose
(or β-D-fructofuranose)

Stability of Chair Conformation in Pyranose Sugars

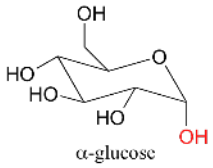
Previously, we have seen the six ring atoms of cyclic glucose drawn in two dimensions. A more accurate depiction shows that the molecule adopts, as expected, a chair conformation.



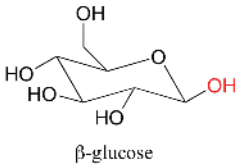
all axial

all equitorial

The conformation in which all substituents are equatorial is lower in energy. The two isomeric forms are referred to by the Greek letters alpha (α) and beta (β).



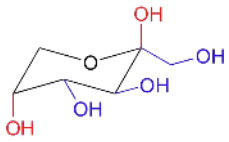
α-glucose



β-glucose

We have not learned about stereoisomerism quite yet, but you can still recognize that the bonding configuration on one carbon is different. On the alpha isomer, one of the hydroxyl groups is axial – this isomer is not able to adopt a chair conformation in which all non-hydrogen substituents are equatorial. The lower energy conformation is the one in which four of the five substituents are equatorial, but the presence of the one axial hydroxyl group means that the alpha isomer is, overall, less stable than the beta isomer.

The most abundant form of fructose in aqueous solution is also a six-membered ring.



fructose
(major form)

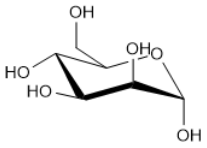
The lower energy chair conformation is the one with three of the five substituents (including the bulky $–CH_2OH$ group) in the equatorial position.

? Exercise 5.1.6.1

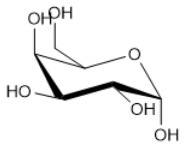
Draw the following in their most stable chair conformation: α-D-galactopyranose and α-D-mannopyranose. Which is expected to be the more stable?

Answer

Because the both have two axial OH's their chair conformations should be roughly the same stability.



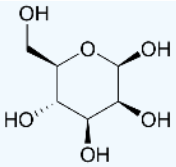
a-D-Mannose



a-D-Galactose

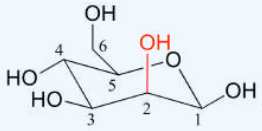
? Exercise 5.1.6.2

Draw the two chair conformations of the sugar called mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

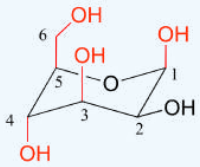


mannose

Answer



major chair form of mannose
(only one substituent axial)

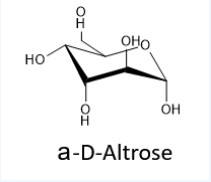


minor chair form of mannose
(four substituents axial)

Exercise 5.1.6.3

Draw the cyclic structure of α-D-altrose.

Answer

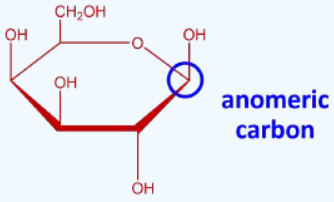


a-D-Altrose

Exercise 5.1.6.4

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer

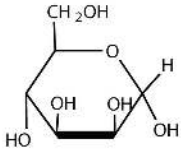


To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. Carbons 2, 3, and 4 are then arranged based on the Fischer projection arrangement at those carbons (C2 right, C3 left, and C4 left).

Exercise 5.1.6.5

Given that the aldohexose D-mannose differs from D-glucose only in the configuration at the second carbon atom, draw the cyclic structure for α-D-mannose.

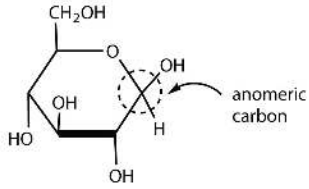
Answer



Exercise 5.1.6.6

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

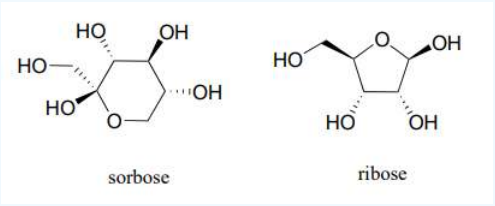
Answer



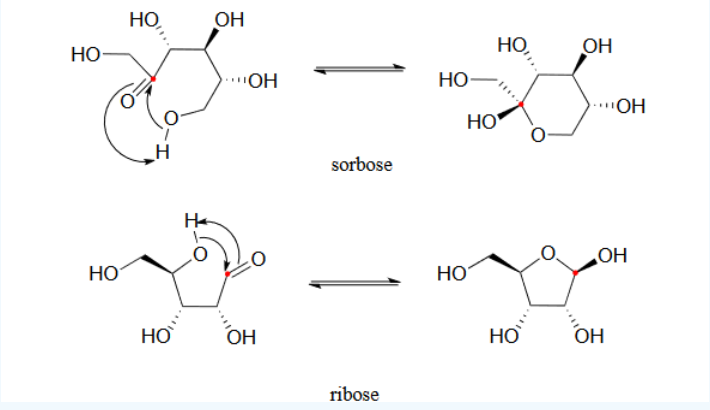
Exercise 5.1.6.7

a) Identify the anomeric carbon of each of the sugars shown below, and specify whether the structure shown is a hemiacetal or hemiketal.

b) Draw mechanisms for cyclization of the open-chain forms to the cyclic forms shown.



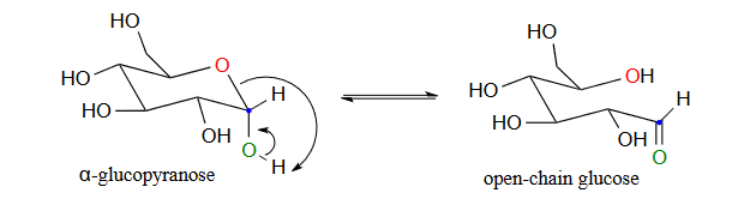
Answer



Exercise 5.1.6.8

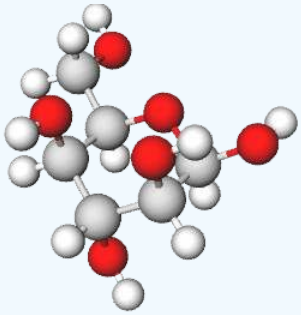
Draw a mechanism for the conversion of α-glucopyranose to open-chain glucose.

Answer



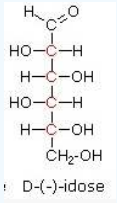
Exercise 5.1.6.9

Identify the following monosaccharide, write its full name, and draw its open-chain form as a Fischer projection.



Answer

β-D-idopyranose.



5.1.6: Cyclic Structures of Monosaccharides - Anomers is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, William Reusch, & William Reusch.

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5.1.7: Reactions of Monosaccharides

Objectives

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

Study Notes

While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

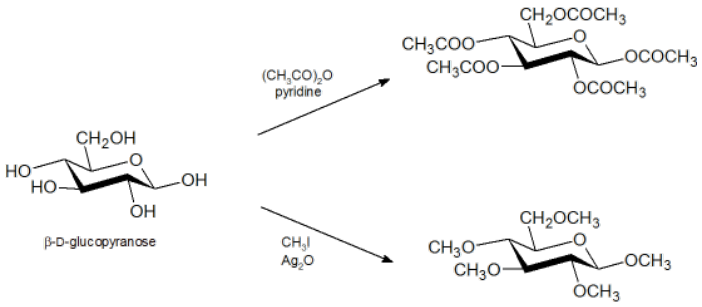
Monosaccharides contain both alcohol and carbonyl functional groups. This allows monosaccharides to undergo many of the reactions typical for these functional groups. In particular, alcohols can be converted to esters, converted to ethers, converted to acetals, or oxidized. Carbonyls can be reacted with nucleophiles, be reduced to form alcohols, or be oxidized to form carboxylic acids.

Ester and Ether Formation

The hydroxyl groups of monosaccharides are often converted to ether or ester groups to increase solubility in organic solvents. Also, the conversion allows the sugar to be easily purified and crystallized.

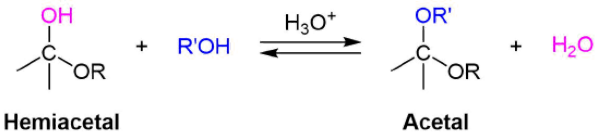
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5) in the presence of a base. During these reactions all of the -OH groups are converted to esters. The monosaccharide, D-glucopyranose can be coverted to the pentacetate through reaction with acetic anhydride.

Treatment of carbohydrates with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the formation of ethers. The strongly basic conditions typically used for the Williamson ether synthesis can degrade some sugar molecules. Instead, milder bases or silver oxide (Ag_2O) are used to provide ethers in high yields. The monosaccharide, D-glucopyranose can be converted to the pentamethyl ether through reaction with iodomethane and silver oxide.

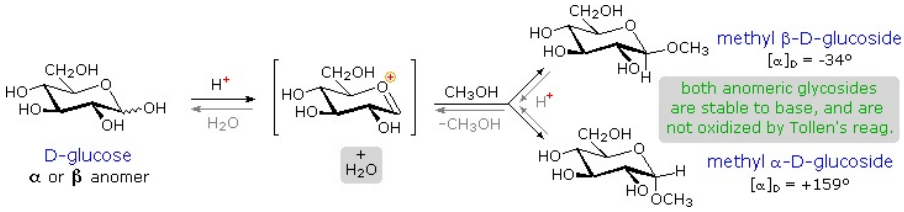


Glycoside Formation

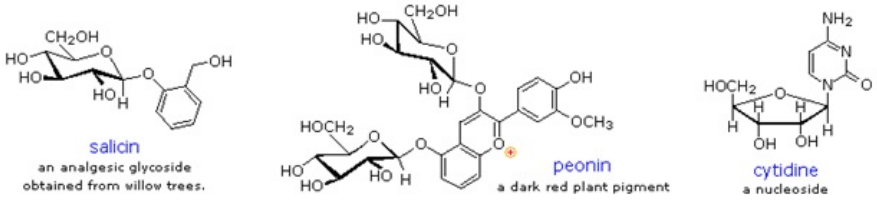
Reacting a hemiacetal with an alcohol and an acid catalyst produces an acetal in which the anomeric hydroxide has been replaced by an ether group.



Monosaccharide acetal derivatives, called glycosides, are formed when a hemiacetal reacts with an alcohol in the presence of an acid catalyst. During the reaction the -OH group from the anomeric carbon is replaced by a -OR group from the alcohol. A mixture of alpha and beta products are formed regardless of the conformation of the reactant. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. This reaction is illustrated below for D-glucopyranose and methanol which forms a mixture of alpha and beta methyl-glucopyranosides. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The acetal product is stable to base and alkaline oxidants such as Tollen's reagent. They are not in equilibrium with the open-chain form and thus do not undergo mutarotation. Since this acid-catalyzed reaction is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.



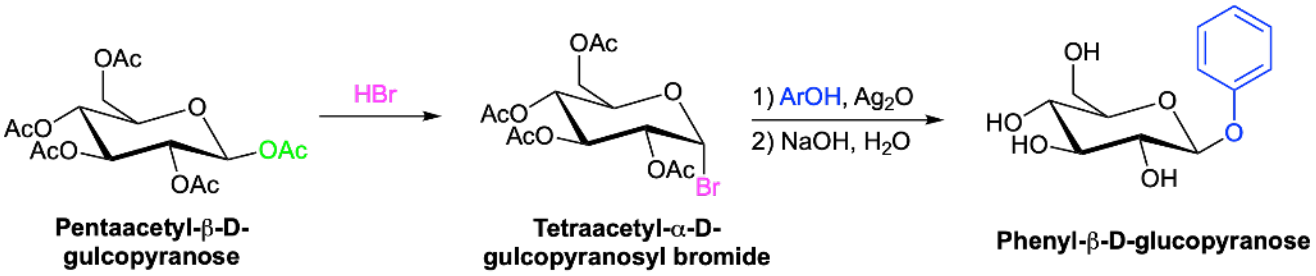
Two examples of naturally occurring glycosides and one example of an amino derivative are displayed below.



- Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin.
- A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins.
- Amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

Koenigs–Knorr Reaction

The presence of multiple -OH groups on a sugar molecular makes the synthesis of glycosides particularly difficult. One of the oldest glycosylation reactions, called the **Koenigs–Knorr reaction**, is effective for preparing the beta-glycosides of glucose. The pathway starts with the reaction of glucose pentaacetate with HBr to form a pyranosyl bromide. Addition of silver oxide allows for the nucleophilic addition of the chosen alcohol. Hydrolysis of the remaning acetal groups forms the beta-glucopyranoside.

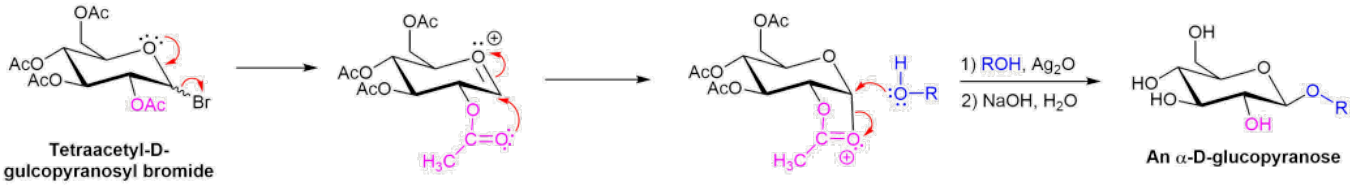


Although the final step of the reaction appears to show the inversion characteristic of an S_N2 reaction, the same product forms if either the alpha or beta anomers of the glucopyranosyl bromide is used. This provides evidence that stereochemical control is lost at some point during the mechanism of the reaction.

Koenigs–Knorr Reaction Mechanism

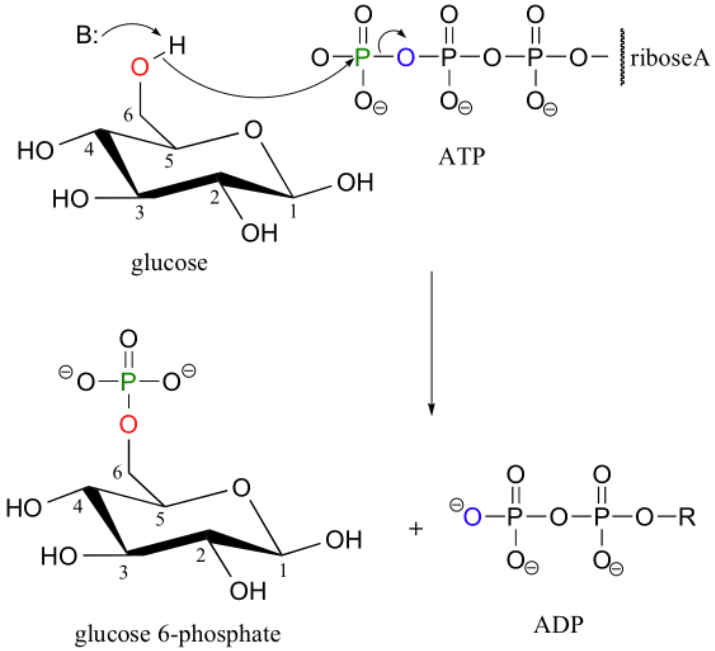
The mechanism starts with the S_N1 like removal of the bromine leaving group which is promoted by the formation of an oxonium ion intermediate. Either anomer of the glucopyranosyl bromide will produce the same oxonium intermediate. Lone pair electrons from the carbonyl oxygen of an adjacent acetate group adds to the oxonium ion in an internal ring-forming reaction. Because the adjacent acetate was on the bottom of the glucose ring the newly form C-O bond is also on the bottom. During this step a new oxonium ion is formed. The alcohol then displaces the oxonium ion as a leaving groups during an S_N2 reaction. The inversion of

configuration of the S_N2 reaction produces a beta-glycoside. Participation of an adjacent acetate group in the mechanism of the Koenigs–Knorr reaction is called a **neighboring-group effect**.



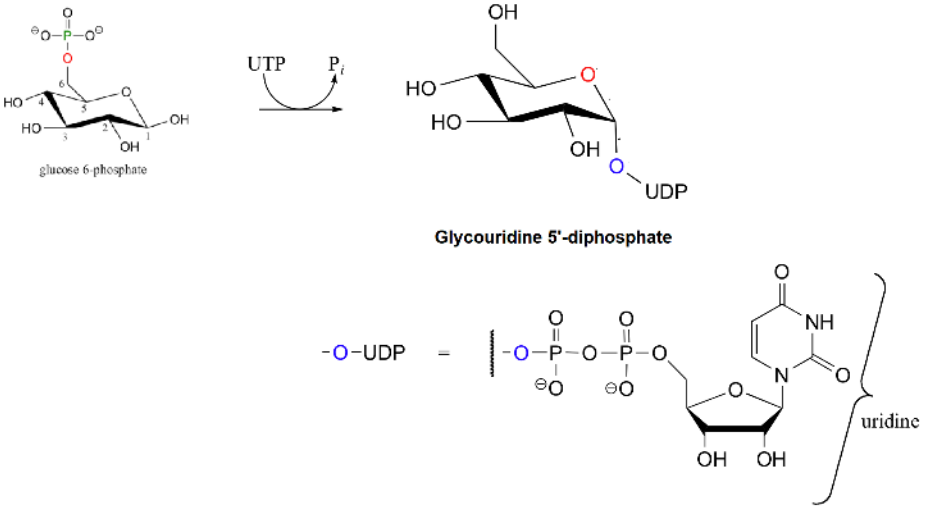
Biological Ester Formation: Phosphorylation

Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP.

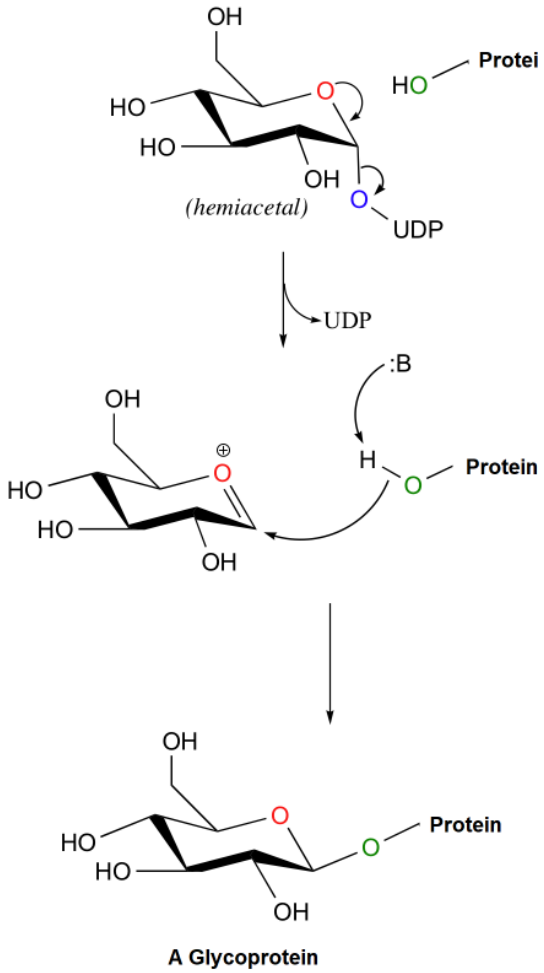


Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Called glycoconjugates these sugar bonded molecules are often found in biological membranes, to which they are anchored through covalent bonds. These compounds are crucial to determine to how different cell types recognized one another which will be discussed further in **Section 25.11**.

Glycoconjugate formation begins with the formation of a phosphorylated sugar such as glucose-6-phosphate which is then reacted with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. The phosphorylation makes the anomeric -OH of the sugar a better leaving group. During nucleophilic substitutions reaction with a protein or a lipid to form a glycoconjugate the anomeric -OH does not leave as a water molecule, but rather as part of a uridine nucleotide diphosphate group.

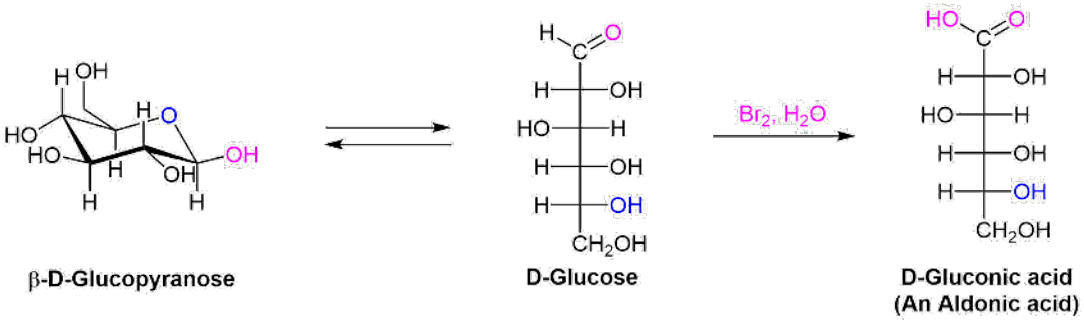


To form a glycoprotein the anomeric carbon of a glucopyranose-UDP derivative is attacked from above by an -OH of -NH_2 group from a protein. The UDP leaving group is displaced, and inversion of stereochemistry results at the anomeric carbon.



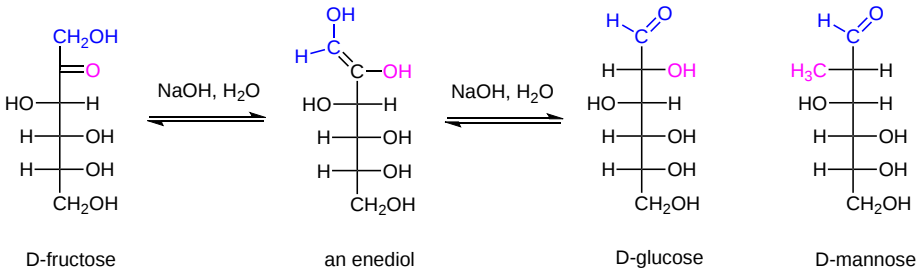
Oxidation of Monosaccharides

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2º hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as aqueous Br_2 can be used for this conversion. The oxidation occurs by reaction of the open-chain form of the sugar. Because of the equilibrium between the open and ring form of the sugar, eventually the entire sample will undergo the reaction.

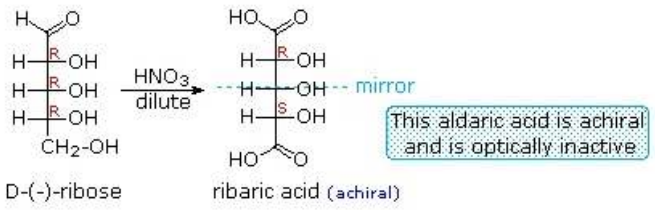


Historically sugars have been classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'** (Ag^+ in NH_3) or **Benedict's** (Cu^{2+} and sodium citrate) reagents. If a sugar is oxidized by these reagents it is called a reducing sugar, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

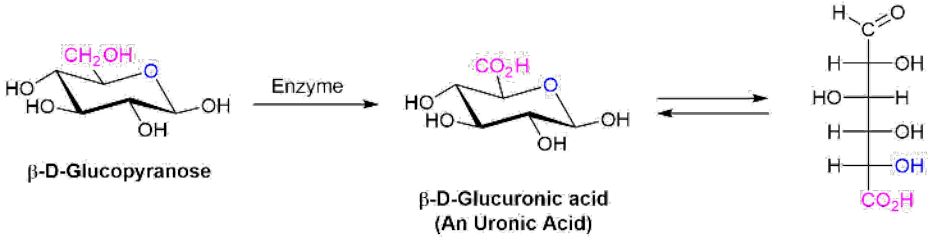
Becuase aldoses contain an aldehyde group they are reducing sugars and will be oxidized by Tollen's and Benedict's reagent. Some ketoses are also reducing sugars. Despite not having an aldehyde groups, fructose is capable of isomerizing to glucose and mannose by keto-enol tautomerism under basic conditions. Once formed, these aldoses are capable of being oxidized by Tollens reagent.



Aldoses can be oxidized to a dicarboxylic acid by dilute nitric acid. Nitric acid is a strong enough oxidizing agent to cause both the aldehyde carbonyl and the -CH_2OH group to be oxidized to carboxylic acids. If both ends of an aldose chain are oxidized to carboxylic acids, the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical. Such an operation will disclose any latent symmetry in the remaining molecule and possibly form an achiral meso compound. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown below.



If the -CH_2OH group of an aldose is oxidized to a carboxylic acid while the aldehyde carbonyl is not affected, the monocarboxylic acid product is called a uronic acid. This selective oxidation is difficult to accomplish and can only be done enzymatically.

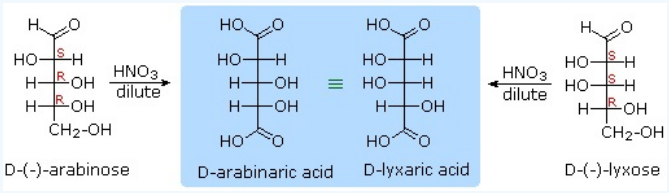


? Exercise 5.1.7.1

D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

Answer

1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.



? Exercise 5.1.7.2

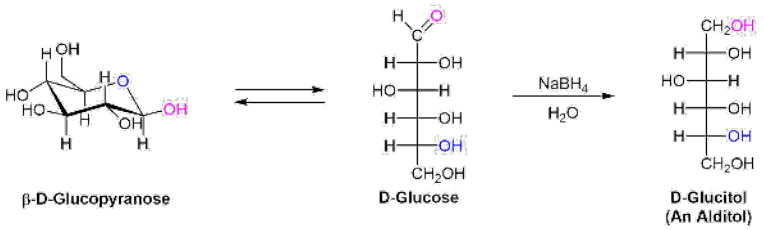
Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer

D-Allose and D-galactose.

Reduction of Monosaccarides

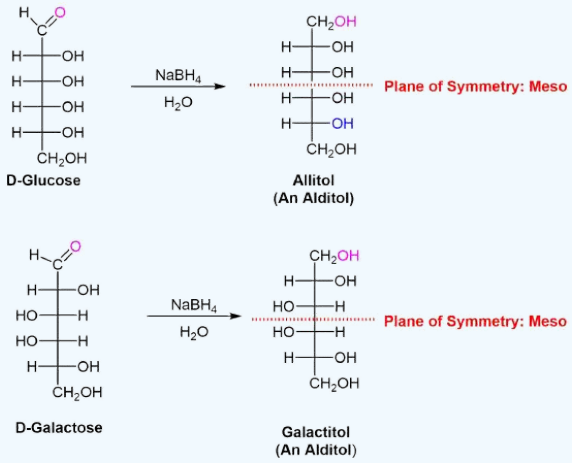
Treatment of an aldose or ketose with sodium borohydride reduces it to a polyalcohol called an alditol. The reduction occurs by reaction of the open-chain form. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction. The reaction products can be formally named by removing the **-ose** ending from the open-chain sugar and replacing it with **-itol**. Note! The alditol products have identical end groups, $HOCH_2(CHOH)_nCH_2OH$ which means that forming an achiral meso compound is possible.



Exercise 5.1.7.3

Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

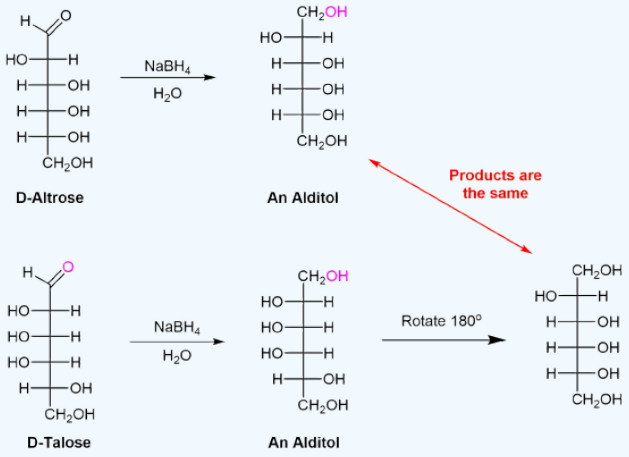
Answer



Exercise 5.1.7.4

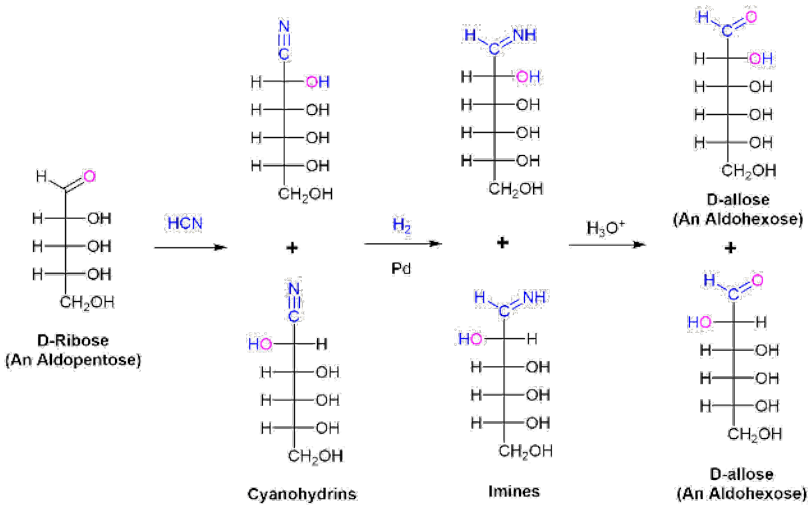
Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer



Chain Lengthening: The Kiliani–Fischer Synthesis

The Kiliani–Fischer synthesis lengthens the carbon chain of an aldose by one carbon atom. In doing this two new sugar epimers are created. The synthesis starts by reacting an aldose with HCN. Nucleophilic addition adds the cyanide nucleophile to the electrophilic carbon of the aldose aldehyde forming a cyanohydrin intermediate. The cyanide nucleophile adds a carbon. Stereochemical control is lost, so a racemic mixture of two cyanohydrins differing in the stereochemistry at C2 is formed. The nitrile group of the cyanohydrin is reduced to an imine intermediate by hydrogenation over a palladium catalyst. Finally, the imine is hydrolyzed to an aldehyde to create two new aldoses with an additional carbon. For example performing the Kiliani–Fischer synthesis on D-ribose produces a mixture of D-allose and D-altrose.



? Exercise 5.1.7.5

What products would you expect from Kiliani–Fischer reaction of D-xylose?

Answer

D-Gluose and D-idose

? Exercise 5.1.7.6

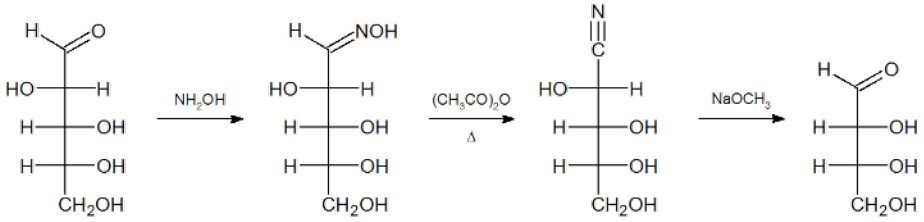
What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer

D-Threose

Chain Shortening: The Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This is commonly accomplished the **Wohl degradation**, which is virtually the reverse of the Kiliani–Fischer synthesis. The aldose aldehyde is converted to an oxime (Section 19-8) by treatment with hydroylamine (NH_2OH). Dehydration of the oxime with acetic anhydride forms a cyanohydrin. Under basic conditions, the cyanohydrine loses HCN to reform an aldehyde carbonyl. The following equation illustrates the application of this procedure to the aldopentose, D-arabinose to form the aldotetrose, D-erythrose.



? Exercise 5.1.7.7

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer

https://chem.libretexts.org/@go/page/413251

D-Ribose and D-arabinose

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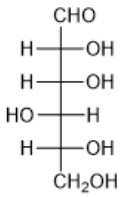
5.1.8: The Eight Essential Monosaccharides

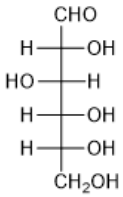
Objectives

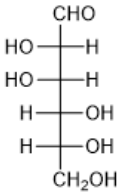
1. identify and draw the eight essential monosaccharides

Eight monosaccharides are required for the proper functioning of human beings. Although they are typically supplied through a healthy diet, they can be biosynthesized if required. The eight monosaccharides are L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, D-glucose, D-mannose, N-acetyl-D-neuraminic acid, and D-xylose.

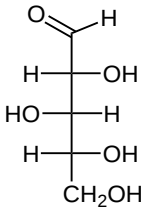
D-Galactose, D-Glucose, and D-Mannose are commonly found aldohexoses:

D-Galactose 

D-Glucose 

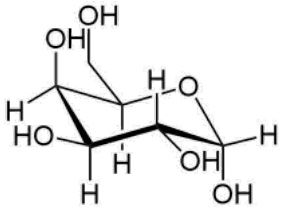
D-Mannose 

D-Xylose is a common aldopentose.

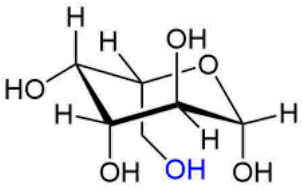


D-Xylose

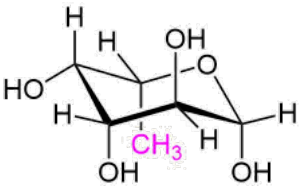
L-Fucose is a deoxy sugar. Fucose is is the monosaccaride L-galactose with the -OH group on C6 replaced with an -H.



α-D-Galactose

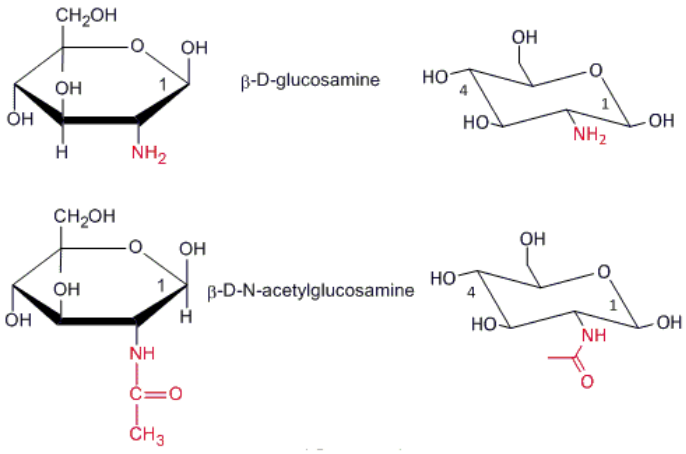


α-L-Galactose

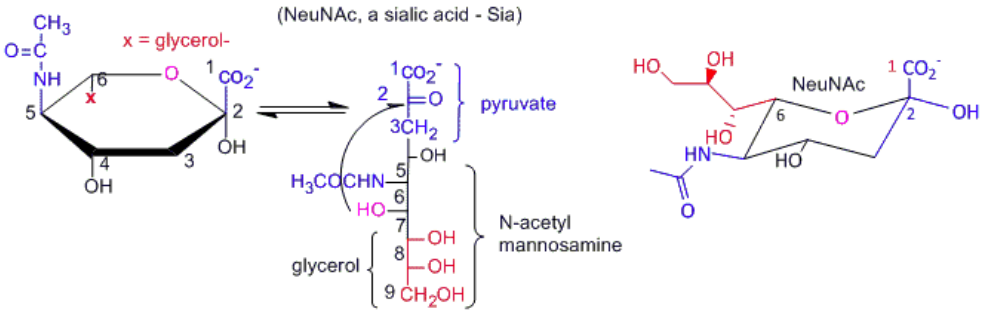


α-L-Fucose

N-acetylgalactosamine and N-acetylglucosamine are derivatives where the corresponding amino sugars have been converted to amides by N-acylation. Amino sugars have had their -OH groups at C2 replaced by an $-NH_2$.

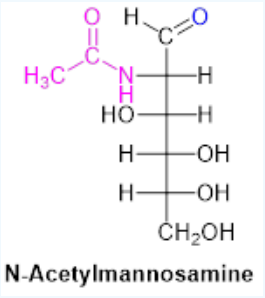


N-Acetylneuraminic acid is nine carbon sugar created by an aldol reaction between N-acetymannosamine and pyruvate. N-acetylneuaminic acid forms a pyranose ring by a intramolecular hemiacetal formation between the -OH on C6 and the ketone functional group in the pyruvate moiety.



Exercise 5.1.8.1

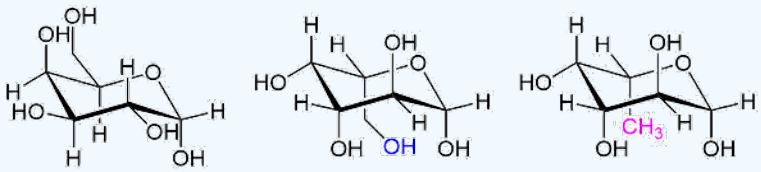
1) Please show the mechanism of the aldol reaction between *N*-acetylmannosamine and pyruvate to form neuraminic acid.



N-Acetylmannosamine

Answer

1)



α-D-Galactose **α-L-Galactose** **α-L-Fucose**

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5.1.9: Disaccharides

Objectives

After completing this section, you should be able to

1. identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
2. identify the two monosaccharide units in a given disaccharide.
3. identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
4. draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.

   Note: If α- or β-D-glucose were one of the monosaccharide units, its structure would not be provided.
5. identify the structural feature that determines whether or not a given disaccharide behaves as a reducing sugar and undergoes mutarotation, and write equations to illustrate these phenomena.
6. identify the products formed from the hydrolysis of a given disaccharide.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

Study Notes

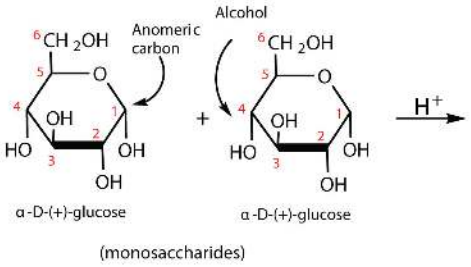
Notice that most of the disaccharides discussed in this section contain one unit of D-glucose. You are not expected to remember the detailed structures of maltose, lactose and sucrose. Similarly, we do not expect you to remember the systematic names of these substances.

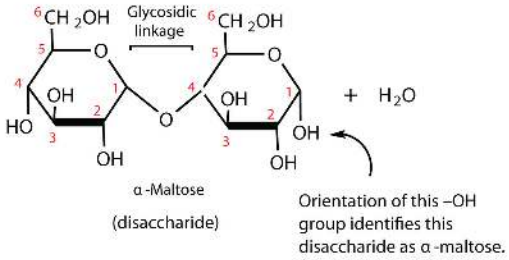
Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol to form a glycoside. When the alcohol component of a glycoside is provided by a hydroxyl function on another monosaccharide, the compound is called a disaccharide. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide. The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water.

Maltose

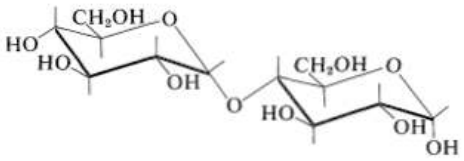
Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units. In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose

The glucopyranose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucopyranose molecule to the fourth carbon atom of the second glucopyranose molecule (an α-1,4-glycosidic linkage). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucopyranose can be in either the α or the β position.





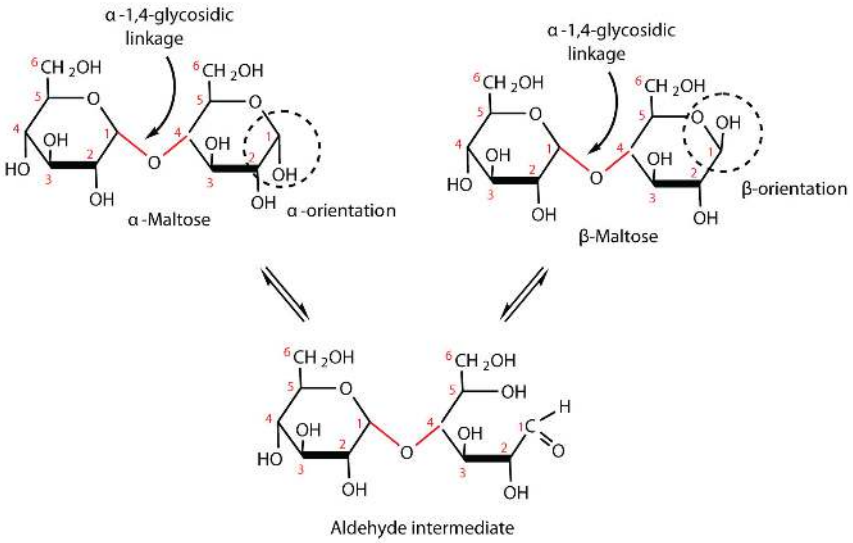
Cellobiose is a disaccharide made up of two D-glucopyranose molecules linked with a β-1,4-glycosidic linkage. Like maltose, the OH group on the anomeric carbon of the second glucopyranose of cellobiose can be in either the α or the β position. Although the difference between maltose and cellobiose seems small they have vastly different biological properties. Maltose can be digested by humans whereas cellobiose cannot.



maltose, **25**

Maltose is a reducing sugar. Thus, its two D-glucopyranose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. Although one anomeric carbon in maltose and cellobiose is used to form the 1,4-glycosidic linkage, the anomeric carbons on the second glucopyranose remain a hemiacetal. Like an individual monosaccharide, the second glucopyranose subunit undergoes mutarotation and thus is in equilibrium with its aldehyde and both anomer forms. For this reason, maltose and cellobiose contain a mixture of α and β anomers of the second glucopyranose.

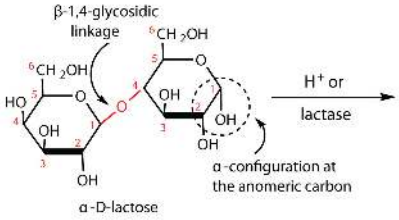
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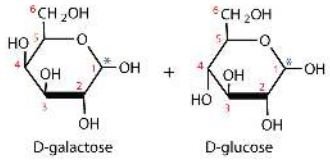


Lactose

Lactose is known as *milk sugar* because it occurs in the milk of humans, cows, and other mammals. In fact, the natural synthesis of lactose occurs only in mammary tissue, whereas most other carbohydrates are plant products. Human milk contains about 7.5% lactose, and cow's milk contains about 4.5%. This sugar is one of the lowest ranking in terms of sweetness, being about one-sixth as sweet as sucrose. Lactose is produced commercially from whey, a by-product in the manufacture of cheese. It is important as an infant food and in the production of penicillin.

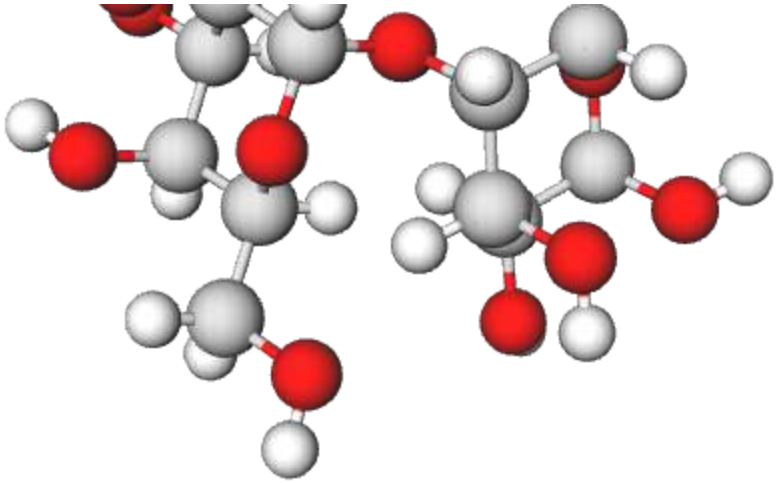
Lactose is a disaccharide composed of one molecule of D-galactopyranose and one molecule of D-glucopyranose joined by a β-1,4-glycosidic bond between the 1 of D-galactopyranose and the C4 of glucose. Lactose is a reducing sugar and undergoes mutarotation to exhibit both anomers of the D-glucopyranose subunit. The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*.





*We use this convention for writing the hydroxyl group on the anomeric carbon when we do not wish to specify either the α or the β anomer.

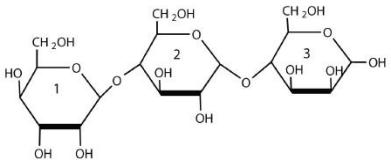




Many adults and some children suffer from a deficiency of lactase. These individuals are said to be lactose intolerant because they cannot digest the lactose found in milk. A more serious problem is the genetic disease galactosemia, which results from the absence of an enzyme needed to convert galactose to glucose. Certain bacteria can metabolize lactose, forming lactic acid as one of the products. This reaction is responsible for the “souring” of milk.

Example 1

For this trisaccharide, indicate whether each glycosidic linkage is α or β.



Solution

The glycosidic linkage between sugars 1 and 2 is β because the bond is directed up from the anomeric carbon. The glycosidic linkage between sugars 2 and 3 is α because the bond is directed down from the anomeric carbon.

To Your Health: Lactose Intolerance and Galactosemia

Lactose makes up about 40% of an infant’s diet during the first year of life. Infants and small children have one form of the enzyme lactase in their small intestines and can digest the sugar easily; however, adults usually have a less active form of the enzyme, and about 70% of the world’s adult population has some deficiency in its production. As a result, many adults experience a reduction in the ability to hydrolyze lactose to galactose and glucose in their small intestine. For some people the inability to synthesize sufficient enzyme increases with age. Up to 20% of the US population suffers some degree of lactose intolerance.

In people with lactose intolerance, some of the unhydrolyzed lactose passes into the colon, where it tends to draw water from the interstitial fluid into the intestinal lumen by osmosis. At the same time, intestinal bacteria may act on the lactose to produce organic acids and gases. The buildup of water and bacterial decay products leads to abdominal distention, cramps, and diarrhea, which are symptoms of the condition.

