STUDY GUIDE

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Organic Chemistry

A Tenth Edition

Preface

What enters your mind when you hear the words "organic chemistry?" Some of you may think, "the chemistry of life," or "the chemistry of carbon." Other responses might include "pre-med," "pressure," "difficult," or "memorization." Although formally the study of the compounds of carbon, the discipline of organic chemistry encompasses many skills that are common to other areas of study. Organic chemistry is as much a liberal art as a science, and mastery of the concepts and techniques of organic chemistry can lead to improved competence in other fields.

Here are several suggestions that may help you with problem solving:

1. The text is organized into chapters that describe individual functional groups. As you study each functional group, *make sure that you understand the structure and reactivity of that group*. In case your memory of a specific reaction fails you, you can rely on your general knowledge of functional groups for help.

2. *Use molecular models*. It is difficult to visualize the three-dimensional structure of an organic molecule when looking at a two-dimensional drawing. Models will help you to appreciate the structural aspects of organic chemistry and are indispensable tools for understanding stereochemistry.

3. *Look through the appendices at the end of the Study Guide*. Some of these appendices contain tables that may help you in working problems; others present information related to the history of organic chemistry.

While the *Study Guide* is written to accompany *Organic Chemistry*, it also contains several unique features. Each chapter of the Study Guide begins with an outline of the text that can be used for a concise review of the text material and can also serve as a reference. After every few chapters a Review Unit is included. In most cases, the chapters covered in the Review Units are related to each other, and the units are planned to appear at approximately the place in the textbook where a test might be given. Each unit lists the vocabulary for the chapters covered, the skills needed to solve problems, and several important points that might need reinforcing or that restate material in the text from a slightly different point of view. Finally, the small self-test that has been included allows you to test yourself on the material from more than one chapter.

I have tried to include many types of study aids in this *Study Guide*. Nevertheless, this book can only serve as an adjunct to the larger and more complete textbook. In addition, please note that a companion to this *Study Guide*, the *Student Solutions Manual*, contains solutions to the problems found in *Organic Chemistry: A Tenth Edition*. I am pleased that this is the first time that these are published by OpenStax and available to you for free in honor of my late son, Peter McMurry.

Susan McMurry

Acknowledgments

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Table of Contents

Chapter 1 – Structure and Bonding

Chapter Outline

I. Atomic Structure (Sections 1.1–1.3).
  A. Introduction to atomic structure (Section 1.1).
    1. An atom consists
    2. of a dense, positively charged nucleus surrounded by negatively charged electrons.
      a. The nucleus is made up of positively charged protons and uncharged neutrons.
      b. The nucleus contains most of the mass of the atom.
      c. Electrons move about the nucleus at a distance of about 2×10^{-10} m (200 pm).
    3. The atomic number (Z) gives the number of protons in the nucleus.
    4. The mass number (A) gives the total number of protons and neutrons.
    5. All atoms of a given element have the same value of Z.
      a. Atoms of a given element can have different values of A.
      b. Atoms of the same element with different values of A are called isotopes.
  B. Orbitals (Section 1.2).
    1. The distribution of electrons in an atom can be described by a wave equation.
      a. The solution to a wave equation is an orbital, represented by Ψ.
      b. Ψ^2 predicts the volume of space in which an electron is likely to be found.
    2. There are four different kinds of orbitals (s, p, d, f).
      a. The s orbitals are spherical.
      b. The p orbitals are dumbbell-shaped.
      c. Four of the five d orbitals are cloverleaf-shaped.
    3. An atom's electrons are organized into electron shells.
      a. The shells differ in the numbers and kinds of orbitals they contain.
      b. Electrons in different orbitals have different energies.
      c. Each orbital can hold up to a maximum of two electrons.
    4. The two lowest-energy electrons are in the 1s orbital.
      a. The 2s orbital is the next higher in energy.
      b. The next three orbitals are $2p_x$, $2p_y$ and $2p_z$, which have the same energy.
        i. Each p orbital has a region of zero density, called a node.
      c. The lobes of a p orbital have opposite algebraic signs.
  C. Electron Configuration (Section 1.3).
    1. The ground-state electron configuration of an atom is a listing of the orbitals occupied by the electrons of the atom in the lowest energy configuration.
    2. Rules for predicting the ground-state electron configuration of an atom:
      a. Orbitals with the lowest energy levels are filled first.
        i. The order of filling is 1s, 2s, 2p, 3s, 3p, 4s, 3d.
      b. Only two electrons can occupy each orbital, and they must be of opposite spin.
      c. If two or more orbitals have the same energy, one electron occupies each until all are half-full (Hund's rule). Only then does a second electron occupy one of the orbitals.
        i. All of the electrons in half-filled shells have the same spin.

II. Chemical Bonding Theory (Sections 1.4–1.5).
  A. Development of chemical bonding theory (Section 1.4).
    1. Kekulé and Couper proposed that carbon has four "affinity units"; carbon is tetravalent.
    2. Kekulé suggested that carbon can form rings and chains.
    3. Van't Hoff and Le Bel proposed that the 4 atoms to which carbon forms bonds sit at the corners of a regular tetrahedron.
    4. In a drawing of a tetrahedral carbon, a wedged line represents a bond pointing toward the viewer, a dashed line points behind the plane of the page, and a solid line lies in the plane of the page.
  B. Covalent bonds.
    1. Atoms bond together because the resulting compound is more stable than the individual atoms.
      a. Atoms tend to achieve the electron configuration of the nearest noble gas.
      b. Atoms in groups 1A, 2A and 7A either lose electrons or gain electrons to form ionic compounds.
      c. Atoms in the middle of the periodic table share electrons by forming covalent bonds.
      d. The neutral collection of atoms held together by covalent bonds is a molecule.
    2. Covalent bonds can be represented two ways.
      a. In electron-dot structures, bonds are represented as pairs of dots.
      b. In line-bond structures, bonds are represented as lines drawn between two bonded atoms.
    3. The number of covalent bonds formed by an atom depends on the number of electrons it has and on the number it needs to achieve an octet.
    4. Valence electrons not used for bonding are called lone-pair (nonbonding) electrons.
      a. Lone-pair electrons are often represented as dots.
  C. Valence bond theory (Section 1.5).
    1. Covalent bonds are formed by the overlap of two atomic orbitals, each of which contains one electron. The two electrons have opposite spins.
    2. Bonds formed by the head-on overlap of two atomic orbitals are cylindrically symmetrical and are called σ bonds.
    3. Bond strength is the measure of the amount of energy needed to break a bond.
    4. Bond length is the optimum distance between nuclei.
    5. Every bond has a characteristic bond length and bond strength.

III. Hybridization (Sections 1.6–1.10).
  A. sp^3 Orbitals (Sections 1.6, 1.7).
    1. Structure of methane (Section 1.6).
      a. When carbon forms 4 bonds with hydrogen, one 2*s* orbital and three 2*p* orbitals combine to form four equivalent atomic orbitals (sp^3 hybrid orbitals).
      b. These orbitals are tetrahedrally oriented.
      c. Because these orbitals are unsymmetrical, they can form stronger bonds than unhybridized orbitals can.

   d. These bonds have a specific geometry and a bond angle of 109.5°.
2. Structure of ethane (Section 1.7).
   a. Ethane has the same type of hybridization as occurs in methane.
   b. The C–C bond is formed by overlap of two sp^3 orbitals.
   c. Bond lengths, strengths and angles are very close to those of methane.

B. sp^2 Orbitals (Section 1.8).
1. If one carbon 2*s* orbital combines with two carbon 2*p* orbitals, three hybrid sp^2 orbitals are formed, and one *p* orbital remains unchanged.
2. The three sp^2 orbitals lie in a plane at angles of 120°, and the unhybridized *p* orbital is perpendicular to them.
3. Two different types of bonds form between two carbons.
   a. A σ bond forms from the overlap of two sp^2 orbitals.
   b. A π bond forms by sideways overlap of two *p* orbitals.
   c. This combination is known as a carbon–carbon double bond.
4. Ethylene is composed of a carbon–carbon double bond and four σ bonds formed between the remaining four sp^2 orbitals of carbon and the 1*s* orbitals of hydrogen.
   a. The double bond of ethylene is both shorter and stronger than the C–C bond of ethane.