The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis of the lactose, so some people with lactose intolerance are still able to enjoy cheese, yogurt, or cooked foods containing milk. The most common treatment for lactose intolerance,

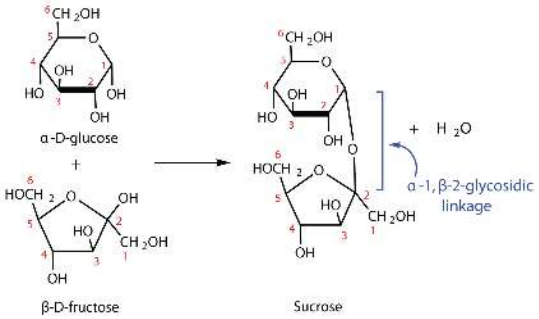
however, is the use of lactase preparations (e.g., Lactaid), which are available in liquid and tablet form at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

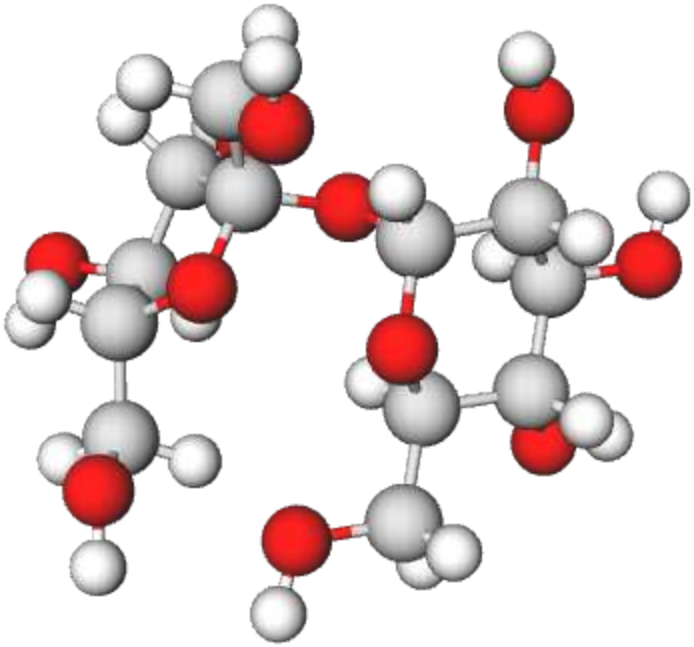
Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite, weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

Sucrose

Sucrose, probably the largest-selling pure organic compound in the world, is known as *beet sugar*, *cane sugar*, *table sugar*, or simply *sugar*. Most of the sucrose sold commercially is obtained from sugar cane and sugar beets (whose juices are 14%–20% sucrose) by evaporation of the water and recrystallization. The dark brown liquid that remains after the recrystallization of sugar is sold as molasses.

The sucrose molecule is unique among the common disaccharides in having an α-1,β-2-glycosidic (head-to-head) linkage. Because this glycosidic linkage is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.





This linkage gives sucrose certain properties that are quite different from those of maltose and lactose. As long as the sucrose molecule remains intact, neither monosaccharide is in equilibrium with its open-chain form. Thus, sucrose is incapable of mutarotation and exists in only one form both in the solid state and in solution. In addition, sucrose does not undergo reactions that are typical of aldehydes and ketones. Therefore, sucrose is a nonreducing sugar.

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

The average American consumes more than 100 lb of sucrose every year. About two-thirds of this amount is ingested in soft drinks, presweetened cereals, and other highly processed foods. The widespread use of sucrose is a contributing factor to obesity and tooth decay. Carbohydrates such as sucrose, are converted to fat when the caloric intake exceeds the body's requirements, and sucrose causes tooth decay by promoting the formation of plaque that sticks to teeth.

Summary

Maltose is composed of two molecules of glucose joined by an α-1,4-glycosidic linkage. It is a reducing sugar that is found in sprouting grain. Lactose is composed of a molecule of galactose joined to a molecule of glucose by a β-1,4-glycosidic linkage. It is a reducing sugar that is found in milk. Sucrose is composed of a molecule of glucose joined to a molecule of fructose by an α-1,β-2-glycosidic linkage. It is a nonreducing sugar that is found in sugar cane and sugar beets.

Exercise 5.1.9.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

a. sucrose
b. maltose
c. lactose

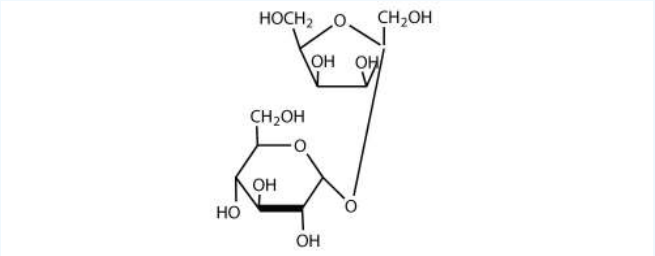
Answer

a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

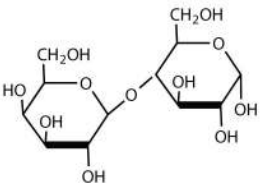
Exercise 5.1.9.2

For each disaccharide, indicate whether the glycosidic linkage is α or β.

a)

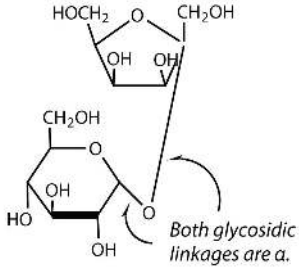


b)

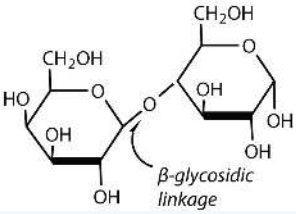


Answer

a)



b)



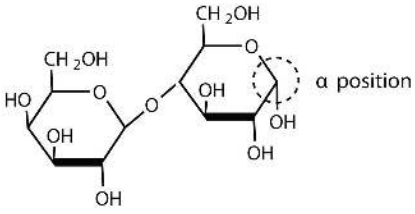
Exercise 5.1.9.3

Identify each disaccharide in Exercise 2 as a reducing or nonreducing sugar. If it is a reducing sugar, draw its structure and circle the anomeric carbon. State if the OH group at the anomeric carbon is in the α or the β position.

Answer

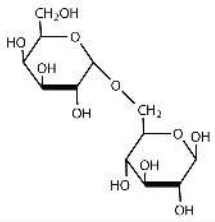
a) nonreducing

b) reducing



Exercise 5.1.9.4

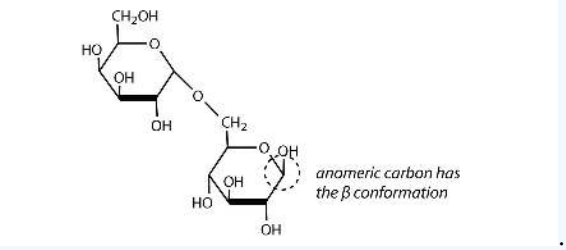
Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



a. What monosaccharide units are incorporated into melibiose?
b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?
c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

Answer

a) galactose and glucose



b) α-glycosidic linkage

c) β.

Contributors and Attributions

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5.1.10: Polysaccharides and Their Synthesis

Objectives

After completing this section, you should be able to

1. identify the structural difference between cellulose and the cold-water-insoluble fraction of starch (amylose), and identify both of these substances as containing many glucose molecules joined by 1,4′-glycoside links.
2. identify the cold-water-soluble fraction of starch (amylopectin) as having a more complex structure than amylose because of the existence of 1,6′-glycoside links in addition to the 1,4′-links.
3. compare and contrast the structures and uses of starch, glycogen and cellulose.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- amylopectin
- amylose
- polysaccharide

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

Starch

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a “starchy” food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

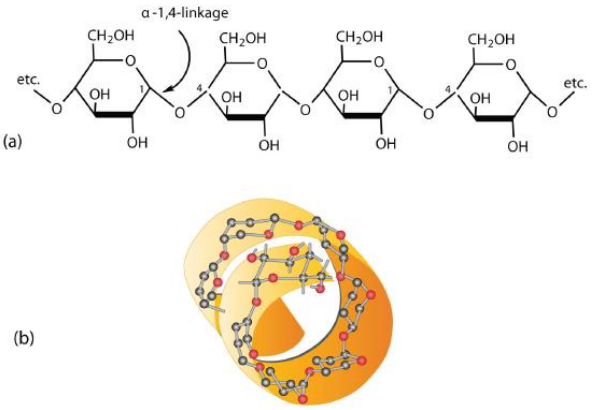


Figure **5.1.10.1**: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we

saw in maltose (part (a) of Figure 5.1.10.1). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure 5.1.10.1). When coiled in this fashion, amylose has just enough room in its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure 5.1.10.2). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

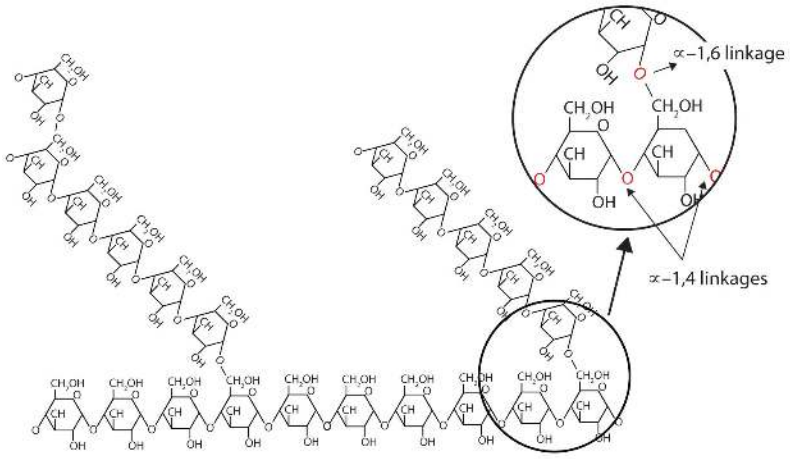


Figure 5.1.10.2: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

Glycogen

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%). Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

> About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.

Cellulose

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products. Although the use of non-cellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure **5.1.10.3**). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure **5.1.10.3**). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

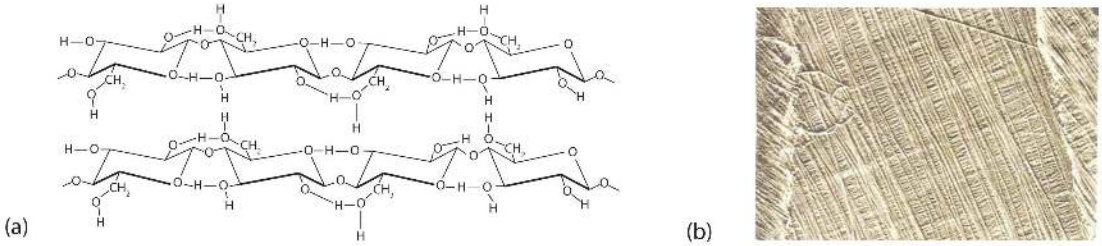
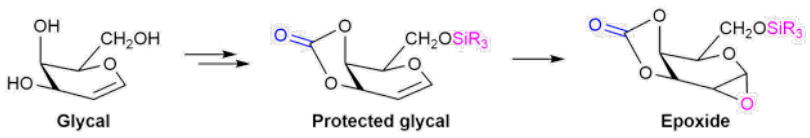


Figure **5.1.10.3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

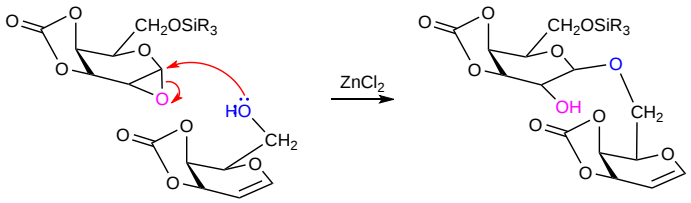
Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

Polysaccaride Synthesis

The presence of multiple -OH groups in monosaccarides makes the laboratory synthesis of polysaccharides difficult. One modern method for the synthesis of polysaccharides is called the **glycal assembly method**. A glycal is a sugar which has been dehydrated to form a double bond. Glycals are typically prepared from the corresponding monosaccharide. As part of the synthesis pathway, the primary alcohol of the glycal is protected by forming a silyl ether (Section 17-8). Also, two adjacent secondary alcohols are protected by forming a cyclic carbonate ester. Now there are no -OH groups remanding in the protected glycal. The double bond of the protected glycal is then converted into a epoxide functional groups.



Epoxides ring can be opened by the acid-catalyzed S_N2 backside attack by an alcohol (section 18-6). This reaction is exploited by reacting a protected glycal epoxide with a second glycal with an unprotected primary alcohol in the presence $ZnCl_2$ as a Lewis acid. The disaccharide formed in this reaction is a glycal so it can be epoxidized and coupled with another glycal to form a trisaccharide etc. Once the monosaccharides are combined to form a chain of the desired length, the remaining silyl ether and cyclic carbonate protecting groups are removed by hydrolysis and the polysaccharide is formed.



Disaccaride glycal

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5.1.11: Other Important Carbohydrates

Objectives

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

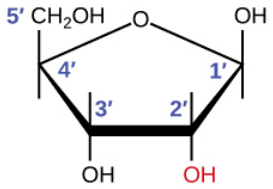
Key Terms

Make certain that you can define, and use in context, the key terms below.

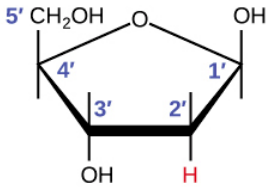
- amino sugar
- deoxy sugar

Deoxy Sugars

As shown in **Section 25-7**, deoxy sugars are missing an oxygen atom. The most common deoxy sugar is 2-deoxyribose, a modified form of another sugar called ribose. When compared to ribose, 2-deoxyribose has an -OH group replaced with an -H at the 2 position. 2-deoxyribose is best known for being the sugar found in the structure of deoxyribonucleic acid (DNA).

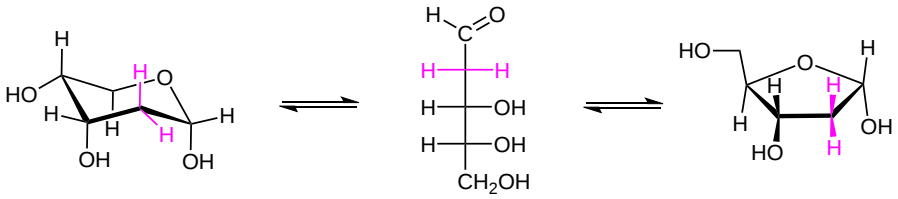


Ribose



Deoxyribose

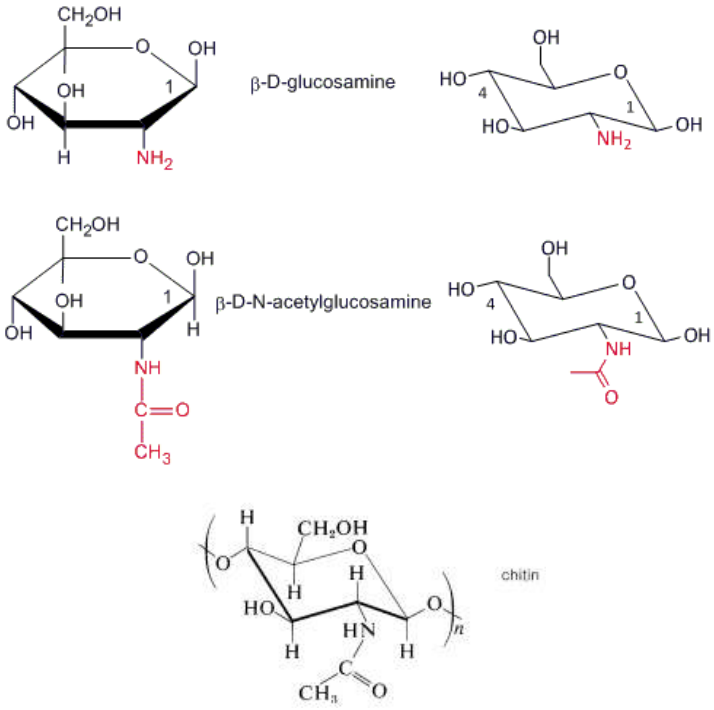
In water, 2-deoxyribose is an equilibrium mixture of both the furanose and pyranose ring forms. The pyranose form the most stable (40% alpha anomer and 35% beta anomer), followed by the furanose structures (13% alpha anomer and 12% beta), with the uncyclized form making up the remaining 0.7%.



Pyranose, uncyclized and furanose forms of 2-deoxyribose. The more stable alpha isomer is shown for both the pyranose and furanose forms. Note the missing hydroxide at the 2 position (highlighted magenta)

Amino Sugars

An amino sugar (or more technically a 2-amino-2-deoxysugar) is a sugar molecule in which a hydroxyl group has been replaced with an amine group. More than 60 amino sugars are known, with one of the most abundant being *N*-acetylglucosamine, which is the main component of chitin.



Chitin is a polymer of 2-deoxy-2- N -ethanamidoglucose (N-acetyl-β-D-glucosamine) and is found in many places throughout the natural world. It is a characteristic component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulae of molluscs, and the beaks and internal shells of cephalopods, including squid and octopuses and on the scales and other soft tissues of fish and lissamphibians. Amino sugars are also found in antibiotics such as amikacin and tobramicin.

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5.1.12: Cell-Surface Carbohydrates and Influenza Viruses

Objectives

After completing this section, you should be able to:

1. Explain how carbohydrates are related to blood type.
2. Explain how influenza works and how it is influenced by carbohydrates.

Oligosaccharides

An **oligosaccharide** is a saccharide polymer containing a small number (typically two to ten) of monosaccharides. Oligosaccharides can have many functions; for example, they are commonly found on the plasma membrane of animal cells where they can play a role in cell-cell recognition. In general, they are found attached to compatible amino acid side-chains in proteins or to lipids. Oligosaccharides are often found as a component of **glycoproteins** or **glycolipids**. They can be used as chemical markers on the outside of cells, often for cell recognition. Oligosaccharides are also responsible for determining blood type.

Glycoproteins

Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Glycoproteins and glycolipids are often found in biological membranes, to which they are anchored by through nonpolar interactions. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect the protein from degradation by enzyme catalysts within the body. However, their main functions arises from the fact that covalently attached carbohydrates that "decorate" the surface of glycoproteins or glycolipids provide new binding site interactions that allow interactions with other biomolecules. Hence glycosylation allows for cell:cell, cell:protein, or protein:protein interactions. Unfortunately, bacteria and viruses often recognize glycosylated molecules on cell membranes as well, allowing for their import into the cell.

Blood Type

Cell markers are carbohydrate chains on the surface of cells where they act as “road signs” allowing molecules to distinguish one cell from another. Blood markers are exclusively made from four monosaccharides: D-galactose, L-fucose, N-acetylgalactosamine, and N-acetylglucosamine.

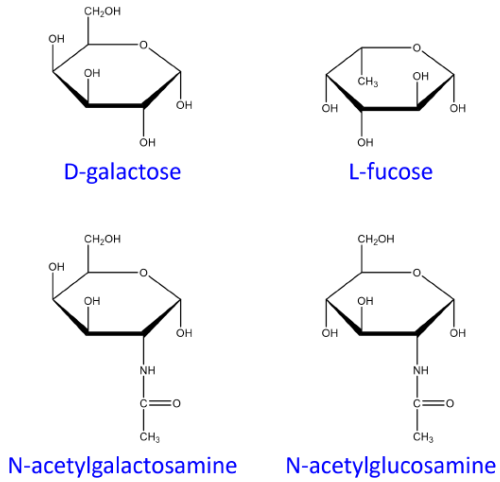


Figure **5.1.12.1**: Structures of monosaccharide units present in ABO blood markers

ABO blood markers found on red blood cells are made up of oligosaccharides that contain either three or four sugar units as shown below. Oligosaccharides attached to red blood cells determine the ABO blood type.

Of the four blood types, type O has the fewest types of saccharides attached to it while type AB has the most. As a result, type O blood is considered the universal donor because it doesn't have any saccharides present that will appear as foreign when transfused

into blood of another type. The reverse is not true. For example:

- If type A blood is given to a patient with type O blood, it will be rejected by the body because there is an unknown species being introduced to the body. Type A blood cells contain N-acetylgalactosamine which is not present in type O blood.
- Since type AB blood has all possible saccharides, type AB blood is considered the **universal acceptor**.

The Rhesus factor (Rh) in blood also affects donor and acceptor properties but it does not depend on carbohydrates. The Rh factor is determined by the presence (Rh+) or absence (Rh-) of a specific protein on the surface of red blood cells.

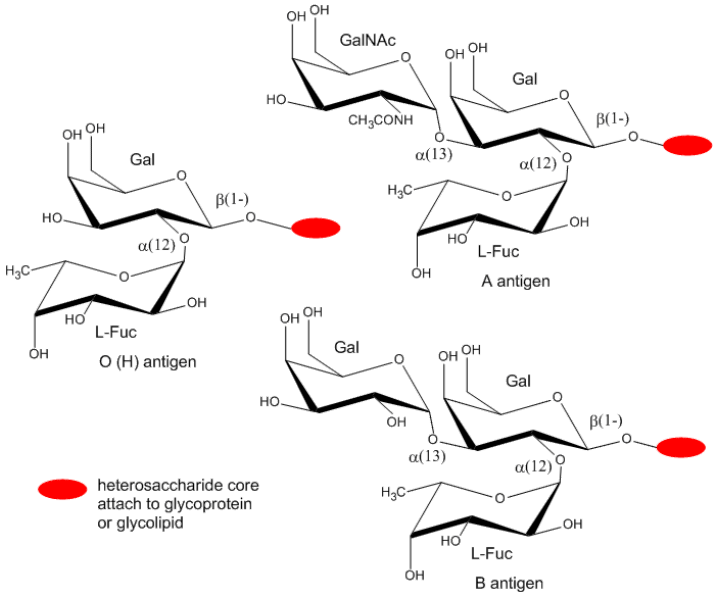


Figure 5.1.12.2: ABO blood types.

Influenza and the Avian Flu

Three pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957;
- the "Hong Kong" flu pandemic of 1968;
- the "Swine" flu pandemic that began in April of 2009.

The influenza virus is a simple yet deadly virus. It interacts with human cells through a surface protein, hemagglutinin (HA). The virus binds to host cells through interaction of HA with cell surface carbohydrates. Once bound the virus internalizes, ultimately leading to release of the RNA genome of the virus into the host cell. The HA protein is the most abundant protein on the viral surface (as surmised by antibody formation).

The influenza virus is typically classified by two kinds of glycoproteins on the surface of the virus: in addition to HA is the enzyme neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1 which stands for hemagglutinin (H: type 5 or type 1) and neuraminidase (N: type 1). 15 avian and mammalian variants have been identified (based on antibody studies). Only 3 adapted to humans in the last 100 yr, giving pandemic strains H1 (1918), H2 (957) and H3 (1968). Three recent avian variants (H5, H7, and H9) have jumped directly to humans recently but have low human to human transmissibility.

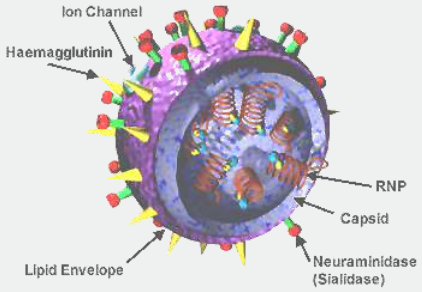
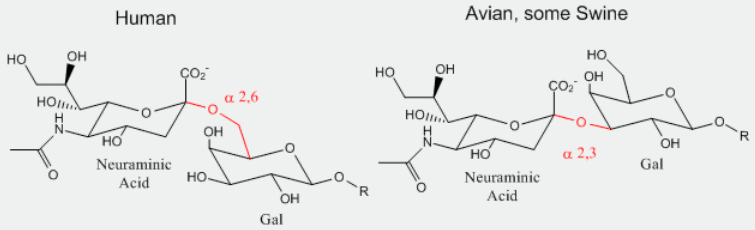


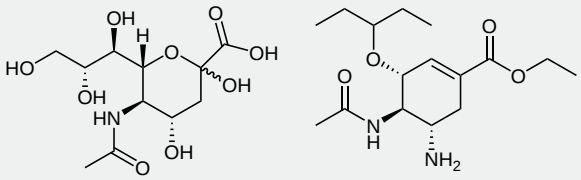
Figure **5.1.12.3**: Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Health via Wikipedia)

Influenza Virus binds to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus. Hemagluttinin binds to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins. The sialic acid is usually connected through an alpha (2,3) or alpha (2,6) link to galactose on N-linked glycoproteins. The subtypes found in avian (and equine) influenza isolates bind preferentially to Sia (alpha 2,3) Gal which predominates in avian GI tract where viruses replicate. Human virus of H1, H2, and H3 subtype (cause of the 1918, 1957, and 1968 pandemics) recognize Sia (alpha 2,6) Gal, as the major form in the human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3) both of which are commonly found in swine.

Binding Site for Influenza Hemagluttinin Protein



The virus, before it leaves the cell, forms a bud on the intracellular side of the cell with the HA and NA in the cell membrane of the host cell. The virus in this state would not leave the cell since its HA molecules would interact with sialic acid residues in the host cell membrane, holding the virus in the membrane. Neuraminidase hydrolyzes sialic acid from cell surface glycoproteins, allowing the virus to complete the budding process and be released from the cell as new viruses. By mimicking the structure of sialic acid, the drugs Oseltamivir (Tamiflu) and zanamivir (Relenza) bind to and inhibit neuraminidase whose activity is necessary for viral release from infected cells. Tamiflu appears to work against N1 of the present H5N1 avian influenza viruses. Governments across the world are stockpiling this drug in case of a pandemic caused by the avian virus jumping directly to humans and becoming transmissible from human to human.



Sialic Acid **Tamiflu**

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5.1.S: Biomolecules- Carbohydrates (Summary)

Concepts & Vocabulary

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes and ketones.
- Examples of carbohydrates are starch, fibers, sugar, and cellulose.
- Green plants use glucose for energy or making larger carbohydrates.
- Carbohydrates are needed for the synthesis of nucleic acids, proteins, and lipids.
- Animals rely on plants to provide them with carbohydrates, which are used for food and clothing.

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynthesis.
- The generic formula is $C_n(H_2O)_n$.
- Carbohydrates play a vital role in a major food source, but are also used as structural material, recognition sites on cells, and other tasks.
- Carbohydrates are called saccharides and can be classified as simple or complex.

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multiple chiral centers are present in a molecule.
- In a Fischer projection:
  - the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines.
  - the two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon).
  - the two vertical bonds are directed behind the central carbon (away from the viewer).
- Determining whether a chiral carbon is R or S
  - If the lowest priority group is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents.
  - If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer, so you reverse it.
- Epimer is used to designate diastereomers that differ in configuration at only one chiral center.

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arbitrary choice that (+)-glucose would be the D-family and related aldoses.
- The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Emil Fischer as the D / L designator site.
- The L-family is the mirror image of the D-family.
- If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family.
- A left directed hydroxyl group then represented the L-family.
- It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L).
- Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

25.5 Configurations of Aldoses

- The aldose family is composed of three to six carbon atoms.
- Emil Fischer determined a way to determine absolute configuration of aldoses.

- In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet, proved that Fischer's choice was correct.

25.6 Anomers

- The preferred structural form of monosaccharides is a cyclic hemiacetal, especially for five and six-membered rings due to low angle strain and eclipsing strain.
- Five-membered cyclic sugars are termed furanose and six-membered cyclic sugars are pyranose.
- By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer.
- The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula.
- In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring.
- The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.
- Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.
- When a straight-chain monosaccharide forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers.
    - When the OH group on the first carbon atom projected downward, this is called the *alpha (α) form*.
    - When the OH group on the first carbon atom pointed upward, is the *beta (β) form*.
- These two stereoisomers of a cyclic monosaccharide are known as anomers.
- You can start with a pure crystalline sample of glucose consisting entirely of one anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer.
- The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation.

25.7 Reactions of Monosaccharides

- The -OH groups on a monosaccharide can be readily converted to esters and ethers.
- Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides.
- Phosphorylation of the -OH group using ATP.
- Oxidation can occur with the monosaccharides, which is why some sugars are classified as reducing.
- When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an aldonic acid.
- If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid.
- Sodium borohydride reduction of an aldose makes the ends of the resulting alditol chain identical like aldaric acid.
- Monosaccharides can react to have the chain length increased or decreased, which can be important in elucidation of the carbohydrate's structure.

25.8 The Eight Essential Monosaccharides

- The eight essential monosaccharides are: L-fructose, D-galactose, D-glucose, D-mannose, N-acetyl-D-glucosamine, N-acetyl-D-galacosamine, D-xylose, N-acetyl-D-neuraminic acid.
- These eight monosaccaharides are obtained through diet.

25.9 Disaccharides

- Disaccharides are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage.
- The glycosidic linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.
- The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them.
- There are three common disaccharides: maltose, lactose, and sucrose.

- Maltose is two glucose molecules linked in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule.
- Lactose is composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond.
- Sucrose is has an α-1,β-2-glycosidic (head-to-head) linkage, which is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages.
- The three most abundant polysaccharides are starch, glycogen, and cellulose.

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated pattern of a sugar group and a phosphate group, the sugar present - deoxyribose.
- An amino sugar is a sugar molecule in which a hydroxyl group has been replaced with an amine group.

25.12 Cell-Surface Carbohydrates and Influenza Viruses

- Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins.
- Glycoproteins and glycolipids are often found in biological membranes that allow other biomolecules to interact and bind to the protein.
- Bacteria and viruses often recognize glycosylated molecules on cell membranes, allowing for their import into the cell.
- This is how the influenza virus enters the body.

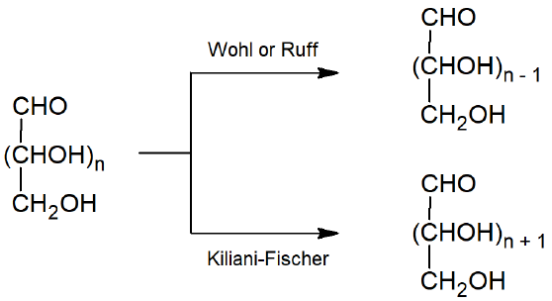
Skills to Master

- Skill 25.1 Determine which molecules can be classified as carbohydrates.
- Skill 25.2 Distinguish between monosaccharide, disaccharide, and trisaccharides given the structure.
- Skill 25.3 Classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.
- Skill 25.4 Draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
- Skill 25.5 Draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
- Skill 25.6 Construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.
- Skill 25.7 Identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
- Skill 25.8 Assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
- Skill 25.9 Draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
- Skill 25.10 Draw configurations of aldoses.
- Skill 25.11 Determine whether a given monosaccharide will exist as a pyranose or furanose.
- Skill 25.12 Draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
- Skill 25.13 Determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
- Skill 25.14 Describe the phenomenon known as mutarotation.
- Skill 25.15 Explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
- Skill 25.16 Predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
- Skill 25.17 Identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
- Skill 25.18 Predict the product that would be produced by the Wohl degradation of a given aldose.
- Skill 25.19 Identify the aldose that would yield a given product following Wohl degradation synthesis.
- Skill 25.20 Identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
- Skill 25.21 Identify the two monosaccharide units in a given disaccharide.
- Skill 25.22 Identify the type of glycoside link (e.g., 1,4′-*β*) present in a given disaccharide structure.

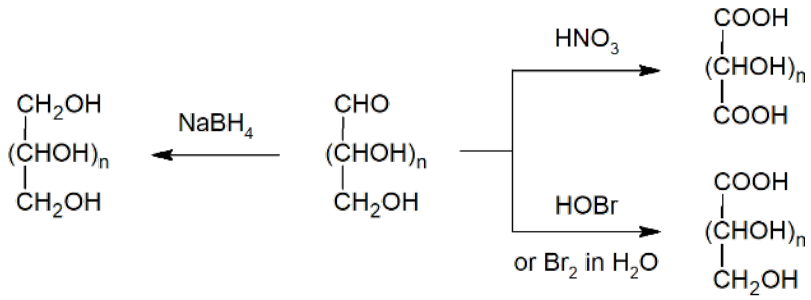
- Skill 25.23 Draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.
- Skill 25.24 Identify the products formed from the hydrolysis of a given disaccharide.

Summary of Reactions

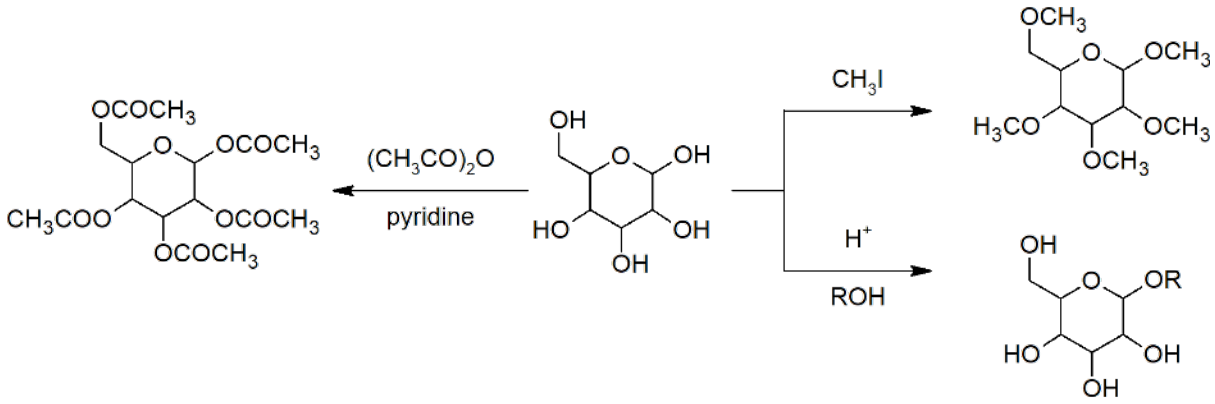
Chain Length



Oxidation - Reduction



Ester and Ether Formation



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SECTION OVERVIEW

5.2: Biomolecules- Amino Acids, Peptides, and Proteins

Learning Objectives

When you have completed Chapter 26, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. use the information provided by an amino acid analysis, an Edman degradation and a carboxypeptidase hydrolysis to determine the structure of an unknown polypeptide.
3. outline the approach that you would use to synthesize a given peptide, providing appropriate mechanistic details if requested to do so.
4. define, and use in context, the key terms introduced in this chapter.

Amino acids are important biochemicals, as they are the building blocks from which proteins and polypeptides are assembled. We begin this chapter with an examination of some of the fundamental chemistry of amino acids: their structures, stereochemistry and synthesis. We then discuss the nature of peptides and of the peptide bond, and present the complex issue of determining the order in which the various amino-acid residues occur in a given peptide. Once a chemist knows the exact order the of the residues in a given peptide, the next challenge is to determine a method by which the same peptide can be prepared in the laboratory. Thus, two sections are devoted to the problem of protein synthesis. The final sections in the chapter deal with the classification, overall structure and denaturation of proteins.

5.2.1: Introduction

5.2.2: Structures of Amino Acids

5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points

5.2.4: Synthesis of Amino Acids

5.2.5: Peptides and Proteins

5.2.6: Amino Acid Analysis of Peptides

5.2.7: The Edman Degradation

5.2.8: Peptide Synthesis

5.2.9: The Merrifield Solid-Phase Technique

5.2.10: Protein Structure

5.2.11: Enzymes and Coenzymes

5.2.12: How do Enzymes Work? Citrate Synthase

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5.2.1: Introduction

Objectives

After completing this section, you should be able to

1. give examples of the various biological roles played by proteins.
2. identify amino acids as being the building blocks from which all proteins are made.
3. show, in a general way, how the joining together of a number of amino acids through the formation of peptide bonds results in the formation of proteins.

Key Terms

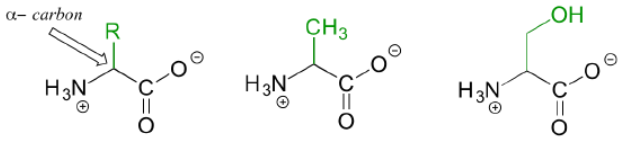
Make certain that you can define, and use in context, the key terms below.

- amino acid
- enzyme
- peptide bond
- protein

Study Notes

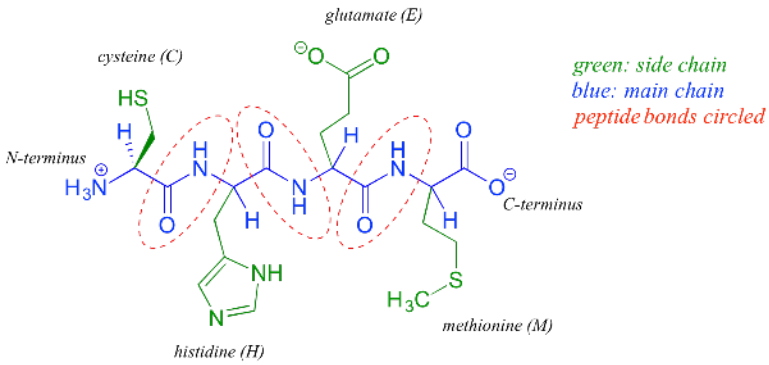
The “peptide bond” or “peptide linkage” that is formed between the amino group of one amino acid and the carboxyl group of a second amino acid is identical to the C$\ce{-}$N bond present in amides (see Section 21.7). We shall review the nature of such bonds in Section 26.4.

Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded to the alpha-carbon.



There are twenty different side chains in naturally occurring amino acids, and it is the identity of the side chain that determines the identity of the amino acid: for example, if the side chain is a -CH_3 group, the amino acid is alanine, and if the side chain is a -CH_2OH group, the amino acid is serine. Many amino acid side chains contain a functional group (the side chain of serine, for example, contains a primary alcohol), while others, like alanine, lack a functional group, and contain only a simple alkane.

The two 'hooks' on an amino acid monomer are the amine and carboxylate groups. Proteins (polymers of ~50 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. Which amino acids are linked, and in what order - the protein **sequence** - is what distinguishes one protein from another, and is coded for by an organism's DNA. Protein sequences are written in the amino terminal (N-terminal) to carboxylate terminal (C-terminal) direction, with either three-letter or single-letter abbreviations for the amino acids (see amino acid table). Below is a four amino acid peptide with the sequence "cysteine - histidine - glutamate - methionine". Using the single-letter code, the sequence is abbreviated CHEM.



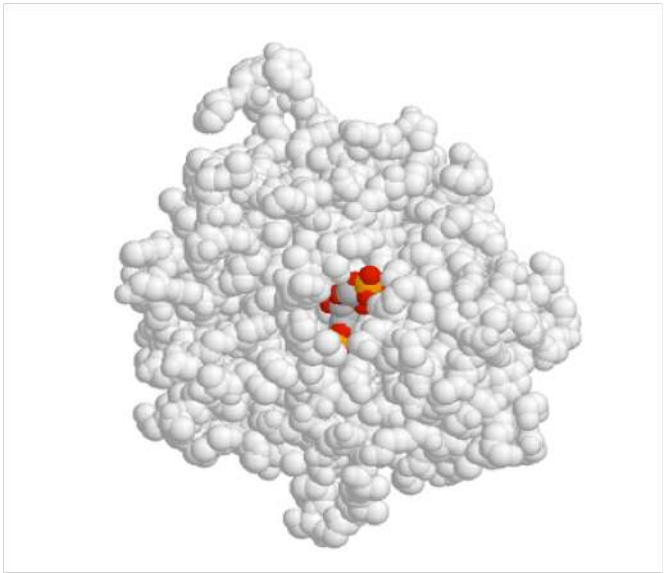
CHEM peptide

When an amino acid is incorporated into a protein it loses a molecule of water and what remains is called a **residue** of the original amino acid. Thus we might refer to the 'glutamate residue' at position 3 of the CHEM peptide above.

Once a protein polymer is constructed, it in many cases folds up very specifically into a three-dimensional structure, which often includes one or more 'binding pockets' in which other molecules can be bound. It is this shape of this folded structure, and the precise arrangement of the functional groups within the structure (especially in the area of the binding pocket) that determines the function of the protein.

Enzymes are proteins which catalyze biochemical reactions. One or more reacting molecules - often called **substrates** - become bound in the **active site** pocket of an enzyme, where the actual reaction takes place. **Receptors** are proteins that bind specifically to one or more molecules - referred to as **ligands** - to initiate a biochemical process. For example, we saw in the introduction to this chapter that the TrpVI receptor in mammalian tissues binds capsaicin (from hot chili peppers) in its binding pocket and initiates a heat/pain signal which is sent to the brain.

Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase (in grey), with the substrate molecule bound inside the active site pocket.



(x-ray crystallographic data are from *Protein Science* **1999**, 8, *291*; pdb code 4ALD. Image produced with JMol First Glance)

Intro to nucleic acids ⇒

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5.2.2: Structures of Amino Acids

Objectives

After completing this section, you should be able to

1. identify the structural features present in the 20 amino acids commonly found in proteins.

   Note: You are not expected to remember the detailed structures of all these amino acids, but you should be prepared to draw the structures of the two simplest members, glycine and alanine.

2. draw the Fischer projection formula of a specified enantiomer of a given amino acid.

   Note: To do so, you must remember that in the *S* enantiomer, the carboxyl group appears at the top of the projection formula and the amino group is on the left.

3. classify an amino acid as being acidic, basic or neutral, given its Kekulé, condensed or shorthand structure.
4. draw the zwitterion form of a given amino acid.
5. account for some of the typical properties of amino acids (e.g., high melting points, solubility in water) in terms of zwitterion formation.
6. write appropriate equations to illustrate the amphoteric nature of amino acids.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- α-amino acids
- amphoteric
- essential amino acids
- zwitterion

Study Notes

This is a good point at which to review some of the principles of stereochemistry presented in Chapter 5. Be sure to make full use of molecular models when any stereochemical issues arise.

You should recognize that a three-letter shorthand code is often used to represent individual amino acids. You need not memorize this code.

The distinction between essential and nonessential amino acids is not as clear-cut as one might suppose. For example, arginine is often regarded as being nonessential.

Introduction to Amino Acids

Amino acids form polymers through a nucleophilic attack by the amino group of an amino acid at the electrophilic carbonyl carbon of the carboxyl group of another amino acid. The carboxyl group of the amino acid must first be activated to provide a better leaving group than OH^-. (We will discuss this activation by ATP later in the course.) The resulting link between the amino acids is an amide link which biochemists call a peptide bond. In this reaction, water is released. In a reverse reaction, the peptide bond can be cleaved by water (hydrolysis).

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

When two amino acids link together to form an amide link, the resulting structure is called a dipeptide. Likewise, we can have tripeptides, tetrapeptides, and other polypeptides. At some point, when the structure is long enough, it is called a protein. There are many different ways to represent the structure of a polypeptide or protein, each showing differing amounts of information.

Figure: Different Representations of a Polypeptide (Heptapeptide)

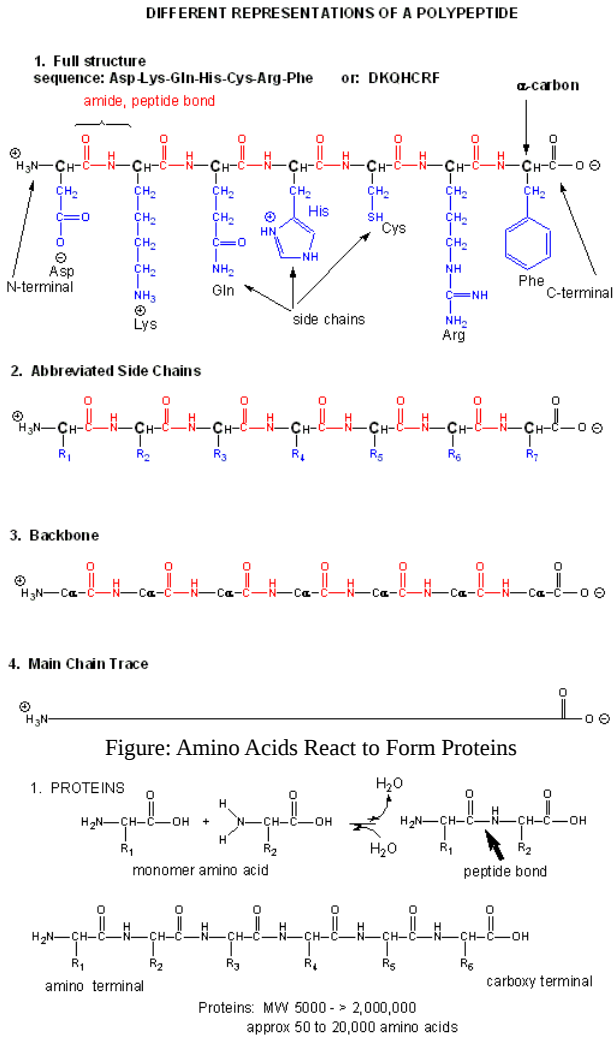


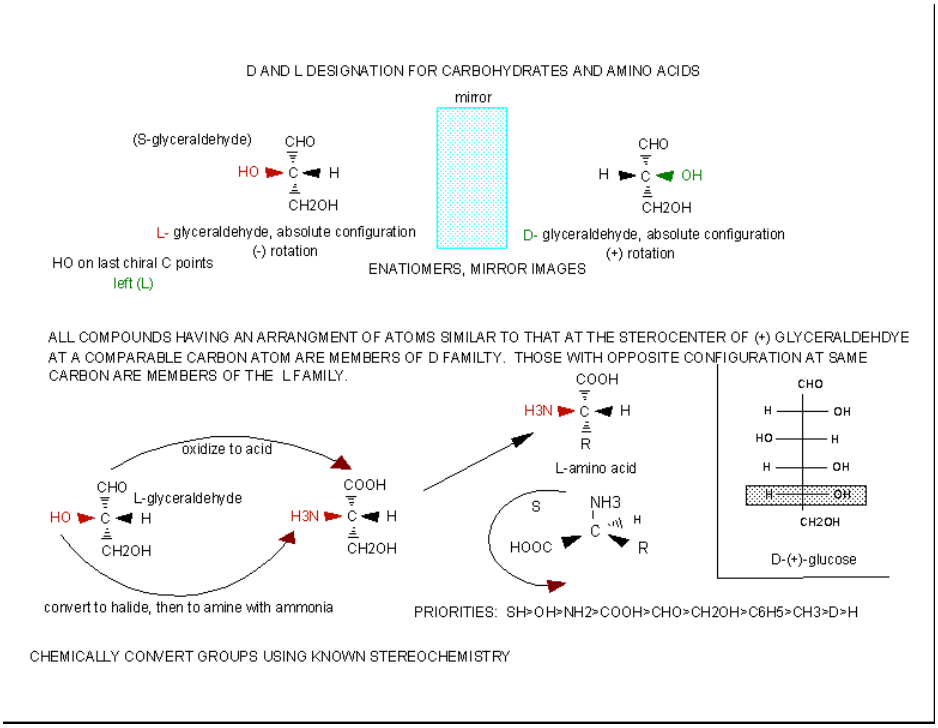
Figure: Amino Acids React to Form Proteins

(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. In contrast, nucleic acids are polymers of just 4 different monomeric nucleotides. Both the sequence of a protein and its total length differentiate one protein from another. Just for an octapeptide, there are over 25 billion different possible arrangements of amino acids. Compare this to just 65536 different oligonucleotides of 8 monomeric units (8mer). Hence the diversity of possible proteins is enormous.