C. *sp* Orbitals (Section 1.10).
1. If one carbon 2*s* orbital combines with one carbon 2*p* orbital, two hybrid *sp* orbitals are formed, and two *p* orbitals are unchanged.
2. The two *sp* orbitals are 180° apart, and the two *p* orbitals are perpendicular to them and to each other.
3. Two different types of bonds form.
   a. A σ bond forms from the overlap of two *sp* orbitals.
   b. Two π bonds form by sideways overlap of four unhybridized *p* orbitals.
   c. This combination is known as a carbon–carbon triple bond.
4. Acetylene is composed of a carbon–carbon triple bond and two σ bonds formed between the remaining two *sp* orbitals of carbon and the 1*s* orbitals of hydrogen.
   a. The triple bond of acetylene is the strongest carbon–carbon bond.

D. Hybridization of nitrogen and oxygen (Section 1.10).
1. Covalent bonds between other elements can be described by using hybrid orbitals.
2. Both the nitrogen atom in ammonia and the oxygen atom in water form sp^3 hybrid orbitals.
3. The bond angles between hydrogen and the central atom is often less than 109° because the lone-pair electrons take up more room than the σ bond.
4. Because of their positions in the third row, phosphorus and sulfur can form more than the typical number of covalent bonds.

IV. Molecular orbital theory (Section 1.11).

A. Molecular orbitals arise from a mathematical combination of atomic orbitals and belong to the entire molecule.
1. Two 1*s* orbitals can combine in two different ways.

    a. The additive combination is a bonding MO and is lower in energy than the two hydrogen 1*s* atomic orbitals.
    b. The subtractive combination is an antibonding MO and is higher in energy than the two hydrogen 1*s* atomic orbitals.
  2. Two *p* orbitals in ethylene can combine to form two π MOs.
    a. The bonding MO has no node; the antibonding MO has one node.
  3. A node is a region between nuclei where electrons aren't found.
    a. If a node occurs between two nuclei, the nuclei repel each other.

V. Chemical structures (Section 1.12).
  A. Drawing chemical structures.
    1. Condensed structures don't show C–H bonds and don't show the bonds between CH_3, CH_2 and CH units.
    2. Skeletal structures are simpler still.
      a. Carbon atoms aren't usually shown.
      b. Hydrogen atoms bonded to carbon aren't usually shown.
      c. Other atoms (O, N, Cl, etc.) are shown.

Chapter 2 – Polar Covalent Bonds; Acids and Bases

Chapter Outline

I. Polar covalent bonds (Sections 2.1–2.3).
- A. Electronegativity (Section 2.1).
  1. Although some bonds are totally ionic and some are totally covalent, most chemical bonds are polar covalent bonds.
     a. In these bonds, electrons are attracted to one atom more than to the other atom.
  2. Bond polarity is due to differences in electronegativity (EN).
     a. Elements on the right side of the periodic table are more electronegative than elements on the left side.
     b. Carbon has an EN of 2.5.
     c. Elements with EN > 2.5 are more electronegative than carbon.
     d. Elements with EN < 2.5 are less electronegative than carbon.
  3. The difference in EN between two elements can be used to predict the polarity of a bond.
     a. If ΔEN < 0.4, a bond is nonpolar covalent.
     b. If ΔEN is between 0.4 and 2.0, a bond is polar covalent.
     c. If ΔEN > 2.0, a bond is ionic.
     d. The symbols $\delta+$ and $\delta-$ are used to indicate partial charges.
     e. A crossed arrow is used to indicate bond polarity.
        i. The tail of the arrow is electron-poor, and the head of the arrow is electron-rich.
  4. Electrostatic potential maps are also used to show electron-rich (red) and electron-poor (blue) regions of molecules.
  5. An inductive effect is an atom's ability to polarize a bond.
- B. Dipole moment (Section 2.2).
  1. Net dipole moment is the measure of a molecule's overall polarity.
  2. Bond dipole moment (μ) = $Q \times r$, where Q = charge and r = distance between charges.
     a. Dipole moment is measured in debyes (D).
  3. Dipole moment can be used to measure charge separation in a bond.
  4. Water and ammonia have large values of D; methane and ethane have D = 0.
- C. Formal charge (Section 2.3).
  1. Formal charge (FC) indicates electron "ownership" in a molecule.
  2. $$(\text{FC}) = [\#\text{ of valence electrons}] - \left[\frac{\#\text{ of bonding electrons}}{2}\right] - [\#\text{ nonbinding electrons}]$$

II. Resonance (Sections 2.4–2.6).
- A. Chemical structures and resonance (Section 2.4).
  1. Some molecules (acetate ion, for example) can be drawn as two (or more) different electron-dot structures.
     a. These structures are called resonance structures.
     b. The true structure of the molecule is intermediate between the resonance structures.

c. The true structure is called a resonance hybrid.

2. Resonance structures differ only in the placement of π and nonbonding electrons.
   a. All atoms occupy the same positions.
3. Resonance is an important concept in organic chemistry.

B. Rules for resonance forms (Section 2.5).
1. Individual resonance forms are imaginary, not real.
2. Resonance forms differ only in the placement of their π or nonbonding electrons.
   a. A curved arrow is used to indicate the movement of electrons, not atoms.
3. Different resonance forms of a molecule don't have to be equivalent.
   a. If resonance forms are nonequivalent, the structure of the actual molecule resembles the more stable resonance form(s).
4. Resonance forms must obey normal rules of valency.
5. The resonance hybrid is more stable than any individual resonance form.

C. A useful technique for drawing resonance forms (Section 2.6).
1. Any three-atom grouping with a multiple bond adjacent to a nonbonding *p* orbital has two resonance forms.
2. One atom in the grouping has a lone electron pair, a vacant orbital or a single electron.
3. By recognizing these three-atom pieces, resonance forms can be generated.

III. Acids and bases (Sections 2.7–2.11).

A. Brønsted–Lowry definition (Section 2.7).
1. A Brønsted–Lowry acid donates an H^+ ion; a Brønsted–Lowry base accepts H^+.
2. The product that results when a base gains H^+ is the conjugate acid of the base; the product that results when an acid loses H^+ is the conjugate base of the acid.
3. Water can act either as an acid or as a base.

B. Acid and base strength (Section 2.8–2.10).
1. A strong acid dissociates almost completely with water (Section 2.8).
2. The strength of an acid in water is indicated by K_a, the acidity constant.
3. Strong acids have large acidity constants, and weaker acids have smaller acidity constants.
4. The pK_a is normally used to express acid strength.
   a. $pK_a = -\log K_a$
   b. A strong acid has a small pK_a, and a weak acid has a large pK_a.
   c. The conjugate base of a strong acid is a weak base, and the conjugate base of a weak acid is a strong base.
5. Predicting acid–base reactions from pK_a (Section 2.9).
   a. An acid with a low pK_a (stronger acid) reacts with the conjugate base of an acid with a high pK_a (stronger base).
   b. In other words, the products of an acid–base reaction are more stable than the reactants.

6. Organic acids and organic bases (Section 2.10).
    a. There are two main types of organic acids:
        i. Acids that contain hydrogen bonded to oxygen.
        ii. Acids that have hydrogen bonded to the carbon next to a C=O group.
    b. The main type of organic base contains a nitrogen atom with a lone electron pair.

C. Lewis acids and bases (Section 2.11).
1. A Lewis acid accepts a pair of nonbinding electrons.
    a. A Lewis acid may have either a vacant low-energy orbital or a polar bond to hydrogen.
    b. Examples include metal cations, halogen acids, group 3 compounds, and transition-metal compounds.
2. A Lewis base has a pair of nonbonding electrons.
    a. Most oxygen- and nitrogen-containing organic compounds are Lewis bases.
    b. Many organic Lewis bases have more than one basic site.
3. A curved arrow shows the movement of electrons from a Lewis base to a Lewis acid.

IV. Noncovalent interactions in molecules (Section 2.12).

A. Dipole–dipole interactions occur between polar molecules as a result of electrostatic interactions among dipoles.
1. These interactions may be either attractive or repulsive.
2. The attractive geometry is lower in energy and predominates.

B. Dispersion forces result from the constantly changing electron distribution within molecules.
1. These forces are transient and weak, but their cumulative effect may be important.

C. Hydrogen bonds.
1. Hydrogen bonds form between a hydrogen bonded to electronegative atoms (O, N, and F) and an unshared electron pair on another electronegative atom.
2. Hydrogen bonds are extremely important in living organisms.
3. Hydrophilic substances dissolve in water because they are capable of forming hydrogen bonds.
4. Hydrophobic substances don’t form hydrogen bonds and usually don’t dissolve in water.