Stereochemistry

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L and D nomenclature. All naturally occuring proteins from all living organisms consist of L amino acids. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids. Most naturally occurring chiral amino acids are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

Figure: *Stereochemistry of Amino Acids.*



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

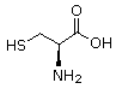
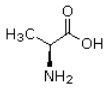
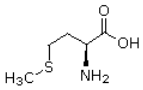
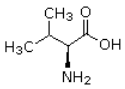
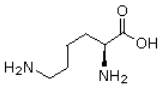
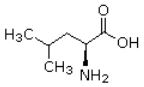
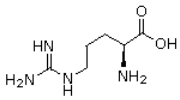
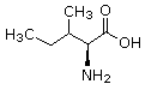
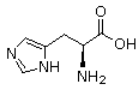
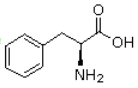
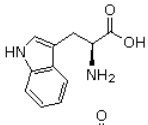
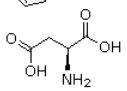
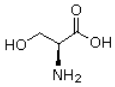
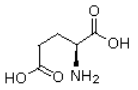
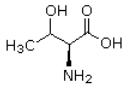
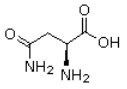
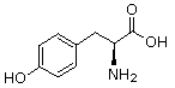
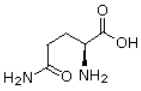
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules. For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), but this just reflects the human decision to give a sulphur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D and L: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like amino acids and simple sugars. "

Natural α-Amino Acids

Hydrolysis of proteins by boiling aqueous acid or base yields an assortment of small molecules identified as α-aminocarboxylic acids. More than twenty such components have been isolated, and the most common of these are listed in the following table. Those amino acids having green colored names are **essential** diet components, since they are not synthesized by human metabolic processes. The best food source of these nutrients is protein, but it is important to recognize that not all proteins have equal nutritional value. For example, peanuts have a higher weight content of protein than fish or eggs, but the proportion of essential amino acids in peanut protein is only a third of that from the two other sources. For reasons that will become evident when discussing the structures of proteins and peptides, each amino acid is assigned a one or three letter abbreviation.

Natural α-Amino Acids

Name	Formula	Abbreviations		Name	Formula	Abbreviations	
Glycine		Gly	G	Cysteine		Cys	C
Alanine		Ala	A	Methionine		Met	M
Valine		Val	V	Lysine		Lys	K
Leucine		Leu	L	Arginine		Arg	R
Isoleucine		Ile	I	Histidine		His	H
Phenylalanine		Phe	F	Tryptophan		Trp	W
Proline		Pro	P	Aspartic Acid		Asp	D
Serine		Ser	S	Glutamic Acid		Glu	E
Threonine		Thr	T	Asparagine		Asn	N
Tyrosine		Tyr	Y	Glutamine		Gln	Q


L-Amino Acid

Some common features of these amino acids should be noted. With the exception of proline, they are all 1°-amines; and with the exception of glycine, they are all chiral. The configurations of the chiral amino acids are the same when written as a Fischer projection formula, as in the drawing on the right, and this was defined as the **L-configuration** by Fischer. The R-substituent in this structure is the remaining structural component that varies from one amino acid to another, and in proline R is a three-carbon chain that joins the nitrogen to the alpha-carbon in a five-membered ring. Applying the Cahn-Ingold-Prelog notation, all these natural chiral amino acids, with the exception of cysteine, have an **S**-configuration. For the first seven compounds in the left column the R-substituent is a hydrocarbon. The last three entries in the left column have hydroxyl functional groups, and the first two amino acids in the right column incorporate thiol and sulfide groups respectively. Lysine and arginine have basic amine functions in their side-chains; histidine and tryptophan have less basic nitrogen heterocyclic rings as substituents. Finally, carboxylic acid side-chains are substituents on aspartic and glutamic acid, and the last two compounds in the right column are their corresponding amides.

The formulas for the amino acids written above are simple covalent bond representations based upon previous understanding of mono-functional analogs. **The formulas are in fact incorrect**. This is evident from a comparison of the physical properties listed in the following table. All four compounds in the table are roughly the same size, and all have moderate to excellent water solubility. The first two are simple carboxylic acids, and the third is an amino alcohol. All three compounds are soluble in organic solvents (e.g. ether) and have relatively low melting points. The carboxylic acids have pK_a's near 4.5, and the conjugate acid of the amine has a pK_a of 10. The simple amino acid alanine is the last entry. By contrast, it is very high melting (with decomposition), insoluble in organic solvents, and a million times weaker as an acid than ordinary carboxylic acids.

Physical Properties of Selected Acids and Amines

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 ºC	5.0
lactic acid	$CH_3CH(OH)CO_2H$	90	complete	complete	53 ºC	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 ºC	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 ºC	9.8

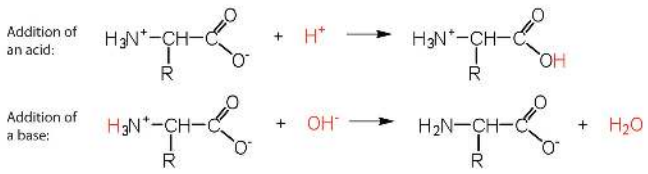
Zwitterion

These differences above all point to internal salt formation by a proton transfer from the acidic carboxyl function to the basic amino group. The resulting ammonium carboxylate structure, commonly referred to as a **zwitterion**, is also supported by the spectroscopic characteristics of alanine.



As expected from its ionic character, the alanine zwitterion is high melting, insoluble in nonpolar solvents and has the acid strength of a 1º-ammonium ion. Examples of a few specific amino acids may also be viewed in their favored neutral zwitterionic form. Note that in lysine the amine function farthest from the carboxyl group is more basic than the alpha-amine. Consequently, the positively charged ammonium moiety formed at the chain terminus is attracted to the negative carboxylate, resulting in a coiled conformation.

The structure of an amino acid allows it to act as both an acid and a base. An amino acid has this ability because at a certain pH value (different for each amino acid) nearly all the amino acid molecules exist as zwitterions. If acid is added to a solution containing the zwitterion, the carboxylate group captures a hydrogen (H^+) ion, and the amino acid becomes positively charged. If base is added, ion removal of the H^+ ion from the amino group of the zwitterion produces a negatively charged amino acid. In both circumstances, the amino acid acts to maintain the pH of the system—that is, to remove the added acid (H^+) or base (OH^-) from solution.

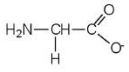


Example 26.1

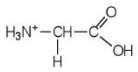
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.

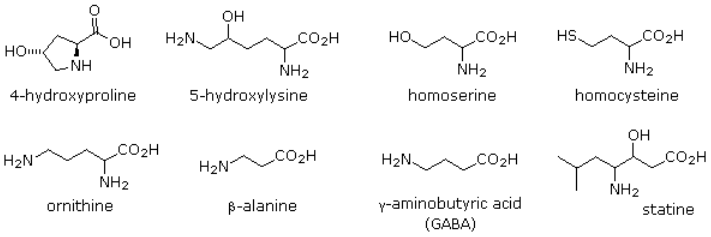


The acid adds H^+ to the carboxylate group.



Other Natural Amino Acids

The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound. These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.



Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

Exercises

Questions

Q26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Q26.1.2

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

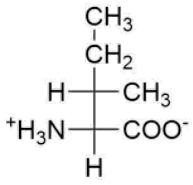
Solutions

S26.1.1

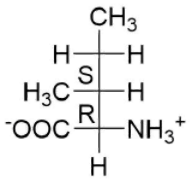
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

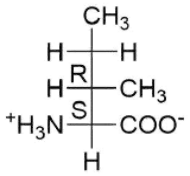
S26.1.2

(a)



(b)





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5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points

Objectives

After completing this section, you should be able to

1. draw the predominant form of a given amino acid in a solution of known pH, given the isoelectric point of the amino acid.
2. describe, briefly, how a mixture of amino acids may be separated by paper electrophoresis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- electrophoresis
- isoelectric point

Since amino acids, as well as peptides and proteins, incorporate both acidic and basic functional groups, the predominant molecular species present in an aqueous solution will depend on the pH of the solution. In order to determine the nature of the molecular and ionic species that are present in aqueous solutions at different pH's, we make use of the **Henderson-Hasselbalch Equation**, written below. Here, the pK_a represents the acidity of a specific conjugate acid function (HA). When the pH of the solution equals pK_a, the concentrations of HA and $A^{(-)}$ must be equal (log 1 = 0).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-]}$$

The titration curve for alanine in Figure **5.2.3.2** demonstrates this relationship. At a pH lower than 2, both the carboxylate and amine functions are protonated, so the alanine molecule has a net positive charge. At a pH greater than 10, the amine exists as a neutral base and the carboxyl as its conjugate base, so the alanine molecule has a net negative charge. At intermediate pH's the zwitterion concentration increases, and at a characteristic pH, called the **isoelectric point** (**pI**), the negatively and positively charged molecular species are present in equal concentration. This behavior is general for simple (difunctional) amino acids. Starting from a fully protonated state, the pK_a's of the acidic functions range from 1.8 to 2.4 for $-CO_2H$, and 8.8 to 9.7 for $-NH_3^{(+)}$. The isoelectric points range from 5.5 to 6.2. Titration curves show the neutralization of these acids by added base, and the change in pH during the titration.

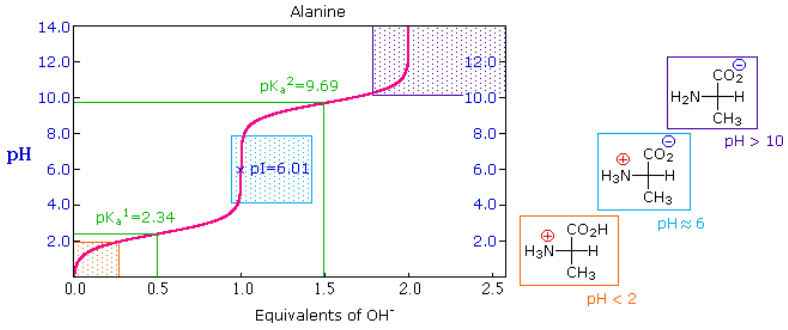


Figure **5.2.3.1**: Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.

The distribution of charged species in a sample can be shown experimentally by observing the movement of solute molecules in an electric field, using the technique of **electrophoresis** (Figure **5.2.3.2**). For such experiments an ionic buffer solution is incorporated in a solid matrix layer, composed of paper or a crosslinked gelatin-like substance. A small amount of the amino acid, peptide or protein sample is placed near the center of the matrix strip and an electric potential is applied at the ends of the strip, as shown in the following diagram. The solid structure of the matrix retards the diffusion of the solute molecules, which will remain where they are inserted, unless acted upon by the electrostatic potential.

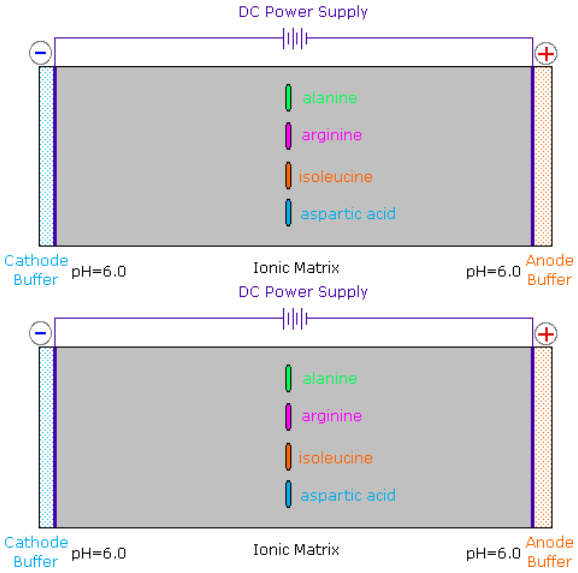
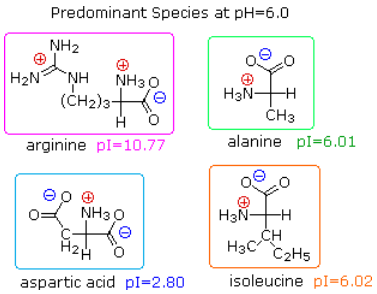


Figure **5.2.3.2**: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

At pH 6.00 alanine and isoleucine exist on average as neutral zwitterionic molecules, and are not influenced by the electric field. Arginine is a basic amino acid. Both base functions exist as "onium" conjugate acids in the pH 6.00 matrix. The solute molecules of arginine therefore carry an excess positive charge, and they move toward the cathode. The two carboxyl functions in aspartic acid are both ionized at pH 6.00, and the negatively charged solute molecules move toward the anode in the electric field. Structures for all these species are shown to the right of the display.



It should be clear that the result of this experiment is critically dependent on the pH of the matrix buffer. If we were to repeat the electrophoresis of these compounds at a pH of 3.80, the aspartic acid would remain at its point of origin, and the other amino acids would move toward the cathode. Ignoring differences in molecular size and shape, the arginine would move twice as fast as the alanine and isoleucine because its solute molecules on average would carry a double positive charge.

As noted earlier, the titration curves of simple amino acids display two inflection points, one due to the strongly acidic carboxyl group (pK_a^1 = 1.8 to 2.4), and the other for the less acidic ammonium function (pK_a^2 = 8.8 to 9.7). For the 2º-amino acid proline, pK_a^2 is 10.6, reflecting the greater basicity of 2º-amines.

Table **5.2.3.1**: pKa Values of Polyfunctional Amino Acids

Amino Acid	α-CO_2H pK_a^1	α-NH_3 pK_a^2	Side Chain pK_a^3	pI
Arginine	2.1	9.0	12.5	10.8
Aspartic Acid	2.1	9.8	3.9	3.0
Cysteine	1.7	10.4	8.3	5.0
Glutamic Acid	2.2	9.7	4.3	3.2
Histidine	1.8	9.2	6.0	7.6
Lysine	2.2	9.0	10.5	9.8
Tyrosine	2.2	9.1	10.1	5.7

Some amino acids have additional acidic or basic functions in their side chains. These compounds are listed in Table **5.2.3.1**. A third pK_a, representing the acidity or basicity of the extra function, is listed in the fourth column of the table. The pI's of these amino acids (last column) are often very different from those noted above for the simpler members. As expected, such compounds display three inflection points in their titration curves, illustrated by the titrations of arginine and aspartic acid (Figure\ (\PageIndex{3}\)). For each of these compounds four possible charged species are possible, one of which has no overall charge. Formulas for these species are written to the right of the titration curves, together with the pH at which each is expected to predominate. The very high pH required to remove the last acidic proton from arginine reflects the exceptionally high basicity of the guanidine moiety at the end of the side chain.

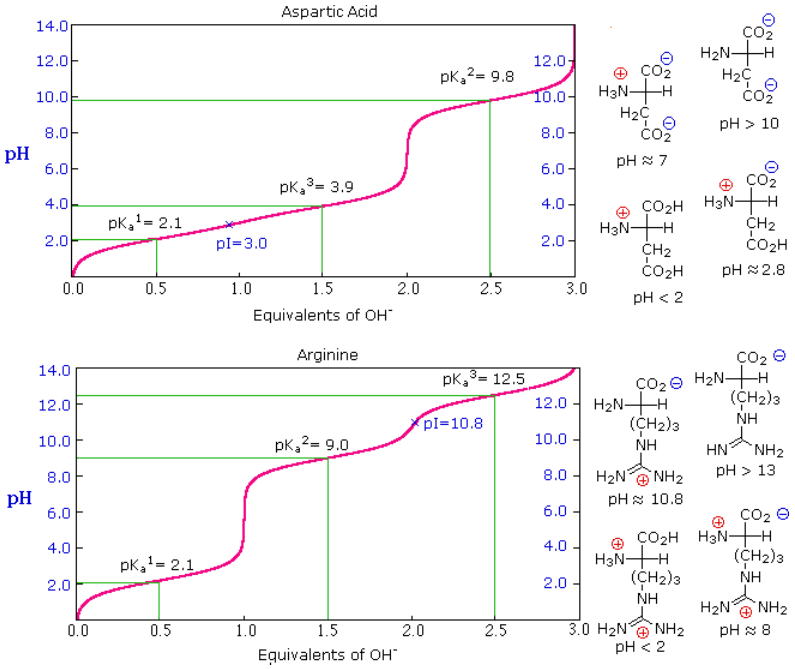


Figure **5.2.3.3**

The Isoelectric Point

The isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value. If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$). In the case of aspartic acid, the similar acids are the alpha-

carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 + 3.9)/2 = 3.0. For arginine, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75

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5.2.4: Synthesis of Amino Acids

Objectives

After completing this section, you should be able to

1. outline, by means of equations, how a racemic mixture of given amino acid can be prepared from a carboxylic acid using reactions you studied earlier in the course.
2. a. outline, by means of equations, the preparation of a given amino acid by the amidomalonate synthesis.
   b. identify the amino acid formed from using a given alkyl halide in an amidomalonate synthesis.
   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
   b. provide a brief example of how a biological method may be employed to resolve a racemic mixture of a given amino acid.
   c. show the enantioselective preparation of an amino acid from the corresponding *Z* enamido acid.

Key Terms

Make certain that you can define, and use in context, the key terms below.

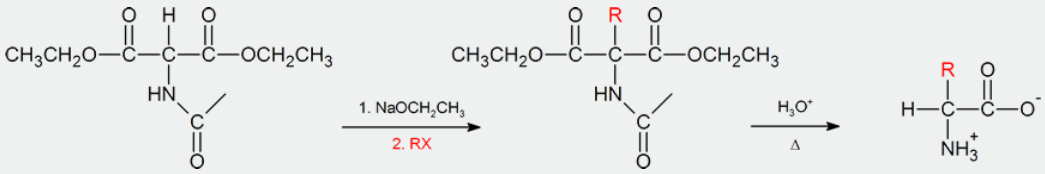
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Study Notes

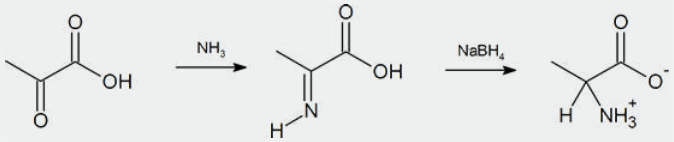
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

To fulfill the requirements of Objective 1, review the Hell-Volhard-Zelinskii reaction (Section 22.4) and the Gabriel phthalimide synthesis (Section 24.6).

The **amidomalonate synthesis** is a simple variation of the malonic ester synthesis (Section 22.7). A base abstracts a proton from the alpha carbon, which is then alkylated with an alkyl halide. Then both the hydrolysis of the esters and the amide protecting group under aqueous acidic conditions generates the α-amino acid.



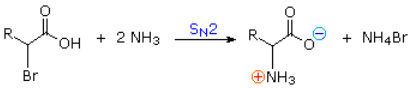
Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).



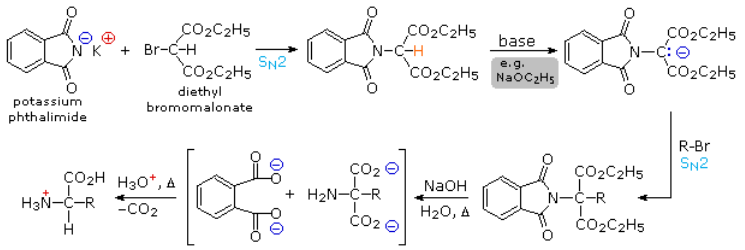
Synthesis of α-Amino Acids

1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with

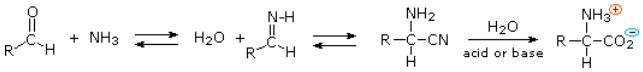
Br_2 + PCl_3. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1º- and many 2º-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).

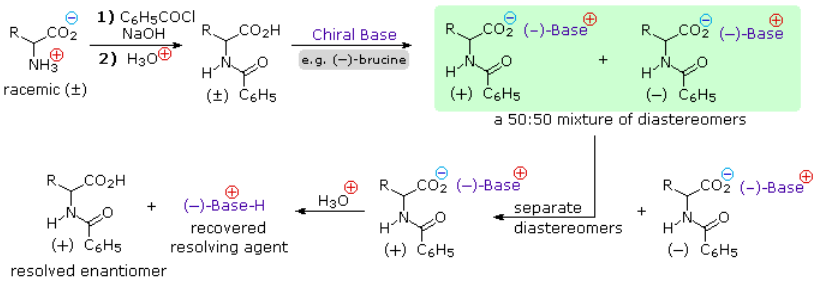


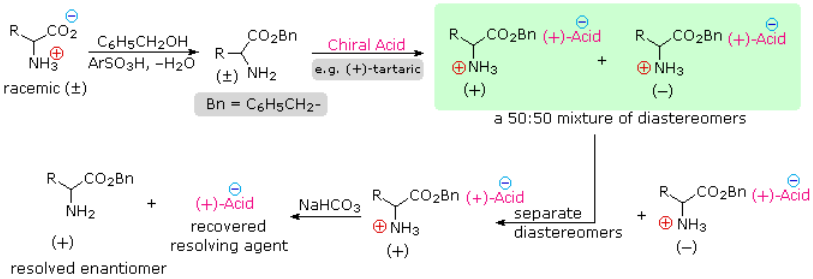
3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.



4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.





Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

Enantioselective Synthesis

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates production of almost pure L-DOPA.

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5.2.5: Peptides and Proteins

Objectives

After completing this section, you should be able to

1. a. show, by means of a diagram, how two different amino acid residues can be combined to give two different dipeptides.
   b. draw the structure of a relatively simple peptide, given its full or abbreviated name and the structures of the appropriate amino acids.
   c. draw, or name, the six possible isomeric tripeptides that can be formed by combining three different amino acid residues (amino acid units) of given structure.
2. account for the fact that there is restricted rotation about the C$\ce{-}$N bonds in peptides.
3. illustrate the formation of a disulfide linkage between two cysteine residues, and show how such bonds can link together two separate peptide chains or can provide a bridge between two cysteine residues present in a single peptide molecule.

Key Terms

Make certain that you can define, and use in context, the key terms below.

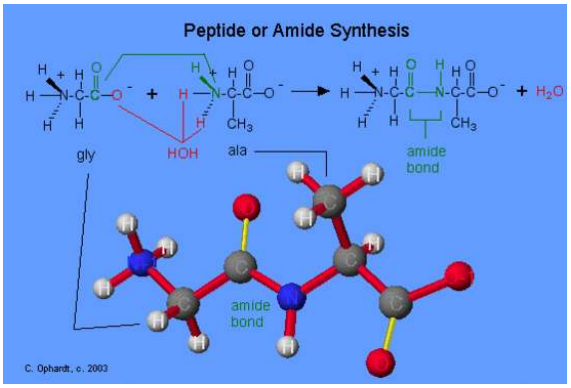
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

Study Notes

If necessary, review the discussion of the delocalization of the nitrogen lone-pair electrons in amides that was presented in Section 24.3. Similarly, you may wish to refer back to Section 18.8 to review the interconversion of thiols and disulfides.

Peptide Bond Formation or Amide Synthesis

The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) is on the right. The reaction of glycine with alanine to form the dipeptide glyclalanine is written as shown in the graphic on the left. Oxygen (red) from the acid and hydrogens (red) on the amine form a water molecule. The carboxyl oxygen (green) and the amine nitrogen (green) join to form the amide bond.



If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

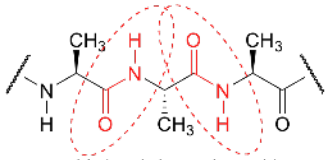
? Exercise 5.2.5.1

Write the reactions for:

a. ala + gly ---> Answer graphic
b. phe + ser ----> Answer graphic

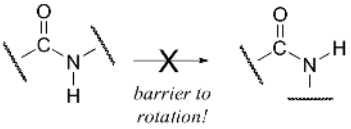
Resonance contributors for the peptide bonds

A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.

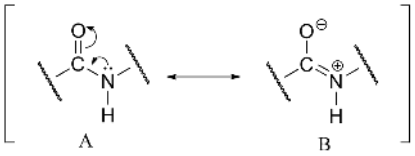


peptide bonds in a polypeptide

Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, the C-N bond in a peptide linkage has a significant barrier to rotation, almost as if it were a double bond.



This, along with the observation that the bonding around the peptide nitrogen has trigonal planar geometry, strongly suggests that the nitrogen is sp^2-hybridized. An important resonance contributor has a C=N double bond and a C-O single bond, with a separation of charge between the oxygen and the nitrogen.



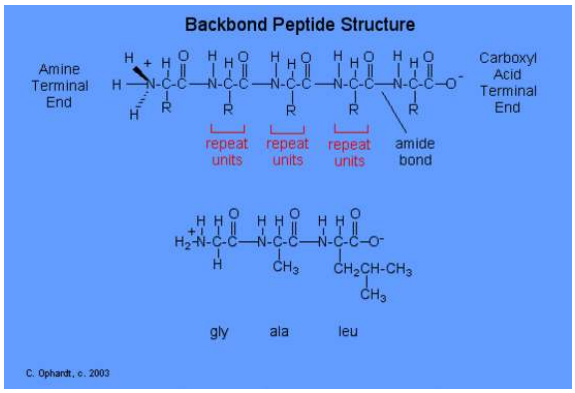
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

Backbone Peptide or Protein Structure

The structure of a peptide can be written fairly easily without showing the complete amide synthesis reaction by learning the structure of the "backbone" for peptides and proteins.

The peptide backbone consists of repeating units of "N-H 2, CH, C double bond O; N-H 2, CH, C double bond O; etc. See the graphic on the left .

After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as gly-ala-leu for this example. The amine end (N terminal) of an amino acid is always on the left (gly), while the acid end (C terminal) is on the right (leu).



? Exercise 5.2.5.2

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Solution

Answer graphic

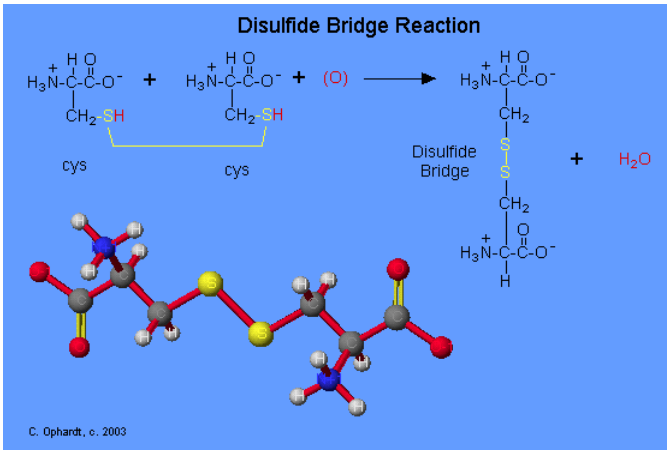
QUES. Write the structure for the tripeptide:

2 a) glu-cys-gly ---> Answer graphic

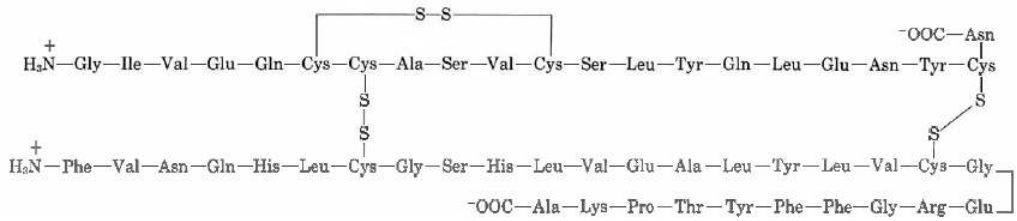
2 b) phe-tyr-asn ---> Answer graphic

Disulfide Bridges and Oxidation-Reduction

The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides an oxygen which reacts with the hydrogen (red) on the -SH group to form water. The sulfurs (yellow) join to make the **disulfide bridge**. This is an important bond to recognize in protein tertiary structure. The reduction of a disulfide bond is the opposite reaction which again leads to two separate cysteine molecules. Remember that reduction is the addition of hydrogen.



Cysteine residues in the the peptide chain can form a loop buy forming the disulfide bond (—S—S—), while cysteine residues in different peptide chains can actually link what were otherwise separate chains. Insulin was the first protein whose amino acid sequence was determined. This pioneering work, completed in 1953 after some 10 years of effort, earned a Nobel Prize for British biochemist Frederick Sanger (born 1918). He found the primary structure to comprise of two chains linked by two cysteine disulfide bridges. Also note the first peptide chain possesses an internal loop.



Insulin

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5.2.6: Amino Acid Analysis of Peptides

Objectives

After completing this section, you should be able to describe, briefly, how the identity and amounts of each amino acid residue present in a peptide of unknown structure may be determined.

Key Terms

Make certain that you can define, and use in context, the key term below.

- amino acid analyzer

Study Notes

You need not memorize the reaction between ninhydrin and an α-amino acid.

Ion-exchange chromatography

When a protein is to be analysed, it is first heated with acid to hydrolyse all the peptide bonds. When such a mixture of amino acids is to be purified and estimated quantitatively, ion-exchange chromatography is the technique of choice. Fully automated amino acid analyzers are now available, which are equipped with a solvent pump to deliver the required buffer(s) in a programmed manner. There is a column, filled with Dowex 50 resin (Fig 26.5.1). This solid support is made up of polymeric beads. Chemically speaking they are polymers bearing arylsulfonic acid groups. The cation exchange resin helps in the separation of amino acids. In a typical run (Fig 26.5.2), the eluent is a buffer. The pH value of the buffer could be varied as step elution or as gradient elution. The chromatogram shown in Fig 26.5.2 is a chromatogram run with gradient elution technique, using **ninhydrin** as the post column treatment. The detector is a UV detector scanning the wavelengths 570 nm and 440 nm.

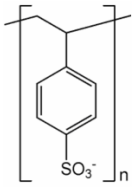


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

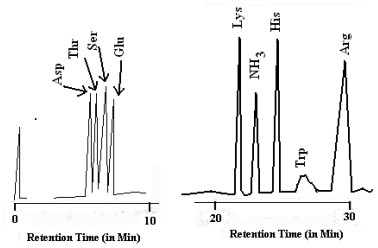
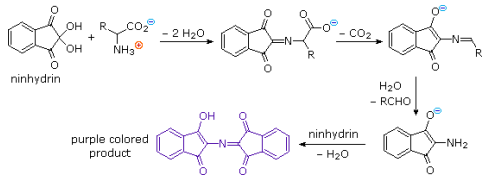


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

The Ninhydrin Reaction

Alpha-amino acids show reactivity at their the carboxylic acid and amine sites typical of those functional groups. In addition to these common reactions of amines and carboxylic acids, common alpha-amino acids, except proline, undergo a unique reaction with the triketohydrindene hydrate known as ninhydrin. Among the products of this unusual reaction (shown on the left below) is a purple colored imino derivative, which provides as a useful color test for these amino acids, most of which are colorless. A common application of the ninhydrin test is the visualization of amino acids in paper chromatography. As shown in the graphic on the right, samples of amino acids or mixtures thereof are applied along a line near the bottom of a rectangular sheet of paper (the baseline). The bottom edge of the paper is immersed in an aqueous buffer, and this liquid climbs slowly toward the top edge. As the solvent front passes the sample spots, the compounds in each sample are carried along at a rate which is characteristic of their functionality, size and interaction with the cellulose matrix of the paper. Some compounds move rapidly up the paper, while others may scarcely move at all. The ratio of the distance a compound moves from the baseline to the distance of the solvent front from the baseline is defined as the retardation (or retention) factor R_f. Different amino acids usually have different R_f's under suitable conditions. In the example on the right, the three sample compounds (1, 2 & 3) have respective R_f values of 0.54, 0.36 & 0.78.



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5.2.7: The Edman Degradation

Objectives

After completing this section, you should be able to

1. describe how an Edman degradation is used to determine the sequence of the amino acid residues in peptides containing up to 20 such residues.
2. describe, briefly, how the procedure is modified to deal with peptides and proteins containing more than 20 amino acid residues.
3. write a detailed mechanism for the Edman degradation.
4. determine the structure of a peptide, given a list of the fragments that are produced by a partial acid hydrolysis.
5. determine the structure of a peptide, given a list of the fragments that are produced when the peptide is cleaved by a specific enzyme and the details of the types of bonds cleaved by that enzyme.
6. predict the fragments that would be produced when a peptide of known structure is cleaved by a specific enzyme, given sufficient information about the types of bonds that are cleaved by the enzyme in question.

Key Terms

Make certain that you can define, and use in context, the key term below.

- Edman degradation

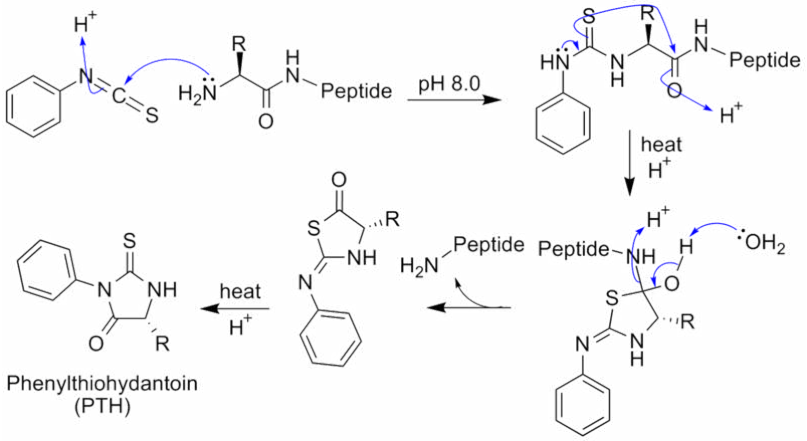
Study Notes

The reagent used in the Edman degradation is phenyl isothiocyanate. You may find it helpful to review the relationship between cyanates, isocyanates, thiocyanates and isothiocyanates.

R–O–C≡N	cyanate (such compounds do not exist)
R–N=C=O	isocyanate
R–S–C≡N	thiocyanate
R–N=C=S	isothiocyanate

You need not memorize the specific peptide bonds that are broken by the enzymes trypsin and chymotrypsin.

Edman degradation is the process of purifying protein by sequentially removing one residue at a time from the amino end of a peptide. To solve the problem of damaging the protein by hydrolyzing conditions, Pehr Edman created a new way of labeling and cleaving the peptide. Edman thought of a way of removing only one residue at a time, which did not damage the overall sequencing. This was done by adding Phenyl isothiocyanate, which creates a phenylthiocarbamoyl derivative with the N-terminal. The N-terminal is then cleaved under less harsh acidic conditions, creating a cyclic compound of phenylthiohydantoin PTH-amino acid. This does not damage the protein and leaves two constituents of the peptide. This method can be repeated for the rest of the residues, separating one residue at a time.



Edman degradation is very useful because it does not damage the protein. This allows sequencing of the protein to be done in less time. Edman sequencing is done best if the composition of the amino acid is known. As we saw in Section 26.5, to determine the composition of the amino acid, the peptide must be hydrolyzed. This can be done by denaturing the protein and heating it and adding HCl for a long time. This causes the individual amino acids to be separated, and they can be separated by ion exchange chromatography. They are then dyed with ninhydrin and the amount of amino acid can be determined by the amount of optical absorbance. This way, the composition but not the sequence can be determined

Sequencing Larger Proteins

Larger proteins cannot be sequenced by the Edman sequencing because of the less than perfect efficiency of the method. A strategy called divide and conquer successfully cleaves the larger protein into smaller, practical amino acids. This is done by using a certain chemical or enzyme which can cleave the protein at specific amino acid residues. The separated peptides can be isolated by chromatography. Then they can be sequenced using the Edman method, because of their smaller size.

In order to put together all the sequences of the different peptides, a method of overlapping peptides is used. The strategy of divide and conquer followed by Edman sequencing is used again a second time, but using a different enzyme or chemical to cleave it into different residues. This allows two different sets of amino acid sequences of the same protein, but at different points. By comparing these two sequences and examining for any overlap between the two, the sequence can be known for the original protein.

For example, trypsin can be used on the initial peptide to cleave it at the carboxyl side of arginine and lysine residues. Using trypsin to cleave the protein and sequencing them individually with Edman degradation will yield many different individual results. Although the sequence of each individual cleaved amino acid segment is known, the order is scrambled. Chymotrypsin, which cleaves on the carboxyl side of aromatic and other bulky nonpolar residues, can be used. The sequence of these segments overlap with those of the trypsin. They can be overlapped to find the original sequence of the initial protein. However, this method is limited in analyzing larger sized proteins (more than 100 amino acids) because of secondary hydrogen bond interference. Other weak intermolecular bonding such as hydrophobic interactions cannot be properly predicted. Only the linear sequence of a protein can be properly predicted assuming the sequence is small enough.

Contributors and Attributions

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5.2.8: Peptide Synthesis

Objectives

After completing this section, you should be able to

1. describe why it is necessary to protect certain amino and carboxyl groups during the synthesis of a peptide.
2. describe, using appropriate equations, how carboxyl groups are protected by ester formation and amino groups are protected by the formation of their *tert*-butoxycarbonyl amide derivatives.
3. write a detailed mechanism for the formation of a peptide link between an amino acid with a protected amino group and an amino acid with a protected carboxyl group using dicyclohexylcarbodiimide.
4. outline the five steps required in order to form a dipeptide from two given amino acids.

In order to synthesize a peptide from its component amino acids, two obstacles must be overcome. The first of these is statistical in nature, and is illustrated by considering the dipeptide Ala-Gly as a proposed target. If we ignore the chemistry involved, a mixture of equal molar amounts of alanine and glycine would generate four different dipeptides. These are: **Ala-Ala, Gly-Gly, Ala-Gly & Gly-Ala**. In the case of tripeptides, the number of possible products from these two amino acids rises to eight. Clearly, some kind of selectivity must be exercised if complex mixtures are to be avoided.

The second difficulty arises from the fact that carboxylic acids and 1º or 2º-amines do not form amide bonds on mixing, but will generally react by proton transfer to give salts (the intermolecular equivalent of zwitterion formation).

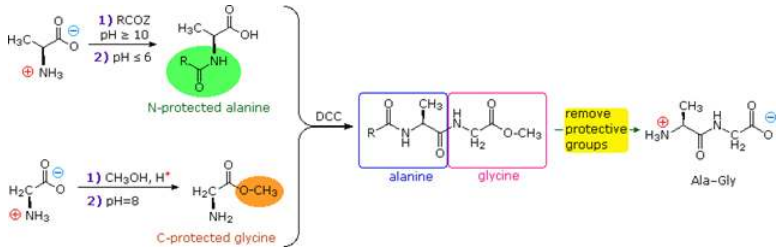
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated carboxyl function so that it will acylate the one remaining free amine. Fortunately, chemical reactions that permit us to accomplish these selections are well known.

First, the basicity and nucleophilicity of amines are substantially reduced by amide formation. Consequently, the acylation of amino acids by treatment with acyl chlorides or anhydrides at pH > 10, as described earlier, serves to protect their amino groups from further reaction.

Second, acyl halide or anhydride-like activation of a specific carboxyl reactant must occur as a prelude to peptide (amide) bond formation. This is possible, provided competing reactions involving other carboxyl functions that might be present are precluded by preliminary ester formation. Remember, esters are weaker acylating reagents than either anhydrides or acyl halides, as noted earlier.

Finally, dicyclohexylcarbodiimide (DCC) effects the dehydration of a carboxylic acid and amine mixture to the corresponding amide under relatively mild conditions. The structure of this reagent and the mechanism of its action have been described. Its application to peptide synthesis will become apparent in the following discussion.

The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.



An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the amino acids in the resulting peptide. This problem strikes at the heart of our strategy, so it is important to give careful thought to the design of specific N-protective groups. In particular, three qualities are desired:

1. The protective amide should be easy to attach to amino acids

1. The protective amide should be easy to attach to amino acids.
2. The protected amino group should not react under peptide forming conditions.
3. The protective amide group should be easy to remove under mild conditions.

A number of protective groups that satisfy these conditions have been devised; and two of the most widely used, **carbobenzoxy** (Cbz) and **t-butoxycarbonyl** (BOC or t-BOC), are described here.

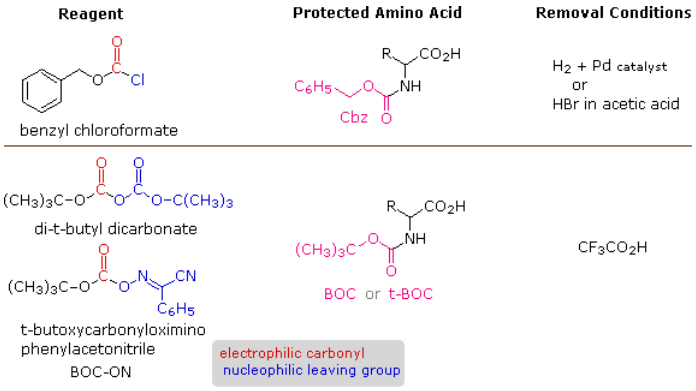


Figure_3.png" />

The reagents for introducing these N-protective groups are the acyl chlorides or anhydrides shown in the left portion of the above diagram. Reaction with a free amine function of an amino acid occurs rapidly to give the "protected" amino acid derivative shown in the center. This can then be used to form a peptide (amide) bond to a second amino acid. Once the desired peptide bond is created the protective group can be removed under relatively mild non-hydrolytic conditions. Equations showing the protective group removal will be displayed above by are shown above. Cleavage of the reactive benzyl or tert-butyl groups generates a common carbamic acid intermediate (HOCO-NHR) which spontaneously loses carbon dioxide, giving the corresponding amine. If the methyl ester at the C-terminus is left in place, this sequence of reactions may be repeated, using a different N-protected amino acid as the acylating reagent. Removal of the protective groups would then yield a specific tripeptide, determined by the nature of the reactants and order of the reactions.

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5.2.9: The Merrifield Solid-Phase Technique

Objectives

After completing this section, you should be able to describe, briefly, the Merrifield solid-phase technique for the synthesis of polypeptides.

Key Terms

Make certain that you can define, and use in context, the key term below.

- solid-phase method (solid-phase synthesis)

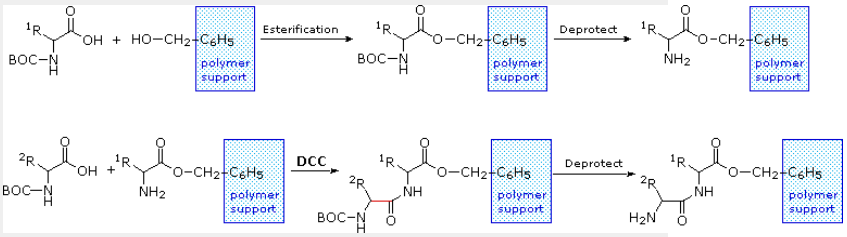
Study Notes

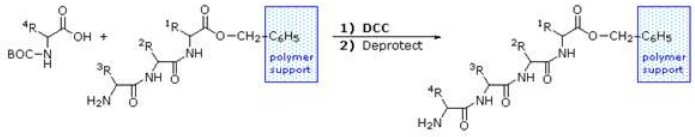
The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

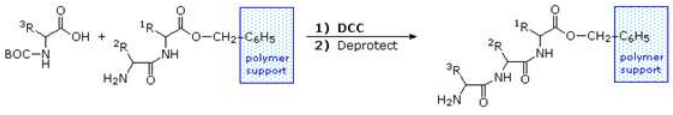
For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

The synthesis of a peptide of significant length (e.g. ten residues) by this approach requires many steps, and the product must be carefully purified after each step to prevent unwanted cross-reactions. To facilitate the tedious and time consuming purifications, and reduce the material losses that occur in handling, a clever modification of this strategy has been developed. This procedure, known as the **Merrifield Synthesis** after its inventor R. Bruce Merrifield, involves attaching the C-terminus of the peptide chain to a polymeric solid, usually having the form of very small beads. Separation and purification is simply accomplished by filtering and washing the beads with appropriate solvents. The reagents for the next peptide bond addition are then added, and the purification steps repeated. The entire process can be automated, and peptide synthesis machines based on the Merrifield approach are commercially available. A series of equations illustrating the Merrifield synthesis may be viewed below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage. This is not shown in the display.

The Merrifield Peptide Synthesis







Two or more moderately sized peptides can be joined together by selective peptide bond formation, provided side-chain functions are protected and do not interfere. In this manner good sized peptides and small proteins may be synthesized in the laboratory. However, even if chemists assemble the primary structure of a natural protein in this or any other fashion, it may not immediately adopt its native secondary, tertiary and quaternary structure. Many factors, such as pH, temperature and inorganic ion concentration influence the conformational coiling of peptide chains. Indeed, scientists are still trying to understand how and why these higher structures are established in living organisms.

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5.2.10: Protein Structure

Objectives

After completing this section, you should be able to

1. discuss, with reference to a suitable example (either given or of your own choice), the structure of proteins, paying particular attention to distinguishing between the primary, secondary, tertiary and quaternary structure.
2. describe the α-helical secondary structure displayed by many proteins.
3. describe the β-pleated-sheet structure displayed by many proteins.

Key Terms

Make certain that you can define, and use in context, the key terms below.

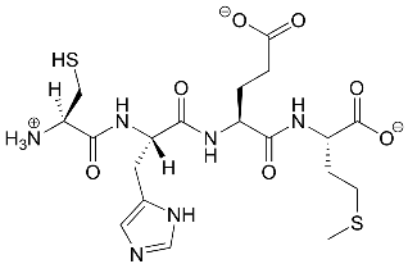
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

Study Notes

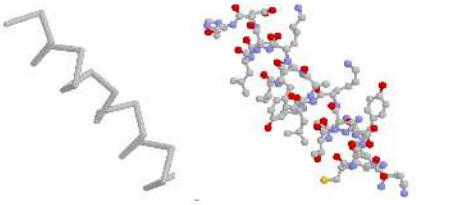
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

The four levels of protein structure

Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)

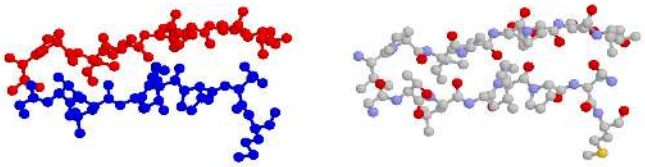


Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.



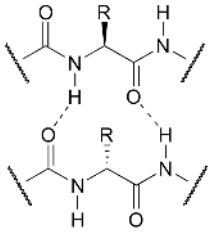
main chain view main chain + side chain

In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



Loops are relatively disordered segments of protein chain, but often assume a very ordered structure when in contact with a second protein or a smaller organic compound.

Both helix and the beta-sheet structures are held together by very specific hydrogen-bonding interactions between the amide nitrogen on one amino acid and the carbonyl oxygen on another. The hydrogen bonding pattern in a section of a beta-strand is shown below.



hydrogen bonding in a β-strand

Secondary structure refers to the shape of a folding protein due exclusively to hydrogen bonding between its backbone amide and carbonyl groups. Secondary structure does not include bonding between the R-groups of amino acids, hydrophobic interactions, or other interactions associated with tertiary structure. The two most commonly encountered secondary structures of a polypeptide chain are α-helices and beta-pleated sheets. These structures are the first major steps in the folding of a polypeptide chain, and they establish important topological motifs that dictate subsequent tertiary structure and the ultimate function of the protein.

α-Helices

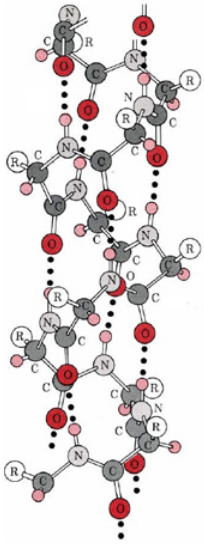


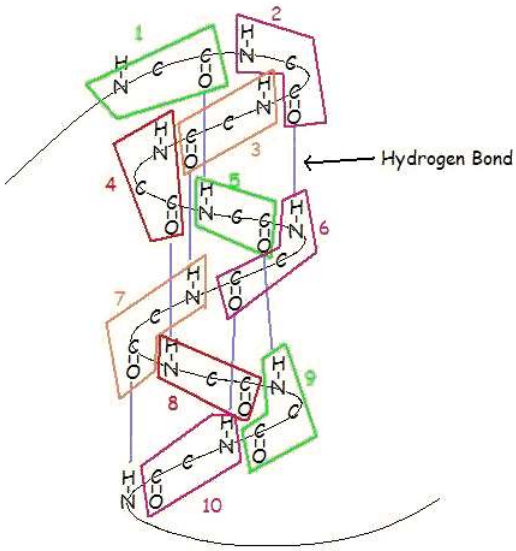
Figure 26.9.1 *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

An α-helix is a right-handed coil of amino-acid residues on a polypeptide chain, typically ranging between 4 and 40 residues. This coil is held together by hydrogen bonds between the oxygen of C=O on top coil and the hydrogen of N-H on the bottom coil. Such

a hydrogen bond is formed exactly every 4 amino acid residues, and every complete turn of the helix is only 3.6 amino acid residues. This regular pattern gives the α-helix very definite features with regards to the thickness of the coil and the length of each complete turn along the helix axis.

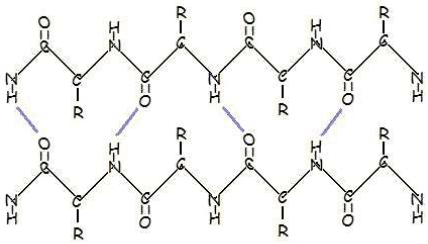
The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the nitrogen of the amide group, which causes steric hindrance. In addition, the lack of a hydrogen on Proline's nitrogen prevents it from participating in hydrogen bonding.

Another factor affecting α-helix stability is the total dipole moment of the entire helix due to individual dipoles of the C=O groups involved in hydrogen bonding. Stable α-helices typically end with a charged amino acid to neutralize the dipole moment.

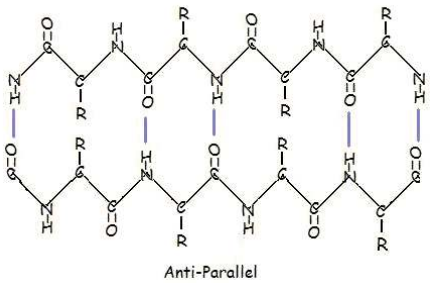


BETA-PLEATED SHEETS

This structure occurs when two (or more, e.g. ψ-loop) segments of a polypeptide chain overlap one another and form a row of hydrogen bonds with each other. This can happen in a parallel arrangement:


Parallel

Or in anti-parallel arrangement:


Anti-Parallel

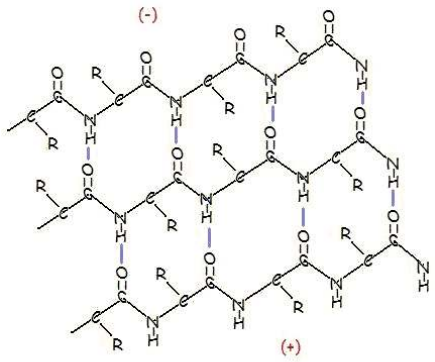
Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards each other to facing opposite directions.

The parallel arrangement is less stable because the geometry of the individual amino acid molecules forces the hydrogen bonds to occur at an angle, making them longer and thus weaker. Contrarily, in the anti-parallel arrangement the hydrogen bonds are aligned directly opposite each other, making for stronger and more stable bonds.

Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of a polypeptide chain to form beta-pleated sheets, but for proximal segments it is a definite requirement. For short distances, the two segments of a beta-pleated sheet are separated by 4+2n amino acid residues, with 4 being the minimum number of residues.

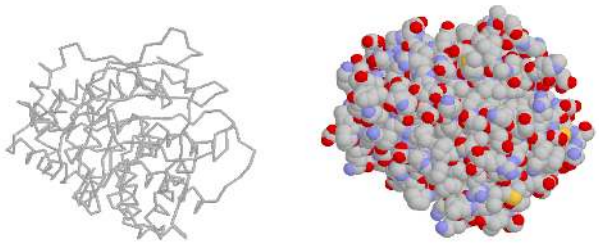
α-PLEATED SHEETS

A similar structure to the beta-pleated sheet is the α-pleated sheet. This structure is energetically less favorable than the beta-pleated sheet, and is fairly uncommon in proteins. An α-pleated sheet is characterized by the alignment of its carbonyl and amino groups; the carbonyl groups are all aligned in one direction, while all the N-H groups are aligned in the opposite direction. The polarization of the amino and carbonyl groups results in a net dipole moment on the α-pleated sheet. The carbonyl side acquires a net negative charge, and the amino side acquires a net positive charge.



Alpha-Pleated Sheet

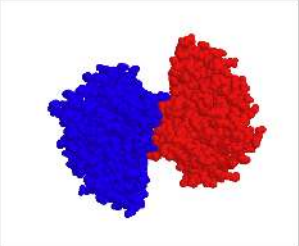
A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.



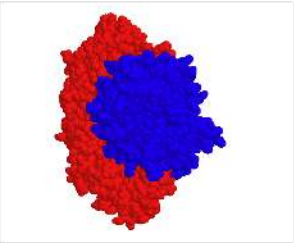
folded protein chain (main chain view)

folded protein chain ('space-filling' view)

While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have no quaternary structure. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers).

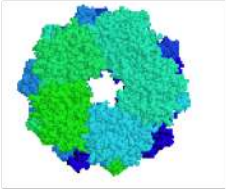


a homodimer

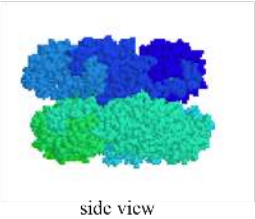


a heterodimer

Quaternary structures can be quite elaborate: below we see a protein whose quaternary structure is defined by ten identical subunits arranged in two five-membered rings, forming what can be visualized as a 'double donut' shape (this is fructose 1,6-bisphosphate aldolase):



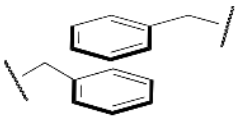
top view



side view

The molecular forces that hold proteins together

The question of exactly how a protein 'finds' its specific folded structure out of the vast number of possible folding patterns is still an active area of research. What *is* known, however, is that the forces that cause a protein to fold properly and to remain folded are the same basic noncovalent forces that we talked about in chapter 2: ion-ion, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic (van der Waals) interactions. One interesting type of hydrophobic interaction is called 'aromatic stacking', and occurs when two or more planar aromatic rings on the side chains of phenylalanine, tryptophan, or tyrosine stack together like plates, thus maximizing surface area contact.



Hydrogen bonding networks are extensive within proteins, with both side chain and main chain atoms participating. Ionic interactions often play a role in protein structure, especially on the protein surface, as negatively charged residues such as aspartate interact with positively-charged groups on lysine or arginine.

One of the most important ideas to understand regarding tertiary structure is that *a protein, when properly folded, is polar on the surface and nonpolar in the interior*. It is the protein's surface that is in contact with water, and therefore the surface must be hydrophilic in order for the whole structure to be soluble. If you examine a three dimensional protein structure you will see many charged side chains (e.g. lysine, arginine, aspartate, glutamate) and hydrogen-bonding side chains (e.g. serine, threonine, glutamine, asparagine) exposed on the surface, in direct contact with water. Inside the protein, out of contact with the surrounding water, there tend to be many more hydrophobic residues such as alanine, valine, phenylalanine, etc. If a protein chain is caused to come unfolded (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as the hydrophobic residues from the interior come into contact with water. You can see this phenomenon for yourself if you pour a little bit of vinegar (acetic acid) into milk. The solid clumps that form in the milk are proteins that have come unfolded due to the sudden acidification, and precipitated out of solution.

In recent years, scientists have become increasing interested in the proteins of so-called 'thermophilic' (heat-loving) microorganisms that thrive in hot water environments such as geothermal hot springs. While the proteins in most organisms (including humans) will rapidly unfold and precipitate out of solution when put in hot water, the proteins of thermophilic microbes remain completely stable, sometimes even in water that is just below the boiling point. In fact, these proteins typically only gain

full biological activity when in appropriately hot water - at room-temperature they act is if they are ‘frozen’. Is the chemical structure of these thermostable proteins somehow unique and exotic? As it turns out, the answer to this question is ‘no’: the overall three-dimensional structures of thermostable proteins look very much like those of ‘normal’ proteins. The critical difference seems to be simply that thermostable proteins have more extensive networks of noncovalent interactions, particularly ion-ion interactions on their surface, that provides them with a greater stability to heat. Interestingly, the proteins of ‘psychrophilic’ (cold-loving) microbes isolated from pockets of water in arctic ice show the opposite characteristic: they have far fewer ion-ion interactions, which gives them greater flexibility in cold temperatures but leads to their rapid unfolding in room temperature water.

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5.2.11: Enzymes and Coenzymes

Objectives

After completing this section, you should be able to

1. describe the catalytic role of an enzyme in a biochemical reaction.
2. give an example of one fat-soluble and one water-soluble vitamin.

Key Terms

Make certain that you can define, and use in context, the key term below.

- coenzyme
- cofactor
- enzyme
- substrate
- vitamin

Study Notes

You should have a general knowledge of the function of enzymes, but you need not memorize specific names or the classification system.

A **catalyst** is any substance that increases the *rate* or speed of a chemical reaction without being changed or consumed in the reaction. **Enzymes** are biological catalysts, and nearly all of them are proteins. In addition, enzymes are highly specific in their action; that is, each enzyme catalyzes only one type of reaction in only one compound or a group of structurally related compounds. The compound or compounds on which an enzyme acts are known as its **substrates**. Enzymes are classified by reaction type into six categories show in Table **5.2.11.1**.

Table **5.2.11.1**: ***Classes of Enzymes***

Class	Type of Reaction Catalyzed	Examples
oxidoreductases	oxidation-reduction reactions	Dehydrogenases catalyze oxidation-reduction reactions involving hydrogen and reductases catalyze reactions in which a subst reduced.
transferases	transfer reactions of groups, such as methyl, amino, and acetyl	Transaminases catalyze the transfer of amino group, and kinases catalyze the transfer of a phosphate group.
hydrolases	hydrolysis reactions	Lipases catalyze the hydrolysis of lipids, and proteases catalyze the hydrolysis of proteins
lyases	reactions in which groups are removed without hydrolysis or addition of groups to a double bond	Decarboxylases catalyze the removal of carboxyl groups.
isomerases	reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a ketose, and mutases catalyze reactions in which a functional group is tr from one atom in a substrate to another.
ligases	reactions in which new bonds are formed between carbon and another atom; energy is required	Synthetases catalyze reactions in which two smaller molecules are linked to form a larger one.

Enzyme-catalyzed reactions occur in at least two steps. In the first step, an enzyme molecule (E) and the substrate molecule or molecules (S) collide and react to form an intermediate compound called the *enzyme-substrate* (E–S) *complex* (Equation 5.2.11.1). This step is reversible because the complex can break apart into the original substrate or substrates and the free enzyme. Once the E–S complex forms, the enzyme is able to catalyze the formation of product (P), which is then released from the enzyme surface (Equation 5.2.11.2):

$$S + E \rightleftharpoons E\text{–}S \tag{5.2.11.1}$$

$$E\text{–}S \rightarrow P + E \tag{5.2.11.2}$$

Hydrogen bonding and other electrostatic interactions hold the enzyme and substrate together in the complex. The structural features or functional groups on the enzyme that participate in these interactions are located in a cleft or pocket on the enzyme surface. This pocket, where the enzyme combines with the substrate and transforms the substrate to product is called the active site of the

enzyme (Figure 5.2.11.1).

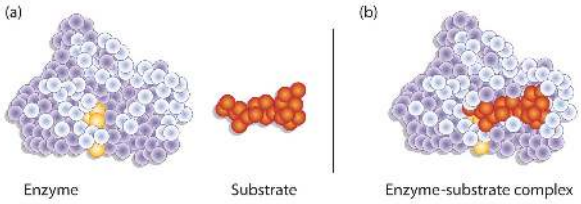


Figure 5.2.11.1: *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

The active site possesses a unique conformation (including correctly positioned bonding groups) that is complementary to the structure of the substrate, so that the enzyme and substrate molecules fit together in much the same manner as a key fits into a tumbler lock. In fact, an early model describing the formation of the enzyme-substrate complex was called the lock-and-key model (Figure 5.2.11.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

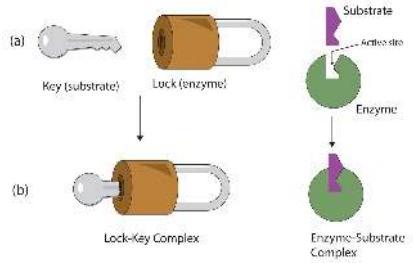


Figure 5.2.11.2: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

Working out the precise three-dimensional structures of numerous enzymes has enabled chemists to refine the original lock-and-key model of enzyme actions. They discovered that the binding of a substrate often leads to a large conformational change in the enzyme, as well as to changes in the structure of the substrate or substrates. The current theory, known as theinduced-fit model, says that enzymes can undergo a change in conformation when they bind substrate molecules, and the active site has a shape complementary to that of the substrate only after the substrate is bound, as shown for hexokinase in Figure 5.2.11.3. After catalysis, the enzyme resumes its original structure.

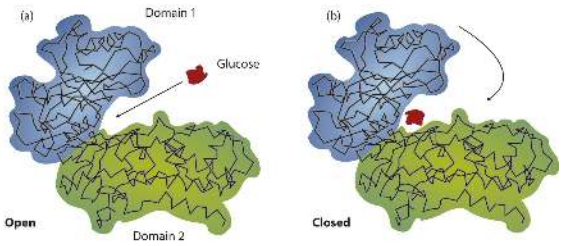


Figure 5.2.11.3: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

The structural changes that occur when an enzyme and a substrate join together bring specific parts of a substrate into alignment with specific parts of the enzyme's active site. Amino acid side chains in or near the binding site can then act as acid or base catalysts, provide binding sites for the transfer of functional groups from one substrate to another or aid in the rearrangement of a substrate. The participating amino acids, which are usually widely separated in the primary sequence of the protein, are brought close together in the active site as a result of the folding and bending of the polypeptide chain or chains when the protein acquires its tertiary and quaternary structure. Binding to enzymes brings reactants close to each other and aligns them properly, which has the same effect as increasing the concentration of the reacting compounds.

Example 5.2.11.1

a. What type of interaction would occur between an OH group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Solution

a. An OH group would most likely engage in hydrogen bonding with an appropriate functional group present in the active site of an enzyme.
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

Exercise 5.2.11.1

a. What type of interaction would occur between an COO^- group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Enzyme Cofactors and Vitamins

Many enzymes are simple proteins consisting entirely of one or more amino acid chains. Other enzymes contain a nonprotein component called a **cofactor** that is necessary for the enzyme's proper functioning. There are two types of cofactors: inorganic ions [e.g., zinc or Cu(I) ions] and organic molecules known as coenzymes. Most **coenzymes** are vitamins or are derived from vitamins.

Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They generally cannot be synthesized at adequate levels by the body and must be obtained from the diet. The absence or shortage of a vitamin may result in a vitamin-deficiency disease. In the first half of the 20th century, a major focus of biochemistry was the identification, isolation, and characterization of vitamins. Despite accumulating evidence that people needed more than just carbohydrates, fats, and proteins in their diets for normal growth and health, it was not until the early 1900s that research established the need for trace nutrients in the diet.

Table 5.2.11.2: Fat-Soluble Vitamins and Physiological Functions

Vitamin	Physiological Function	Effect of Deficien
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (softening of the bones); kn
vitamin E (tocopherol)	fat-soluble antioxidant	damage to cell memb
vitamin K (phylloquinone)	formation of prothrombin, a key enzyme in the blood-clotting process	increases the time required fo

Because organisms differ in their synthetic abilities, a substance that is a vitamin for one species may not be so for another. Over the past 100 years, scientists have identified and isolated 13 vitamins required in the human diet and have divided them into two broad categories: the *fat-soluble vitamins* (Table **5.2.11.2**), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table **5.2.11.3**). All fat-soluble vitamins contain a high proportion of hydrocarbon structural components. There are one or two oxygen atoms present, but the compounds as a whole are nonpolar. In contrast, water-soluble vitamins contain large numbers of electronegative oxygen and nitrogen atoms, which can engage in hydrogen bonding with water. Most water-soluble vitamins act as coenzymes or are required for the synthesis of coenzymes. The fat-soluble vitamins are important for a variety of physiological functions.

Table **5.2.11.3**: ***Water-Soluble Vitamins and Physiological Functions***

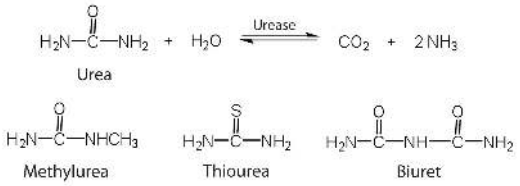
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Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vitamin B_3 (niacin)	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra
vitamin B_6 (py	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
riboxine)			
vitamin B_{12} (cyanocobalamin)	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia
pantothenic Acid	coenzyme A	carrier of acyl groups	—
vita	none	antioxidant; formation of collagen, a protein found in tendons, ligaments, and bone	scurvy

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
minC (ascorbic acid)			

One characteristic that distinguishes an enzyme from all other types of catalysts is its *substrate specificity*. An inorganic acid such as sulfuric acid can be used to increase the reaction rates of many different reactions, such as the hydrolysis of disaccharides, polysaccharides, lipids, and proteins, with complete impartiality. In contrast, enzymes are much more specific. Some enzymes act on a single substrate, while other enzymes act on any of a group of related molecules containing a similar functional group or chemical bond. Some enzymes even distinguish between D- and L-stereoisomers, binding one stereoisomer but not the other. Urease, for example, is an enzyme that catalyzes the hydrolysis of a single substrate—urea—but not the closely related compounds methyl urea, thiourea, or biuret. The enzyme carboxypeptidase, on the other hand, is far less specific. It catalyzes the removal of nearly any amino acid from the carboxyl end of any peptide or protein.



Enzyme specificity results from the uniqueness of the active site in each different enzyme because of the identity, charge, and spatial orientation of the functional groups located there. It regulates cell chemistry so that the proper reactions occur in the proper place at the proper time. Clearly, it is crucial to the proper functioning of the living cell.

Concept Review Exercises

1. Distinguish between the lock-and-key model and induced-fit model of enzyme action.
2. Which enzyme has greater specificity—urease or carboxypeptidase? Explain.

Answers

1. The lock-and-key model portrays an enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site. The induced fit model portrays the enzyme structure as more flexible and is complementary to the substrate only after the substrate is bound.
2. Urease has the greater specificity because it can bind only to a single substrate. Carboxypeptidase, on the other hand, can catalyze the removal of nearly any amino acid from the carboxyl end of a peptide or protein.

Takeaways

- A substrate binds to a specific region on an enzyme known as the active site, where the substrate can be converted to product.
- The substrate binds to the enzyme primarily through hydrogen bonding and other electrostatic interactions.
- The induced-fit model says that an enzyme can undergo a conformational change when binding a substrate.
- Enzymes exhibit varying degrees of substrate specificity.

Exercises

1. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. COOH
   b. NH_3^+
   c. OH
   d. $CH(CH_3)_2$
2. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. SH
   b. NH_2
   c. C_6H_5
   d. COO^-
3. For each functional group in Exercise 1, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.
4. For each functional group in Exercise 2, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.

Answers

1. a. hydrogen bonding
   b. ionic bonding
   c. hydrogen bonding
   d. dispersion forces

3. a. The amino acid has a polar side chain capable of engaging in hydrogen bonding; serine (answers will vary).
   b. The amino acid has a negatively charged side chain; aspartic acid (answers will vary).
   c. The amino acid has a polar side chain capable of engaging in hydrogen bonding; asparagine (answers will vary).
   d. The amino acid has a nonpolar side chain; isoleucine (answers will vary).

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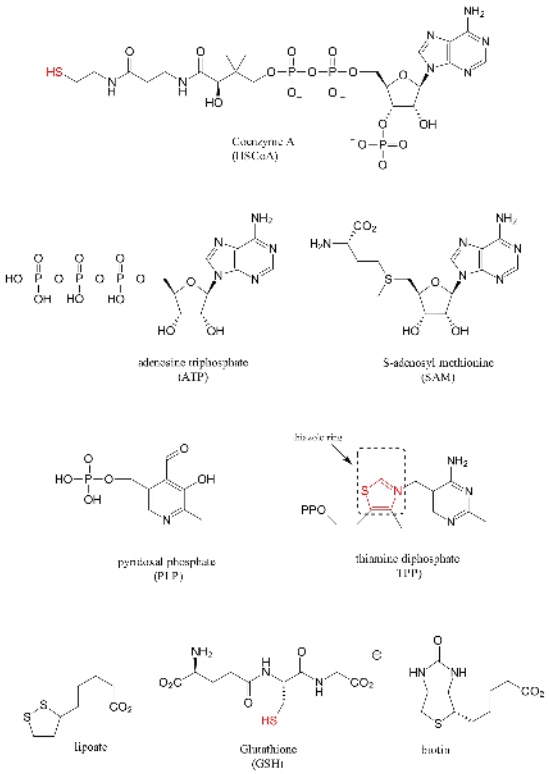
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5.2.12: How do Enzymes Work? Citrate Synthase

Objectives

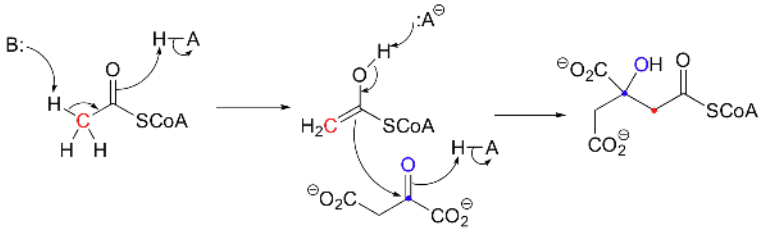
After completing this section, you should be able to

1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.

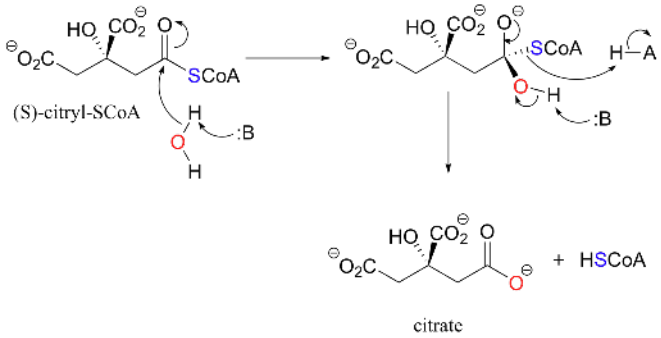


Oxaloacetate to Citrate Catalyzed by Citrate Synthase

Citrate synthase is a protein with 433 amino acids with various functional groups that can react with substrates. This enzyme catalyzes oxaloacetate to eventually produce citrate as part of the citric acid (Krebs) cycle. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA. The carboxylate group of an aspartic acid (B:) on citrate synthase removes the acidic alpha proton on acetyl CoA, while a histidine site (H-A) donates a proton to form the enol. Then a second histidine site (H-A) protonates the carbonyl oxygen of oxaloacetate, while the carbon of the carbonyl is attacked by the enol. Simultaeously, that first histidine ($:A^-$) deprotonates the acetyl CoA enol. (S)-citryl CoA is generated.



The acyl group of a thioester of (S)-citryl CoA can be transferred to a water molecule in a hydrolysis reaction to converting (S)-citryl CoA to citrate. Again histidine sites on citrate synthase are an integral part of the mechanism and assist with removal and addition of protons.



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5.3: Biomolecules - Lipids

Learning Objectives

- When you have completed Chapter 27, you should be able to
- fulfill all of the detailed objectives listed under each individual section.
- distinguish among fats and oils, phospholipids, prostaglandins, terpenes and steroids, and be familiar with the sources and biological roles of these substances.
- define, and use in context, the key terms introduced in this chapter.

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5.3.1: Introduction to Lipids

Objectives

After completing this section, you should be able to identify fats and steroids as being examples of lipids.

Key Terms

Make certain that you can define, and use in context, the key term below.

- lipid

Lipids are naturally occurring organic compounds that can be extracted from cells and tissues using nonpolar solvents. Although many lipids have complex structures, their chemistry can often be understood quite readily by applying the basic concepts you have studied in previous chapters. We begin the chapter with a study of fats and oils, and explain the different origins of these structurally similar substances. A discussion of soaps follows, as soap is obtained by the reaction of a fat with sodium hydroxide. Phospholipids are substances whose structures are somewhat similar to those of fats, except that the former contain a phosphate group. Prostaglandins are lipids that play important roles in biological systems and are of great interest to those involved in the medical and pharmaceutical professions. Terpenoids form a series of compounds whose structural similarity can be seen through the application of the isoprene rule. The chapter concludes with a discussion of steroids, with particular attention being paid to the stereochemistry of these substances.

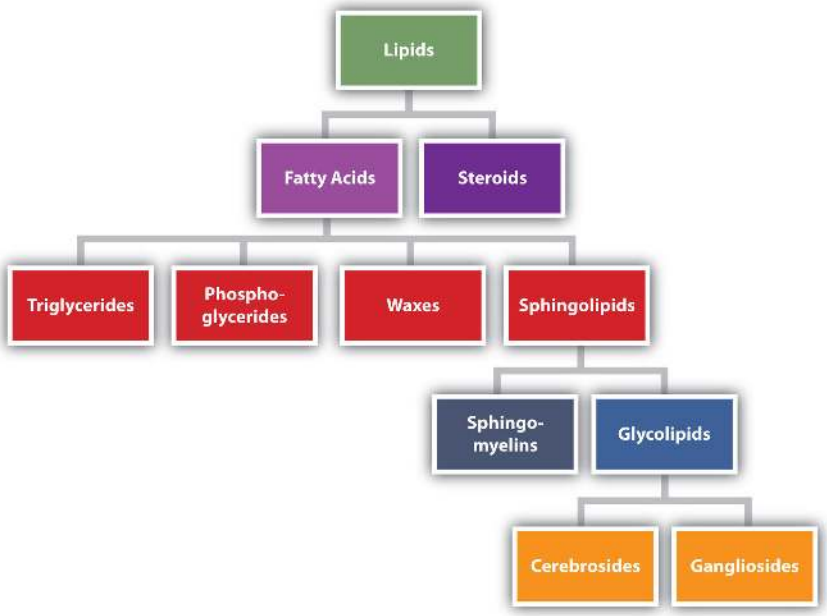


Figure **5.3.1.1**: Lipid Organization Based on Structural Relationships

Lipids are not defined by the presence of specific functional groups, as carbohydrates are, but by a physical property—solubility. Compounds isolated from body tissues are classified as lipids if they are more soluble in organic solvents, such as dichloromethane, than in water. By this criterion, the lipid category includes not only **fats and oils**, which are esters of the trihydroxy alcohol glycerol and fatty acids, but also compounds that incorporate functional groups derived from phosphoric acid, carbohydrates, or amino alcohols, as well as **steroid compounds** such as cholesterol. Figure **5.3.1.1** presents one scheme for classifying the various kinds of lipids.

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5.3.2: Waxes, Fats, and Oils

Objectives

After completing this section, you should be able to

1. identify waxes as being mixtures of long-chain esters, and write the general structure for such compounds.
2. identify fats and oils as being triacylglycerols, and write a general structure for such compounds.
3. relate the physical properties of animal fats and vegetable oils to their structures.
4. predict the behaviour of a given fat or oil when it is subjected to some of the more common reactions discussed in previous units; examples would include hydrolysis, reduction and ozonolysis.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- fat
- fatty acids
- triacylglycerols

Study Notes

You are not expected to memorize the trivial names or formulas of the fatty acids listed in Table **5.3.2.1**. The systematic names for these compounds are shown in the tables below.

Saturated Fatty Acids

Table **5.3.2.1**: Systematic names of some common saturated fatty acids

Trivial Name	Systematic Name
lauric acid	dodecanoic acid
myristic acid	tetradecanoic acid
palmitic acid	hexadecanoic acid
stearic acid	octadecanoic acid
arachidic acid	eicosanoic acid

Unsaturated Fatty Acids

Table **5.3.2.2**: Systematic names of some common unsaturated fatty acids

Trivial Name	Systematic Name
palmitoleic acid	(*Z*)-9-hexadecenoic acid
oleic acid	(*Z*)-9-octadecenoic acid
ricinoleic acid	(*Z*)-12-hydroxy-9-octadecenoic acid
linoleic acid	(*Z*,*Z*)-9,12-octadecadienoic acid
linolenic acid	(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid
arachidonic acid	(*Z*,*Z*,*Z*,*Z*)-5,8,11,14-eicosatetraenoic acid

The systematic names in these tables may be somewhat unfamiliar, but they are derived in exactly the same way as the names of the simpler carboxylic acids that we discussed in Chapter 20. You may wish to review the alkane names (Section 3.2) and the *E*,*Z* system (Section 7.5) to satisfy yourself that you understand how these names originate.

In many older textbooks, the term “fatty acid” is used to describe all carboxylic acids, not only those that are obtained from the hydrolysis of triacylglycerols.

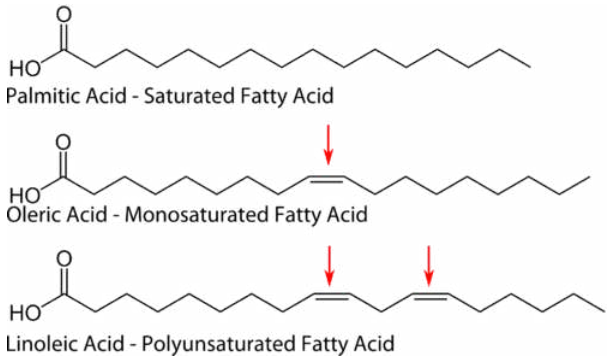
Fats play an important role in human nutrition, and most people are aware of the desirability of limiting their dietary intake of saturated fats, as these compounds have been associated with heart disease. Unsaturated fats are generally considered to be much more desirable from the point of view of good health. Notice that all the fatty acids derived from naturally occurring fats have a *Z* (i.e., cis) configuration.

Linoleic acid is an “essential” nutrient; that is, it cannot be made by the body in sufficient quantity to meet our physiological needs, and must be obtained from food. A deficiency in linoleic acid results in skin problems and liver abnormalities. Historically, linolenic and arachidonic acids were also thought to be essential nutrients, but recent research suggests that they can be synthesized in the body if sufficient linoleic acid is present.

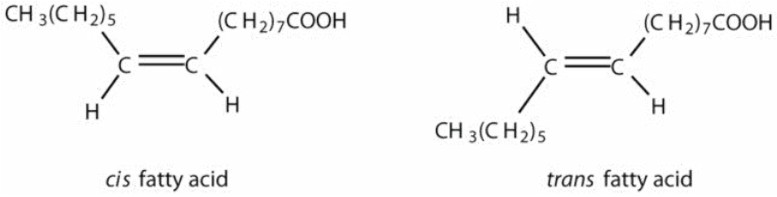
Fatty Acids

Fatty acids are structural components of fats, oils, and all other categories of lipids, except steroids. **Fatty acids** are long-chain carboxylic acids that have the general formula $CH_3(CH_2)_nCOOH$, where n usually ranges from 2 to 28 and is always an even number. More than 70 have been identified in nature. They are generally unbranched, and can be classified by the presence and number of carbon-to-carbon double bonds.

A **saturated fat** is a fat that consists of triglycerides whose carbon chains consist entirely of carbon-carbon single bonds. Therefore, the carbon chains are saturated with the maximum number of hydrogen atoms possible. An **unsaturated fat** is a fat that consists of triglycerides whose carbon chains contain one or more carbon-carbon double bonds. A fat with one double bond is called monounsaturated, while a fat with multiple double bonds is called polyunsaturated (see figure below).



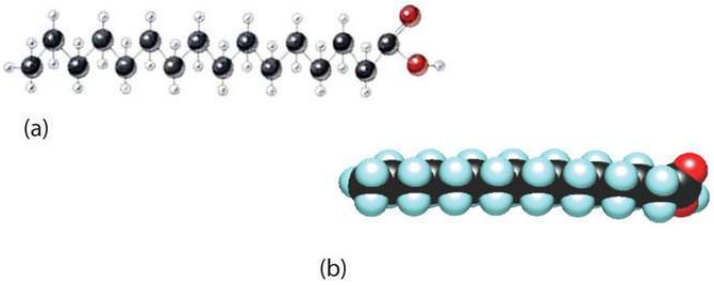
Each of the double bonds in unsaturated fatty acids can have either cis or trans stereochemistry and the type of fatty acid is further defined as a **cis fatty acid** or **trans fatty acid**. These are what are commonly referred to in food as cis or trans fats.



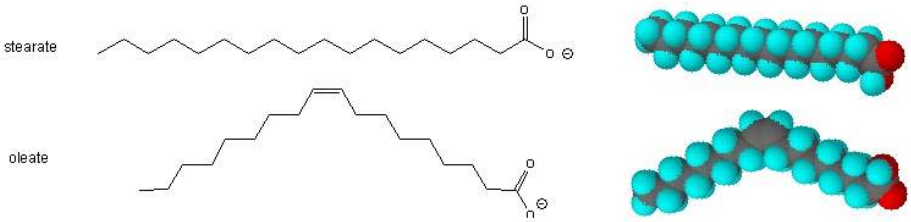
Saturated Fatty Acids		
Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

Unsaturated Fatty Acids		
Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

The higher melting points of the saturated fatty acids reflect the uniform rod-like shape of their molecules. Viewed as a whole, however, the saturated fatty acid molecule is relatively straight (Figure 17.1.2b). Such molecules pack closely together into a crystal lattice, maximizing the strength of dispersion forces and causing fatty acids and the fats derived from them to have relatively high melting points.



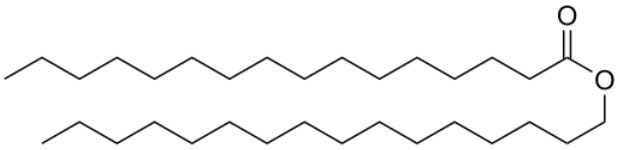
The cis-double bond(s) in the unsaturated fatty acids introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.



Waxes

Waxes are esters of long-chain fatty acids with long-chain monohydric alcohols (one hydroxyl group). The carboxylic acid and the alcohol typically each have an even number of carbons. Cetyl palmitate is a typical wax, it is the ester of cetyl alcohol (

$CH_3(CH_2)_{15}OH$) and palmitic acid ($CH_3(CH_2)_{14}COOH$). Most waxes have a similar structure.



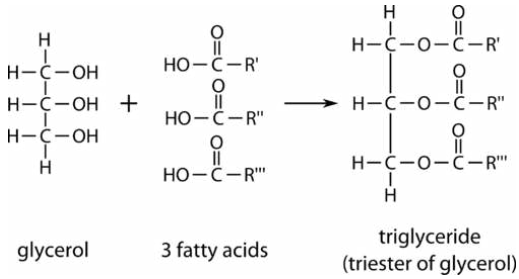
Cetyl palmitate, a typical wax ester.

Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water repellent. Carnauba wax is valued for its toughness and water resistance. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

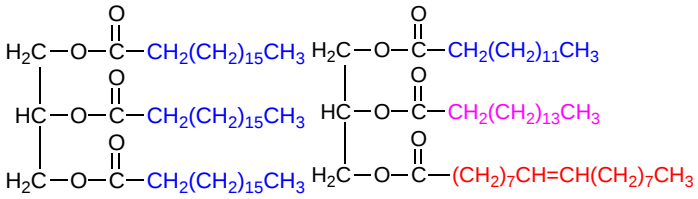
	Spermaceti	Beeswax	Carnauba wax
Alcohol	$CH_3(CH_2)_{14}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH
Fatty Acid	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{24}COOH$
Wax	$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

Triglycerides

Fats and oils often exist as **triglycerides** (or ***triacylcylgerols*** because they are esters composed of three fatty acid units joined to *glycerol*, a trihydroxy alcohol (IUPAC name is 1,2,3-propanetriol)):



If all three OH groups on the glycerol molecule are esterified with the same fatty acid, the resulting ester is called a ***simple triglyceride***. Although simple triglycerides have been synthesized in the laboratory, they rarely occur in nature. Instead, a typical triglyceride obtained from naturally occurring fats and oils contains two or three different fatty acid components and is thus termed a ***mixed triglyceride***.



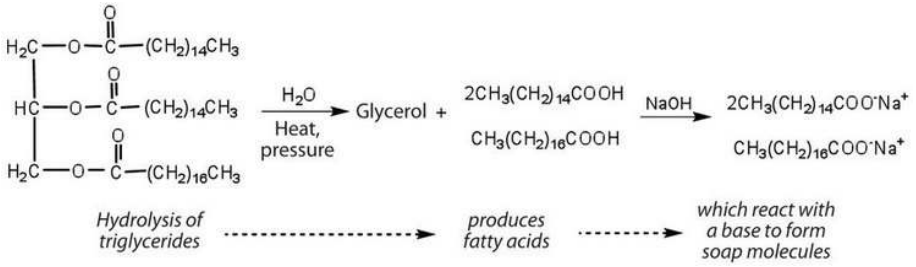
Tristearin: a simple triglyceride (left) and a mixed triglyceride (right)

A triglyceride is called a **fat** if it is a solid at 25°C; it is called an **oil** if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation (as discussed above) and number of carbon atoms in the constituent fatty acids. Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils. No single formula can be written to represent the naturally occurring fats and oils because they are highly complex mixtures of triglycerides in which many different fatty acids are represented. The table below shows the fatty acid compositions of some common fats and oils. The composition of any given fat or oil can vary depending on the plant or animal species it comes from as well as on dietetic and climatic factors.

Table **5.3.2.3**: Some common fats and oils including fatty acid content are listed below.

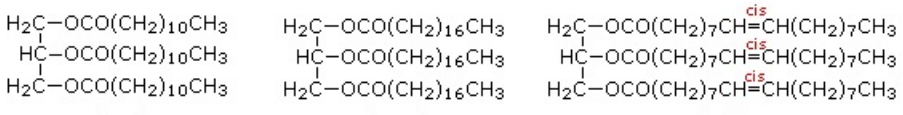
glycerides					
Fat or Oil	**Saturated**		**Unsaturated**		
	Palmitic	Stearic	Oleic	Linoleic	Other
Animal Origin					
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
Vegetable Origin					
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

Fats and oils can participate in a variety of chemical reactions—for example, because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The hydrolysis of fats and oils in the presence of a base is used to make soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [(~50 atm or 5,000 kPa) and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts (soap molecules):

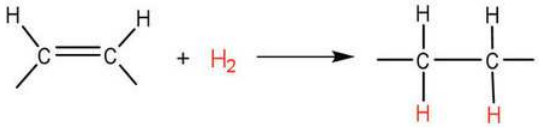


Chemical reaction of the saponification (base hydrolysis) of a triglyceride.

As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



The double bonds in fats and oils can undergo hydrogenation and also oxidation. The hydrogenation of vegetable oils to produce semisolid fats is an important process in the food industry. Chemically, it is essentially identical to the catalytic hydrogenation reaction described for alkenes.



In commercial processes, the number of double bonds that are hydrogenated is carefully controlled to produce fats with the desired consistency (soft and pliable). Inexpensive and abundant vegetable oils (canola, corn, soybean) are thus transformed into margarine and cooking fats.

Many people have switched from butter to margarine or vegetable shortening because of concerns that saturated animal fats can raise blood cholesterol levels and result in clogged arteries. However, during the hydrogenation of vegetable oils, an isomerization reaction occurs that produces the trans fatty acids mentioned in the opening essay. However, studies have shown that trans fatty acids also raise cholesterol levels and increase the incidence of heart disease. Trans fatty acids do not have the bend in their structures, which occurs in cis fatty acids and thus pack closely together in the same way that the saturated fatty acids do. Consumers are now being advised to use polyunsaturated oils and soft or liquid margarine and reduce their total fat consumption to less than 30% of their total calorie intake each day.

? Exercise 5.3.2.1

Why do unsaturated fatty acids have lower melting points than saturated fatty acids?

Answer

Unsaturated fatty acids cannot pack as tightly together as saturated fatty acids due to the presence of the cis double bond that puts a “kink” or bend in the hydrocarbon chain.

? Exercise 5.3.2.2

Classify each fatty acid as saturated or unsaturated and indicate the number of carbon atoms in each molecule.

a. palmitoleic acid
b. myristic acid
c. linoleic acid

Answer

a. unsaturated; 16 carbon atoms
b. saturated; 14 carbon atoms
c. unsaturated; 18 carbon atoms

? Exercise 5.3.2.3

Write the condensed structural formula for each fatty acid.

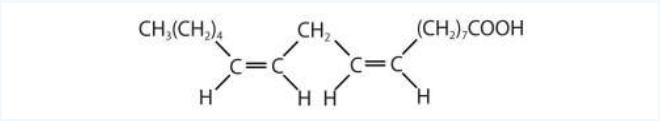
a. lauric acid
b. palmitoleic acid
c. linoleic acid

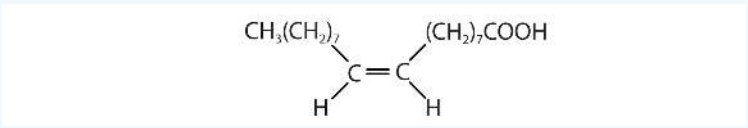
Answer

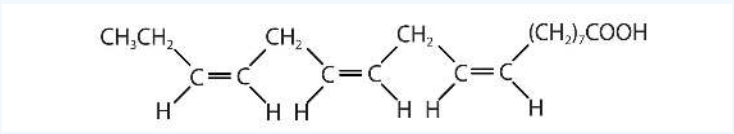
a. $CH_3(CH_2)_{10}COOH$
b. $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
c. $CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$

Exercise 5.3.2.4

Arrange these fatty acids (all contain 18 carbon atoms) in order of increasing melting point. Justify your arrangement.

a) 

b) 

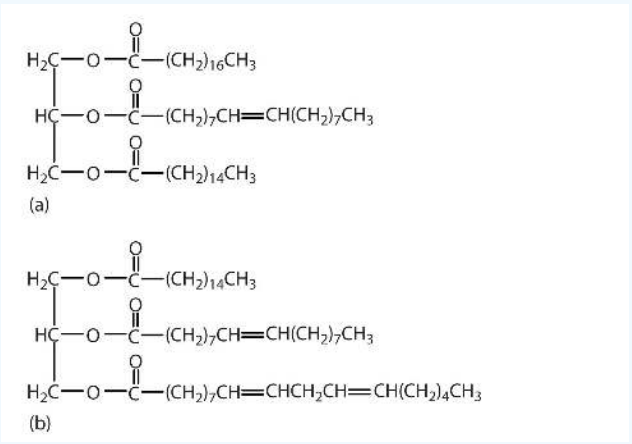
c) 

Answer

c < a < b; an increase in the number of double bonds will lower the melting point because it is more difficult to closely pack the fatty acids together.