Review Unit 1: Bonds and Bond Polarity

Major Topics Covered (with vocabulary:)

Atomic Structure:
atomic number mass number wave equation orbital shell node electron configuration

Chemical Bonding Theory:
covalent bond Lewis structure lone-pair electrons line-bond structure valence-bond theory sigma (σ) bond bond strength bond length molecular orbital theory bonding MO antibonding MO

Hybridization:
sp^3 hybrid orbital bond angle sp^2 hybrid orbital pi (π) bond sp hybrid orbital

Polar covalent bonds:
polar covalent bond electronegativity (EN) electrostatic potential maps inductive effect dipole moment formal charge dipolar molecule

Resonance:
resonance form resonance hybrid

Acids and Bases:
Brønsted-Lowry acid Brønsted-Lowry base conjugate acid conjugate base acidity constant K_a pK_a organic acid organic base Lewis acid Lewis base

Chemical Structures:
condensed structure skeletal structure space-filling models ball-and-stick models

Types of Problems:

After studying these chapters, you should be able to:

- Predict the ground state electronic configuration of atoms.
- Draw Lewis electron-dot structures of simple compounds.
- Predict and describe the hybridization of bonds in simple compounds.
- Predict bond angles and shapes of molecules.
- Predict the direction of polarity of a chemical bond, and predict the dipole moment of a simple compound.
- Calculate formal charge for atoms in a molecule.
- Draw resonance forms of molecules.
- Predict the relative acid/base strengths of Brønsted acids and bases.
- Predict the direction of Brønsted acid/base reactions.
- Calculate: pK_a from K_a, and vice versa.
  pH of a solution of a weak acid.
- Identify Lewis acids and bases.
- Draw chemical structures from molecular formulas, and vice versa.

Points to Remember:

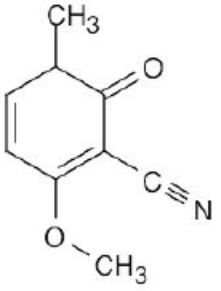
* In order for carbon, with valence shell electron configuration of $2s^2 2p^2$, to form four sp^3 hybrid orbitals, it is necessary that one electron be promoted from the 2*s* subshell to the 2*p* subshell. Although this promotion requires energy, the resulting hybrid orbitals are able to form stronger bonds, and compounds containing these bonds are more stable.

* Assigning formal charge to atoms in a molecule is helpful in showing where the electrons in a bond are located. Even if a bond is polar covalent, in some molecules the electrons "belong" more to one of the atoms than the other. This "ownership" is useful for predicting the outcomes of chemical reactions, as we will see in later chapters.

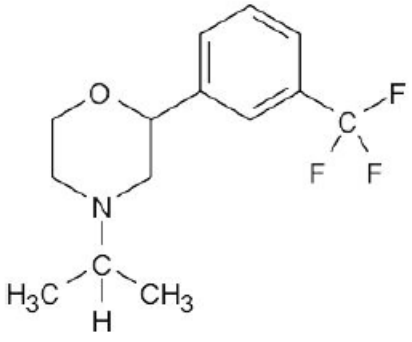
* Resonance structures are representations of the distribution of π and nonbonding electrons in a molecule. Resonance structures are an attempt to show, by conventional line-bond drawings, the electron distribution of a molecule that can't be represented by any one structure.

* As in general chemistry, acid-base reactions are of fundamental importance in organic chemistry. Organic acids and bases, as well as inorganic acids and bases, occur frequently in reactions, and large numbers of reactions are catalyzed by Brønsted acids and bases and Lewis acids and bases.

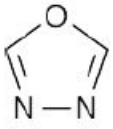
Self-Test:



A
Ricinine
(a toxic component of castor beans)



B
Oxaflozane
(an antidepressant)



C
1,3,4-Oxadiazole

For **A** (ricinine) and **B** (oxaflozane): Add all missing electron lone pairs. Identify the hybridization of all carbons. Indicate the direction of bond polarity for all bonds with $\Delta EN \geq 0.5$. In each compound, which bond is the most polar? Convert **A** and **B** to molecular formulas.

Draw a resonance structure for **B**. Which atom (or atoms) of **B** can act as a Lewis base?

Add missing electron lone pairs to **C**. Is it possible to draw resonance forms for **C**? If so, draw at least one resonance form, and describe it.

Multiple Choice:

1. Which element has $4s^2 4p^2$ as its valence shell electronic configuration?
   (a) Ca (b) C (c) Al (d) Ge

2. Which compound (or group of atoms) has an oxygen with a +1 formal charge?
   (a) NO_3^- (b) O_3 (c) acetone anion (d) acetate anion

The following questions (3–7) involve these acids: (i) HW ($pK_a = 2$); (ii) HX ($pK_a = 6$); (iii) HY ($pK_a = 10$); (iv) HZ ($pK_a = 20$).

3. Which of the above acids react almost completely with water to form hydroxide ion?
   (a) none of them (b) all of them (c) HY and HZ (d) HZ

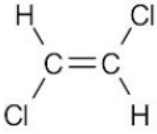
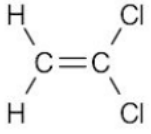
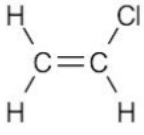
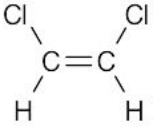
4. The conjugate bases of which of the above acids react almost completely with water to form hydroxide ion?
   (a) none of them (b) all of them (c) HZ (d) HY and HZ

5. If you want to convert HX to X^-, which bases can you use?
   (a) W^- (b) Y^- (c) Z^- (d) Y^- or Z^-

6. If you add equimolar amounts of HW, X^- and HY to a solution, what are the principal species in the resulting solution?
   (a) HW, HX, HY (b) W^-, HX, HY (c) HW, X^-, HY (d) HW, HX, Y^-

7. What is the approximate pH difference between a solution of 1 M HX and a solution of 1 M HY?
   (a) 2 (b) 3 (c) 4 (d) 6

8. If you wanted to write the structure of a molecule that shows carbon and hydrogen atoms as groups, without indicating many of the carbon-hydrogen bonds, you would draw a:
   (a) molecular formula (b) Kekulé structure (c) skeletal structure (d) condensed structure

9. Which of the following molecules has zero net dipole moment?
   (a)  (b)  (c)  (d) 

10. In which of the following bonds is carbon the more electronegative element?
    (a) C — Br (b) C — I (c) C — P (d) C — S

Chapter 3 – Organic Compounds: Alkanes and Their Stereochemistry

Chapter Outline

I. Functional Groups (Section 3.1).
   A. Functional groups are groups of atoms within a molecule that have a characteristic chemical behavior.
   B. The chemistry of every organic molecule is determined by its functional groups.
   C. Functional groups described in this text can be grouped into three categories:
      1. Functional groups with carbon–carbon multiple bonds.
      2. Groups in which carbon forms a single bond to an electronegative atom.
      3. Groups with a carbon–oxygen double bond.

II. Alkanes (Sections 3.2–3.5).
   A. Alkanes and alkane isomers (Section 3.2).
      1. Alkanes are formed by overlap of carbon sp^3 orbitals.
      2. Alkanes are described as saturated hydrocarbons.
         a. They are hydrocarbons because they contain only carbon and hydrogen.
         b. They are saturated because all bonds are single bonds.
         c. The general formula for alkanes is C_nH_{2n+2}.
      3. For alkanes with four or more carbons, the carbons can be connected in more than one way.
         a. If the carbons are in a row, the alkane is a straight-chain alkane.
         b. If the carbon chain has a branch, the alkane is a branched-chain alkane.
      4. Alkanes with the same molecular formula can exist in different forms known as isomers.
         a. Isomers whose atoms are connected differently are constitutional isomers.
            i. Constitutional isomers are always different compounds with different properties but with the same molecular formula.
         b. Most alkanes can be drawn in many ways.
      5. Straight-chain alkanes are named according to the number of carbons in their chain.
   B. Alkyl groups (Section 3.3).
      1. An alkyl group is the partial structure that results from the removal of a hydrogen atom from an alkane.
         a. Alkyl groups are named by replacing the -ane of an alkane name with -yl.
         b. *n*-Alkyl groups are formed by removal of an end hydrogen atom of a straight chain alkane.
         c. Branched-chain alkyl groups are formed by removal of a hydrogen atom from an internal carbon.
            i. The prefixes *sec*- and *tert*- refer to the degree of substitution at the branching carbon atom.
      2. There are four possible degrees of alkyl substitution for carbon.
         a. A primary carbon is bonded to one other carbon (RCH_3).
         b. A secondary carbon is bonded to two other carbons (R_2CH_2).

   c. A tertiary carbon is bonded to three other carbons (R_3CH_1).
   d. A quaternary carbon is bonded to four other carbons (R_4C).
   e. The symbol **R** refers to the rest of the molecule.
3. Hydrogens are also described as primary, secondary and tertiary.
   a. Primary hydrogens are bonded to primary carbons (RCH_3).
   b. Secondary hydrogens are bonded to secondary carbons (R_2CH_2).
   c. Tertiary hydrogens are bonded to tertiary carbons (R_3CH).