Exercise 5.3.2.5

Which of these triglycerides would you expect to find in higher amounts in oils? In fats? Justify your choice.



Answer

The triglyceride labeled as (a) is expected to be present in higher amounts in fats because it is composed of a greater number of saturated fatty acids. The triglyceride labeled as (b) is expected to be present in higher amounts in oils because it is composed of a greater number of unsaturated fatty acids.

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5.3.3: Soap

Learning Objectives

After completing this section, you should be able to

- write an equation to represent the formation of a soap.
  - identify the structure of the fat required to produce a given soap.
  - identify the structure of a soap, given the structure of the fat from which it is produced.
- describe the mechanism by which soaps exert their cleansing action.
- give a chemical explanation of the problems encountered when carboxylate soaps are used in hard-water areas, and explain how they may be overcome by the use of sulphonate detergents.

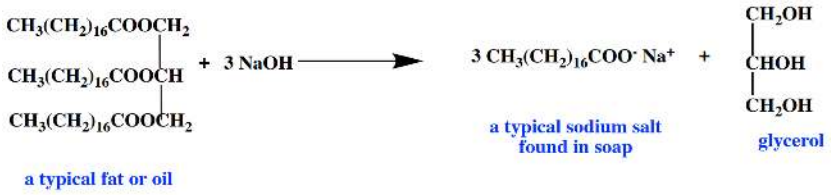
Key Terms

Make certain that you can define, and use in context, the key terms below.

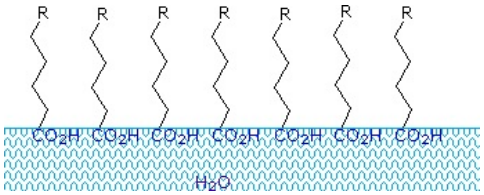
- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

Soap making has remained unchanged over the centuries. The ancient Roman tradition called for mixing rain water, potash and animal tallow (rendered form of beef or mutton fat). Making soap was a long and arduous process. First, the fat had to be rendered (melted and filtered). Then, potash solution was added. Since water and oil do not mix, this mixture had to be continuously stirred and heated sufficiently to keep the fat melted. Slowly, a chemical reaction called saponification would take place between the fat and the hydroxide which resulted in a liquid soap. When the fat and water no longer separated, the mixture was allowed to cool. At this point salt, such as sodium chloride, was added to separate the soap from the excess water. The soap came to the top, was skimmed off, and placed in wooden molds to cure. It was aged many months to allow the reaction to run to completion.

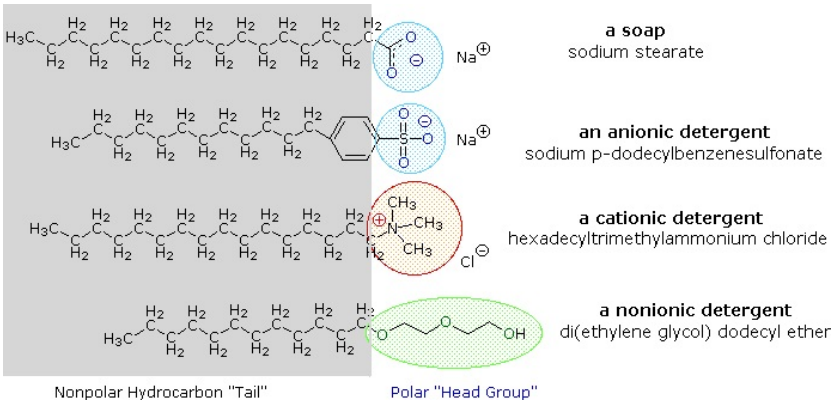
All soap is made from fats and oils, mixed with alkaline (basic) solutions. There are many kinds of fats and oils, both animal and vegetable. As previously discussed, fats are usually solid at room temperature, but many oils are liquid at room temperature. Liquid cooking oils originate from corn, peanuts, olives, soybeans, and many other plants. For making soap, all different types of fats and oils can be used – anything from lard to exotic tropical plant oils.



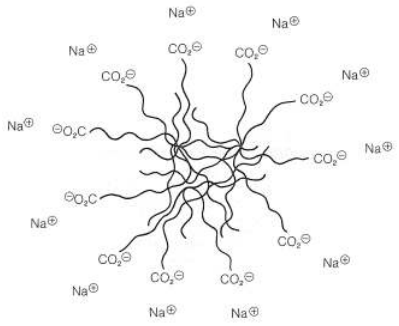
Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids made up of ten or more carbon atoms are nearly insoluble in water, and because of their lower density, float on the surface when mixed with water. Unlike paraffin or other alkanes, which tend to puddle on the waters surface, these fatty acids spread evenly over an extended water surface, eventually forming a monomolecular layer in which the polar carboxyl groups are hydrogen bonded at the water interface, and the hydrocarbon chains are aligned together away from the water. This behavior is illustrated in the diagram on the right. Substances that accumulate at water surfaces and change the surface properties are called **surfactants**.



Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules has a nonpolar hydrocarbon chain, the "tail", and a polar (often ionic) "head group". The use of such compounds as cleaning agents is facilitated by their surfactant character, which lowers the surface tension of water, allowing it to penetrate and wet a variety of materials.



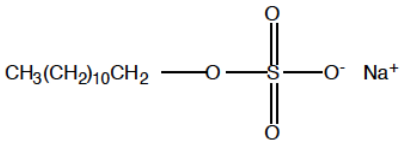
When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface tension of the water and contributes to the startling properties of soap films and bubbles. At higher concentrations, the solutions become turbid as the result of **micelle** formation. Micelles are spherical aggregates of soap molecules, wherein the hydrocarbon chains form a region of low polarity that is stabilized by having the polar salt ends of the molecules in contact with the water. By gathering the hydrophobic chains together in the center of the micelle, disruption of the hydrogen bonded structure of liquid water is minimized, and the polar head groups extend into the surrounding water where they participate in hydrogen bonding.



The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pKa ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the pH of a soap solution is lowered by acidic contaminants, insoluble fatty acids precipitate and form a scum. A second problem soaps are less effective in hard water, which is water that contains a significant concentration of magnesium, calcium and iron ions. These ions form precipitates with soap molecules, and this precipitate is often seen as a gray line on a bathtub or sink and is often called “soap scum”. Since soap forms a precipitate with these ions, it means that many of the soap molecules are no longer present in the solution. Therefore, soap will form fewer suds in hard water. “Soft

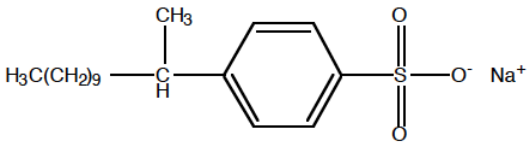
water" is water that contains very few or no ions that precipitate with soap. Soap will therefore be much more effective in soft water than in hard water.

These problems have been alleviated by the development of synthetic soaps called detergents. Detergents are similar to soaps in that they have a charged head group and a long nonpolar tail group, but they are not prepared from natural fats or oils. Detergents are useful because they do not form precipitates with magnesium, iron or calcium ions, which means that they work in both soft and hard water. By using a much stronger acid for the polar head group, water solutions of detergents are less sensitive to pH changes. Also the sulfonate functions used for virtually all anionic detergents confer greater solubility on micelles incorporating the alkaline earth cations found in hard water. Variations on the detergent theme have led to the development of other classes, such as the cationic and nonionic detergents shown above. Cationic detergents often exhibit germicidal properties, and their ability to change surface pH has made them useful as fabric softeners and hair conditioners. These versatile chemical "tools" have dramatically transformed the household and personal care cleaning product markets over the past fifty years



Sodium Lauryl Sulfate (a non-biodegradable detergent)

After detergents started being widely used, it was discovered that they were not broken down in sewage treatment plants. Many streams and lakes became contaminated with detergents and large amounts of foam appeared in natural waters. Biodegradable detergents were then developed. Shown below is an example of a biodegradable detergent, sodium laurylbenzenesulfonate.



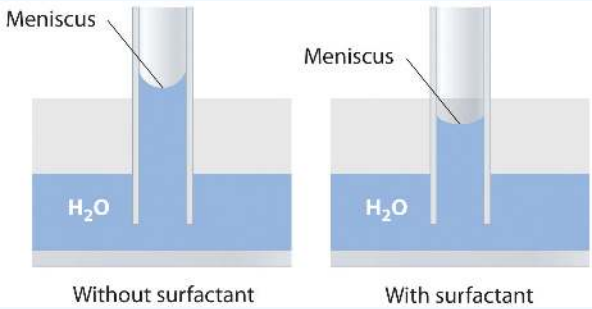
Sodium Laurylbenzenesulfonate (a biodegradable detergent)

? Exercise 5.3.3.1

Explain how soaps or surfactants decrease the surface tension of a liquid. How does the meniscus of an aqueous solution in a capillary change if a surfactant is added? Illustrate your answer with a diagram.

Answer

Adding a soap or a surfactant to water disrupts the attractive intermolecular interactions between water molecules, thereby decreasing the surface tension. Because water is a polar molecule, one would expect that a soap or a surfactant would also disrupt the attractive interactions responsible for adhesion of water to the surface of a glass capillary. As shown in the sketch, this would decrease the height of the water column inside the capillary, as well as making the meniscus less concave.



Exercise 5.3.3.2

Draw the structure of calcium stearate, a component of soap scum.

Answer

$(C_{17}H_{35}COO)_2Ca^{2+}$

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5.3.4: Phospholipids

Learning Objectives

After completing this section, you should be able to

- draw the general structure of a phosphoglyceride.
- describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

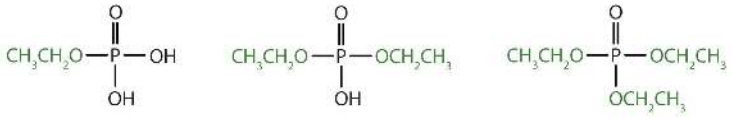
Key Terms

Make certain that you can define, and use in context, the key terms below.

- phosphoglyceride
- phospholipid

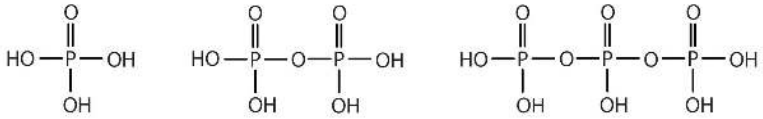
Phosphate Esters

Similarly to carboxylic acids, inorganic acids such as nitric acid (HNO_3), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4) also can form esters. The esters of phosphoric acid are especially important in biochemistry. A phosphoric acid molecule can form a monoalkyl, a dialkyl, or a trialkyl ester by reaction with one, two, or three molecules of an alcohol.



Ethyl dihydrogen phosphate | Diethyl hydrogen phosphate | Triethyl phosphate

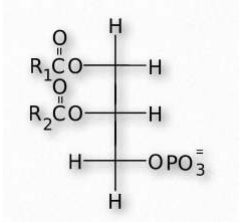
Esters of pyrophosphoric acid and triphosphoric acid are also important in biochemistry.



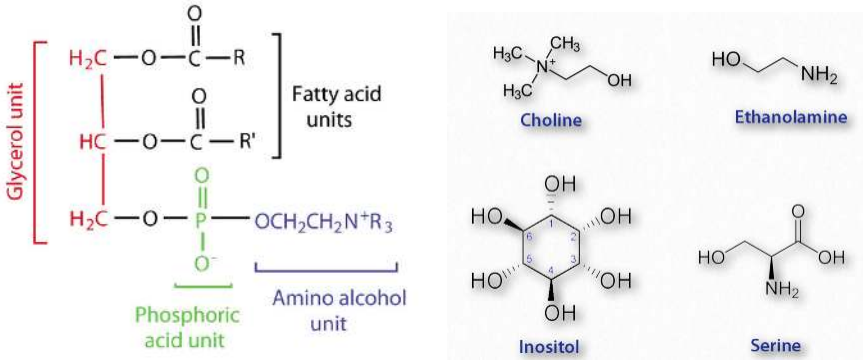
Phosphoric acid | Pyrophosphoric acid | Triphosphoric acid

Phospholipids

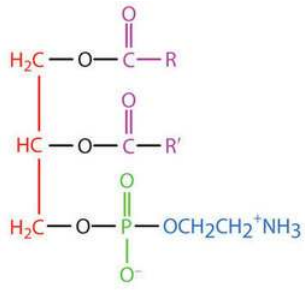
The two main types of phospholipids are **glycerophospholipids** and **sphingomyelins**. Glycerophospholipids are important components of the lipid bilayer of cellular membranes. Glycerophospholipids are structurally related to fats, as both are derived from phosphatidic acid, which has the basic structure of glycerol with two ester bonds with fatty acids and one ester bond with phosphoric acid.



Phosphatidic acid is converted into a glycerophospholipid by esterifying various groups, such as ethanolamine, serine, choline, inositol, and others to the phosphate of phosphatidic acid. These compounds have a chiral center at C2 and have an R configuration when found in nature.

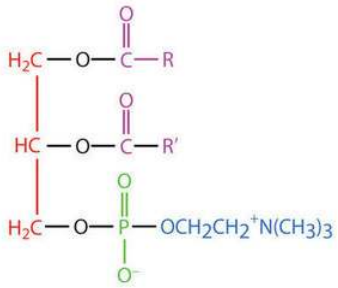


The **phosphatidylethanolamines** are found in all living cells and are one of the most common phosphatides. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially located on the inner leaflet (closest to the cytoplasm) of the plasma membrane.



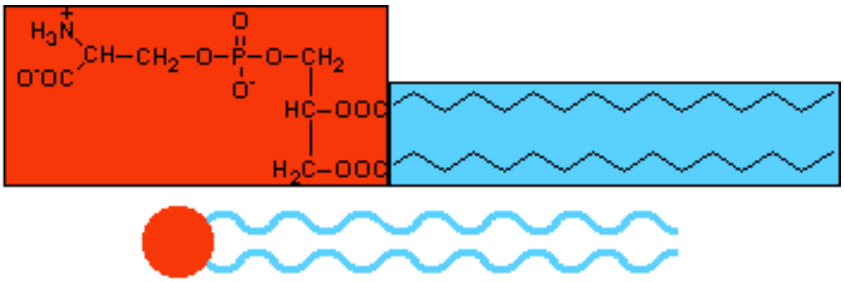
Phosphatidylethanolamine
(cephalin)

Metabolically, phosphatidylethanloamines are precursors of **phosphatidylcholines**. Phosphatidylcholines are another group of important membrane components. They tend to be found more commonly on the outer leaflet of the plasma membrane. Nutritionally, the compounds are readily obtained from eggs and soybeans. Phosphatidylcholines are moved across membranes by Phosphatidylcholine transfer protein (PCTP).



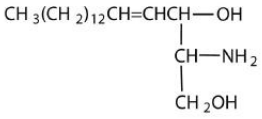
Phosphatidycholine
(lecithin)

Like the phosphatidylethanolamines, **phosphatidylserines** are preferentially located on the inner leaflet of the plasma membrane. When apoptosis (cell suicide) occurs, the preferential distribution is lost and the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell.

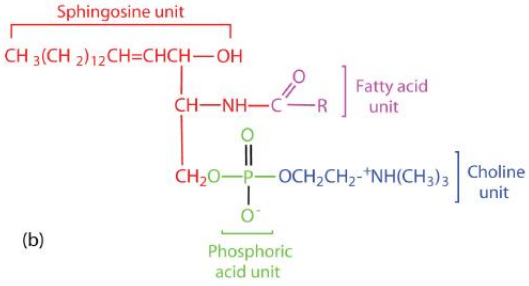


Phosphatidylserine, a polar phospholipid. A serine head group has been added on to a phosphate group on a glycerol functional group, all shown in orange. The fatty acid chains are in blue.

Sphingomyelins, the simplest sphingolipids, each contain a fatty acid, a phosphoric acid, sphingosine, and choline. Because they contain phosphoric acid, they are also classified as phospholipids. Sphingomyelins are important constituents of the myelin sheath surrounding the axon of a nerve cell. Multiple sclerosis is one of several diseases resulting from damage to the myelin sheath.



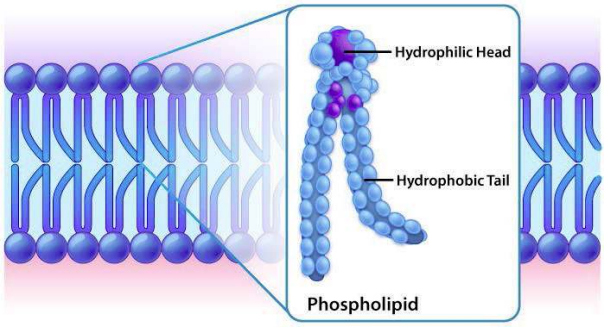
(a) Sphingosine



(b)

Lipid Bilayer

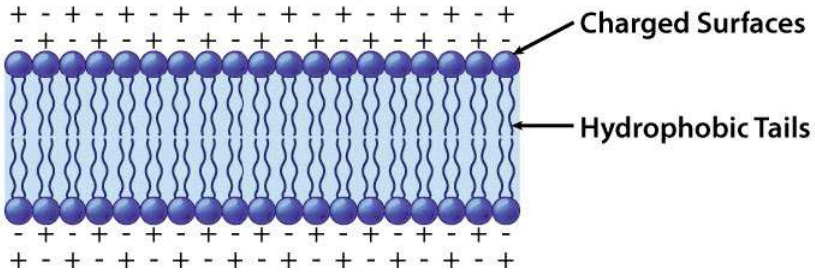
In one sense the polar lipids are like the anions of fatty acids, only more so. They contain two hydrophobic hydrocarbon tails and a head which may have several electrically charged sites. As in the case of soap and detergent molecules, the tails of polar lipids tend to avoid water and other polar substances, but the heads are quite compatible with such environments.



Lipid bilayer closeup Image by Aleia Kim

As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head

groups, micelle formation is unfavorable relative to a bilayer structure. If a phospholipid is smeared over a small hole in a thin piece of plastic immersed in water, a stable planar bilayer of phospholipid molecules is created at the hole. As shown in the following diagram, the polar head groups on the faces of the bilayer contact water, and the hydrophobic alkyl chains form a nonpolar interior.



Organization of the lipid bilayer Image by Aleia Ki

The polar lipids are most commonly found as components of cell walls and other membranes. Nearly all hypotheses regarding membrane structure take as a fundamental component a lipid bilayer. Bilayers made in the laboratory have many properties in common with membranes. Ions such as Na^+, K^+, and Cl^- cannot pass through them, but water molecules can. Certain carrier molecules can transport K^+ and other ions across a bilayer, apparently by wrapping a hydrophobic cloak around them to disguise their charges. Membrane proteins in a bilayer also allow for transport of ions and other molecules across the bilayer which could not cross otherwise.

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- **20.6: Polar Lipids** by Ed Vitz, John W. Moore, Justin Shorb, Xavier Prat-Resina, Tim Wendorff, & Adam Hahn is licensed CC BY-NC-SA 4.0.

5.3.5: Prostaglandins and Other Eicosanoids

Learning Objectives

After completing this section, you should be able to

- describe the general structure of the prostaglandins, and identify a prostaglandin from a given list of organic structures.
- identify at least two important biological functions of prostaglandins.

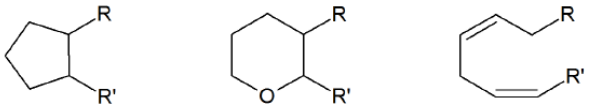
Key Terms

Make certain that you can define, and use in context, the key terms below.

- eicosanoid
- prostaglandin

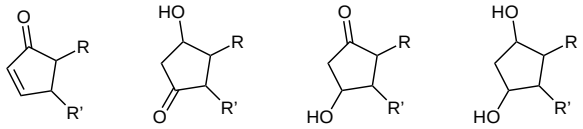
Eicosanoids

The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as **eicosanoids**. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones. Eicosanoids include prostaglandins, leukotrienes, and thromboxanes.



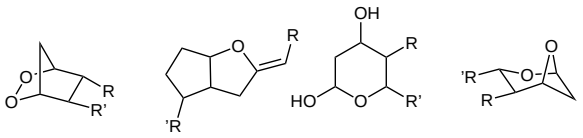
prostaglandin (PG) thromboxane (TX) leukotriene (LT)

Eicosanoids are primarily named off the ring system present in the molecule prostaglandin (PG), thromboxane (TX), leukotriene (LT). Common substitution patterns on the ring system are indicated with a letter in the name. Also, the number of double bonds in the molecule is indicated with a subscript number.



PGA PGD PGE PGF

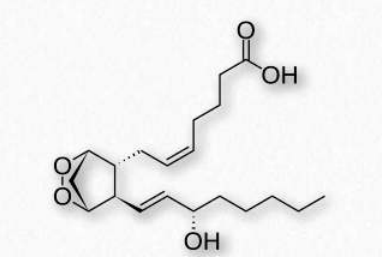
Prostaglandin structures for PGA, PGD, PGE and PGF



PGG, PGH PGI TXB TXA

Structures for prostaglandins PGG, PGH and PGI and thromboxanes TXA and TXB

Thus the molecule PGH_2 means that it has the prostaglandin ring system with a type H Substitution pattern. The subscript 2 indicated that the molecule contains two double bonds.



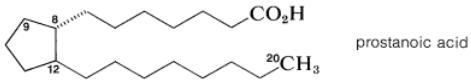
Prostaglandin PGH_2

Prostaglandins

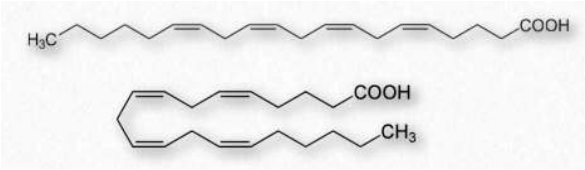
Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon prostanoic acid, which is a C20 fatty acid in which there is a cyclopentane ring formed by connecting the C8 and C12 positions.

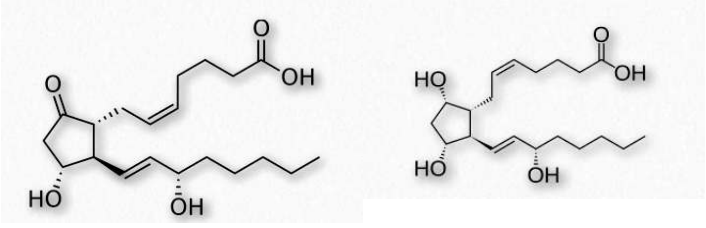


They are biochemically synthesized from the fatty acid, arachidonic acid. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring of the prostaglandin.



Arachidonic acid

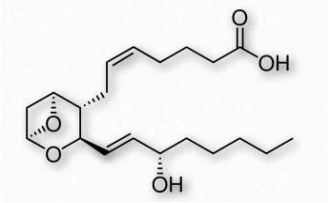
There are a variety of functional groups present in prostaglandin structures. The can have one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. Some typical structures are shown below.



Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

Thromboxanes

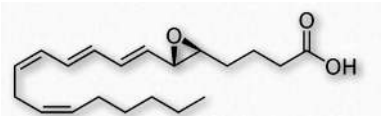
Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

Leukotrienes

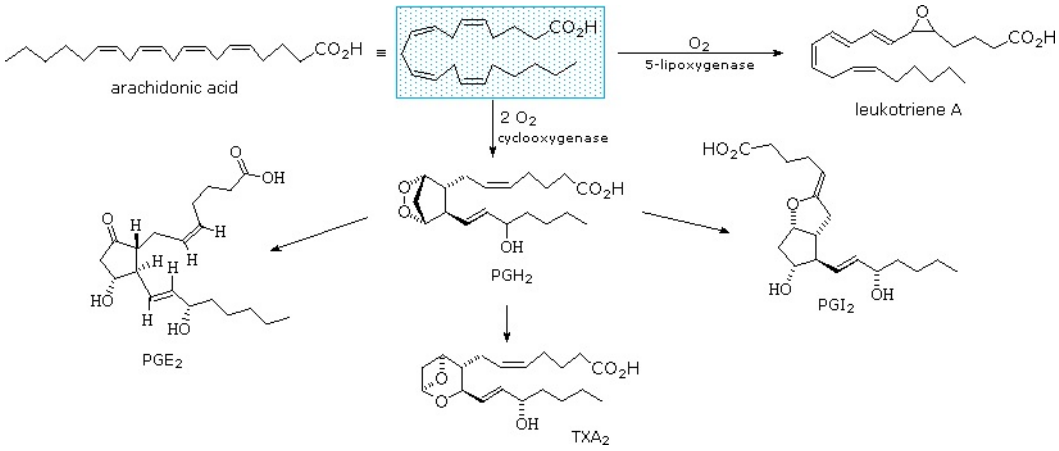
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.



Leukotriene A_4 (LTA_4)

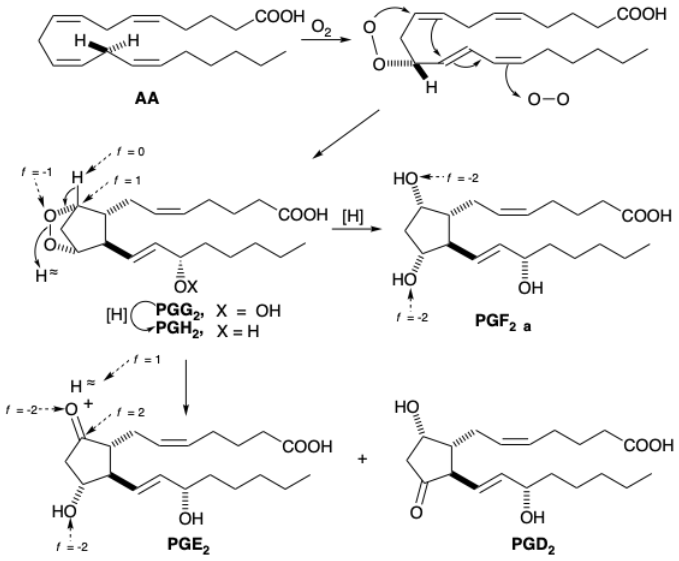
Eicosanoid Biosynthesis

The biosynthesis of eicosanoids begins with the reaction of arachidonic acid with O_2 which can be catalyzed by two different cyclooxygenase enzymes (COX-1 & COX-2).



In nature, prostaglandins arise by an oxidative cyclization of poly-unsaturated twenty-carbon fatty acids, which begins with enantiospecific removal of the L-hydrogen atom of the prochiral methylene group at C-13 coupled with enantiospecific introduction of oxygen at the allylic C-15 position. Subsequent cyclization and termination by addition of a second molecule of oxygen leads to a 15-hydroperoxy bicyclic peroxide (PGG), that is reduced to a 15-hydroxy bicyclic peroxide (PGH). These intermediates, known as prostaglandin endoperoxides, have been isolated and shown to yield prostaglandins. Reduction of the peroxy bridge gives PGF, while disproportionation gives β-hydroxy ketones PGE and PGD. The carbons in prostaglandins are

numbered one to twenty starting at the carboxyl carbon and following the numbering system of the biosynthetic precursor fatty acids.



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5.3.6: Terpenoids

Objectives

After completing this section, you should be able to

1. identify a terpene from a given list of organic structures.
2. analyze the structure of a given terpene in terms of the isoprene rule.
3. classify a given terpene structure according to the number of isoprene units present; that is, determine whether a given terpene is a monoterpene, sesquiterpene, diterpene, etc.
4. identify and draw the structure of the precursors of isopentenyl diphosphate: (*R*) mevalonate or 1-deoxy-D-xylulose 5-phosphate.

Key Terms

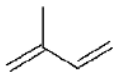
Make certain that you can define, and use in context, the key terms below.

- isoprene rule
- terpenoid
- terpene

Study Notes

You are not expected to memorize all the details of the synthetic mechanisms for terpenoids. However, you should know the overall general synthetic pathway illustrated under "Terpenoid Biosynthesis." As you read through the details of these mechanisms, realize that they may be complex, but they are based on experimental evidence. You should also note the important role of enzymes in many natural systems transformations. Finally, you will recognize that essentially, individual steps are often reactions you have already encountered in previous sections.

The terpenoids (aka isoprenoids) are a large (estimated 60% of known natural products) and diverse group of lipids derived from five-carbon isoprene units assembled in thousands of combinations. Technically a terpenoid contains oxygen, while a terpene is a hydrocarbon. Often the two terms are used to refer collectively to both groups.



isoprene

Isoprene Rule

Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals. Terpenes incorporating most of the common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons is a definitive characteristic. Terpenes may be considered to be made up of isoprene (more accurately isopentane) units, an empirical feature known as the isoprene rule. Because of this, terpenes usually have $5n$ carbon atoms (n is an integer), and are subdivided as follows:

Classification	Isoprene Units	Carbon Atoms
monoterpenes	2	C_{10}
sesquiterpenes	3	C_{15}
diterpenes	4	C_{20}
sesterterpenes	5	C_{25}
triterpenes	6	C_{30}

Isoprene itself, a C_5H_8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism. Next to methane it is the most common volatile organic compound found in the atmosphere. Examples of C10 and higher terpenes, representing the four most common classes are shown in the following diagrams. Most terpenes may be structurally dissected into isopentane segments. How this is done can be seen in the diagram directly below.

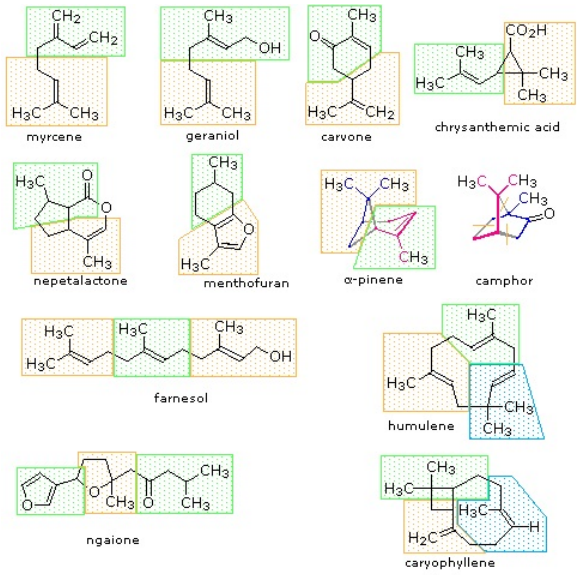


Figure 27.5.1: Monoterpenes and sesquiterpenes

The isopentane units in most of these terpenes are easy to discern, and are defined by the shaded areas. In the case of the monoterpene camphor, the units overlap to such a degree it is easier to distinguish them by coloring the carbon chains. This is also done for alpha-pinene. In the case of the triterpene lanosterol we see an interesting deviation from the isoprene rule. This thirty carbon compound is clearly a terpene, and four of the six isopentane units can be identified. However, the ten carbons in center of the molecule cannot be dissected in this manner. Evidence exists that the two methyl groups circled in magenta and light blue have moved from their original isoprenoid locations (marked by small circles of the same color) to their present location. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

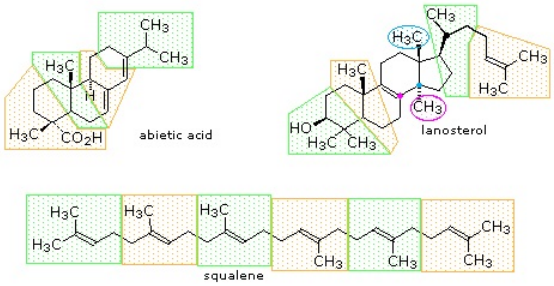
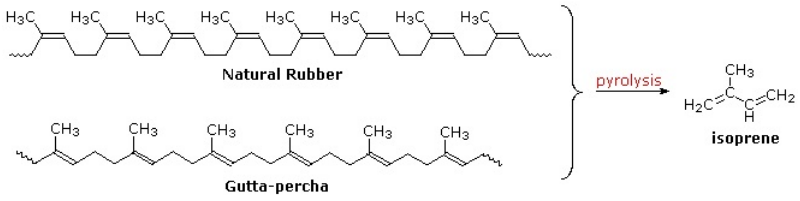


Figure 27.5.2: Triterpenes

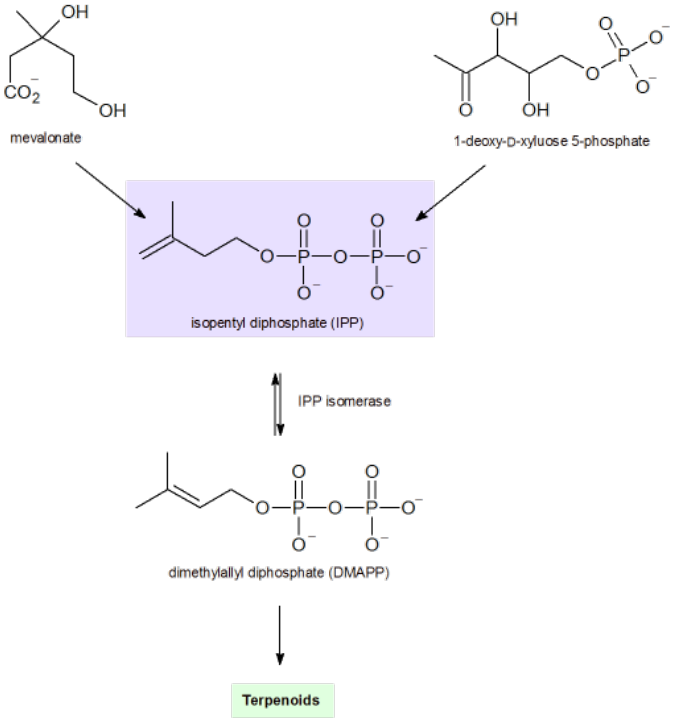
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride and hydrogen all add with a stoichiometry of one molar equivalent per isoprene unit. Ozonolysis of rubber generates a mixture of levulinic acid ($CH_3COCH_2CH_2CO_2H$) and the corresponding aldehyde. Pyrolysis of rubber produces the diene isoprene along with other products.



The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure above) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

Terpenoid Biosynthesis

While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.

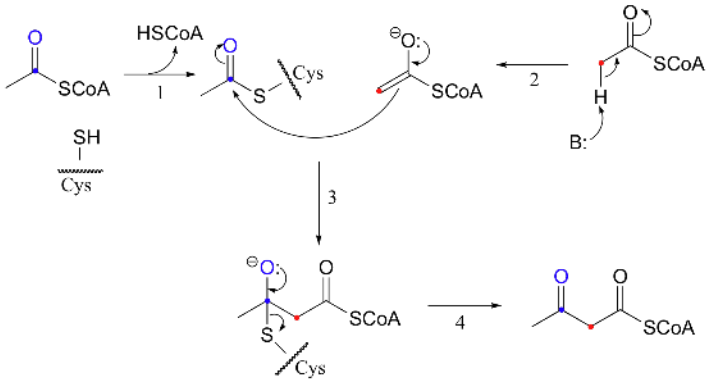


Mevalonate Pathway

Step 1 - Claisen Condensation

An early step in the biosynthesis of cholesterol and other 'isoprenoid' compounds is a Claisen condensation between two acetyl CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine

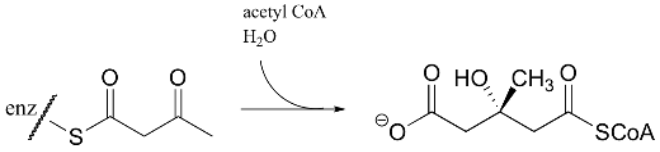
(Reaction 1). In the Claisen condensation phase of the reaction, the alpha-carbon of a second acetyl CoA is deprotonated, forming an enolate (Reaction 2).



The enolate carbon attacks the electrophilic thioester carbon, forming a tetrahedral intermediate (Reaction 3) which quickly collapses to expel the cysteine thiol (Reaction 4) and produce acetoacetyl CoA.

Step 2 - Aldol Condensation

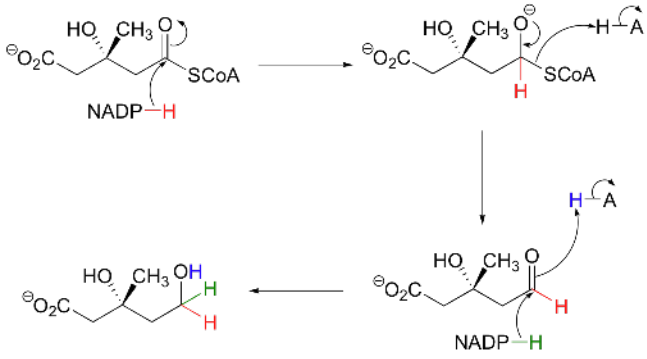
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - Reduction of the Thioester

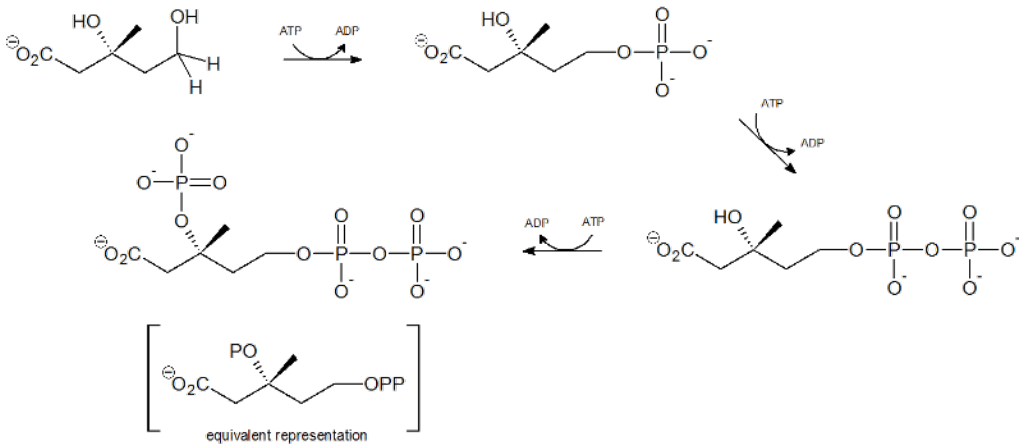
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

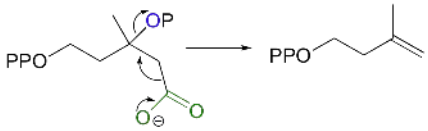
Step 4 - Mevalonate Phosphorylation

Two phsophorylations by adenosine triphosphate (ATP) occur at the terminal hydroxyl/phosphorus group through nucleophilic substitution, followed by a third ATP phosphorylation of the tertiary hydroxyl group.



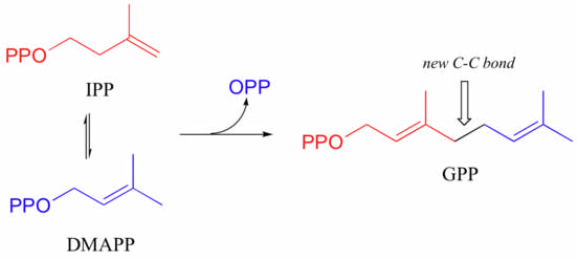
Step 5 - **Decarboxylation**

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

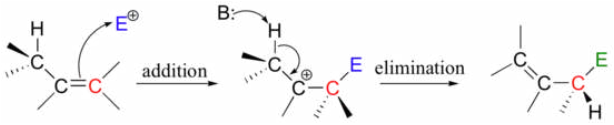


Conversion of IPP to Terpenoids

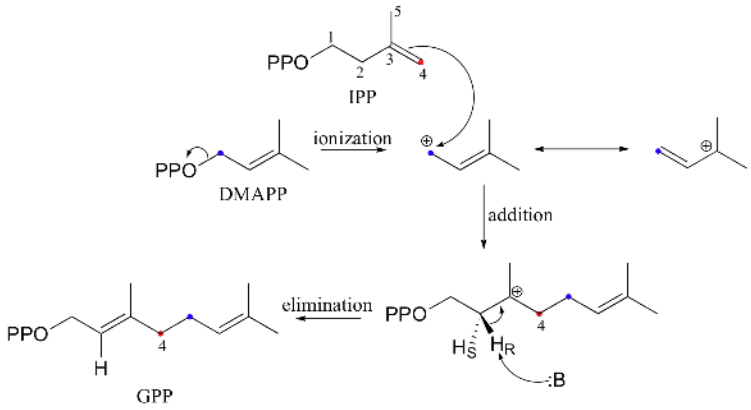
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

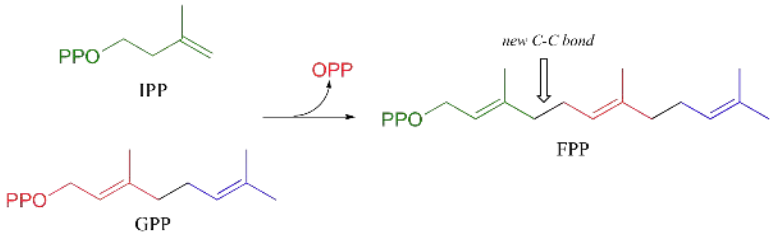


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

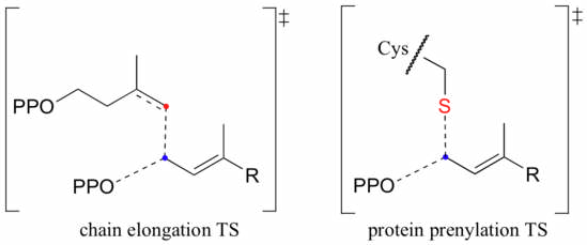


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).

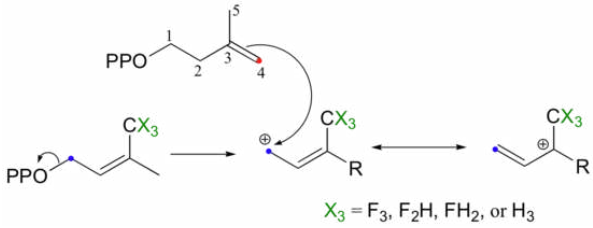


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction. The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

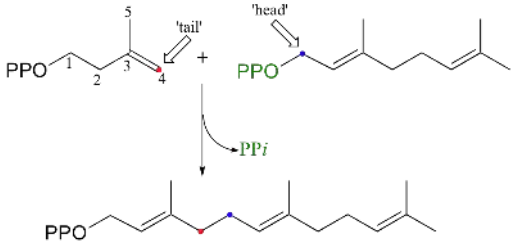
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



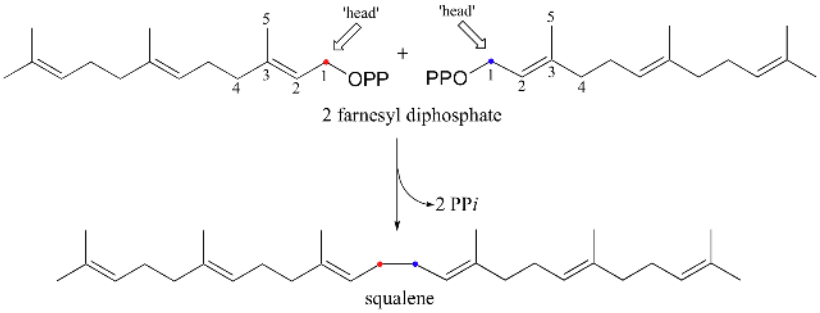
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc*. **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

In this section, we will briefly examine the reaction catalyzed by an enzyme called squalene synthase, an important enzymatic transformation that involves some very interesting and unusual electrophilic additions, rearrangements, and reactive intermediates. This particular enzyme is also of interest because it represents a potential new target for cholesterol-lowering drugs.

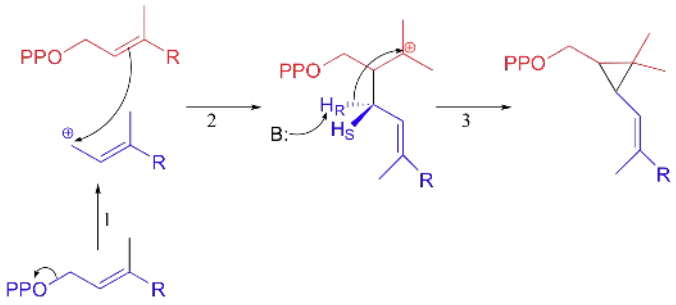
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, or 'head to tail' electrophilic condensation of isoprenoid chains:



The condensation of two molecules of FPP to form squalene, however, is something different: this is a 'head to head' condensation, where C_1 of the first molecule forms a bond to C_1 of the second. The chemistry involved is quite a bit more complicated.

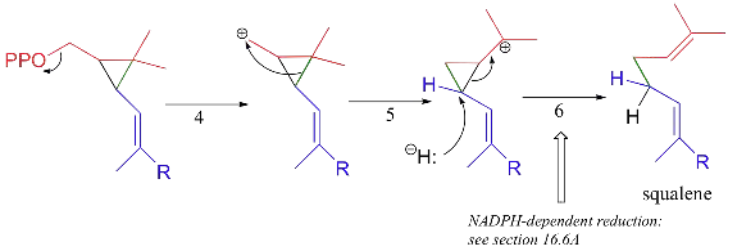


The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).

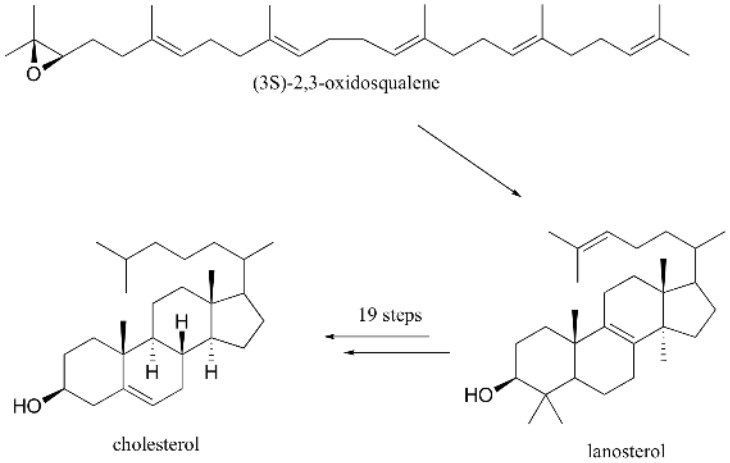


This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl intermediate.