C. Naming alkanes (Section 3.4).
1. The system of nomenclature used in this book is the IUPAC system.
   In this system, a chemical name has a locant, a prefix, a parent and a suffix.
   a. The locant shows the location of substituents and functional groups.
   b. The prefix indicates the type of substituent or functional group.
   c. The parent shows the number of carbons in the principal chain.
   d. The suffix identifies the functional group family.
2. Naming an alkane:
   a. Find the parent hydrocarbon.
      i. Find the longest continuous chain of carbons, and use its name as the parent name.
      ii. If two chains have the same number of carbons, choose the one with more branch points.
   b. Number the atoms in the parent chain.
      i. Start numbering at the end nearer the first branch point.
      ii. If branching occurs an equal distance from both ends, begin numbering at the end nearer the second branch point.
   c. Identify and number the substituents.
      i. Give each substituent a number that corresponds to its position on the parent chain.
      ii. Two substituents on the same carbon receive the same number.
   d. Write the name as a single word.
      i. Use hyphens to separate prefixes and commas to separate numbers.
      ii. Use the prefixes, *di-*, *tri-*, *tetra-* if necessary, but don't use them for alphabetizing.
   e. Name a complex substituent as if it were a compound, and set it off within parentheses.
      i. Some simple branched-chain alkyl groups have common names.
      ii. The prefix *iso* is used for alphabetizing, but *sec-* and *tert-* are not.

D. Properties of alkanes (Section 3.5).
1. Alkanes are chemically inert to most laboratory reagents.
2. Alkanes react with O_2 (combustion) and Cl_2 (substitution).

3. The boiling points and melting points of alkanes increase with increasing molecular weight.
    a. This effect is due to weak dispersion forces.
    b. The strength of these forces increases with increasing molecular weight.
4. Increased branching lowers an alkane's boiling point.

III. Conformations of straight-chain alkanes (Sections 3.6–3.7).

A. Conformations of ethane (Section 3.6).
1. Rotation about a single bond produces isomers that differ in conformation.
    a. These isomers (conformers) have the same connections of atoms and can't be isolated.
2. These isomers can be represented in two ways:
    a. Sawhorse representations view the C–C bond from an oblique angle.
    b. Newman projections view the C–C bond end-on and represent the two carbons as a circle.
3. There is a barrier to rotation that makes some conformers of lower energy than others.
    a. The lowest energy conformer (staggered conformation) occurs when all C–H bonds are as far from each other as possible.
    b. The highest energy conformer (eclipsed conformation) occurs when all C–H bonds are as close to each other as possible.
    c. Between these two conformations lie an infinite number of other conformations.
4. The staggered conformation is 12 kJ/mol lower in energy than the eclipsed conformation.
    a. This energy difference is due to torsional strain from interactions between C–H bonding orbitals on one carbon and C–H antibonding orbitals on an adjacent carbon, which stabilize the staggered conformer.
    b. The torsional strain resulting from a single C–H interaction is 4.0 kJ/mol.
    c. The barrier to rotation can be represented on a graph of potential energy vs. angle of rotation (dihedral angle).

B. Conformations of other alkanes (Section 3.7).
1. Conformations of propane.
    a. Propane also shows a barrier to rotation that is 14 kJ/mol.
    b. The eclipsing interaction between a C–C bond and a C–H bond is 6.0 kJ/mol.
2. Conformations of butane.
    a. Not all staggered conformations of butane have the same energy; not all eclipsed conformations have the same energy.
        i. In the lowest energy conformation (anti) the two large methyl groups are as far from each other as possible.
        ii. The eclipsed conformation that has two methyl–hydrogen interactions and a H–H interaction is 16 kJ/mol higher in energy than the anti-conformation.
        iii. The conformation with two methyl groups 60° apart (gauche conformation) is 3.8 kJ/mol higher in energy than the anti-conformation.

(a) This energy difference is due to steric strain – the repulsive interaction that results from forcing atoms to be closer together than their atomic radii allow.

iv. The highest energy conformations occur when the two methyl groups are eclipsed.

(a) This conformation is 19 kJ/mol less stable than the anti-conformation. The value of a methyl–methyl eclipsing interaction is 11 kJ/mol.

b. The most favored conformation for any straight-chain alkane has carbon–carbon bonds in staggered arrangements and large substituents anti to each other.

c. At room temperature, bond rotation occurs rapidly, but a majority of molecules adopt the most stable conformation.

Chapter 4 – Organic Compounds: Cycloalkanes and Their Stereochemistry

Chapter Outline

I. Cycloalkanes – alicyclic compounds – (Sections 4.1–4.2).
   A. Cycloalkanes have the general formula C_nH_{2n}, if they have one ring.
   B. Naming cycloalkanes (Section 4.1).
      1. Find the parent.
         a. If the number of carbon atoms in the ring is larger than the number in the largest substituent, the compound is named as an alkyl-substituted cycloalkane.
         b. If the number of carbon atoms in the ring is smaller than the number in the largest substituent, the compound is named as a cycloalkyl-substituted alkane.
      2. Number the substituents.
         a. Start at a point of attachment and number the substituents so that the second substituent has the lowest possible number.
         b. If necessary, proceed to the next substituent until a point of difference is found.
         c. If two or more substituents might potentially receive the same number, number them by alphabetical priority.
         d. Halogens are treated in the same way as alkyl groups.
   C. Cis–trans isomerism in cycloalkanes (Section 4.2).
      1. Unlike open-chain alkanes, cycloalkanes have much less rotational freedom.
         a. Very small rings are rigid.
         b. Large rings have more rotational freedom.
      2. Cycloalkanes have a "top" side and a "bottom" side.
         a. If two substituents are on the same side of a ring, the ring is cis-disubstituted.
         b. If two substituents are on opposite sides of a ring, the ring is trans-disubstituted.
      3. Substituents in the two types of disubstituted cycloalkanes are connected in the same order but differ in spatial orientation.
         a. These cycloalkenes are stereoisomers that are known as cis–trans isomers.
         b. Cis–trans isomers are stable compounds that can't be interconverted.

II. Conformations of cycloalkanes (Sections 4.3–4.9).
   A. General principles (Section 4.3).
      1. Ring strain.
         a. A. von Baeyer suggested that rings other than those of 5 or 6 carbons were too strained to exist.
         b. This concept of angle strain is true for smaller rings, but larger rings can be easily prepared.
      2. Heats of combustion of cycloalkanes.
         a. To measure strain, it is necessary to measure the total energy of a compound and compare it to a strain-free reference compound.
         b. Heat of combustion measures the amount of heat released when a compound is completely burned in oxygen.
            i. The more strained the compound, the higher the heat of combustion.
            ii. Strain per CH_2 unit can be calculated and plotted as a function of ring size.

    c. Graphs show that only small rings have serious strain.
  3. The nature of ring strain.
    a. Rings tend to adopt puckered conformations.
    b. Several factors account for ring strain.
      i. Angle strain occurs when bond angles are distorted from their normal values.
      ii. Torsional strain is due to eclipsing of bonds.
      iii. Steric strain results when atoms approach too closely.

B. Conformations of small rings (Section 4.4).
  1. Cyclopropane.
    a. Cyclopropane has bent bonds.
    b. Because of bent bonds, cyclopropane is more reactive than other cycloalkanes.
  2. Cyclobutane.
    a. Cyclobutane has less angle strain than cyclopropane but has more torsional strain.
    b. Cyclobutane has almost the same total strain as cyclopropane.
    c. Cyclobutane is slightly bent to relieve torsional strain, but this increases angle strain.
  3. Cyclopentane.
    a. Cyclopentane has little angle strain but considerable torsional strain.
    b. To relieve torsional strain, cyclopentane adopts a puckered conformation.
      i. In this conformation, one carbon is bent out of plane; hydrogens are nearly staggered.

C. Conformations of cyclohexane (Sections 4.5–4.8).
  1. Chair cyclohexane (Section 4.5).
    a. The chair conformation of cyclohexane is strain-free.
    b. In a standard drawing of cyclohexane, the lower bond is in front, and the upper bond is in back.
    c. The twist-boat conformation of cyclohexane has little angle strain but experiences both steric strain and torsional strain.
  2. Axial and equatorial bonds in cyclohexane (Section 4.6).
    a. There are two kinds of positions on a cyclohexane ring.
      i. Six axial hydrogens are perpendicular to the plane of the ring.
      ii. Six equatorial hydrogens are roughly in the plane of the ring.
    b. Each carbon has one axial hydrogen and one equatorial hydrogen.
    c. Each side of the ring has alternating axial and equatorial hydrogens.
    d. All hydrogens on the same face of the ring are cis.
  3. Conformational mobility of cyclohexanes.
    a. Different chair conformations of cyclohexanes interconvert by a ring-flip.
    b. After a ring-flip, an axial bond becomes an equatorial bond, and vice versa.
    c. The energy barrier to interconversion is 45 kJ/mol, making interconversion rapid at room temperature.