In the second stage of squalene synthesis, the second pyrophosphate group leaves, generating a cyclopropylcarbinyl cation (step 4). Because this is a primary carbocation, you probably are wondering about how stable it could be (and thus how likely an intermediate). As it turns out, such carbocations are remarkably stable, due to favorable interactions between the empty orbital and orbitals on the three-membered ring (the level of bonding theory needed to really understand this idea is beyond the scope of this text, but you may learn about it if you take a class in advanced organic chemistry). What occurs next is an alkyl shift leading to a tertiary carbocation (step 5).

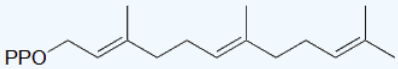


Discussion of the final step (step 6) will need to be put off - this is a reduction with a hydride nucleophile derived from a coenzyme called NADPH. Although this may seem like an extremely convoluted (and perhaps unlikely!) mechanism, there is much experimental evidence to back it up.



? Exercise 5.3.6.1

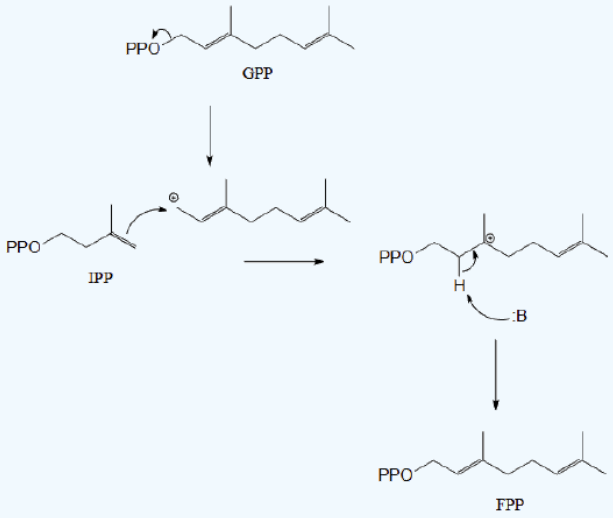
Farnesyl diphosphate (FPP) is synthesized by adding another five-carbon building block to geranyl diphosphate. What is this building block - IPP or DMAPP? Draw a mechanism for the formation of FPP.



farnesyl diphosphate

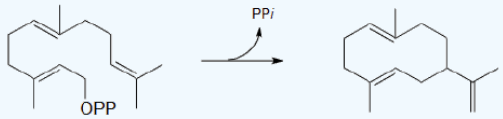
Answer

IPP is the five-carbon species added to geranyl diphosphate to make the 15-carbon farnesyl diphosphate.



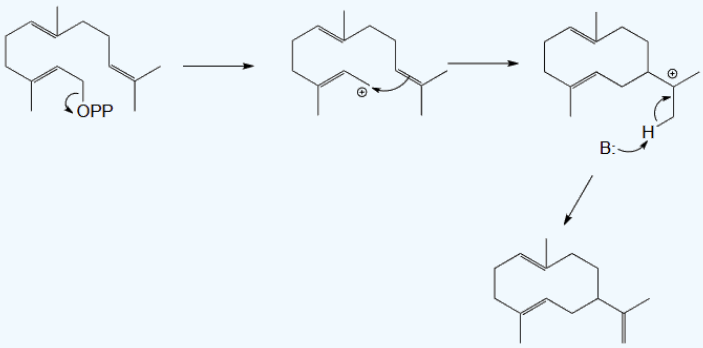
Exercise 5.3.6.2

Propose a likely mechanism for the following transformation, which is the first stage in a somewhat complex reaction in the synthesis of an isoprenoid compound in plants. (Science 1997, 277, 1815)



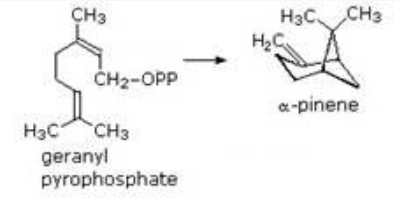
farnesyl diphosphate

Answer

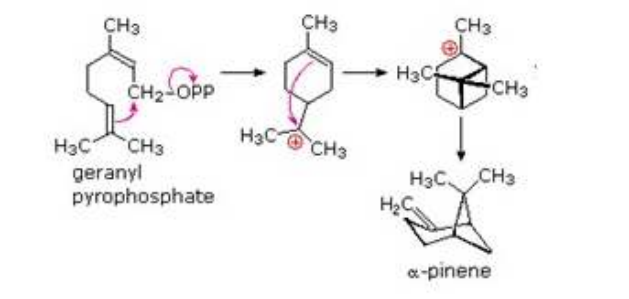


Exercise 5.3.6.3

Propose a likely mechanism for the following transformation.



Answers



5.3.6: Terpenoids is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Tim Soderberg, William Reusch, & William Reusch.

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5.3.7: Steroids

Objectives

After completing this section, you should be able to

1. draw the tetracyclic ring system on which the structure of all steroids is based.
2. identify the occurrence and biological roles of at least two common steroids.
3. sketch the stereochemical conformation of a steroid, given an adequate wedge and dash structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.
4. construct a molecular model of a steroid, given a suitable written description or a wedge and dash structure from which to work.

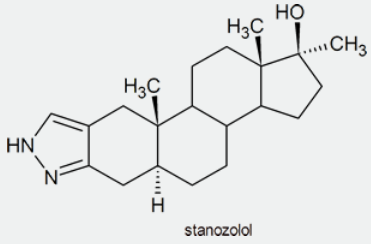
Key Terms

Make certain that you can define, and use in context, the key term below.

- steroid

Study Notes

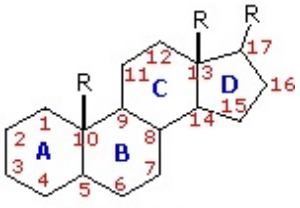
Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word “steroid” and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

General Steroid Structure

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram below. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.

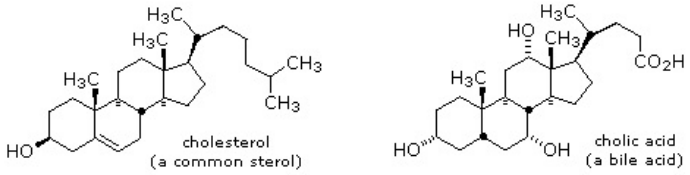


The Steroid
Carbon Skeleton

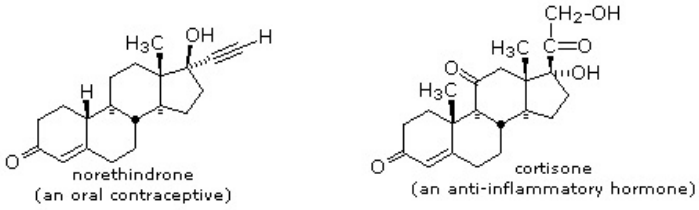
Common Steroids

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally.

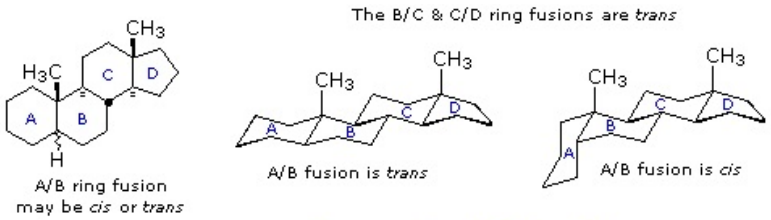
The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration.



Typical Animal Steroids



Medicinally Useful Steroids

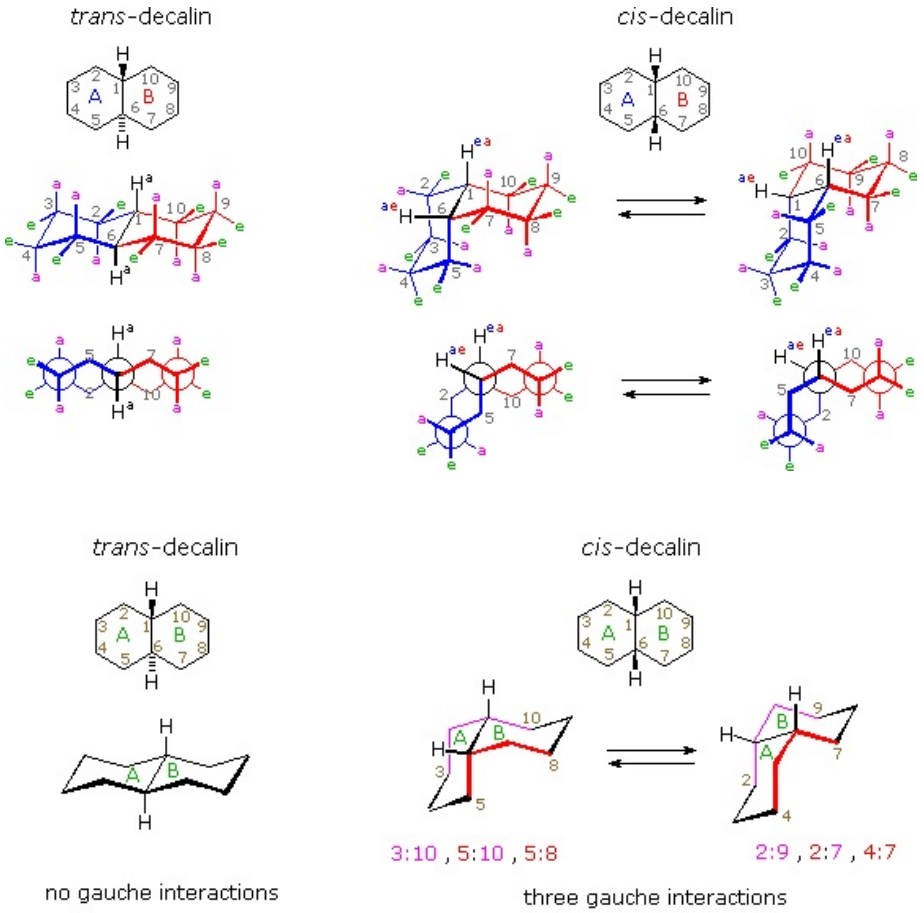


Common Steroid Conformations

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

Decalin as a model system

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion and the angular hydrogens are black.



The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above the plane of the two rings alternate from axial to equatorial and back if we proceed around the rings from C-1 to C-10 in numerical order. The bonds directed below the rings also alternate in a complementary fashion.

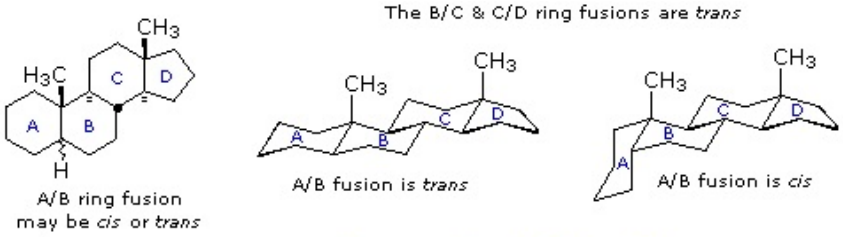
Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by one axial and one equatorial bond, and the overall structure is bent at the ring fusion. In the conformer on the left, the red ring (B) is attached to the blue ring (A) by an axial bond to C-1 and an equatorial bond to C-6 (these terms refer to ring A substituents). In the conformer on the right, the carbon bond to C-1 is equatorial and the bond to C-6 is axial. Each of the angular hydrogens (Hae or Hea) is oriented axial to one of the rings and equatorial to the other. This relationship reverses when double ring flipping converts one cis-conformer into the other.

Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following button. This difference is roughly three times the energy of a gauche butane conformer relative to its anti conformer. Indeed three gauche butane interactions may be identified in each of the cis-decalin conformations, as will be displayed by clicking on the above conformational diagram. These gauche interactions are also shown in the model.

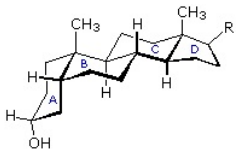
Steroid Conformations

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the same conformational mobility exhibited by cis-decalin. The fusion of ring C to ring B in a trans configuration prevents ring B from undergoing a conformational flip to another chair form. If this were to occur, ring C would have to be attached to ring B by two adjacent axial bonds directed

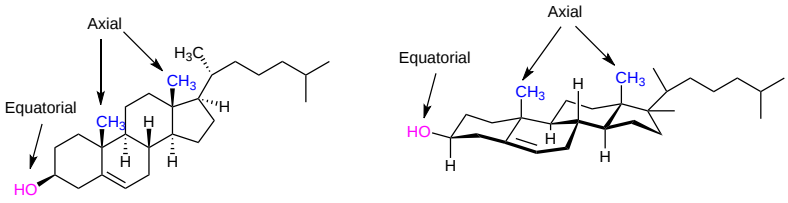
180º apart. This is too great a distance to be bridged by the four carbon atoms making up ring C. Consequently, the steroid molecule is locked in the all chair conformation shown here. Of course, all these steroids and decalins may have one or more six-membered rings in a boat conformation. However the high energy of boat conformers relative to chairs would make such structures minor components in the overall ensemble of conformations available to these molecules.



Common Steroid Conformations



Much like cyclohexanes substituents (**Section 4-7**) on a steroid ring system can be either an axial or equatorial position. Fused rings makes steroids ridge and unable to undergo cyclohexane ring-flips Because of sterics, substituents in the equatorial posltion tend to be more energetically favorable. The -OH group present in cholesterol is in the more stable equatorial position while the two -CH_3 groups on the steroid ring are both in an axial position.

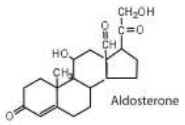
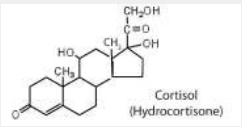
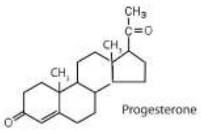
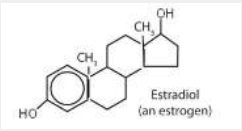
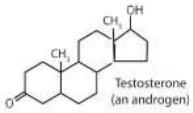


Steroid Hormones

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table 27.6.1), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table 27.6.1 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

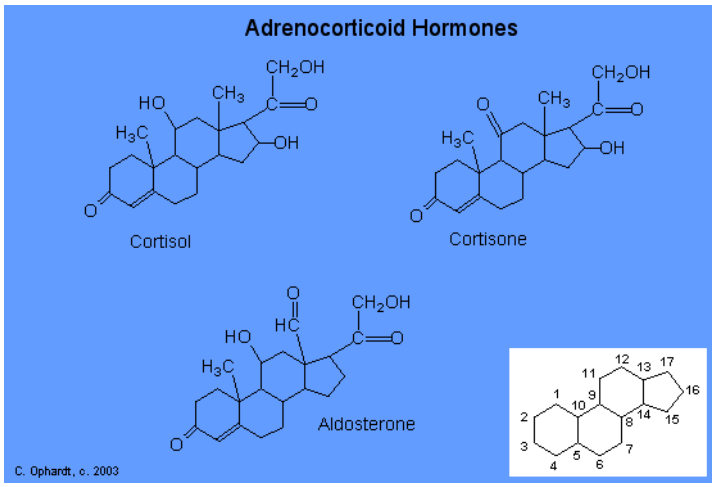
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

Adrenocorticoid Hormones

The adrenocorticoid hormones are products of the adrenal glands ("adrenal" means adjacent to the renal (kidney). The most important adrenocorticoid is **aldosterone**, which regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions. Aldosterone is secreted when blood sodium ion levels are too low to cause the kidney to retain sodium ions. If sodium levels are elevated, aldosterone is not secreted, so that some sodium will be lost in the urine. Aldosterone also controls swelling in the tissues.

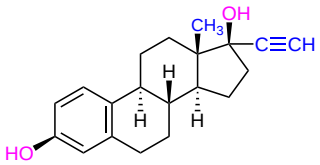
Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to inflammatory effects. Cortisone or similar synthetic derivatives such as prednisolone are used to treat inflammatory diseases, rheumatoid arthritis, and bronchial asthma. There are many side effects with the use of cortisone drugs, so there use must be monitored carefully.

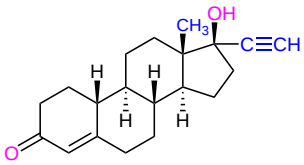


Synthetic Steroids

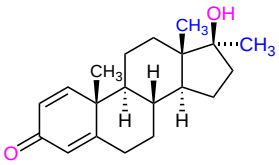
In the hope of producing new drugs, thousands of steroid derivatives have been synthesized and test by pharmaceutical companies. The two classes of synthetic steroids most commonly know by the public are oral contraceptives and anabolic steroids. Oral contraceptives contain synthetic versions of the hormones estrogen (ethynylestradiol*)* and progestin (norethindrone*)*. They prevent pregnancy by interfering with ovulation, fertilization, and/or implantation of the fertilized egg. Anabolic steroids (methandrostenolone) mimic the effects of natural testosterone.



Ethynylestradiol
(A synthetic estrogen)



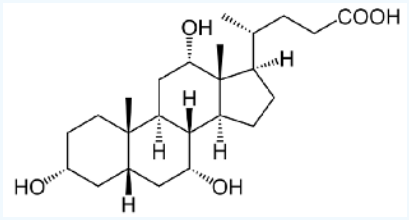
Norethindrone
(A synthetic progestin)



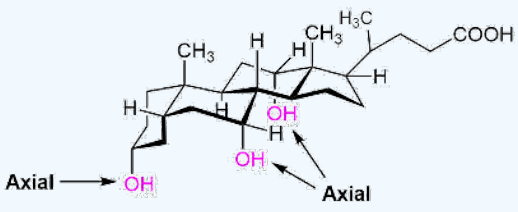
Methandrostenolone
(A synthetic androgen)

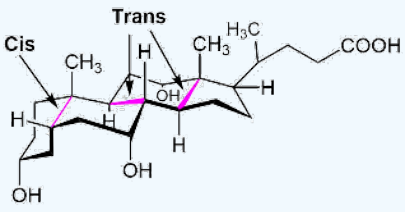
? Exercise 5.3.7.1

The following molecule is cholic acid. Draw it showing the chair conformations. Determine if the three fused bonds have a *cis* or *trans* configuration. Determine if the OH groups are axial or equatorial.



Answer

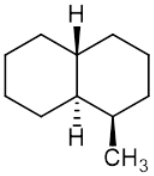




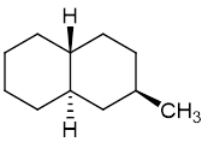
Exercise 5.3.7.2

Draw the following decalin molecules in chair conformations. Determine if the -CH_3 groups are axial or equatorial.

a)

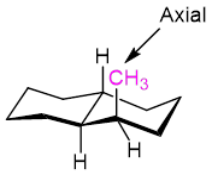


b)

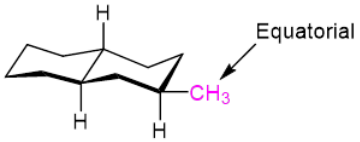


Answer

a)



b)



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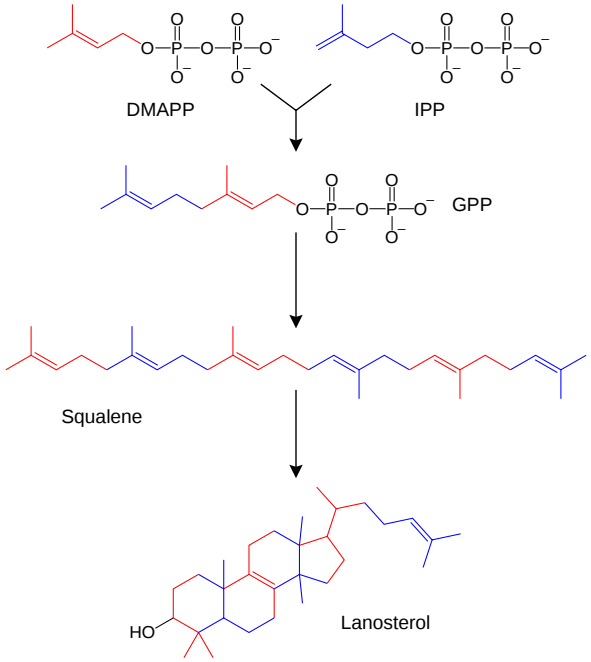
5.3.8: Biosynthesis of Steroids

Objectives

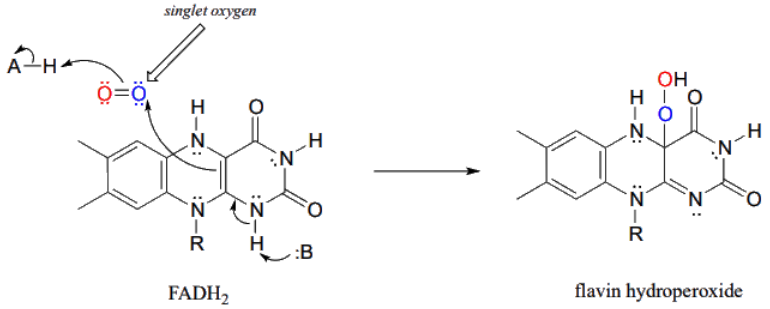
After completing this section, you should be able to

- give an overview of how steroids are synthsized.
- describe changes to molecules through the biosynthesis of steroids.

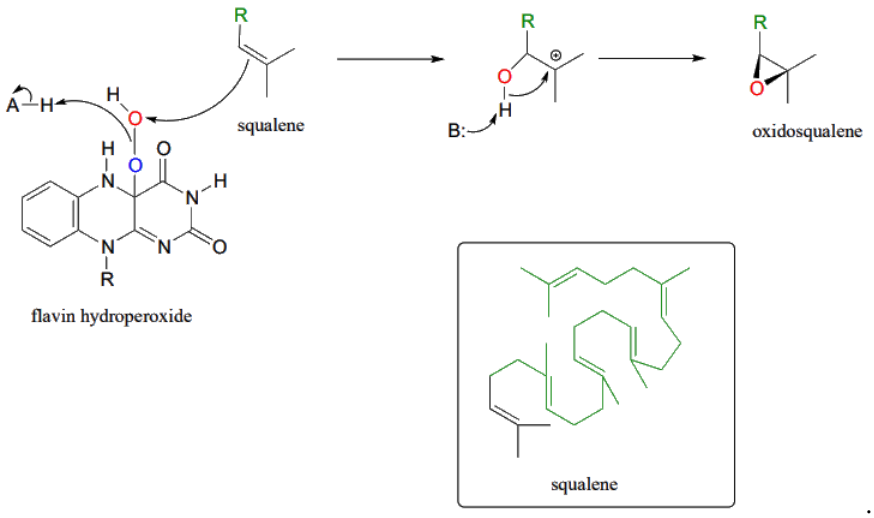
Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors. A unique biosynthetic pathway is followed in animals compared to many other organisms, making the pathway a common target for antibiotics and other anti-infective drugs. In humans and other animals, the biosynthesis of steroids follows the **mevalonate pathway** that uses acetyl-CoA as building blocks to form dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP). These two compounds are coupled to form geranyl pyrophosphate (GPP) which is then converted to the hydrocarbon polyene squalene. After an oxidation and multiple rearrangements, lanosterol the first steroid in the pathway is formed. Further conversions can yield different steroids.



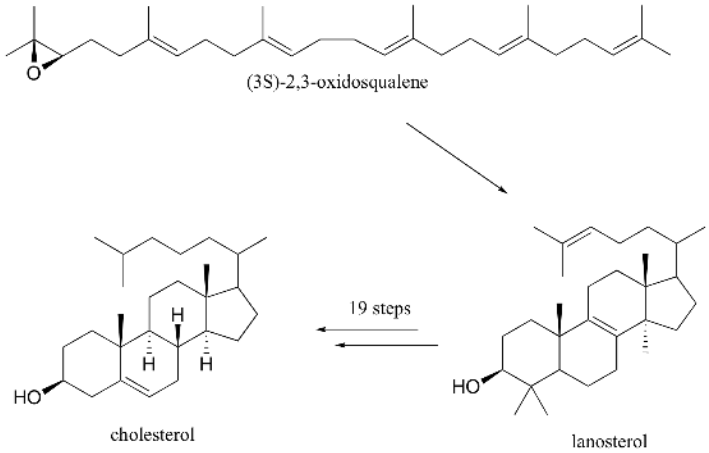
The key step in the biosynthesis of lanosterol is the regioselective epoxidation of squalene to give (3*S*)-2,3-oxidosqualene. This reaction is catalyzed by the monooxygenase enzyme squalene epoxidase. In this step, flavin hydroperoxide serves as the direct oxidizing agent. In flavin hydroperoxide, the peroxide group is linked to one of the carbons of the reactive triple-ring system of the coenzyme. A possible mechanism for the formation of flavin peroxide from $FADH_2$ and molecular oxygen is shown below.



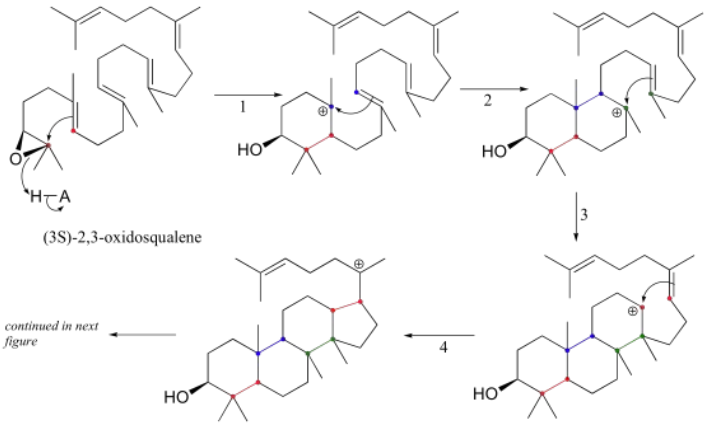
The mechanism for the flavin-hydroperoxide-dependent epoxidation of squalene is initiated by the nucleophilic attack of the pi electrons of a squalene double bond on the electrophilic terminal hydroperoxide oxygen.



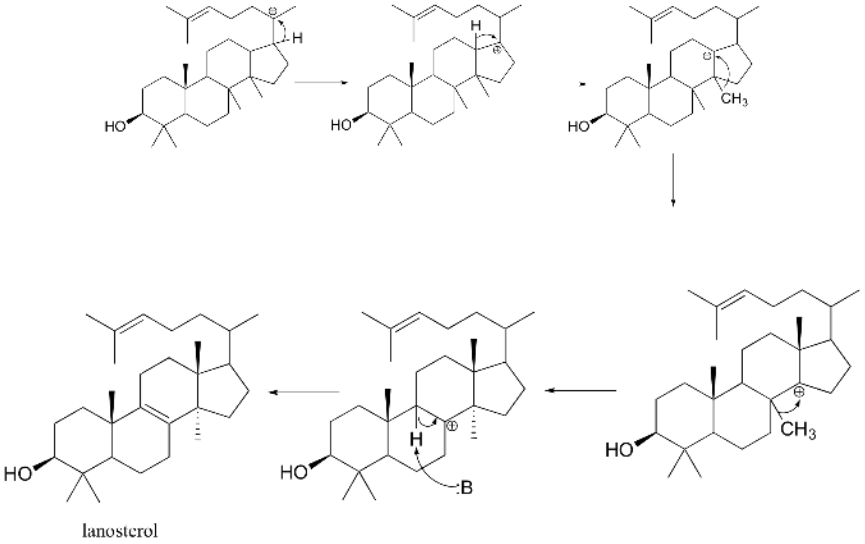
Oxidosqualene goes on to cyclize to lanosterol in a complex and fascinating electrophilic reaction which catalyzed by oxidosqualene-lanosterol cyclase. This reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet carbocation intermediates) or in a concerted manner. For the sake of clarity, we will show the reaction proceeding stepwise. After lanosterol is formed the pathway continued to form cholesterol which is the precursor that all other steroids are derived.



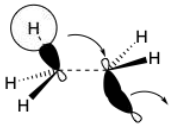
The cyclization phase begins with attack by pi electrons on an epoxide electrophile. The epoxide ring opens to form an alcohol after protonation. A relatively stable tertiary carbocation is also formed. Steps 2, 3, and 4 are simply successive attacks by pi electrons on the carbocation generated by the previous attack. The overall result of this electrophilic cascade is the opening of the epoxide ring, and closure of three six-membered and one five-membered ring.

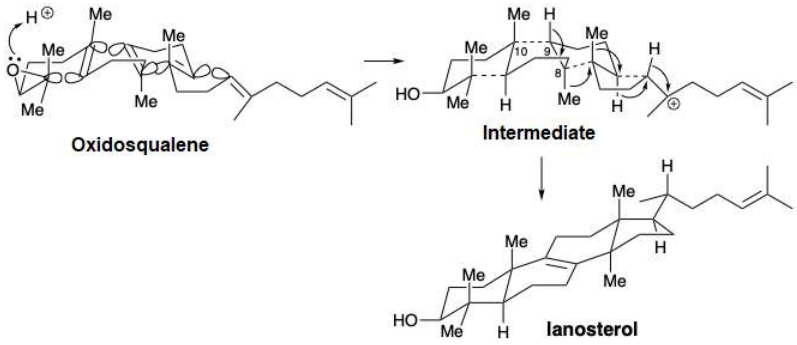


Next comes the rearrangement phase of the reaction in which a series of two 1,2-hydride and two 1,2-methyl shifts to give lanosterol after proton loss from the 9 position.



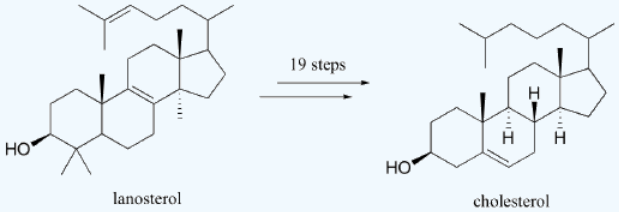
Especially interesting are the stereochemical details of the polyene cyclization and subsequent rearrangement. The polyene cyclization involves stereospecific **anti-periplanar** addition across three C=C bonds in oxidosqualene (see below). The folded conformation of oxidosqualene, required for cyclization is probably imposed by the enzyme involved since appreciable steric congestion is present in both oxidosqualene and the intermediate. Relief of steric strain provides a large driving force for the rearrangements to lanosterol that involves stereospecific inversion of configuration at each stereocenter during 1,2-hydrogen or methyl shifts. Thus, each 1,2-hydride or 1,2-methyl shift occurs to the backside of the orbital connected to the leaving group in what can be viewed as a series of nucleophilic substitution reactions – where σ-bonding electron pairs serve as the nucleophiles.





? Exercise 5.3.8.1

What changes must be made to the structure of lanosterol to convert it to cholesterol?



Answer

Three methyl groups and a double bond are removed. Another double bond is moved to the other side of a six-membered ring.

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- **4.7: Biosynthesis and Total Synthesis of Steroids** by Robert G. Salomon is licensed CC BY-NC 4.0.

5.3.S: Biomolecules - Lipids (Summary)

Concepts & Vocabulary

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrog

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynt

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multip

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arb

25.5 Configurations of Aldoses

- The aldos

25.6 Anomers

- The preferred structural form of mon

25.7 Reactions of Monosaccharides

- The -OH groups on a monosacc

25.8 The Eight Essential Monosaccharides

- The eight essential monos

25.9 Disaccharides

- Disaccharides are sugars com

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers co

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated

25.12 Cell-Surface Carbohydrates and Influenza Viruses

- Carbohydrates a

Skills to Master

- Skill 25.1 Determine which molecules can be classified as carbohydr
-

Summary of Reactions

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SECTION OVERVIEW

5.4: Biomolecules - Nucleic Acids

Learning Objectives

When you have completed Chapter 28, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the structure of a given nucleotide.
3. discuss the structure of DNA and RNA.
4. describe the processes involved in DNA replication, transcription, translation, and protein synthesis.
5. define, and use in context, the key terms introduced in this chapter.

Two types of nucleic acids are found in cells—deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). These highly complex substances are built up from a number of simpler units, called nucleotides. Each nucleotide consists of three parts: a phosphoric acid residue, a sugar and a nitrogen-containing heterocyclic base. Thus, in order to understand the biochemistry of the nucleic acids, you must first study the chemistry of the sugars (see Chapter 25) and simple heterocyclic systems. We have already discussed certain aspects of the structure of heterocyclic ring systems during our study of aromaticity (Sections 15.5–15.6). You may find it helpful to review this chapter.

Chapter 28 examines the structure and replication of DNA and then describes the structure and synthesis of RNA. The chapter closes with a brief study of the role played by RNA in the biosynthesis of proteins.

5.4.1: Nucleotides and Nucleic Acids

5.4.2: Base Pairing in DNA - The Watson-Crick Model

5.4.3: Replication of DNA

5.4.4: Transcription of DNA

5.4.5: Translation of RNA - Protein Biosynthesis

5.4.6: DNA Sequencing

5.4.7: DNA Synthesis

5.4.8: The Polymerase Chain Reaction

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5.4.1: Nucleotides and Nucleic Acids

Objectives

After completing this section, you should be able to

- outline the relationship between nucleic acids, nucleotides and nucleosides.
- identify, in general terms, the enzymatic hydrolysis products of nucleosides.
- explain the structural difference between the sugar components of DNA and RNA.
- identify by name the four heterocyclic amine bases found in deoxyribonucleotides.
- identify by name the four heterocyclic amine bases found in ribonucleotides.
- draw the general structure of a nucleotide and a nucleoside.
- indicate the nitrogen atom by which a given purine or pyrimidine base attaches to the sugar component in nucleotides and nucleosides.
- sketch a section of nucleic acid to show how the nucleotide units are joined together.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- deoxyribonucleic acid (DNA)
- nucleosides nucleotides
- ribonucleic acid (RNA)

Study Notes

The five bases that are found in nucleotides are often represented by their initial letter: adenine, A; guanine, G; cytosine, C; thymine, T; and uracil, U. Note that A, G, C and T occur in DNA; A, G, C and U occur in RNA. You are not required to memorize the structures of these bases, but you must know how each one bonds to the sugar unit in a nucleotide.

To fulfill Objective 6, you should be able to reproduce the figure below.

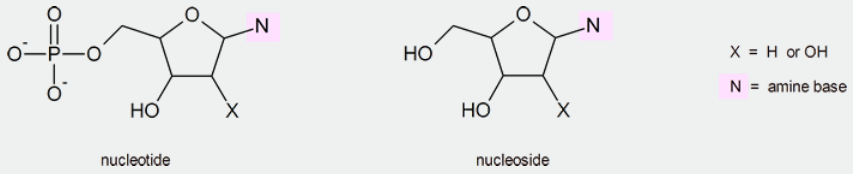


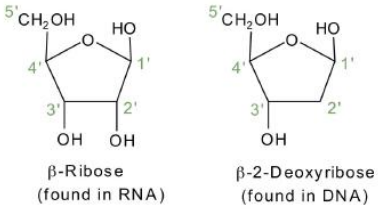
Figure **5.4.1.0** The Pyrimidine and Purine Nucleotides below.

The Learning Objective of this Module is to identify the different molecules that combine to form nucleotides.

The repeating, or monomer, units that are linked together to form **nucleic acids** are known as **nucleotides**. The deoxyribonucleic acid (DNA) of a typical mammalian cell contains about 3×10^9 nucleotides. Nucleotides can be further broken down to a phosphate group (PO_4^{-3}) and a nucleoside which is composed of a aldopentose sugar (a sugar with five carbon atoms), and a heterocyclic purine or pyrimidine base (a base containing nitrogen atoms).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar}$$

If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleosides are used in ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleoside are used in deoxyribonucleic acid (DNA). The prefix -deoxy implies that there is an oxygen missing from the 2' position of ribose.



The nitrogenous bases found in nucleotides are classified as pyrimidines or purines. Pyrimidines are heterocyclic amines with two nitrogen atoms in a six-member ring and include uracil, thymine, and cytosine. Purines are heterocyclic amines consisting of a pyrimidine ring fused to a five-member ring with two nitrogen atoms. Adenine and guanine are the major purines found in nucleic acids (Figure **5.4.1.1**). The numbering convention is that primed numbers designate the atoms of the pentose ring, and unprimed numbers designate the atoms of the purine or pyrimidine ring.

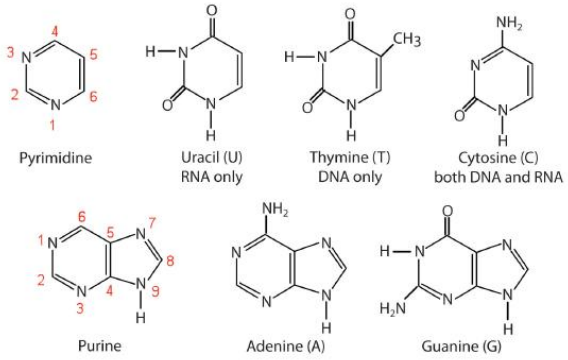
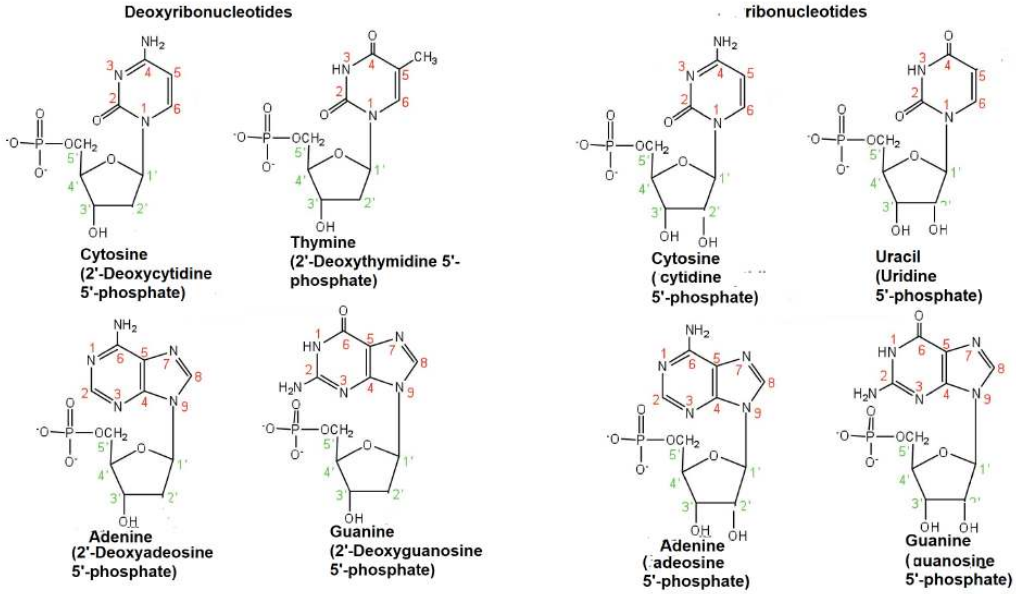


Figure **5.4.1.1**: The Nitrogenous Bases Found in DNA and RNA

Nucleosides are formed by a bond between the anomeric C1′ of the pentose sugar and N1 position of the pyrimidine base or the N9 position of the purine base. The addition of a phospate groups at the 5' position of a nucleoside creates a corresponding nucleotide. DNA is made from four deoxyribonucleotides (Cytosine, Thymine, Adenine, Guanine) and RNA is made from four ribonucleotides Cytosine, Uracil, Adenine, Guanine. The names and structures of the major ribonucleotides and deoxyribonucleotides are given in Figure **5.4.1.2**.



Apart from being the monomer units of DNA and RNA, the nucleotides and some of their derivatives have other functions as well. Adenosine diphosphate (ADP) and adenosine triphosphate (ATP), shown in Figure **5.4.1.3**, have a role in cell metabolism.

Moreover, a number of coenzymes, including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+), and coenzyme A, contain adenine nucleotides as structural components.

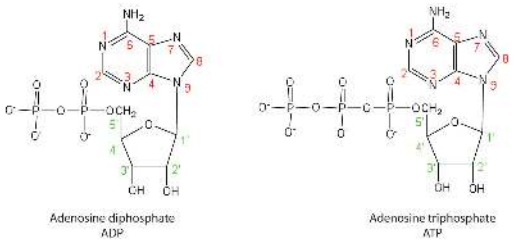


Figure 5.4.1.3: Structures of Two Important Adenine-Containing Nucleotides

Primary Structure of Nucleic Acids

Nucleotides are joined together through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the 3' carbon atom of the sugar unit of a second nucleotide. This unit joins to a third nucleotide, and the process is repeated to produce a long nucleic acid chain (Figure 28.1.4). The backbone of the chain consists of alternating phosphate and sugar units (2-deoxyribose in DNA and ribose in RNA). The purine and pyrimidine bases branch off this backbone.

Like proteins, nucleic acids have a primary structure that is defined as the sequence of their nucleotides. Unlike proteins, which have 20 different kinds of amino acids, there are only 4 different kinds of nucleotides in nucleic acids. For amino acid sequences in proteins, the convention is to write the amino acids in order starting with the N-terminal amino acid. In writing nucleotide sequences for nucleic acids, the convention is to write the nucleotides (usually using the one-letter abbreviations for the bases, shown in Figure 28.1.4) starting with the nucleotide having a free phosphate group, which is known as the 5′ end, and indicate the nucleotides in order. For DNA, a lowercase *d* is often written in front of the sequence to indicate that the monomers are deoxyribonucleotides. The final nucleotide has a free OH group on the 3′ carbon atom and is called the *3′ end*. The sequence of nucleotides in the DNA segment shown in Figure 28.1.4 would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

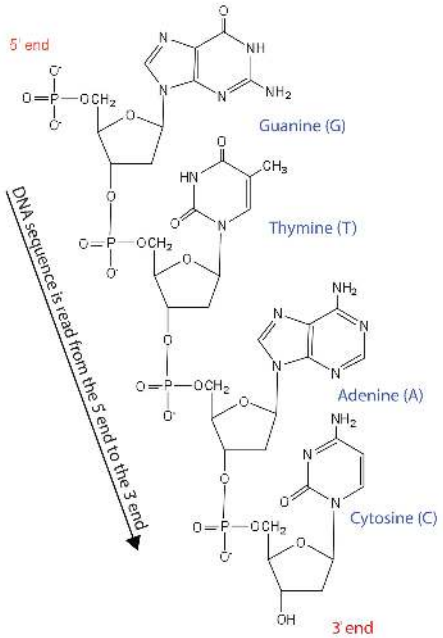


Figure 5.4.1.4: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

Note

Each phosphate group has one acidic hydrogen atom that is ionized at physiological pH. This is why these compounds are known as nucleic acids.

Exercise 5.4.1.1

Classify each compound as a pentose sugar, a purine, or a pyrimidine.

a. adenine
b. guanine
c. deoxyribose
d. thymine
e. ribose
f. cytosine

Answer

a. purine
b. purine
c. pentose sugar
d. pyrimidine
e. pentose sugar
f. pyrimidine

Exercise 5.4.1.2

Identify the three molecules needed to form the nucleotides in each nucleic acid.

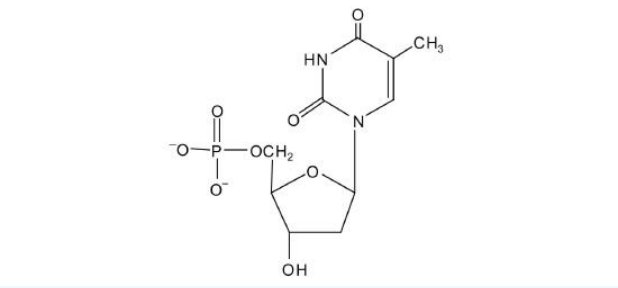
a. DNA
b. RNA

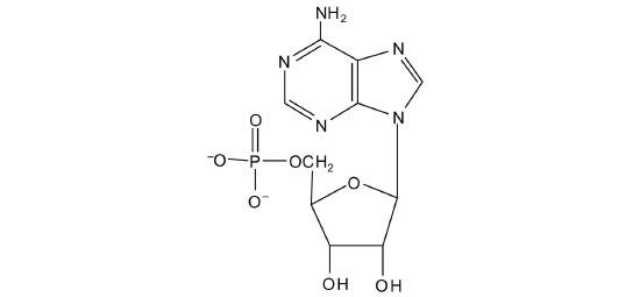
Answer

a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4

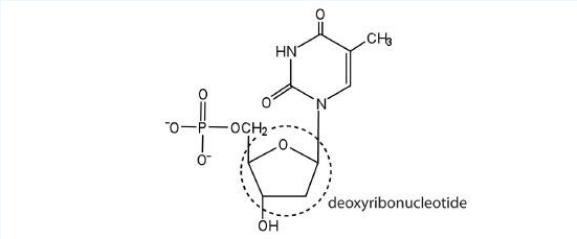
Exercise 5.4.1.3

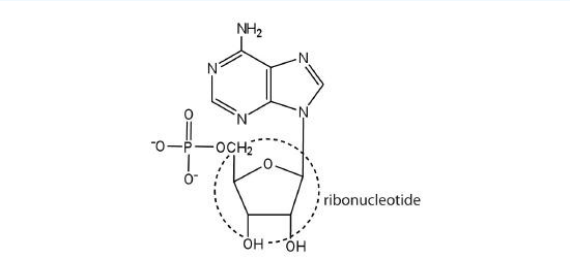
For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

- 

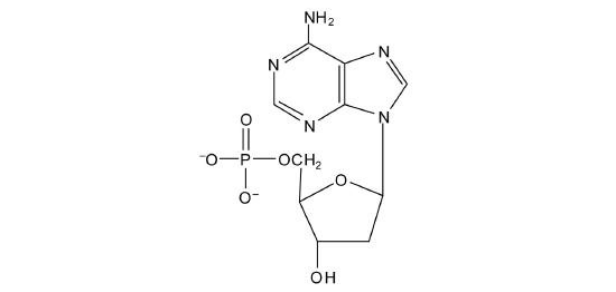
Answer

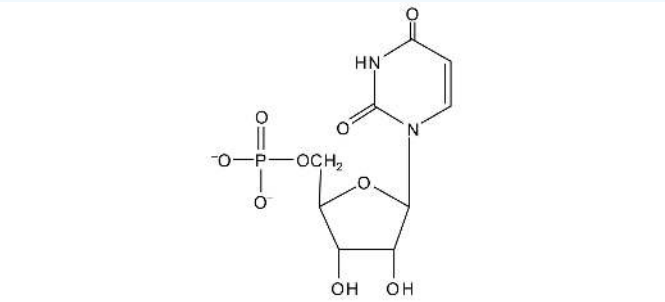
a. 

b. 

Exercise 5.4.1.4

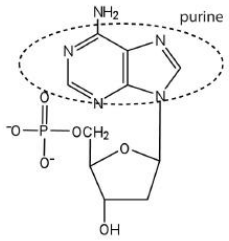
For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

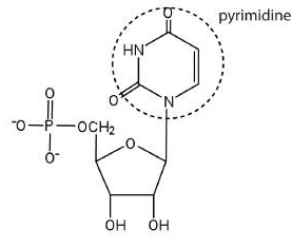
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Answer

a.



b.



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5.4.2: Base Pairing in DNA - The Watson-Crick Model

Objectives

After completing this section, you should be able, given the necessary Kekulé structures, to show how hydrogen bonding can occur between thymine and adenine, and between guanine and cytosine; and to explain the significance of such interactions to the primary and secondary structures of DNA.

Study Notes

Watson and Crick received the Nobel Prize in 1962 for elucidating the structure of DNA and proposing the mechanism for gene reproduction. Their work rested heavily on X-ray crystallographic work done on RNA and DNA by Franklin and Wilkins. Wilkins shared the Nobel Prize with Watson and Crick, but Franklin had been dead four years at the time of the award (you cannot be awarded the Nobel Prize posthumously).

The history of Watson and Crick's proposed DNA model is controversial and a travesty of scientific ethics. Rosalind Franklin was deeply involved in the determination of the structure of DNA, and had collected numerous diffraction patterns. Watson attended a departmental colloquium at King's College given by Franklin, and came into possession of an internal progress report she had written. Both departmental colloquia and progress reports are merely methods of discussion between colleagues; works presented in these fora are not considered by scientists to be "published" works, and therefore are not in the public domain. Watson and Crick not only were aware of Franklin's work, but used her unpublished data, presented in confidence within her own college.

The final blow came about a year after the colloquium. Watson visited Wilkins at King's College, and Wilkins inexplicably handed over Franklin's diffraction photographs without her consent. Had Franklin's work not been secretly taken from her, she might quite possibly have solved the DNA structure before Watson and Crick, who at the time did not yet have their own photographs. This is truly one of the sadder episodes of questionable scientific ethics and discovery that I have ever encountered.

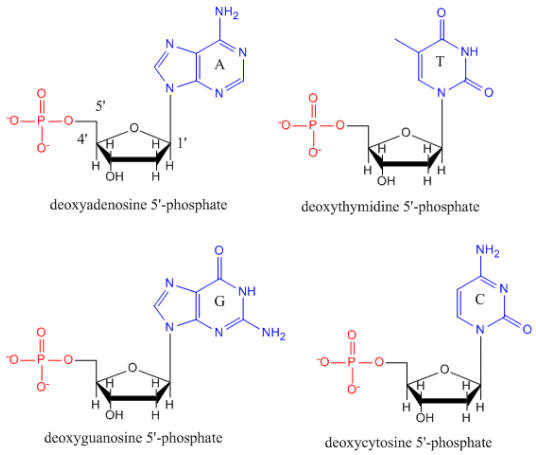
References

Kass-Simon, G., and P. Farnes. Women of Science: Righting the Record. Bloomington, IN: Indiana University Press, 1990.

Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

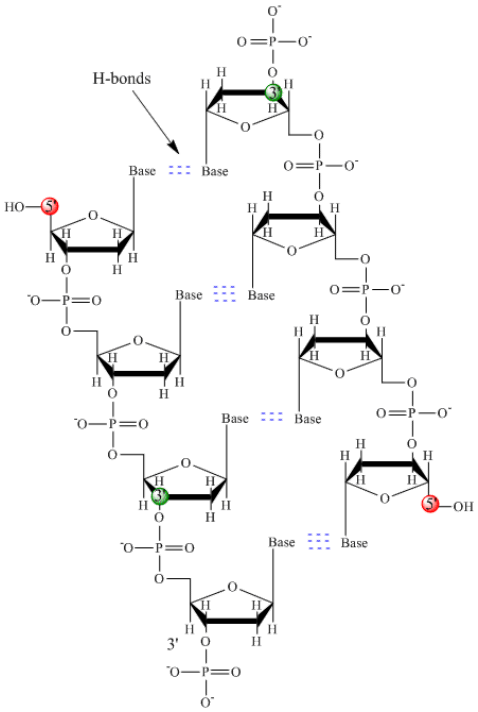
Intermolecular Forces in Nucleic Acids

The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices while RNA typically is a single-stranded molecule which can fold in 3D space to form complex secondary (double-stranded helices) and tertiary structures in a fashion similar to proteins. The complex 3D structures formed by RNA allow it to perform functions other than simple genetic information storage, such as catalysis. Hence most scientists believe that RNA preceded both DNA and proteins in evolution as it can both store genetic information and catalyze chemical reactions.

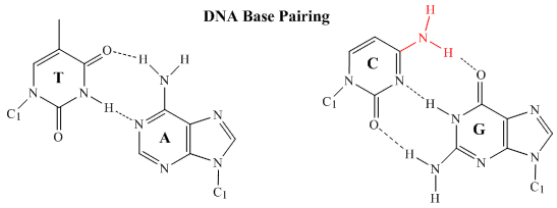


DNA

DNA is a polymer, consisting of monomers call deoxynucleotides. The monomer contains a simple sugar (deoxyribose, shown in black above), a phosphate group (in red), and a cyclic organic R group (in blue) that is analogous to the side chain of an amino acid. Only four bases are used in DNA (in contrast to the 20 different side chains in proteins) which we will abbreviate, for simplicity, as A, G, C and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with one base attached to each sugar molecule. As with proteins, the DNA backbone is polar but also charged. It is a polyanion. The bases, analogous to the side chains of amino acids, are predominately polar. Given the charged nature of the backbone, you might expect that DNA does not fold to a compact globular (spherical) shape, even if positively charged cations like Mg bind to and stabilize the charge on the polymer. Instead, DNA exists usually as a double-stranded (ds) structure with the sugar-phosphate backbones of the two different strands running in opposite directions (5'-3' and the other 3'-5'). The strands are held together by hydrogen bonds between bases on complementary strands. Hence like proteins, DNA has secondary structure but in this case, the hydrogen bonds are not within the backbone but between the "side chain" bases on opposing strands. It is actually a misnomer to call dsDNA a molecule, since it really consists of two different, complementary strands held together by hydrogen bonds. A structure of ds-DNA showing the opposite polarity of the strands is shown below.



In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff's findings clearly indicate that some type of heterocyclic amine base pairing exists in the DNA structure. In double stranded DNA, the guanine (G) base on one strand can form three H-bonds with a cytosine (C) base on another strand (this is called a GC base pair). The thymine (T) base on one strand can form two H-bonds with an adenine (A) base on the other strand (this is called an AT base pair). Double-stranded DNA has a regular geometric structure with a fixed distance between the two backbones. This requires the bases pairs to consists of one base with a two-ring (bicyclic) structure (these bases are called purines) and one with a single ring structure (these bases are called pyrimidines). Hence a G and A or a T and C are not possible base pair partners.

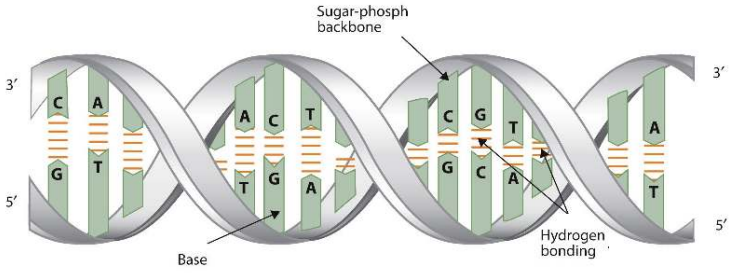


A and T base pair through Hydrogen bonds

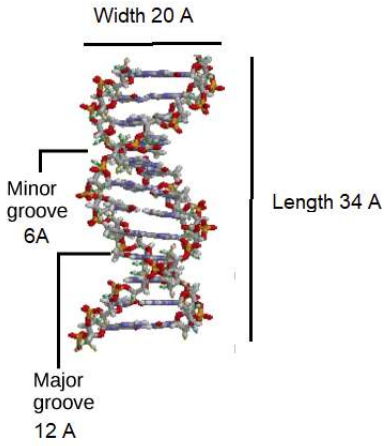
G and C base pair through Hydrogen bonds

Secondary Structure of DNA

The three-dimensional structure of DNA was the subject of an intensive research effort in the late 1940s to early 1950s. DNA exists as a double-stranded molecule that twists around its axis to form a helical structure,stabilized through Watson-Crick hydrogen bonding between purines and pyrimidines, and through pi-pi stacking interactions among the bases arranged in structure. helical column. Each strand is a complement to the other; the nucleotides on one strand hydrogen-bond with complementary nucleotides on the opposite strand—that is, side-by-side with the 5′ end of one chain next to the 3′ end of the other. The purine and pyrimidine bases face the inside of the helix, with guanine always opposite cytosine and adenine always opposite thymine. The double helical "twist" occurs because of the angular geometry of each bonded nucleotide.



Initial work revealed the DNA polymer had a regular repeating pattern X-ray diffraction data shows that a repeating helical pattern is 20 Angstrom units wide and occurs every 34 Angstrom units with 10 nucleotide subunits per turn. Each subunit occupies 3.4 Angstrom units which is the same amount of space occupied by a single nucleotide unit. The helix is Under most conditions, the two strands are slightly offset, which creates a 12 Angstrom major groove on one face of the double helix, and a 6 Angstrom minor groove on the other. The overall DNA polymer varies in length (number of sugar-phosphate units connected), base composition (how many of each set of bases) and sequence (the order of the bases in the backbone).



What do we mean when we say information is encoded in the DNA molecule? An organism's DNA can be compared to a book containing directions for assembling a model airplane or for knitting a sweater. Letters of the alphabet are arranged into words, and these words direct the individual to perform certain operations with specific materials. If all the directions are followed correctly, a model airplane or sweater is produced.

In DNA, the particular sequences of nucleotides along the chains encode the directions for building an organism. Just as *saw* means one thing in English and *was* means another, the sequence of bases CGT means one thing, and TGC means something different. Although there are only four letters—the four nucleotides—in the genetic code of DNA, their sequencing along the DNA strands can vary so widely that information storage is essentially unlimited.

Deoxyribonucleic acid (DNA) stores genetic information, while ribonucleic acid (RNA) is responsible for transmitting or expressing genetic information by directing the synthesis of thousands of proteins found in living organisms. But how do the nucleic acids perform these functions?

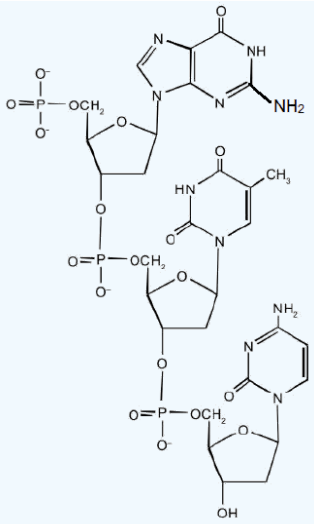
Three processes are required:

1. ***Replication***, in which new copies of DNA are made.
2. ***Transcription***, in which a segment of DNA is used to produce RNA.
3. ***Translation***, in which the information in RNA is translated into a protein sequence.

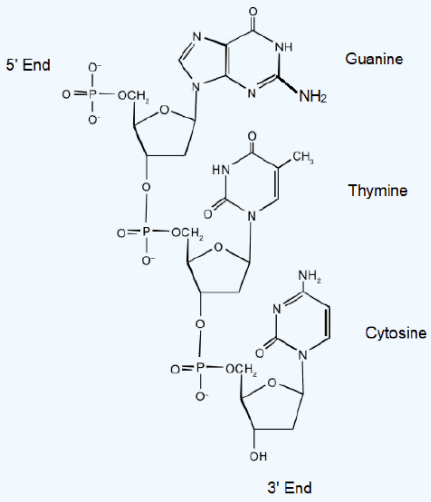
? Exercise 5.4.2.1

For this short DNA segment,

a. Identify the 5′ end and the 3′ end of the molecule.
b. Circle the atoms that comprise the backbone of the nucleic acid chain.
c. Write the nucleotide sequence of this DNA segment.



Answer



Exercise 5.4.2.2

Which nitrogenous base in DNA pairs with each listed nitrogenous base?

a. Cytosine
b. Adenine
c. Guanine
d. Thymine

Answer

a. Guanine
b. Thymine
c. Cytosine
d. Adenine

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Exercise 5.4.2.3

How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

Answer

22 (2 between each AT base pair and 3 between each GC base pair).

Exercise 5.4.2.4

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Answer

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

5.4.2: Base Pairing in DNA - The Watson-Crick Model is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Chris Schaller, Steven Farmer, Dietmar Kennepohl, Henry Jakubowski, & Henry Jakubowski.

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- **19.2: Nucleic Acid Structure** by Anonymous is licensed CC BY-NC-SA 3.0. Original source: https://2012books.lardbucket.org/books/introduction-to-chemistry-general-organic-and-biological.

5.4.3: Replication of DNA

Objectives

After completing this section, you should be able to describe, very briefly, the replication of DNA.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- replication
- semiconservative replication

Study Notes

Notice that the objective for this section requires only that you be able to describe the replication process briefly.

According to the central dogma of molecular genetics, DNA is the genetically active component of the chromosomes of a cell. That is, DNA in the cell nucleus contains all the information necessary to control synthesis of the proteins, enzymes, and other molecules which are needed as that cell grows, carries on metabolism, and eventually reproduces. Thus when a cell divides, its DNA must pass on genetic information to both daughter cells. It must somehow be able to divide into duplicate copies. This process is called **replication**. Given the complementary double strands of DNA, it is relatively easy to see how DNA as a molecule is well structured for replication, as is show in Figure 5.4.3.1. Each strand serves as a template for a new strand. Thus, after DNA is replicated, each new DNA double helix will have one strand from the original DNA molecule, and one newly synthesized molecule. This is referred to as **semiconservative replication**.

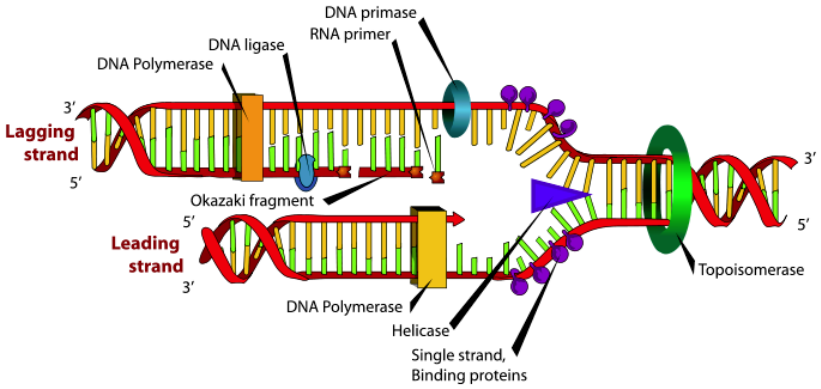


Figure 5.4.3.1: The replication of DNA. Replication occurs by means of partial unwinding of the two strands accompanied by synthesis of a new strand complementary to each of the originals. (CC BY 4.0; Aida Khakimova, Oleg Zolotarev, and Igor Zatsman via the Open Public Health Journal)

A rather complex mechanism exists for DNA replication, involving many different enzymes and protein factors. Let us consider some of the more important aspects of DNA replication. First, the double strand needs to be opened up to replicate each template strand. To do this, a set of proteins and enzymes bind to and open up the double helix at an origin point in the molecule. This forms **replication forks**, points where double stranded DNA opens up, allowing replication to occur. A helicase enzyme binds at the replication forks, with the function of further unwinding the DNA and allowing the replication fork to move along the double strand as DNA is replicated. Another enzyme, DNA gyrase, is also required to relieve stress on the duplex caused by unwinding the double strand. Further, single strand binding proteins are needed to prevent the single strands from reforming a double strand. Another essential enzyme in this initiation phase is primase, which creates an RNA primer on each single strand of DNA to begin replication from.

All of these initial functions are necessary to prepare the DNA for the main enzyme which builds then new strands, DNA polymerase. Multiple polymerase enzymes exist, but for the moment we will DNA polymerase III, the main DNA polymerase in *E.*

coli. DNA polymerase III catalyzes the reaction by which a new nucleotide is added to a growing DNA strand. That reaction is seen in Figure **5.4.3.2**. The DNA polymerase enzymes need a free 3' OH group in order to begin synthesizing a new strand, which explains the necessity of the RNA primer, which gives a 3'OH group for DNA polymerase III to start from.

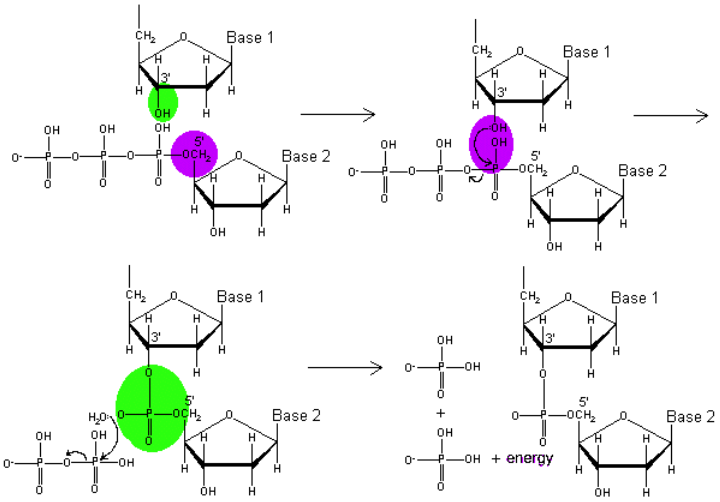


Figure **5.4.3.3**: The polymerization of DNA nucleotides. The 3' hydroxyl group attacks the triphosphate group on the incoming nucleotide. A new phosphodiester bond is formed, and a pyrophosphate group leaves. This leaves two phosphates, the energy released from breaking down a the high energy phosphate group, and a elongated strand of DNA with a new 3' hydroxyl group to which another nucleotide may be added.
(Copyright; author via source)

This leads to another constraint on DNA polymerase III. One strand, the **leading strand** can be polymerized continuously since the new strand being created goes 5' to 3' from the replication fork, but since the original strands are anti-parallel, the other strand, the **lagging strand** is going in the wrong direction for polymerization. In this case, the polymerization reaction starts away from the replication fork and works back toward it. This means that the lagging strand is synthesized in disconnected segments, known as **Okazaki fragments**, instead of continuously. Later, another DNA polymerase, in the case of *E. coli*, DNA polymerase I, removes RNA primers and fills in the missing discontinuities. Then, *another* enzyme, DNA ligase, connects breaks between 3'OH groups and 5' phosphate groups in the newly synthesized strands that exist due to these discontinuities. While the enzymes of this process differ in eukaryotes, they fulfill similar mechanisms. Even with this complexity of this process, DNA polymerase III is able to add new nucleotides at a rate of 250-1,000 nucleotides per second.[3]

A number of advantages of the double-stranded structure held together by hydrogen bonds is evident in the process of replication. Complementary base pairing, A to T and G to C, insures that the two new DNA molecules will be the same as the original. The large number of hydrogen bonds, each of which is relatively weak, makes complete separation of the two strands unlikely, but one hydrogen bond, or even a few, can be broken rather easily. The helicase portion of the replication complex can therefore separate the two strands in much the same way that a zipper operates. Like the teeth of a zipper, hydrogen bonds provide great strength when all work together, but the proper tool can separate them one at a time.

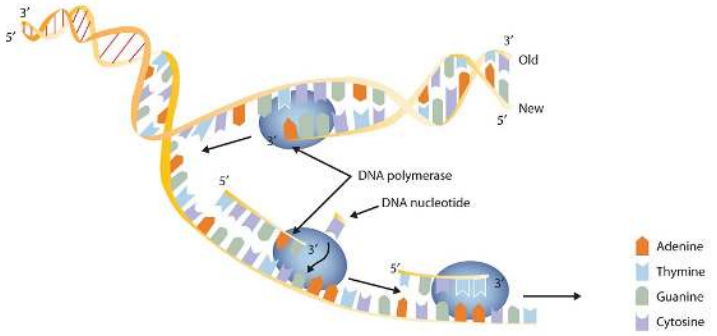


Figure **5.4.3.4**: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix.

The Scope of the Problem of DNA Replication

The 46 chromosomes of the human genome consists of roughly 6.5 billion base pairs of DNA if one considers the full diploid genome (i.e. if you count the DNA inherited from both parents). Considering that this DNA can be copied in just a few hours shows that the rate of DNA replication is staggering.

Although DNA replication is typically a highly accurate process and proofreading DNA polymerases help to keep the error rate low (about one per 10 billion bases), mistakes still occur. In addition to errors of replication, environmental damage may also occur to the DNA. Such uncorrected errors of replication or environmental DNA damage may lead to serious consequences. Therefore, Nature has evolved several mechanisms for detecting and repairing damaged or incorrectly synthesized DNA.

Example 5.4.3.1

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Solution

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

Exercise 28.3.1

A segment of one strand from a DNA molecule has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

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5.4.4: Transcription of DNA

Objectives

After completing this section, you should be able to

- describe, very briefly, how RNA is synthesized in the nucleus of the cell by transcription of DNA.
- identify the important structural differences between DNA and DNA.
- given the appropriate Kekulé structures, show how uracil can form strong hydrogen bonds to adenine.
- identify the base sequence in RNA that would be complementary to a given base sequence in DNA.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- messenger RNA
- RNA polymerase
- ribosomal RNA
- transcription
- transfer RNA

Study Notes

"Messenger RNA" (mRNA) carries the genetic information from the DNA in the nucleus to the cytoplasm where protein synthesis occurs. The code carried by mRNA is read by "transfer RNA" (tRNA) in a process called translation (see Section 28.5).

"Ribosomal RNA" (rRNA) is the term used to describe the RNA molecules which, together with proteins, make up the ribosomes on which proteins are synthesized.

Three types of RNA are formed during transcription: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). These three types of RNA differ in function, size, and percentage of the total cell RNA (Table **5.4.4.1**). mRNA makes up only a small percent of the total amount of RNA within the cell, primarily because each molecule of mRNA exists for a relatively short time; it is continuously being degraded and resynthesized. The molecular dimensions of the mRNA molecule vary according to the amount of genetic information a given molecule contains. After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Elsewhere, we shall see how mRNA directly determines the sequence of amino acids during protein synthesis.

Table **5.4.4.1**: Properties of Cellular RNA in Escherichia coli

Type	Function	Approximate Number of Nucleotides	Percentage of Total Cell RNA
mRNA	codes for proteins	100–6,000	~3
rRNA	component of ribosomes	120–2900	83
tRNA	adapter molecule that brings the amino acid to the ribosome	75–90	14

For the hereditary information in DNA to be useful, it must be "expressed," that is, used to direct the growth and functioning of an organism. The flow of genetic information in cells goes from DNA to mRNA to protein, by genes which specify the sequences of mRNAs, which in turn specify the sequences of proteins.

The first step in the processes that constitute DNA expression is the synthesis of RNA, by a template mechanism that is in many ways analogous to DNA replication. Because the RNA that is synthesized is a complementary copy of information contained in

DNA, RNA synthesis is referred to as transcription. Transcription requires the DNA double helix to partially unwind in the region of mRNA synthesis. The region of unwinding is called a **transcription bubble**. The DNA sequence has patterns which indicate where RNA polymerase should start and end transcription. A DNA sequence at which the RNA polymerase binds to start transcription is called a **promoter**. The DNA sequence that indicates the endpoint of transcription, where the RNA polymerase should stop adding nucleotides and dissociate from the template is known as a **terminator** sequence. The promoter and terminator, thus, bracket the region of the DNA that is to be transcribed.

In bacteria, the promotor sequence contains two 6 bp region called **consensus** sequences. One sequence is centered about 10 bp upstream from the transcription start site. The second sequence at about 35 basepairs upstream from the start of transcription. The consensus sequences at -10 and -35 are necessary for recognition of the promoter region by RNA polymerase.

The DNA sequence that is transcribed to make RNA is called the antisense strand (also called template, anticoding, or transcribed strand), while the complementary sequence on the other DNA strand is called the sense strand (also called the coding or informational strand). To initiate RNA synthesis, the two DNA strands unwind at specific sites along the DNA molecule. Ribonucleotides are attracted to the uncoiling region of the DNA molecule, beginning at the 3′ end of the template strand, according to the rules of base pairing. Thymine in DNA calls for adenine in RNA, cytosine specifies guanine, guanine calls for cytosine, and adenine requires uracil. RNA polymerase—an enzyme—binds the complementary ribonucleotide and catalyzes the formation of the ester linkage between ribonucleotides, a reaction very similar to that catalyzed by DNA polymerase (Figure 5.4.4.1). Synthesis of the RNA strand takes place in the 5′ to 3′ direction, antiparallel to the template strand. Only a short segment of the RNA molecule is hydrogen-bonded to the template strand at any time during transcription. When transcription is completed, the RNA is released, and the DNA helix reforms. The nucleotide sequence of the RNA strand formed during transcription is identical to that of the corresponding coding strand of the DNA, except that U replaces T.

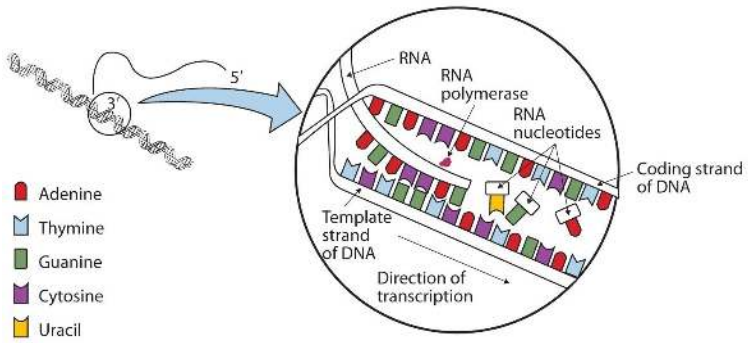


Figure 5.4.4.1: A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The genes of eukaryotes (animals and plants) usually done have continuous segments of coding DNA. Rather they have intervening sequences of DNA (introns) within a given gene that separate coding fragments of DNA (exons). In a process called **splicing**, a primary transcript is made from the DNA, and then splicesomes cut out the introns and join the exons to form a contiguous stretch to form messenger RNA, mRNA. Once formed the mRNA leaves the nucleus is to be translated into a protein sequence..

New findings make it even more complicated to define a gene, especially if the transcripts of a "gene region" are studied. Cheng et al studied all transcripts from 10 different human chromosomes and 8 different cell lines. They found a large number of different transcripts, many of which overlapped. Splicing often occur between nonadjacent introns. Transcripts were found from both strands and were from regions containing introns and exons. Other studies found up to 5% of transcripts continued through the end of "gene" into other genes. 63% of the entire mouse genome, which is comprised of only 2% exons, is transcribed.

? Exercise 5.4.4.1

A portion of the template strand of a gene has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Answer

Four things must be remembered in answering this question: (1) the DNA strand and the RNA strand being synthesized are antiparallel; (2) RNA is synthesized in a 5′ to 3′ direction, so transcription begins at the 3′ end of the template strand; (3) ribonucleotides are used in place of deoxyribonucleotides; and (4) thymine (T) base pairs with adenine (A), A base pairs with uracil (U; in RNA), and cytosine (C) base pairs with guanine (G). The sequence is determined to be 3′-AGGUACUCAACU-5′ (can also be written as 5′-UCAACUCAUGGA-3′).

? Exercise 5.4.4.2

What would be the DNA base sequence of the coding strand required to transcribe the following RNA sequence?

5′-AUGAGCGACUUUGCGGGAUUA-3′

Answer

5′-ATGAGCGACTTTGCGGGATTA-3′.

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5.4.5: Translation of RNA - Protein Biosynthesis

Objectives

After completing this section, you should be able to describe, very briefly, the roles of messenger RNA and transfer RNA in the biosynthesis of proteins.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- anticodon
- codon
- translation

Study Notes

As in the preceding section, you should not be too concerned about trying to memorize details. The objective requires you to have a general understanding of the roles played by mRNA and tRNA in the biosynthesis of proteins, and that you be able to describe this process.

After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Ribosomes are cellular substructures where proteins are synthesized. They contain about 65% rRNA and 35% protein, held together by numerous noncovalent interactions, such as hydrogen bonding, in an overall structure consisting of two globular particles of unequal size. We turn now to the question of how the sequence of nucleotides in a molecule of ribonucleic acid (RNA) is translated into an amino acid sequence.

How can a molecule containing just 4 different nucleotides specify the sequence of the 20 amino acids that occur in proteins? If each nucleotide coded for 1 amino acid, then obviously the nucleic acids could code for only 4 amino acids. What if amino acids were coded for by groups of 2 nucleotides? There are 4^2, or 16, different combinations of 2 nucleotides (AA, AU, AC, AG, UU, and so on). Such a code is more extensive but still not adequate to code for 20 amino acids. However, if the nucleotides are arranged in groups of 3, the number of different possible combinations is 4^3, or 64. Here we have a code that is extensive enough to direct the synthesis of the primary structure of a protein molecule.

The **genetic code** can therefore be described as the identification of each group of three nucleotides and its particular amino acid. The sequence of these triplet groups in the mRNA dictates the sequence of the amino acids in the protein. Each individual three-nucleotide coding unit, as we have seen, is called a **codon**.

First base	Second base: U	Second base: C	Second base: A	Second base: G	Third base
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Figure 5.4.5.1: The Genetic Code

Early experimenters were faced with the task of determining which of the 64 possible codons stood for each of the 20 amino acids. The cracking of the genetic code was the joint accomplishment of several well-known geneticists—notably Har Khorana, Marshall Nirenberg, Philip Leder, and Severo Ochoa—from 1961 to 1964. The genetic dictionary they compiled, summarized in Figure 5.4.5.3, shows that 61 codons code for amino acids, and 3 codons serve as signals for the termination of polypeptide synthesis (much like the period at the end of a sentence). Notice that only methionine (AUG) and tryptophan (UGG) have single codons. All other amino acids have two or more codons.

Protein synthesis is accomplished by orderly interactions between mRNA and the other ribonucleic acids (transfer RNA [tRNA] and ribosomal RNA [rRNA]), the ribosome, and more than 100 enzymes. The mRNA formed in the nucleus during transcription is transported across the nuclear membrane into the cytoplasm to the ribosomes—carrying with it the genetic instructions. The process in which the information encoded in the mRNA is used to direct the sequencing of amino acids and thus ultimately to synthesize a protein is referred to as *translation*.

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. The carboxylic acid group of the amino acid forms an ester linkage with with the 3' hydroxyl group on the riboses bonded at the 3' end of the tRNA. This crucial process requires an enzyme known as aminoacyl-tRNA synthetase (Figure 5.4.5.1). There is a specific aminoacyl-tRNA synthetase for each amino acid. This high degree of specificity is vital to the incorporation of the correct amino acid into a protein. After the amino acid molecule has been bound to its tRNA carrier, protein synthesis can take place.

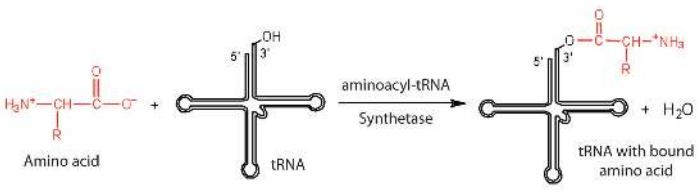


Figure 5.4.5.2 Binding of an Amino Acid to Its tRNA

The two-dimensional structure of a tRNA molecule is reminiscent of a cloverleaf. At one end of the tRNA molecule is the acceptor stem, where the amino acid is attached. The tRNA Molecule has three distinctive loops. One of these is called the anticodon loop which holds a sequence of three nucleotides called the **anticodon**. Each anticodon corresponds to the amino acid each is tRNA molecule is specifically designed to carry. For example, the amino acid lysine has the codon AAG, so the anticodon is UUC. Therefore, lysine would be carried by a tRNA molecule with the anticodon UUC. Each of the 20 amino acids found in proteins has at least one corresponding kind of tRNA, and most amino acids have more than one.

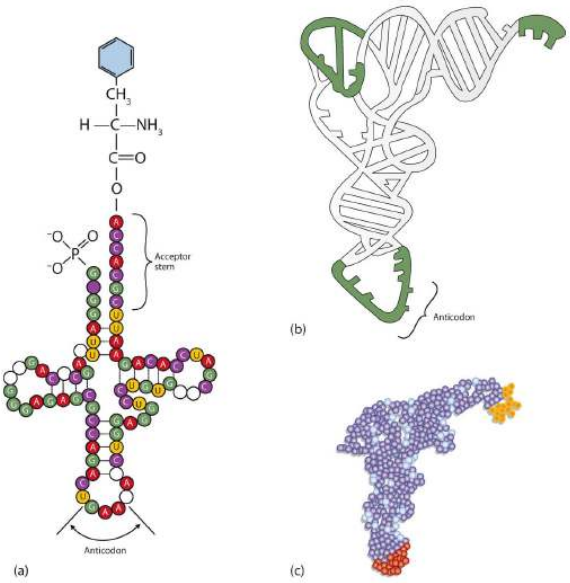
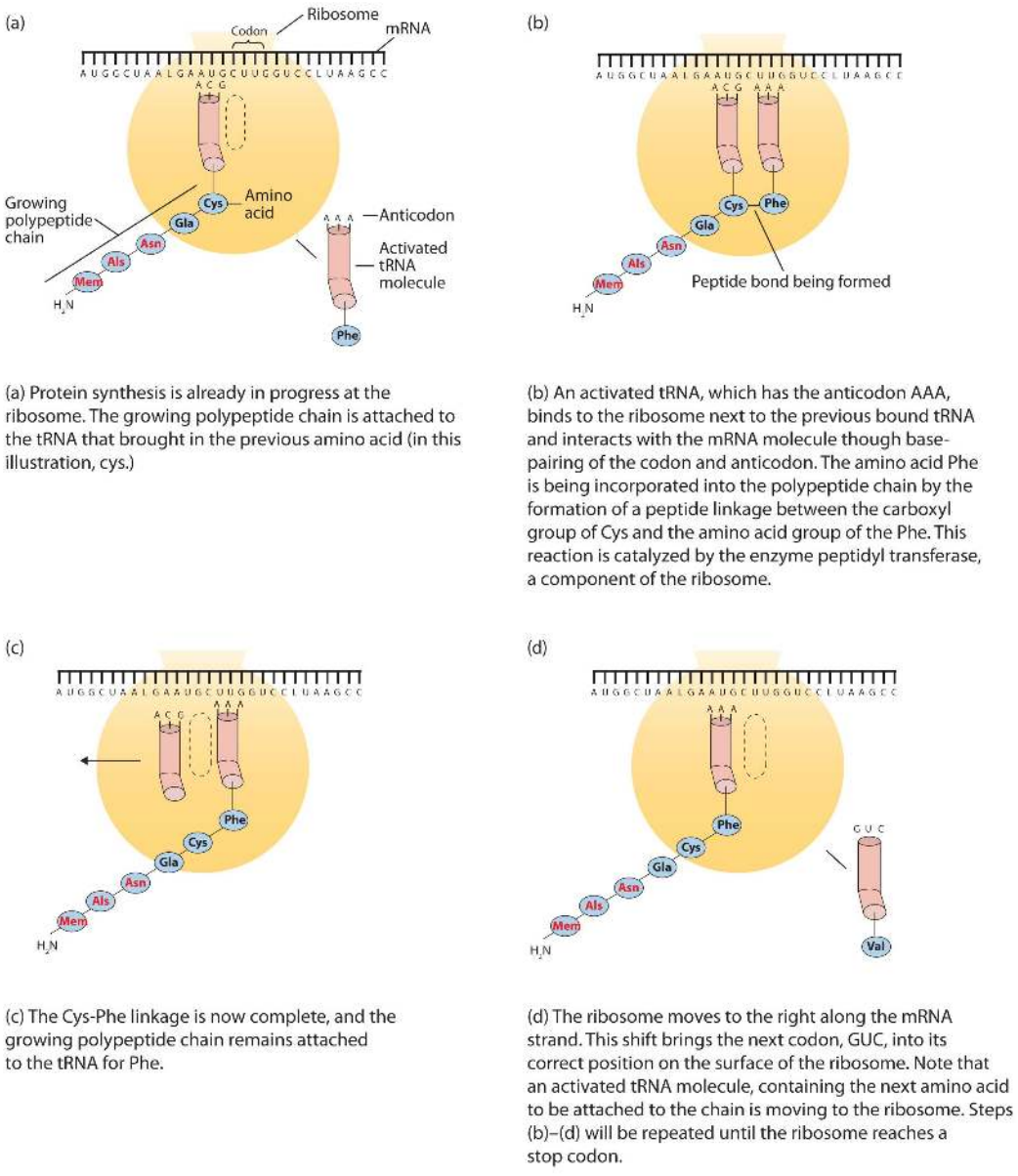


Figure 5.4.5.3: Transfer RNA (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common ribonucleotides A, U, C, and G.) (b) In the three-dimensional structure of yeast phenylalanine tRNA, note that the anticodon loop is at the bottom and the acceptor stem is at the top right. (c) This shows a space-filling model of the tRNA.

During protein synthesis the codon on the mRNA determines which kind of tRNA will add its amino acid to the growing chain. Wherever the codon AAG appears in mRNA, a UUC anticodon on a tRNA temporarily binds to the codon ect. As each different tRNA brings an amino acid into position an enzyme adds it to the growing protein chain. The protein is released from the ribosome once it is completed. Figure 5.4.5.2 depicts a schematic stepwise representation of this all-important process.



(a) Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)

(b) An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though base-pairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide chain by the formation of a peptide linkage between the carboxyl group of Cys and the amino acid group of the Phe. This reaction is catalyzed by the enzyme peptidyl transferase, a component of the ribosome.

(c) The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.

(d) The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached to the chain is moving to the ribosome. Steps (b)–(d) will be repeated until the ribosome reaches a stop codon.

Figure **5.4.5.4**: The Elongation Steps in Protein Synthesis

? Exercise 5.4.5.1

What are the roles of mRNA and tRNA in protein synthesis?

Answer

mRNA provides the code that determines the order of amino acids in the protein; tRNA transports the amino acids to the ribosome to incorporate into the growing protein chain.

? Exercise 5.4.5.2

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Answer

Use Figure 5.4.5.1 to determine what amino acid each set of three nucleotides (codon) codes for. Remember that the sequence is read starting from the 5′ end and that a protein is synthesized starting with the N-terminal amino acid. The sequence 5′-AUGCCACGAGUUGAC-3′ codes for met-pro-arg-val-asp.

? Exercise 5.4.5.3

Write the anticodon on tRNA that would pair with each mRNA codon.

a. 5′-UUU-3′
b. 5′-CAU-3′
c. 5′-AGC-3′
d. 5′-CCG-3′

Answer

a. 3′-AAA-5′
b. 3′-GUA-5′
c. 3′-UCG-5′
d. 3′-GGC-5′

? Exercise 5.4.5.4

The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?

Answer

27 nucleotides (3 nucleotides/codon)

? Exercise 5.4.5.5

Determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.

Answer

met-ser-asp-phe-ala-gly-leu

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5.4.6: DNA Sequencing

Objectives

After completing this section, you should be able to

- Describe briefly how DNA sequencing is carried out.

DNA sequencing determines the order of nucleotide bases within a given fragment of DNA. This information can be used to infer the RNA or protein sequence encoded by the gene, from which further inferences may be made about the gene's function and its relationship to other genes and gene products. DNA sequence information is also useful in studying the regulation of gene expression. If DNA sequencing is applied to the study of many genes, or even a whole genome, it is considered an example of genomics.

While techniques to sequence proteins have been around since the 1950s, techniques to sequence DNA were not developed until the mid-1970s, when two distinct sequencing methods were developed almost simultaneously, one by Walter Gilbert's group at Harvard University, the other by Frederick Sanger's group at Cambridge University. However, until the 1990s, the sequencing of DNA was a relatively expensive and long process. Using radiolabeled nucleotides also compounded the problem through safety concerns. With currently-available technology and automated machines, the process is cheaper, safer, and can be completed in a matter of hours. The Sanger sequencing method was used for the human genome sequencing project, which was finished its sequencing phase in 2003, but today both it and the Gilbert method have been largely replaced by better methods.

Restriction Enzymes

To be able to sequence DNA, it is first necessary to cut it into smaller fragments. What is needed is a way to cleave the DNA molecule at a few precisely-located sites so that a small set of homogeneous fragments are produced. To cut DNA at known locations, researchers use **restriction endonucleases** enzymes that have been purified from various bacterial species, and which can be purchased from various commercial sources. REs occur naturally in bacteria, where they specifically recognize short stretches of nucleotides in DNA and catalyze double-strand breaks at or near the recognition site (also known as a restriction site). These enzymes are usually named after the bacterium from which they were first isolated. For example, ***EcoRI*** and *EcoRV* are both enzymes from *E. coli*.

Restriction enzymes like EcoRI are frequently called 6-cutters, because they recognize a 6-nucleotide sequence. Assuming a random distribution of A, C, G and Ts in DNA, probability predicts that a recognition site for a 6-cutter should occur about once for every 4096 bp (4^6) in DNA. Of course, the distribution of nucleotides in DNA is not random, so the actual sizes of DNA fragments produced by EcoRI range from hundreds to many thousands of base pairs, but the mean size is close to 4000 bp. DNA fragments of this length are useful in the lab, since they long enough to contain the coding sequence for proteins and are well-resolved on agarose gels.

EcoRI recognizes the sequence G A A T T C in double stranded DNA. This recognition sequence is a palindrome with a two-fold axis of symmetry, because reading from 5' to 3' on either strand of the helix gives the same sequence. The palindromic nature of the restriction site is more obvious in the figure below. The dot in the center of the restriction site denotes the axis of symmetry. EcoRI catalyzes the hydrolysis of the phosphodiester bonds between G and A on both DNA strands. The restriction fragments generated in the reaction have short single-stranded tails at the 5'-ends. These ends are often referred to as "sticky ends," because of their ability to form hydrogen bonds with complementary DNA sequences.



Figure 5.4.6.1: The recognition sequence for EcoRI (blue) is cleaved by the enzyme (grey). This particular enzyme cuts DNA at a position offset from the center of the restriction site. This creates an overhanging, sticky-end. (Original-Deyholos-CC:AN)

Reading DNA Sequences

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. Sanger sequencing, also known as chain-termination sequencing, requires a single-stranded DNA template, a DNA primer, a DNA polymerase, normal deoxynucleotidetriphosphates (dNTPs), and modified nucleotides (dideoxyNTPs - ddNTP) that terminate DNA strand elongation. These chain-terminating nucleotides lack a 3′-OH group required for the formation of a phosphodiester bond between two nucleotides, causing DNA polymerase to cease extension of DNA when a ddNTP is incorporated.

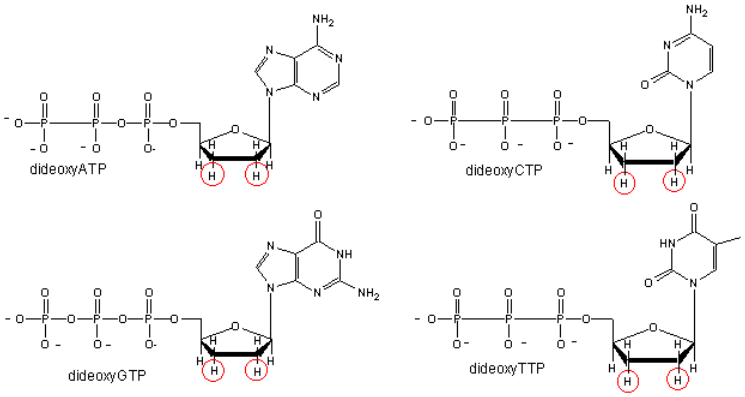


Figure 5.4.6.2: Didexoynucleotides

Four reaction tubes are set up, each containing the template DNA to be sequenced, a *primer* of known sequence, all four of the standard deoxynucleotides (dATP, dGTP, dCTP and dTTP), and the DNA polymerase. To each reaction is added only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP) which has been fluorescently labeled. Most of the time in a Sanger sequencing reaction, DNA Polymerase will add a proper dNTP to the growing strand it is synthesizing in vitro. But at random locations, it will instead add a ddNTP. When it does, that strand will be terminated at the ddNTP just added. If enough template DNAs are included in the reaction mix, each one will have the labeled ddNTP inserted at a different random location, and there will be at least one DNA terminated at each different nucleotide along its length for as long as the in vitro reaction can take place (about 900 nucleotides under optimal conditions.)

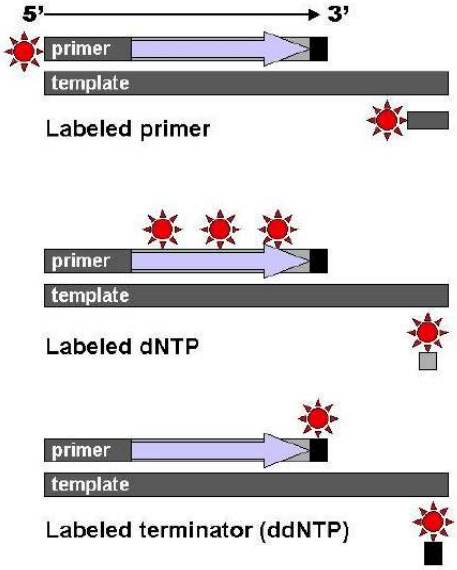


Figure **5.4.6.3**: Sanger sequencing: Different types of Sanger sequencing, all of which depend on the sequence being stopped by a terminating dideoxynucleotide (black bars).