4. Conformations of monosubstituted cyclohexanes (Section 4.7).
    a. Both conformations aren't equally stable at room temperature.
        i. In methylcyclohexane, 95% of molecules have the methyl group in the equatorial position.
    b. The energy difference is due to 1,3-diaxial interactions.
        i. These interactions, between an axial group and a ring hydrogen two carbons away, are due to steric strain.
        ii. They are the same interactions as occur in gauche butane.
    c. Axial methylcyclohexane has two gauche interactions that cause it to be 7.6 kJ/mol less stable than equatorial methylcyclohexane.
    d. All substituents are more stable in the equatorial position.
        i. The size of the strain depends on the nature and size of the group.
5. Conformations of disubstituted cyclohexanes (Section 4.8).
    a. In *cis*-1,2-dimethylcyclohexane, one methyl group is axial and one is equatorial in both chair conformations, which are of equal energy.
    b. In *trans*-1,2-dimethylcyclohexane, both methyl groups are either both axial or both equatorial.
        i. The conformation with both methyl groups axial is 15.2 kJ/mol less stable than the conformation with both groups equatorial due to 1,3 diaxial interactions.
        ii. The trans isomer exists almost exclusively in the diequatorial conformation.
    c. This type of conformational analysis can be carried out for most substituted cyclohexanes.

D. Conformations of polycyclic (fused-ring) molecules (Section 4.9).
1. Decalin has two rings that can be either cis-fused or trans-fused.
    a. The two decalins are nonconvertible.
2. Steroids have four fused rings.
3. Bicyclic ring systems have rings that are connected by bridges.
    a. In norbornane, the six-membered ring is locked into a boat conformation.

Chapter 5 – Stereochemistry at Tetrahedral Centers

Chapter Outline

I. Handedness (Sections 5.1–5.4).
   A. Enantiomers and tetrahedral carbon (Section 5.1).
      1. When four different groups are bonded to a carbon atom, two different arrangements are possible.
         a. These arrangements are mirror images.
         b. The two mirror-image molecules are enantiomers.
   B. The reason for handedness in molecules: chirality (Section 5.2).
      1. Molecules that are not superimposable on their mirror-images are chiral.
         a. A molecule is not chiral if it contains a plane of symmetry.
         b. A molecule with no plane of symmetry is chiral.
      2. A carbon bonded to four different groups is a chirality center.
      3. It is sometimes difficult to locate a chirality center in a complex molecule.
      4. The groups $–CH_2–$, $–CH_3$, C=O, C=C, and C≡C cannot be chirality centers.
   C. Optical activity (Section 5.3).
      1. Solutions of certain substances rotate the plane of plane-polarized light.
         a. These substances are said to be optically active.
      2. The angle of rotation can be measured with a polarimeter.
      3. The direction of rotation can also be measured.
         a. A compound whose solution rotates plane-polarized light to the right is termed dextrorotatory.
         b. A compound whose solution rotates plane-polarized light to the left is termed levorotatory.
      4. Specific rotation.
         a. The extent of rotation depends on concentration, path length, and wavelength.
         b. Specific rotation is the observed rotation of a sample with concentration = 1 g/mL, sample path length of 1 dm, and light of wavelength = 589 nm.
         c. Specific rotation is a physical constant characteristic of a given optically active compound.
   D. Pasteur's discovery of enantiomerism (Section 5.4).
      1. Pasteur discovered two different types of crystals in a solution that he was evaporating.
      2. The crystals were mirror images.
      3. Solutions of each of the two types of crystals were optically active, and their specific rotations were equal in magnitude but opposite in sign.
      4. Pasteur postulated that some molecules are handed and thus discovered the phenomenon of enantiomerism.
II. Stereoisomers and configurations (Sections 5.5–5.8).
   A. Specification of configurations of stereoisomers (Section 5.5).
      1. Rules for assigning configurations at a chirality center:

a. Assign priorities to each group bonded to the carbon by using Cahn–Ingold–Prelog rules.
    i. Rank each atom by atomic number.
        (a). An atom with a higher atomic number receives a higher priority than an atom with a lower atomic number.
    ii. If a decision can't be reached based on the first atom, look at the second or third atom until a difference is found.
    iii. Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.
b. Orient the molecule so that the group of lowest priority is pointing to the rear.
c. Draw a curved arrow from group 1 to group 2 to group 3.
d. If the arrow rotates clockwise, the chirality center is *R*, and if the arrow rotates counterclockwise, the chirality center is *S*.

2. The sign of optical rotation is not related to *R,S* designation.
3. X-ray experiments have proven *R,S* conventions to be correct.

B. Diastereomers (Section 5.6).
1. A molecule with two chirality centers can have four possible stereoisomers.
    a. The stereoisomers group into two pairs of enantiomers.
    b. A stereoisomer from one pair is the diastereomer of a stereoisomer from the other pair.
2. Diastereomers are stereoisomers that are not mirror images.
3. Epimers are diastereomers whose configuration differs at only one chirality center.

C. Meso compounds (Section 5.7).
1. A meso compound occurs when a compound with two chirality centers possesses a plane of symmetry.
2. A meso compound is achiral despite having two chirality centers.
3. The physical properties of meso compounds, diastereomers and racemic mixtures differ from each other and from the properties of enantiomers.

D. Racemic mixtures and the resolution of enantiomers (Section 5.8).
1. A racemic mixture (racemate) is a 50:50 mixture of two enantiomers.
    a. Racemic mixtures show zero optical rotation.
2. Some racemic mixtures can be resolved into their component enantiomers.
    a. If a racemic mixture of a carboxylic acid reacts with a chiral amine, the product ammonium salts are diastereomers.
    b. The diastereomeric salts differ in chemical and physical properties and can be separated.
    c. The original enantiomers can be recovered by acidification.

III. A review of isomerism (Section 5.9).

A. Constitutional isomers differ in connections between atoms.
1. Skeletal isomers have different carbon skeletons.
2. Functional isomers contain different functional groups.
3. Positional isomers have functional groups in different positions.

B. Stereoisomers have the same connections between atoms, but different geometry.
   1. Enantiomers have a mirror-image relationship.
   2. Diastereomers are non-mirror-image stereoisomers.
      a. Configurational diastereomers.
      b. Cis–trans isomers differ in the arrangement of substituents on a ring or a double bond.

IV. Chirality at atoms other than carbon (Section 5.10).
   A. Other elements with tetrahedral atoms can be chirality centers.
   B. Trivalent nitrogen can, theoretically, be chiral, but rapid inversion of the nitrogen lone pair interconverts the enantiomers.
   C. Chiral phosphines and trivalent sulfur compounds can be isolated because their rate of inversion is slower.

V. Prochirality (Section 5.11).
   A. A molecule is prochiral if it can be converted from achiral to chiral in a single chemical step.
   B. Identifying prochirality.
      1. For sp^2 carbon, draw the plane that includes the atoms bonded to the sp^2 carbon.
         a. Assign priorities to the groups bonded to the carbon.
         b. Draw a curved arrow from group 1 to group 2 to group 3.
         c. The face of the plane on which the curved arrow rotates clockwise is the Re face.
         d. The face on which the arrow rotates counterclockwise is the Si face.
      2. An atom that is sp^3-hybridized may have a prochirality center if, when one of its attached groups is replaced, it becomes a chirality center.
         a. For $–CH_2X$, imagine a replacement of one hydrogen with deuterium.
         b. Rank the groups, including the deuterium.
         c. If the replacement leads to *R* chirality, the atom is pro-*R*.
         d. If the replacement leads to *S* chirality, the atom is pro-*S*.
   C. Many biochemical reactions involve prochiral compounds.

VI. Chirality in nature and chiral environments (Section 5.12).
   A. Different enantiomers of a chiral molecule have different properties in nature.
      1. (+)-Limonene has the odor of oranges, and (–)-limonene has the odor of lemons.
      2. Racemic fluoxetine is an antidepressant, but the *S* enantiomer is effective against migraines.
   B. In nature, a molecule must fit into a chiral receptor, and only one enantiomer usually fits.