After the reactions are over, the newly synthesized strands can be denatured from the template, and then separated by capillary electrophoresis or other equivalent methods. Since each band differs in length by one nucleotide, and the identity of that nucleotide is known from its fluorescence, the DNA sequence can be read simply from the order of the colors in successive bands.

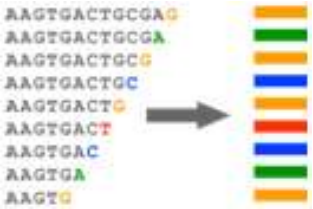


Figure **5.4.6.4**: Fluorescently labeled products can be separated electrophoretically based on their length. (Original-Deyholos-CC:AN)

As each differently-sized fragment exits the capillary column, a laser excites the florescent tag on its terminal nucleotide. From the color of the resulting florescence, a computer can keep track of which nucleotide was present as the terminating nucleotide. The computer also keeps track of the order in which the terminating nucleotides appeared, which is the sequence of the DNA used in the original reaction. In practice, the maximum length of sequence that can be read from a single sequencing reaction is about 700 bp.

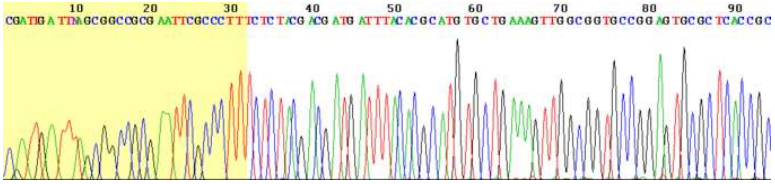


Figure **5.4.6.5**: Chromatograph: This is an example of the output of a Sanger sequencing read using fluorescently labeled dye-terminators. The four DNA bases are represented by different colors which are interpreted by the software to give the DNA sequence above.

Scientists now know the sequence of all the 3 billion DNA base pairs in the entire human genome. This knowledge was attained by the **Human Genome Project (HGP),** a $3 billion, international scientific research project that was formally launched in 1990. The project was completed in 2003, two years ahead of its 15-year projected deadline. Determining the sequence of the billions of base pairs that make up human DNA was the main goal of the HGP. Another goal was mapping the location and determining the function of all the genes in the human genome. There are only about 20,500 genes in human beings. If modern methods were used it might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.

Example 5.4.6.1

You will pretend to sequence a single stranded piece of DNA as shown below. The new nucleotides are added by the enzyme DNA polymerase to the primer, GACT, in the 5' to 3' direction. You will set up 4 reaction tubes, Each tube contains all the dXTP's. In addition, add ddATP to tube 1, ddTTP to tube 2, ddCTP to tube 3, and ddGTP to tube 4. For each separate reaction mixture, determine all the possible sequences made by writing the possible sequences on one of the unfinished complementary sequences below. Cut the completed sequences from the page, determine the size of the polynucleotide sequences made, and place them as they would migrate (based on size) in the appropriate lane of a imaginary gel which you have drawn on a piece of paper. Lane 1 will contain the nucleotides made in tube 1, etc. Then draw lines under the positions of the cutout nucleotides to represent DNA bands in the gel. Read the sequence of the complementary DNA synthesized. Then write the sequence of the ssDNA that was to be sequenced.

- 5' T C A A C G A T C T G A 3' (STAND TO SEQUENCE)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)

Since the DNA fragments have no detectable color, they can not be directly visualized in the gel. Alternative methods are used. In the one described above, radiolabeled ddXTP's where used. Once the sequencing gel is run, it can be dried and the bands visualized by radioautography (also called autoradiography). A place of x-ray film is placed over the dried gel in a dark environment. The radiolabeled bands will emit radiation which will expose the x-ray film directly over the bands. The film can be developed to detect the bands. In a newer technique, the primer can be labeled with a flourescent dye. If a different dye is used for each reaction mixture, all the reaction mixtures can be run in one lane of a gel. (Actually only one reaction mix containing all the ddXTP's together need be performed.) The gel can then be scanned by a laser, which detects fluorescence from the dyes, each at a different wavelength.

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5.4.7: DNA Synthesis

Objectives

After completing this section, you should be able to

- describe, briefly, the steps required for chemical synthesis of DNA segments.

DNA must be synthesized to study genes, the sequence of genomes, and many other studies. This occurs in two fashions, by polymerase chain reaction (PCR) and chemical synthesis. PCR is covered in Section 28.8. Here we will focus on chemical synthesis of short DNA segments, which which are called oligonucleotides. Oligonucleotide synthesis is the chemical synthesis of relatively short fragments of nucleic acids, both DNA and RNA with a defined chemical structure (sequence). The technique is extremely useful in current laboratory practice because it provides a rapid and inexpensive access to custom-made oligonucleotides of the desired sequence.

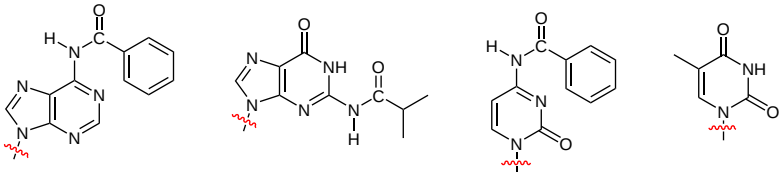
The synthesis of DNA is more difficult than peptide synthesis (Section 26-8) because of the complexity of nucleotide monomers. Commercial automated DNA synthesizers are available which allow for DNA segments to be made quickly and at a low cost. DNA synthesizers typically uses solid-phase techniques similar to the Merrifield solid-phase peptide synthesizer. Nucleotides are protected then covalently bonded to a solid support. Nucleotides are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, it is then deprotected, and collected. The occurrence of side reactions sets practical limits for the length of synthetic oligonucleotides (up to about 200 nucleotide residues) because the number of errors accumulates with the length of the oligonucleotide being synthesized. Products are often isolated by HPLC to obtain the desired oligonucleotides in high purity. Typically, synthetic oligonucleotides are single-stranded DNA or RNA molecules around 15–25 bases in length.

DNA Chemical Synthesis

The synthesis of DNA involves five steps:

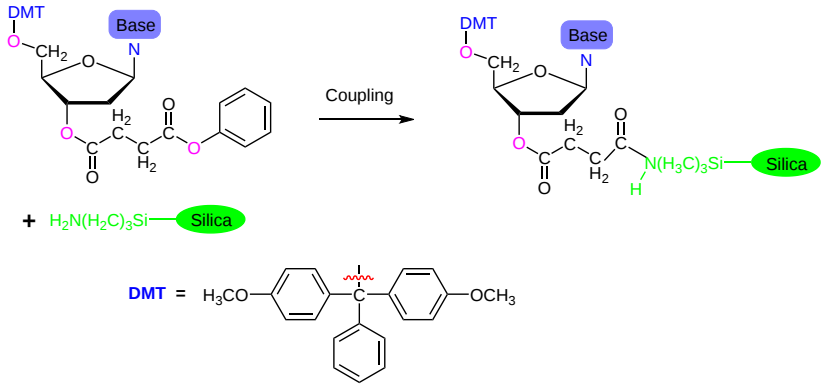
Step 1

Nucleosides used for this synthesis are modified with a linking agent at the 3' hydroxyl group of deoxyribose. The 5' hydroxyl group of the nucleosides is protected with *p*-dimethoxytrityl (DMT) ether. The amine groups on the nucleoside's heterocyclic bases are also protected. The amines of adenine and cytosine bases are protected with benzoyl groups. Guanine's amine are protected by a isobutyryl group and thymine has no amine groups so protection is not required.



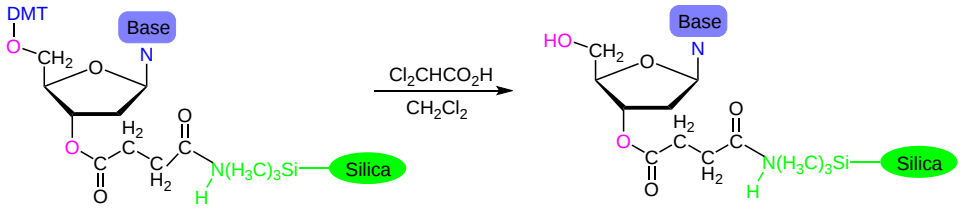
N-Protected Adenine **N-Protected Guanine** **N-Protected Cytosine** **Thymine**

The solid phase support used for DNA synthesis is commonly silica (SO_2) spheres which have been functionalized with (3-aminopropyl)triethoxysilane such that an amine group is available for reaction on the surface. A protected nucleoside is coupled to the solid phase support through an ester linkage with the 3' hydroxyl group of the nucleoside and an amide linkage with amine group from the silica surface.



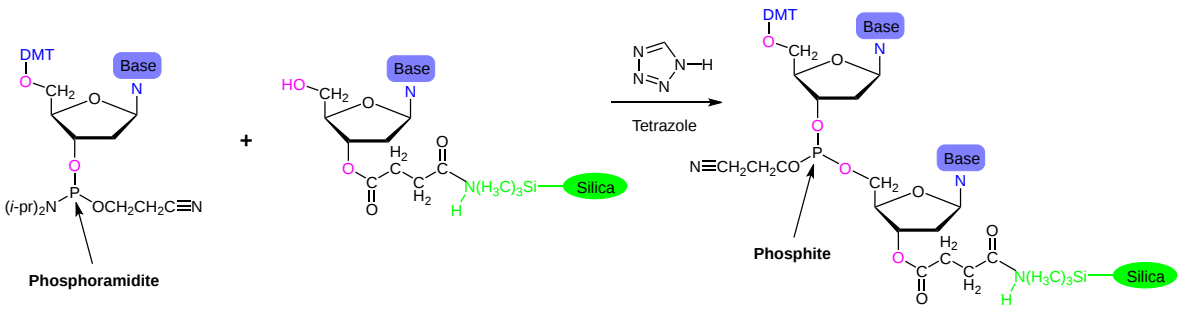
Step 2

Reaction with with dichloroacetic acid removes the DMT protecting group from the 5' hydroxyl of the nucleoside attached to the silica surface. The *p*-dimethoxytrityl leaving group forms a relatively stable dimethoxytrityl cation which is both tertiary and benzylic. The reaction proceeds rapidly through a S_N1 mechanism.



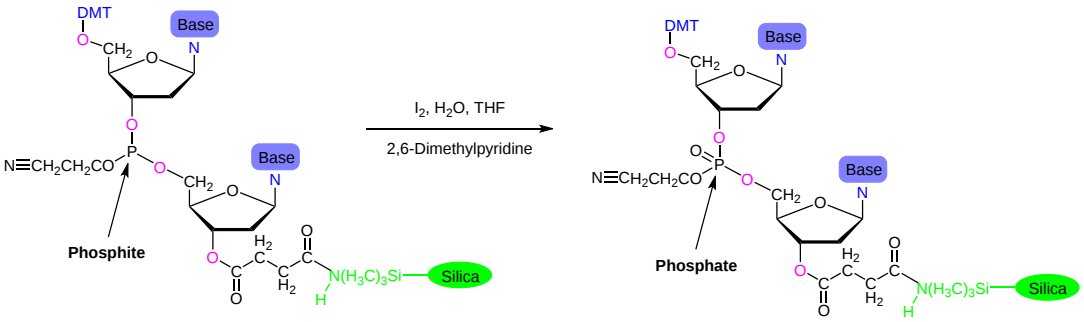
Step 3

The nucleoside attached to the silica surface is then reacted with a protected nucleoside which has a **phosphoramidite** functional group [$R_2NP(OR)_2$] attached to the 3' hydroxyl group of its deoxyribose moiety. In addition, one of the phosphorus oxygen atoms of the phosphoramidite group is protected with a beta-cyanoethyl group (-OCH_2CH_2CN). The two nucleosides are coupled in a reaction which uses acetonitrile as a polar aprotic solvent, tetrazole as a heterocyclic amine catalyst, and produces a product with a phosphite functional group [$P(OR)_3$].



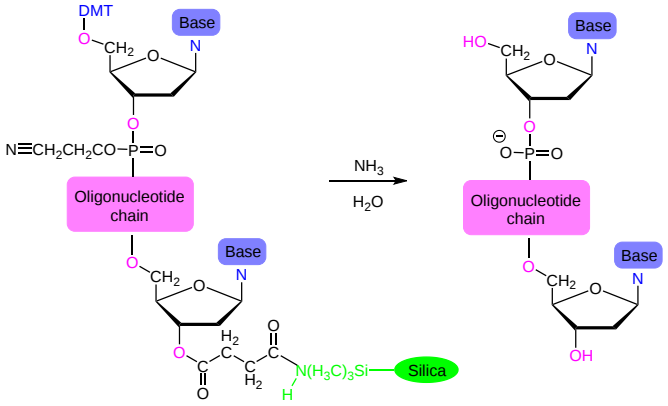
Step 4

Next the phosphite product of the previous step is oxidized to a phosphate by reaction with iodine (I_2) along with 2,6-dimethylpyridine in aqueous tetrahydrofuran (THF). Additional nucleosides can now be added by repeating the **phosphoramidite oligodeoxynucleotide synthesis cycle** of (1) DMT deprotection, (2) phosphoramidite coupling, and (3) oxidation to a phosphite.



Step 5

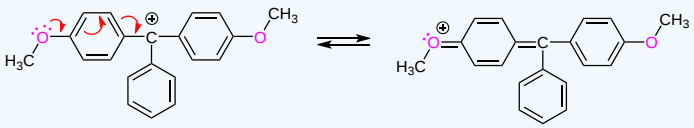
After the oligonucleotide chain of the desired sequence has been made, the final step is the removal of all the protecting groups and the linkage to silica by reaction with aqueous ammonia (NH_3).



Exercise 5.4.7.1

Draw a mechanism which shows why dimethoxytrityl cation produced by the cleavage of a *p*-dimethoxytrityl protecting group is exceptionally stable.

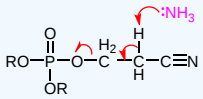
Answer



Exercise 5.4.7.2

When the beta-cyanoethyl protecting group is cleaved with aqueous ammonia, Acrylonitrile, H_2CCHCN , is also produced as a by-product. Draw a mechanism for the reaction.

Answer



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5.4.8: The Polymerase Chain Reaction

Objectives

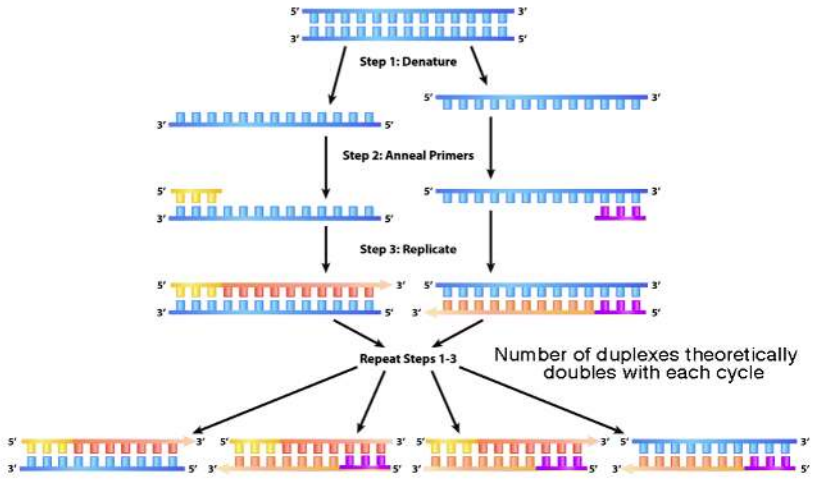
After completing this section, you should be able to

1. describe, briefly the three steps of PCR.

The polymerase chain reaction (PCR), allows one to use the power of DNA replication to amplify DNA enormously in a short period of time. As you know, cells replicate their DNA before they divide, and in doing so, double the amount of the cell's DNA. PCR essentially mimics cellular DNA replication in the test tube, repeatedly copying the target DNA over and over, to produce large quantities of the desired DNA. Kary B. Mullis was awarded a Nobel Prize in 1993 for his development of PCR, which is now the basis of innumerable research studies of gene structure, function and evolution as well as applications in criminal forensics, medical diagnostics and other commercial uses.

PCR requires a DNA fragment, some primers, which are short synthetic oligonucleotides whose sequence matches a region flanking the target sequence. All four deoxynucleotide triphosphates (dATP, dCTP, dGTP, dTTP), are added along with a heat stable DNA polymerase, **Taq**, from the organism *Thermophilus aquaticus* (which lives in hot springs).

PCR is run in a repeating cycle which involves three steps, template denaturing, primer annealing and primer extension.



Template Denaturing

This step is the first regular cycling event and consists of heating the reaction to 94-98°C. It causes denaturing of the DNA template by disrupting the hydrogen bonds between complementary bases, yielding single-stranded DNA molecules. The Taq polymerase is heat-stable so it is not denatured by the high temperature needed to separate the DNA template strands.

Primer Annealing

Next, the solution is cooled to 50-65°C, a temperature that favors complementary DNA sequences finding each other and making base pairs, a process called **annealing**. Since the primers are present in great excess, the complementary sequences they target are readily found and base-paired to the primers. These primers direct the synthesis of DNA. Only where primer anneals to a DNA strand will replication occur, since DNA polymerases require a primer to begin synthesis of a new strand.

Primer Extension

The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75-80°C, and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5′ to 3′ direction, condensing the 5′-phosphate group of the dNTPs with the 3′-hydroxyl group at the end of the nascent (extending) DNA strand. On

completion of this step there are two copies of the DNA template. The new DNA then be denatured to start the cycle again. Each cycle doubles the amount of DNA. Using automated equipment, each cycle of replication can be completed in less than 5 minutes. After 30 cycles, what began as a single molecule of DNA has been amplified into more than a billion copies.

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Index

A

absolute configuration
5.1.5: Configurations of Aldoses
activated charcoal
2.2.4.5C: Charcoal
adsorption
2.1.3: Chromatography
alcohol
3.1.1: Introduction
aldose
5.1.2: Classification of Carbohydrates
alkoxymercuration
3.2.3: Preparing Ethers
alpha cleavage
3.1.12: Spectroscopy of Alcohols and Phenols
amide synthesis reaction
5.2.5: Peptides and Proteins
amides
4.2.6: Chemistry of Amides
amidomalonate synthesis
5.2.4: Synthesis of Amino Acids
amino acid analyzer
5.2.6: Amino Acid Analysis of Peptides
amino sugar
5.1.11: Other Important Carbohydrates
amphoteric
5.2.2: Structures of Amino Acids
amylopectin
5.1.10: Polysaccharides and Their Synthesis
amylose
5.1.10: Polysaccharides and Their Synthesis
Anionic Polymerization
1.4.5: Polymerization of Alkenes
anomers
5.1.6: Cyclic Structures of Monosaccharides - Anomers
anticodon
5.4.5: Translation of RNA - Protein Biosynthesis
Assessing Purity
2.1.5B: Uses of Gas Chromatography
Aufbau principle
1.8.2: Atomic Structure - Electron Configurations
Author Bars
5.2.6: Amino Acid Analysis of Peptides
azide synthesis
3.3.3: Synthesis of Amines

B

Baeyer theory
1.3.2: Stability of Cycloalkanes - Ring Strain
boiling stick
2.2.4.3A: Ideal Temperature Profile
Boiling stones
2.2.4.5B: Heat Source and Bump Prevention
Bromocresol Green
2.1.4F: Visualizing TLC Plates
Bump Prevention
2.2.4.5B: Heat Source and Bump Prevention

C

carbohydrate
5.1.1: Introduction
carbohydrates
5.1.2: Classification of Carbohydrates
carboxylic acids
4.2.2: Naming Carboxylic Acids and Nitriles
carrier gas
2.1.3: Chromatography
cationic polymerization
1.4.5: Polymerization of Alkenes
chromatography
2.1.3: Chromatography
citrate synthase
5.2.12: How do Enzymes Work? Citrate Synthase
Claisen rearrangement
3.2.5: Reactions of Ethers- Claisen Rearrangement
codon
5.4.5: Translation of RNA - Protein Biosynthesis
coenzyme
5.2.11: Enzymes and Coenzymes
cofactor
5.2.11: Enzymes and Coenzymes
column
2.1.3: Chromatography
column chromatography
2.2: Column Chromatography
Coordination Polymerization
1.4.5: Polymerization of Alkenes
Cortisone
5.3.7: Steroids
crystallization
2.2.4: Crystallization
2.2.4.3B: General Procedures for Removing Impurities
2.2.4.3C: Determining Which Solvent to Use
Curtius rearrangement
3.3.3: Synthesis of Amines
cyclic ethers
3.2.1: Introduction
cycloalkanes
1.3.1: Naming Cycloalkanes

D

D sugar
5.1.4: D, L Sugars
D2O shake
3.1.12: Spectroscopy of Alcohols and Phenols
dehydration
3.1.12: Spectroscopy of Alcohols and Phenols
deoxy sugar
5.1.11: Other Important Carbohydrates
deoxyribonucleic acid
5.4.1: Nucleotides and Nucleic Acids
Disaccharide
5.1.2: Classification of Carbohydrates
5.1.9: Disaccharides
DNA
5.4.1: Nucleotides and Nucleic Acids
DNA sequencing
5.4.6: DNA Sequencing
DNA Sequnecing
5.4.6: DNA Sequencing
DNA synthesis
5.4.7: DNA Synthesis

E

Edman degradation
5.2.7: The Edman Degradation
eicosanoids
5.3.5: Prostaglandins and Other Eicosanoids
electrophoresis
5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points
eluent
2.1.4D: Separation Theory
enantioselective synthesis
5.2.4: Synthesis of Amino Acids
enol
3.1.1: Introduction
enzyme
5.2.11: Enzymes and Coenzymes
esters
4.2.5: Chemistry of Esters
ether
3.2.1: Introduction
ethers
3.2.2: Names and Properties of Ethers

F

fats
5.3.2: Waxes, Fats, and Oils
Fischer projection
5.1.3: Depicting Carbohydrate Stereochemistry - Fischer Projections
Flash chromatography
2.2: Column Chromatography
fractional distillation
1.2.3: Fractional Distillation
1.2.3.1: Theory of Fractional Distillation
1.2.3.2: Fractionating Columns
1.2.3.3: Uses of Fractional Distillation
1.2.3.4: Step-by-Step Procedures for Fractional Distillation
fractionating column
1.2.3.1: Theory of Fractional Distillation
Fremy's salt
3.1.11: Reactions of Phenols

G

Gabriel synthesis
3.3.3: Synthesis of Amines
gas chromatography
2.1.3: Chromatography
2.1.5: Gas Chromatography (GC)
2.1.5A: Overview of GC
2.1.5D: Quantitating with GC
glycoproteins
5.1.12: Cell-Surface Carbohydrates and Influenza Viruses
Grignard reagents
3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents

H

hemiacetal
5.1.6: Cyclic Structures of Monosaccharides - Anomers

Hofmann Elimination
3.3.4: Reactions of Amines

Hofmann rearrangement
3.3.3: Synthesis of Amines

hormones
5.3.7: Steroids

hund's rule
1.8.2: Atomic Structure - Electron Configurations

hydroquinone
3.1.11: Reactions of Phenols

I

imide
3.3.3: Synthesis of Amines

insoluble solvent
2.2.4.3F: Mixed Solvents
2.2.4.6D: Mixed Solvent Crystallization

invert sugar
5.1.9: Disaccharides

iodine
2.1.4F: Visualizing TLC Plates

Iron(III) Chloride
2.1.4F: Visualizing TLC Plates

isoelectric point
5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points

isomers
1.7.1: Isomerism Introduction

isoprene rule
5.3.6: Terpenoids

K

ketose
5.1.2: Classification of Carbohydrates

L

lactone
4.2.5: Chemistry of Esters

M

Macroscale Columns
2.2.1: Macroscale Columns

Merrifield synthesis
5.2.9: The Merrifield Solid-Phase Technique

messenger RNA
5.4.4: Transcription of DNA

Microscale Columns
2.2.2: Microscale (Pipette) Columns

Mixed Solvent Crystallization
2.2.4.6D: Mixed Solvent Crystallization

Mixed Solvents
2.2.4.3F: Mixed Solvents

mobile phase
2.1.3: Chromatography

Monosaccharide
5.1.2: Classification of Carbohydrates

monosaccharides
5.1.7: Reactions of Monosaccharides

mother liquor
2.2.4: Crystallization

N

Ninhydrin reaction
5.2.6: Amino Acid Analysis of Peptides

nitriles
4.2.2: Naming Carboxylic Acids and Nitriles

nucleosides
5.4.1: Nucleotides and Nucleic Acids

nucleotides
5.4.1: Nucleotides and Nucleic Acids

O

oiling out
2.2.4.3C: Determining Which Solvent to Use

oils
5.3.2: Waxes, Fats, and Oils

Okazaki fragments
5.4.3: Replication of DNA

oligosaccharide
5.1.12: Cell-Surface Carbohydrates and Influenza Viruses

oxymercuration
3.2.3: Preparing Ethers

P

paper chromatography
2.1.3: Chromatography
2.1.4: Thin Layer Chromatography (TLC)

Pasteur Pipettes
2.2.2: Microscale (Pipette) Columns

pauli exclusion principle
1.8.2: Atomic Structure - Electron Configurations

PCR
5.4.8: The Polymerase Chain Reaction

peptide synthesis
5.2.8: Peptide Synthesis

permanganate
2.1.4F: Visualizing TLC Plates

petroleum refining
1.2.3.3: Uses of Fractional Distillation

phenol
3.1.1: Introduction

phenyl isothiocyanate
5.2.7: The Edman Degradation

Phosphomolybdic Acid (PMA)
2.1.4F: Visualizing TLC Plates

Pipette Columns
2.2.2: Microscale (Pipette) Columns

polycyclic compounds
1.3.1: Naming Cycloalkanes

polymerase chain reaction
5.4.8: The Polymerase Chain Reaction

polymerization
1.4.5: Polymerization of Alkenes

polymers
1.4.5: Polymerization of Alkenes

polysaccharide
5.1.2: Classification of Carbohydrates
5.1.10: Polysaccharides and Their Synthesis

prostaglandins
5.3.5: Prostaglandins and Other Eicosanoids

protein structure
5.2.10: Protein Structure

Purification of Product Mixtures
2.2.4.2B: Purification of Product Mixtures

pyramidal inversion
3.3.2: Structure and Properties of Amines

Q

quinones
3.1.11: Reactions of Phenols

R

racemic mixture
5.2.4: Synthesis of Amino Acids

radical polymerization
1.4.5: Polymerization of Alkenes

Reagent Purification
2.2.4.2A: Reagent Purification

reductive amination
3.3.3: Synthesis of Amines

replication
5.4.3: Replication of DNA

resonance
1.9.2: Resonance

restriction endonucleases
5.4.6: DNA Sequencing

Restriction Enzymes
5.4.6: DNA Sequencing

retention time
2.1.4C: The Retention Factor

ribonucleic acid
5.4.1: Nucleotides and Nucleic Acids

ribosomal RNA
5.4.4: Transcription of DNA

ring strain
1.3.2: Stability of Cycloalkanes - Ring Strain

RNA
5.4.1: Nucleotides and Nucleic Acids

RNA polymerase
5.4.4: Transcription of DNA

RNA translation
5.4.5: Translation of RNA - Protein Biosynthesis

S

sample injector
2.1.3: Chromatography

saponification
4.2.5: Chemistry of Esters

Second Crop Crystallization
2.2.4.4F: Second Crop Crystallization

semiconservative replication
5.4.3: Replication of DNA

Separation Theory
2.1.4D: Separation Theory
2.1.5C: Separation Theory

Solubility Data
2.2.4.3D: Using Solubility Data

stationary phase
2.1.3: Chromatography

steroids
5.3.7: Steroids
5.3.8: Biosynthesis of Steroids

substrate
5.2.11: Enzymes and Coenzymes
sulfide
3.2.1: Introduction
sulfides
3.2.6: Thiols and Sulfides

T

Temperature Profile
2.2.4.3A: Ideal Temperature Profile
terpenes
5.3.6: Terpenoids
terpenoids
5.3.6: Terpenoids
theoretical plate
1.2.3.1: Theory of Fractional Distillation
thin layer chromatography
2.1.4E: Step-by-Step Procedures for Thin Layer Chromatography
thiol
3.2.1: Introduction
thiols
3.2.6: Thiols and Sulfides
TLC
2.1.4: Thin Layer Chromatography (TLC)
2.1.4A: Overview of TLC
2.1.4B: Uses of TLC
2.1.4D: Separation Theory
TLC Plates
2.1.4F: Visualizing TLC Plates
transcription
5.4.4: Transcription of DNA
transfer RNA
5.4.4: Transcription of DNA
translation
5.4.5: Translation of RNA - Protein Biosynthesis

U

ubiquinone
3.1.11: Reactions of Phenols

V

valence bond theory
1.8.4: Describing Chemical Bonds - Valence Bond Theory
vanillin
2.1.4F: Visualizing TLC Plates
Vigreux column
1.2.3.1: Theory of Fractional Distillation
1.2.3.2: Fractionating Columns
Visualizing TLC
2.1.4F: Visualizing TLC Plates
vitamin
5.2.11: Enzymes and Coenzymes

W

Waxes
5.3.2: Waxes, Fats, and Oils
Williamson Ether Synthesis
3.2.3: Preparing Ethers

Glossary

Sample Word 1 | Sample Definition 1

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Overview

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By Page

- Organic Chemistry - MLC - *Undeclared*
  - Front Matter - *Undeclared*
    - TitlePage - *Undeclared*
    - InfoPage - *Undeclared*
    - Table of Contents - *Undeclared*
    - Licensing - *Undeclared*
  - 1: Introduction to Organic Chemistry and Structure - *Undeclared*
    - 1.1: Introduction to Organic Chemistry - *Undeclared*
      - 1.1.1: History - *Undeclared*
    - 1.2: Fractional Distillation and Alkanes - *Undeclared*
      - 1.2.1: Hydrocarbons and the Homologous Series - *Undeclared*
      - 1.2.2: Overview of Distillation - *CC BY-NC-ND 4.0*
      - 1.2.3: Fractional Distillation - *CC BY-NC-ND 4.0*
        - 1.2.3.1: Theory of Fractional Distillation - *CC BY-NC-ND 4.0*
        - 1.2.3.2: Fractionating Columns - *CC BY-NC-ND 4.0*
        - 1.2.3.3: Uses of Fractional Distillation - *CC BY-NC-ND 4.0*
        - 1.2.3.4: Step-by-Step Procedures for Fractional Distillation - *CC BY-NC-ND 4.0*
      - 1.2.4: Structural Formulas - Lewis, Kekule, Bond-line, Condensed, and Perspective - *Undeclared*
      - 1.2.5: Alkanes and Alkane Isomers - *Undeclared*
      - 1.2.6: Alkyl Groups - *Undeclared*
      - 1.2.7: Naming Alkanes - *Undeclared*
      - 1.2.8: Properties of Alkanes - *Undeclared*
    - 1.3: Cyclic Hydrocarbons - *Undeclared*
      - 1.3.1: Naming Cycloalkanes - *Undeclared*
      - 1.3.2: Stability of Cycloalkanes - Ring Strain - *Undeclared*
    - 1.4: Alkenes - *Undeclared*
      - 1.4.1: Bond Rotation - *Undeclared*
      - 1.4.2: Introduction to Alkenes - *Undeclared*
      - 1.4.3: Industrial Preparation and Use of Alkenes - *Undeclared*
      - 1.4.4: Naming Alkenes - *Undeclared*
      - 1.4.5: Polymerization of Alkenes - *Undeclared*
    - 1.5: Alkynes and Benzene - *Undeclared*
      - 1.5.1: Naming Alkynes - *Undeclared*
      - 1.5.2: Introduction - *Undeclared*
      - 1.5.3: Naming Aromatic Compounds - *Undeclared*
      - 1.5.4: Structure and Stability of Benzene - *Undeclared*
    - 1.6: Halides - *Undeclared*
      - 1.6.1: Introduction to Organohalides - *Undeclared*
      - 1.6.2: Names and Properties of Alkyl Halides - *Undeclared*
    - 1.7: Isomers - *Undeclared*
      - 1.7.1: Isomerism Introduction - *Undeclared*
    - 1.8: Polarity and Lewis Structures - *Undeclared*
      - 1.8.1: Atomic Structure - Orbitals - *CC BY-NC-SA 4.0*
      - 1.8.2: Atomic Structure - Electron Configurations - *CC BY-NC-SA 4.0*
      - 1.8.3: Development of Chemical Bonding Theory - *Undeclared*

- 1.8.4: Describing Chemical Bonds - Valence Bond Theory - *Undeclared*
- 1.8.5: Polar Covalent Bonds - Electronegativity - *Undeclared*
- 1.9: Formal Charge and Resonance - *Undeclared*
  - 1.9.1: Lewis Structures and Formal Charges - *Undeclared*
  - 1.9.2: Resonance - *Undeclared*
- 1.10: Common Bonding Patterns for Organic Chemistry - *Undeclared*

2: Tools of Organic Chemistry - *Undeclared*

- 2.1: Intermolecular Forces (IMFs) - Review - *Undeclared*
  - 2.1.1: Intermolecular Forces and Relative Boiling Points (bp) - *Undeclared*
  - 2.1.2: Intermolecular Forces and Solubilities - *Undeclared*
  - 2.1.3: Chromatography - *CC BY-NC-SA 4.0*
  - 2.1.4: Thin Layer Chromatography (TLC) - *CC BY-NC-ND 4.0*
    - 2.1.4A: Overview of TLC - *CC BY-NC-ND 4.0*
    - 2.1.4B: Uses of TLC - *CC BY-NC-ND 4.0*
    - 2.1.4C: The Retention Factor - *CC BY-NC-ND 4.0*
    - 2.1.4D: Separation Theory - *CC BY-NC-ND 4.0*
    - 2.1.4E: Step-by-Step Procedures for Thin Layer Chromatography - *CC BY-NC-ND 4.0*
    - 2.1.4F: Visualizing TLC Plates - *CC BY-NC-ND 4.0*
  - 2.1.5: Gas Chromatography (GC) - *CC BY-NC-ND 4.0*
    - 2.1.5A: Overview of GC - *CC BY-NC-ND 4.0*
    - 2.1.5B: Uses of Gas Chromatography - *CC BY-NC-ND 4.0*
    - 2.1.5C: Separation Theory - *CC BY-NC-ND 4.0*
    - 2.1.5D: Quantitating with GC - *CC BY-NC-ND 4.0*
    - 2.1.5E: GC Parameters - *CC BY-NC-ND 4.0*
    - 2.1.5F: Sample Preparation for Gas Chromatography - *CC BY-NC-ND 4.0*
- 2.2: Column Chromatography - *CC BY-NC-ND 4.0*
  - 2.2.1: Macroscale Columns - *CC BY-NC-ND 4.0*
  - 2.2.2: Microscale (Pipette) Columns - *CC BY-NC-ND 4.0*
  - 2.2.3: 5.5 Polarimetry - *Undeclared*
  - 2.2.4: Crystallization - *CC BY-NC-ND 4.0*
    - 2.2.4.1: Overview of Crystallization - *CC BY-NC-ND 4.0*
    - 2.2.4.2: Uses of Crystallization - *CC BY-NC-ND 4.0*
      - 2.2.4.2A: Reagent Purification - *CC BY-NC-ND 4.0*
      - 2.2.4.2B: Purification of Product Mixtures - *CC BY-NC-ND 4.0*
    - 2.2.4.3: Choice of Solvent - *CC BY-NC-ND 4.0*
      - 2.2.4.3A: Ideal Temperature Profile - *CC BY-NC-ND 4.0*
      - 2.2.4.3B: General Procedures for Removing Impurities - *CC BY-NC-ND 4.0*
      - 2.2.4.3C: Determining Which Solvent to Use - *CC BY-NC-ND 4.0*
      - 2.2.4.3D: Using Solubility Data - *CC BY-NC-ND 4.0*
      - 2.2.4.3E: Experimentally Testing Solvents - *CC BY-NC-ND 4.0*
      - 2.2.4.3F: Mixed Solvents - *CC BY-NC-ND 4.0*
    - 2.2.4.4: Crystallization Theory - *CC BY-NC-ND 4.0*
      - 2.2.4.4A: Purification - *CC BY-NC-ND 4.0*
      - 2.2.4.4B: Cooling Slowly - *CC BY-NC-ND 4.0*
      - 2.2.4.4C: Using the Minimum Amount of Hot Solvent - *CC BY-NC-ND 4.0*
      - 2.2.4.4D: The Unavoidable Loss of Recovery - *CC BY-NC-ND 4.0*
      - 2.2.4.4E: Quantitating Crystallization - *CC BY-NC-ND 4.0*
      - 2.2.4.4F: Second Crop Crystallization - *CC BY-NC-ND 4.0*
    - 2.2.4.5: Procedural Generalities - *CC BY-NC-ND 4.0*
      - 2.2.4.5A: General Procedure - *CC BY-NC-ND 4.0*
      - 2.2.4.5B: Heat Source and Bump Prevention - *CC BY-NC-ND 4.0*
      - 2.2.4.5C: Charcoal - *CC BY-NC-ND 4.0*
      - 2.2.4.5D: Cooling Slowly - *CC BY-NC-ND 4.0*
      - 2.2.4.5E: Initiating Crystallization - *CC BY-NC-ND 4.0*
    - 2.2.4.6: Step-by-Step Procedures - *CC BY-NC-ND 4.0*

- 2.2.4.6A: Single Solvent Crystallization - *CC BY-NC-ND 4.0*
- 2.2.4.6B: Crystallization Summary - *CC BY-NC-ND 4.0*
- 2.2.4.6C: Using Solvents Other Than Water - *CC BY-NC-ND 4.0*
- 2.2.4.6D: Mixed Solvent Crystallization - *CC BY-NC-ND 4.0*
- 2.2.4.6E: Mixed Solvent Summary - *CC BY-NC-ND 4.0*
- 2.2.4.6F: Troubleshooting - *CC BY-NC-ND 4.0*

- 3: Alcohols, Ethers, Thiols, Sulfides, and Amines - *Undeclared*
  - 3.1: Alcohols and Phenols - *CC BY-SA 4.0*
    - 3.1.1: Introduction - *CC BY-SA 4.0*
    - 3.1.2: Naming Alcohols and Phenols - *CC BY-SA 4.0*
    - 3.1.3: Properties of Alcohols and Phenols - *CC BY-SA 4.0*
    - 3.1.4: Preparation of Alcohols- A Review - *CC BY-SA 4.0*
    - 3.1.5: Alcohols from Carbonyl Compounds- Reduction - *CC BY-SA 4.0*
    - 3.1.6: Alcohols from Carbonyl Compounds- Grignard Reagents - *CC BY-SA 4.0*
    - 3.1.7: Reactions of Alcohols - *CC BY-SA 4.0*
    - 3.1.8: Oxidation of Alcohols - *CC BY-SA 4.0*
    - 3.1.9: Protection of Alcohols - *CC BY-SA 4.0*
    - 3.1.10: Phenols and Their Uses - *CC BY-SA 4.0*
    - 3.1.11: Reactions of Phenols - *CC BY-SA 4.0*
    - 3.1.12: Spectroscopy of Alcohols and Phenols - *CC BY-SA 4.0*
    - 3.1.S: Alcohols and Phenols (Summary) - *CC BY-SA 4.0*
  - 3.2: Ethers and Epoxides; Thiols and Sulfides - *CC BY-SA 4.0*
    - 3.2.1: Introduction - *CC BY-SA 4.0*
    - 3.2.2: Names and Properties of Ethers - *CC BY-SA 4.0*
    - 3.2.3: Preparing Ethers - *CC BY-SA 4.0*
    - 3.2.4: Reactions of Ethers- Acidic Cleavage - *CC BY-SA 4.0*
    - 3.2.5: Reactions of Ethers- Claisen Rearrangement - *CC BY-SA 4.0*
    - 3.2.6: Thiols and Sulfides - *CC BY-SA 4.0*
  - 3.3: Amines and Heterocycles - *CC BY-SA 4.0*
    - 3.3.1: Naming Amines - *CC BY-SA 4.0*
    - 3.3.2: Structure and Properties of Amines - *CC BY-SA 4.0*
    - 3.3.3: Synthesis of Amines - *CC BY-SA 4.0*
    - 3.3.4: Reactions of Amines - *CC BY-SA 4.0*
- 4: Carbonyls - *Undeclared*
  - 4.1: Aldehydes and Ketones- Nucleophilic Addition Reactions - *CC BY-SA 4.0*
    - 4.1.1: Chapter Objectives and Preview of Carbonyl Chemistry - *CC BY-SA 4.0*
    - 4.1.2: Naming Aldehydes and Ketones - *CC BY-SA 4.0*
    - 4.1.3: Preparing Aldehydes and Ketones - *CC BY-SA 4.0*
    - 4.1.4: Oxidation of Aldehydes and Ketones - *CC BY-SA 4.0*
    - 4.1.5: Nucleophilic Addition Reactions of Aldehydes and Ketones - *CC BY-SA 4.0*
    - 4.1.6: Nucleophilic Addition of Water- Hydration - *CC BY-SA 4.0*
  - 4.2: Carboxylic Acids - *CC BY-SA 4.0*
    - 4.2.1: Chapter Objectives and Introduction to Carboxylic Acids - *CC BY-SA 4.0*
    - 4.2.2: Naming Carboxylic Acids and Nitriles - *CC BY-SA 4.0*
    - 4.2.3: Structure and Properties of Carboxylic Acids - *CC BY-SA 4.0*
    - 4.2.4: Reactions of Carboxylic Acids - An Overview - *CC BY-SA 4.0*
    - 4.2.5: Chemistry of Esters - *CC BY-SA 4.0*
    - 4.2.6: Chemistry of Amides - *CC BY-SA 4.0*
- 5: Biomolecules - *Undeclared*
  - 5.1: Biomolecules- Carbohydrates - *CC BY-SA 4.0*
    - 5.1.1: Introduction - *CC BY-SA 4.0*
    - 5.1.2: Classification of Carbohydrates - *CC BY-SA 4.0*
    - 5.1.3: Depicting Carbohydrate Stereochemistry - Fischer Projections - *CC BY-SA 4.0*
    - 5.1.4: D, L Sugars - *CC BY-SA 4.0*
    - 5.1.5: Configurations of Aldoses - *CC BY-SA 4.0*
    - 5.1.6: Cyclic Structures of Monosaccharides - Anomers - *CC BY-SA 4.0*
    - 5.1.7: Reactions of Monosaccharides - *CC BY-SA 4.0*
    - 5.1.8: The Eight Essential Monosaccharides - *CC BY-SA 4.0*
    - 5.1.9: Disaccharides - *CC BY-SA 4.0*
    - 5.1.10: Polysaccharides and Their Synthesis - *CC BY-SA 4.0*

- 5.1.11: Other Important Carbohydrates - *CC BY-SA 4.0*
- 5.1.12: Cell-Surface Carbohydrates and Influenza Viruses - *CC BY-SA 4.0*
- 5.1.S: Biomolecules- Carbohydrates (Summary) - *CC BY-SA 4.0*

- 5.2: Biomolecules- Amino Acids, Peptides, and Proteins - *CC BY-SA 4.0*
  - 5.2.1: Introduction - *CC BY-SA 4.0*
  - 5.2.2: Structures of Amino Acids - *CC BY-SA 4.0*
  - 5.2.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points - *CC BY-SA 4.0*
  - 5.2.4: Synthesis of Amino Acids - *CC BY-SA 4.0*
  - 5.2.5: Peptides and Proteins - *CC BY-SA 4.0*
  - 5.2.6: Amino Acid Analysis of Peptides - *CC BY-SA 4.0*
  - 5.2.7: The Edman Degradation - *CC BY-SA 3.0*
  - 5.2.8: Peptide Synthesis - *CC BY-SA 4.0*
  - 5.2.9: The Merrifield Solid-Phase Technique - *CC BY-SA 4.0*
  - 5.2.10: Protein Structure - *CC BY-SA 4.0*
  - 5.2.11: Enzymes and Coenzymes - *CC BY-SA 4.0*
  - 5.2.12: How do Enzymes Work? Citrate Synthase - *Undeclared*
- 5.3: Biomolecules - Lipids - *Undeclared*
  - 5.3.1: Introduction to Lipids - *CC BY-SA 4.0*
  - 5.3.2: Waxes, Fats, and Oils - *CC BY-SA 4.0*
  - 5.3.3: Soap - *CC BY-SA 4.0*
  - 5.3.4: Phospholipids - *CC BY-SA 4.0*
  - 5.3.5: Prostaglandins and Other Eicosanoids - *CC BY-SA 4.0*
  - 5.3.6: Terpenoids - *CC BY-SA 4.0*
  - 5.3.7: Steroids - *CC BY-SA 4.0*
  - 5.3.8: Biosynthesis of Steroids - *CC BY-SA 4.0*
  - 5.3.S: Biomolecules - Lipids (Summary) - *CC BY-SA 4.0*
- 5.4: Biomolecules - Nucleic Acids - *CC BY-SA 4.0*
  - 5.4.1: Nucleotides and Nucleic Acids - *CC BY-SA 4.0*
  - 5.4.2: Base Pairing in DNA - The Watson-Crick Model - *CC BY-SA 4.0*
  - 5.4.3: Replication of DNA - *CC BY-SA 4.0*
  - 5.4.4: Transcription of DNA - *CC BY-SA 4.0*
  - 5.4.5: Translation of RNA - Protein Biosynthesis - *CC BY-SA 4.0*
  - 5.4.6: DNA Sequencing - *CC BY-SA 4.0*
  - 5.4.7: DNA Synthesis - *CC BY-SA 4.0*
  - 5.4.8: The Polymerase Chain Reaction - *CC BY-SA 4.0*

- Back Matter - *Undeclared*
  - Index - *Undeclared*
  - Glossary - *Undeclared*
  - Detailed Licensing - *Undeclared*