Review Unit 2: Alkanes and Stereochemistry

Major Topics Covered (with vocabulary):

Functional Groups.
Alkanes:
saturated aliphatic straight-chain alkane branched-chain alkane isomer constitutional isomer alkyl group primary, secondary, tertiary, quaternary carbon IUPAC system of nomenclature primary, secondary, tertiary hydrogen paraffin cycloalkane *cis-trans* isomer stereoisomer

Alkane Stereochemistry:
conformer sawhorse representation Newman projection staggered conformation eclipsed conformation torsional strain dihedral angle anti conformation gauche conformation steric strain angle strain heat of combustion chair conformation axial group equatorial group ring-flip 1,3-diaxial interaction conformational analysis boat conformation twist-boat conformation polycyclic molecules bicycloalkane

Handedness:
stereoisomer enantiomer chiral plane of symmetry achiral chirality center plane-polarized light optical activity levorotatory dextrorotatory specific rotation

Stereoisomers and configuration:
configuration Cahn–Ingold–Prelog rules absolute configuration diastereomer meso compound racemate resolution prochirality Re face Si face prochirality center pro-*R* pro-*S*

Types of Problems:

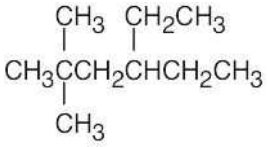
After studying these chapters, you should be able to:

- Identify functional groups, and draw molecules containing a given functional group.
- Draw all isomers of a given molecular formula.
- Name and draw alkanes and alkyl groups.
- Identify carbons and hydrogens as being primary, secondary or tertiary.
- Draw energy vs. angle of rotation graphs for single bond conformations.
- Draw Newman projections of bond conformations and predict their relative stability.
- Understand the geometry of, and predict the stability of, cycloalkanes having fewer than 6 carbons.
- Draw and name substituted cyclohexanes, indicating cis/trans geometry.
- Predict the stability of substituted cyclohexanes by estimating steric interactions.
- Calculate the specific rotation of an optically active compound.
- Locate chirality centers, assign priorities to substituents, and assign *R,S* designations to chirality centers.
- Given a stereoisomer, draw its enantiomer and/or diastereomers.
- Locate the symmetry plane of a meso compound.
- Assign pro-*R* and pro-*S* designations to prochiral groups.
- Identify the face of an sp^2-hybridized carbon as pro-*R* or pro-*S.*

Points to Remember:

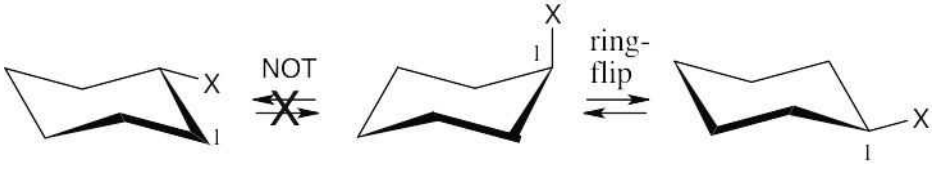
* In identifying the functional groups in a compound, some groups have different designations that depend on the number and importance of other groups in the molecule. For example, a compound containing an –OH group and few other groups is probably named as an alcohol, but when several other groups are present, the –OH group is referred to as a hydroxyl group. There is a priority list of functional groups in the Appendix of the textbook, and this priority order will become more apparent as you progress through the text.

* It is surprising how many errors can be made in naming compounds as simple as alkanes. Why is this? Often the problem is a result of just not paying attention. It is very easy to undercount or overcount the $–CH_2–$ groups in a chain and to misnumber substituents. Let's work through a problem, using the rules in Section 3.4.



Find the longest chain. In the above compound, the longest chain is a hexane (Try all possibilities; there are two different six-carbon chains in the compound.) Identify the substituents. The compound has two methyl groups and an ethyl group. It's a good idea to list these groups to keep track of them. Number the chain and the groups. Try both possible sets of numbers, and see which results in the lower combination of numbers. The compound might be named either as a 2,2,4-trisubstituted hexane or a 3,5,5-trisubstituted hexane, but the first name has a lower combination of numbers. Name the compound, remembering the prefix *di-* and remembering to list substituents in alphabetical order. The correct name for the above compound is 4-ethyl-2,2-dimethylhexane. The acronym FINN (from the first letters of each step listed above) may be helpful.

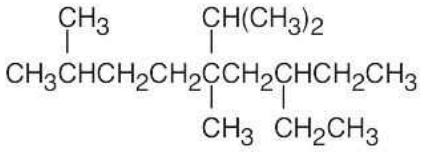
* When performing a ring-flip on a cyclohexane ring, keep track of the positions on the ring.



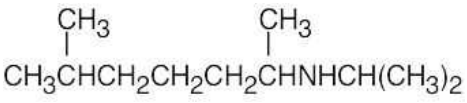
* A helpful strategy for assigning *R,S* designations: Using models, build two enantiomers by adding four groups to each of two tetrahedral carbons. Number the groups 1–4, to represent priorities of groups at a tetrahedral carbon, and assign a configuration to each carbon. Attach a label that indicates the configuration of each enantiomer. Keep these two enantiomers, and use them to check your answer every time that you need to assign *R,S* configurations to a chiral atom.

* When assigning pro-*R* or pro-*S* designations to a hydrogen, mentally replace the hydrogen that points out of the plane of the page. The other hydrogen is then positioned for prochirality assignment without manipulating the molecule. If the designation is *R*, the replaced hydrogen is pro-*R*; if the designation is *S*, the replaced hydrogen is pro-*S*.

Self-Test



A

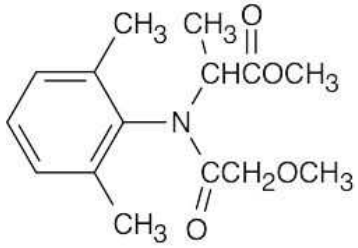


B

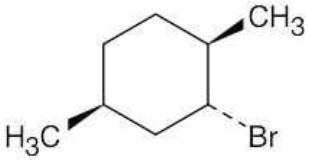
Metron S (an antihistamine)

Name **A**, and identify carbons as primary, secondary, tertiary, or quaternary.

B is an amine with two alkyl substituents. Name these groups and identify alkyl hydrogens as primary, secondary, or tertiary.



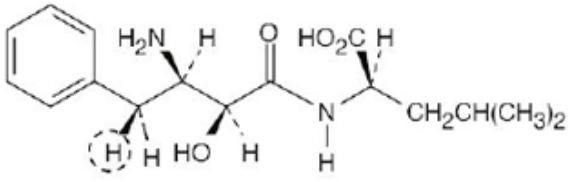
C Metalaxyl (a fungicide)



D

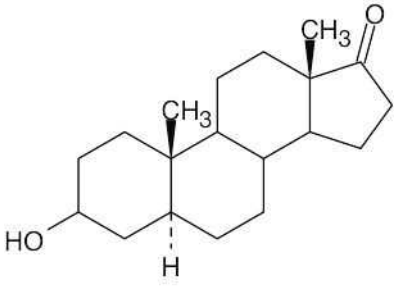
Identify all functional groups of **C** (metalaxyl).

Name **D** and indicate the cis/trans relationship of the substituents. Draw both possible chair conformations, and calculate the energy difference between them.



E

Ubenimex
(an antitumor drug)



F

Epiandosterone
(an androgen)

Assign *R,S* designations to the chiral carbons in **E**. Label the circled hydrogen as pro-*R* or pro-*S*. Indicate the chirality centers in **F**. How many stereoisomers of **F** are possible?

Multiple Choice

1. Which of the following functional groups doesn't contain a carbonyl group?
   (a) aldehyde (b) ester (c) ether (d) ketone

2. Which of the following compounds contains primary, secondary, tertiary, and quaternary carbons?
   (a) 2,2,4-Trimethylhexane (b) Ethylcyclohexane
   (c) 2-Methyl-4-ethylcyclohexane (d) 2,2-Dimethylcyclohexane

3. How many isomers of the formula $C_4H_8Br_2$ are there?
   (a) 4 (b) 6 (c) 8 (d) 9

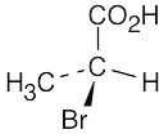
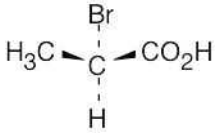
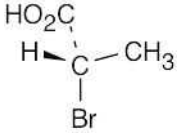
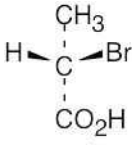
4. The lowest energy conformation of 2-methylbutane occurs:
   (a) when all methyl groups are anti (b) when all methyl groups are gauche
   (c) when two methyl groups are anti (d) when two methyl groups are eclipsed

5. The strain in a cyclopentane ring is due to:
   (a) angle strain (b) torsional strain (c) steric stain (d) angle strain and torsional strain

6. In which disubstituted cyclohexane do the substituents in the more stable conformation have a diequatorial relationship?
   (a) cis-1,2 disubstituted (b) cis-1,3 disubstituted
   (c) trans-1,3-disubstituted (d) cis-1,4 disubstituted

7. Which group is of lower priority than $–CH=CH_2$?
   (a) $–CH(CH_3)_2$ (b) $–CH=C(CH_3)_2$ (c) $–C\equiv CH$ (d) $–C(CH_3)_3$

8. A meso compound and a racemate are identical in all respects except:
   (a) molecular formula (b) degree of rotation of plane-polarized light
   (c) connectivity of atoms (d) physical properties

9. Which of the following projections represents an *R* enantiomer?
   (a) 
   (b) 
   (c) 
   (d) 

10. How many prochirality centers does 1-bromobutane have?
    (a) none (b) 1 (c) 2 (d) 3

Chapter 6 – An Overview of Organic Reactions

Chapter Outline

I. Organic Reactions (Sections 6.1–6.6).

A. Kinds of organic reactions (Section 6.1).

1. Addition reactions occur when two reactants add to form one product.
2. Elimination reactions occur when a single reactant splits into two products.
3. Substitution reactions occur when two reactants exchange parts to yield two new products.
4. Rearrangement reactions occur when a single product undergoes a rearrangement of bonds to yield an isomeric product.

B. Reaction mechanisms - general information (Section 6.2).

1. A reaction mechanism describes the bonds broken and formed in a chemical reaction, and accounts for all reactants and products.
2. Bond breaking and formation in chemical reactions.
   a. Bond breaking is symmetrical (homolytic) if one electron remains with each fragment.
   b. Bond breaking is unsymmetrical (heterolytic) if both electrons remain with one fragment and the other fragment has a vacant orbital.
   c. Bond formation is symmetrical if one electron in a covalent bond comes from each reactant.
   d. Bond formation is unsymmetrical if both electrons in a covalent bond come from one reactant.
3. Types of reactions.
   a. Radical reactions involve symmetrical bond breaking and bond formation.
   b. Polar reactions involve unsymmetrical bond breaking and bond formation.
   c. Pericyclic reactions will be studied later.

C. Polar reactions (Sections 6.3–6.5).

1. Characteristics of polar reactions (Section 6.3).
   a. Polar reactions occur as a result of differences in bond polarities within molecules.
   b. These polarities are usually due to electronegativity differences between atoms.
      i. Differences may also be due to interactions of functional groups with solvents, as well as with Lewis acids or bases.
      ii. Some bonds in which one atom is polarizable may also behave as polar bonds.
   c. In polar reactions, electron-rich sites in one molecule react with electron-poor sites in another molecule.
   d. The movement of an electron pair in a polar reaction is shown by a curved, full-headed arrow.
      i. An electron pair moves from an atom at the tail of the arrow to a second atom at the head of the arrow.
   e. The reacting species:
      i. A nucleophile is a compound with an electron-rich atom.
      ii. An electrophile is a compound with an electron-poor atom.
      iii. Some compounds can behave as both nucleophiles and as electrophiles

f. Many polar reactions can be explained in terms of acid-base reactions.

2. An example of a polar reaction: addition of HBr to ethylene (Section 6.4).
   a. This reaction is known as an electrophilic addition.
   b. The π electrons in ethylene behave as a nucleophile.
   c. The reaction begins by the attack of the π electrons on the electrophile H^+.
   d. The resulting intermediate carbocation reacts with Br^- to form bromoethane.
3. Rules for using curved arrows in polar reaction mechanisms (Section 6.5).
   a. Electrons must move from a nucleophilic source to an electrophilic sink.
   b. The nucleophile can be either negatively charged or neutral.
   c. The electrophile can be either positively charged or neutral.
   d. The octet rule must be followed.

D. Radical reactions (Section 6.6).
1. Radicals are highly reactive because they contain an atom with an unpaired electron.
2. A substitution reaction occurs when a radical abstracts an atom and a bonding electron from another molecule.
3. An addition reaction occurs when a radical adds to a double bond.
4. Steps in a radical reaction.
   a. The *initiation step* produces radicals by the symmetrical cleavage of a bond.
   b. The *propagation steps* occur when a radical abstracts an atom to produce a new radical and a stable molecule.
      i. This sequence of steps is a chain reaction.
   c. A *termination step* occurs when two radicals combine.
5. In radical reactions, all bonds are broken and formed by reactions of species with odd numbers of electrons.

II. Describing a reaction (Sections 6.7–6.10).

A. Equilibria, rates, and energy changes (Section 6.7).
1. All chemical reactions are equilibria that can be expressed by an equilibrium constant K_{eq} that shows the ratio of products to reactants.
   a. If $K_{eq} > 1$, [products] > [reactants].
   b. If $K_{eq} < 1$, [reactants] > [products].
2. For a reaction to proceed as written, the energy of the products must be lower than the energy of the reactants.
   a. The energy change that occurs during a reaction is described by $\Delta G°$, the Gibbs free-energy change.
   b. Favorable reactions have negative $\Delta G°$ and are exergonic.
   c. Unfavorable reactions have positive $\Delta G°$ and are endergonic.
   d. $\Delta G° = -RT \ln K_{eq}$.
3. $\Delta G°$ is composed of two terms $-\Delta H°$, and $\Delta S°$, which is temperature-dependent.
   a. $\Delta H°$ is a measure of the change in total bonding energy during a reaction.

i. If $\Delta H°$ is negative, a reaction is exothermic.
ii. If $\Delta H°$ is positive, a reaction is endothermic.

b. $\Delta S°$ (entropy) is a measure of the freedom of motion of a reaction.
i. A reaction that produces two product molecules from one reactant molecule has positive entropy.
ii. A reaction that produces one product molecule from two reactant molecules has negative entropy.

c. $\Delta G° = \Delta H° - T\Delta S°$.

4. None of these expressions predict the rate of a reaction.

B. Bond dissociation energies (Section 6.8).
1. The bond dissociation energy (D) measures the heat needed to break a bond to produce two radical fragments.
2. Each bond has a characteristic strength.
3. In exothermic reactions, the bonds formed are stronger than the bonds broken.

C. Energy diagrams and transition states (Section 6.9).
1. Reaction energy diagrams show the energy changes that occur during a reaction.
a. The vertical axis represents energy changes, and the horizontal axis (reaction coordinate) represents the progress of a reaction.
2. The transition state is the highest-energy species in this reaction.
a. It is possible for a reaction to have more than one transition state.
b. The difference in energy between the reactants and the transition state is the energy of activation $\Delta G^‡$.
c. Values of $\Delta G^‡$ range from 40 – 150 kJ/mol.
3. After reaching the transition state, the reaction can go on to form products or can revert to starting material.
4. Every reaction has its own energy profile.

D. Reaction Intermediates (Section 6.10).
1. In a reaction of at least two steps, an intermediate is the species that lies at the energy minimum between two transition states.
2. Even though an intermediate lies at an energy minimum between two transition states, it is a high-energy species and usually can't be isolated.
3. Each step of a reaction has its own $\Delta G^‡$ and $\Delta G°$, but the total reaction has an overall $\Delta G°$.
4. Biological reactions take place in several small steps, each of which has a small value of $\Delta G^‡$.

III. A Comparison of biological and laboratory reactions (Section 6.11).

A. Laboratory reactions are carried out in organic solvents; biological reactions occur in aqueous medium.
B. Laboratory reactions take place over a wide variety of temperatures; biological reactions take place at the temperature of the organism, usually within narrow limits.
C. Laboratory reactions are uncatalyzed, or use simple catalysts; biological reactions are enzyme-catalyzed.
D. Laboratory reagents are usually small and simple; biological reactions involve large, complex coenzymes.
E. Biological reactions have high specificity for substrate, whereas laboratory reactions are relatively nonspecific.

Chapter 7 – Alkenes: Structure and Reactivity

Chapter Outline

I. Introduction to alkene chemistry (Sections 7.1–7.7).

A. Industrial preparation and use of alkenes (Section 7.1).

1. Ethylene and propylene are the two most important organic chemicals produced industrially.
2. Ethylene, propylene and butene are synthesized by thermal cracking.
   a. Thermal cracking involves homolytic breaking of C–H and C–C bonds.
   b. Thermal cracking reactions are dominated by entropy.

B. Calculating a molecule's degree of unsaturation (Section 7.2).

1. The degree of unsaturation of a molecule describes the number of multiple bonds and/or rings in a molecule.
2. To calculate degree of unsaturation of a compound, first determine the equivalent hydrocarbon formula of the compound.
   a. Add the number of halogens to the number of hydrogens.
   b. Subtract one hydrogen for every nitrogen.
   c. Ignore the number of oxygens.
3. Calculate the number of pairs of hydrogens that would be present in an alkane C_nH_{2n+2} that has the same number of carbons as the equivalent hydrocarbon of the compound of interest. The difference is the degree of unsaturation.

C. Naming alkenes (Section 7.3).

1. Find the longest chain containing the double bond, and name it, using "ene" as a suffix.
2. Number the carbon atoms in the chain, beginning at the end nearer the double bond.
3. Number the substituents and write the name.
   a. Name the substituents alphabetically.
   b. Indicate the position of the double bond.
   c. Use the suffixes -diene, -triene, etc… if more than one double bond is present.
4. A newer IUPAC naming system places the number locant of the double bond immediately before the *-ene* suffix (not used in this book).
5. For cycloalkenes, the double bond is between C1 and C2, and substituents receive the lowest possible numbers.
6. A $–CH_2–$ substituent is a methylene group, a $H_2C{=}CH–$ group is a vinyl group, and a $H_2C{=}CHCH_2–$ group is an allyl group.

D. Double bond geometry (Sections 7.4–7.5).

1. Cis–trans isomerism in alkenes (Section 7.4).
   a. Carbon atoms in a double bond are sp^2-hybridized.
   b. The two carbons in a double bond form one σ bond and one π bond.
   c. Free rotation does not occur around double bonds.
   d. 350 kJ/mol of energy is required to break a π bond.
2. Cis–trans isomerism.

a. A disubstituted alkene can have substituents either on the same side of the double bond (cis) or on opposite sides (trans).
b. These isomers do not interconvert because free rotation about a double bond is not possible.
c. Cis–trans isomerism does not occur if one carbon in the double bond is bonded to identical substituents.

3. *E,Z* isomerism (Section 7.5).
   a. The *E,Z* system is used to describe the arrangement of substituents around a double bond that cannot be described by the cis–trans system.
   b. Sequence rules for *E,Z* isomers:
      i. For each double bond carbon, rank its substituents by atomic number.
         (a) An atom with a higher atomic number receives a higher priority than an atom with a lower atomic number.
      ii. If a decision can't be reached based on the first atom, look at the second or third atom until a difference is found.
      iii. Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.
   c. If the higher-ranked groups are on the same side of the double bond, the alkene has *Z* geometry.
   d. If the higher-ranked groups are on opposite sides of the double bond, the alkene has *E* geometry.

E. Stability of alkenes (Section 7.6).
1. Cis alkenes are less stable than trans alkenes because of steric strain between double bond substituents.
2. Stabilities of alkenes can be determined experimentally by measuring:
   a. Cis–trans equilibrium constants.
   b. Heats of hydrogenation – the most useful method.
3. The heat of hydrogenation of a cis isomer is a larger negative number than the heat of hydrogenation of a trans isomer.
   a. This indicates that a cis isomer is of higher energy and is less stable than a trans isomer.
4. Alkene double bonds become more stable with increasing substitution for two reasons:
   a. Hyperconjugation – a stabilizing interaction between the antibonding π orbital of the C–C bond and a filled C–H σ orbital on an adjacent substituent.
   b. More substituted double bonds have more of the stronger sp^2–sp^3 bonds.

II. Electrophilic addition reactions (Sections 7.7–7.11).

A. Addition of H–X to alkenes (Sections 7.7–7.8).
1. Mechanism of addition (Section 7.7).
   a. The electrons of the nucleophilic π bond attack the H atom of the electrophile H–X (X = Cl, Br, I, OH).
   b. Two electrons from the π bond form a new σ bond between –H and an alkene carbon.

   c. The carbocation intermediate reacts with X^- to form a C–X bond.
2. The energy diagram has two peaks separated by a valley (carbocation intermediate).
   a. The reaction is exergonic.
   b. The first step is slower than the second step.
3. Organic reactions are often written in different ways to emphasize different points.
4. Orientation of addition: Markovnikov's rule (Section 7.8).
   a. In the addition of HX to a double bond, H attaches to the carbon with fewer substituents, and X attaches to the carbon with more substituents (regiospecific).
   b. If the carbons have the same number of substituents, a mixture of products results.

B. Carbocation structure and stability (Section 7.9).
1. Carbocations are planar; the unoccupied *p* orbital extends above and below the plane containing the cation.
2. The stability of carbocations increases with increasing substitution.
   a. Carbocation stability can be measured by studying gas-phase dissociation enthalpies.
   b. Carbocations can be stabilized by inductive effects of neighboring alkyl groups.
   c. Carbocation can be stabilized by hyperconjugation: The more alkyl groups on the carbocation, the more opportunities there are for hyperconjugation.

C. The Hammond postulate (Section 7.10).
1. The transition state for an endergonic reaction step resembles the product of that step because it is closer in energy.
2. The transition state for an exergonic reaction step resembles the reactant for that step because it is closer in energy.
3. In an electrophilic addition reaction, the transition state for alkene protonation resembles the carbocation intermediate.
4. More stable carbocations form faster because their transition states are also stabilized.

D. Carbocation rearrangements (Section 7.11).
1. In some electrophilic addition reactions, products from carbocation rearrangements are formed.
2. The appearance of these products supports the two-step electrophilic addition mechanism, in which an intermediate carbocation is formed.
3. Intermediate carbocations can rearrange to more stable carbocations by either a hydride shift (H with its electron pair) or by an alkyl shift (alkyl group with its electron pair).
4. In both cases a group moves to an adjacent positively charged carbon, taking its bonding electron pair with it.

Chapter 8 – Alkenes: Reactions and Synthesis

Chapter Outline

I. Preparation of alkenes (Section 8.1).
   A. Dehydrohalogenation.
      1. Reaction of an alkyl halide with a strong base forms an alkene, with loss of HX.
   B. Dehydration.
      1. Treatment of an alcohol with a strong acid forms an alkene, with loss of H_2O.

II. Addition reactions of alkenes (Sections 8.2–8.6).
   A. Addition of halogens (halogenation) (Section 8.2).
      1. Br_2 and Cl_2 react with alkenes to yield 1,2-dihaloalkanes.
      2. Reaction occurs with anti-stereochemistry: Both halogens come from opposite sides of the molecule.
      3. The reaction intermediate is a cyclic halonium intermediate that is formed in a single step by interaction of an alkene with Br^+ or Cl^+.
   B. Addition of hypohalous acids (Section 8.3).
      1. Alkenes add HO–X (X = Br or Cl), forming halohydrins, when they react with halogens in the presence of H_2O.
      2. The added nucleophile (H_2O) intercepts the halonium ion to yield a halohydrin.
      3. Bromohydrin formation is usually achieved by NBS in aqueous DMSO.
      4. Aromatic rings are inert to halohydrin reagents.
   C. Addition of water to alkenes (Section 8.4).
      1. Hydration.
         a. Water adds to alkenes to yield alcohols in the presence of a strong acid catalyst.
         b. Although this reaction is important industrially, reaction conditions are too severe for most molecules.
      2. Oxymercuration.
         a. Addition of $Hg(OAc)_2$, followed by $NaBH_4$, converts an alkene to an alcohol.
         b. The mechanism of addition proceeds through a mercurinium ion.
         c. The reaction follows Markovnikov regiochemistry.
   D. Addition of water to alkenes: hydroboration/oxidation (Section 8.5).
      1. BH_3 adds to an alkene to produce an organoborane.
         a. Three molecules of alkene add to BH_3 to produce a trialkylborane.
      2. Treatment of the trialkylborane with H_2O_2 forms 3 molecules of an alcohol.
      3. Addition occurs with syn stereochemistry.
      4. Addition occurs with non-Markovnikov regiochemistry.
         a. Hydroboration is complementary to oxymercuration/reduction.
      5. The mechanism of hydroboration involves a four-center, cyclic transition state.
         a. This transition state explains syn addition.
         b. Attachment of boron to the less sterically crowded carbon atom of the alkene also explains non-Markovnikov regiochemistry.

III. Reduction and oxidation of alkenes (Sections 8.6–8.8).
   A. Reduction of alkenes (Section 8.6).

1. In organic chemistry, reduction increases electron density on carbon either by forming C–H bonds or by breaking C–O, C–N, or C–X bonds.
2. Catalytic hydrogenation reduces alkenes to saturated hydrocarbons.
    a. The catalysts most frequently used are Pt and Pd.
    b. Catalytic hydrogenation is a heterogeneous process that takes place on the surface of the catalyst.
    c. Hydrogenation occurs with syn stereochemistry.
    d. The reaction is sensitive to the steric environment around the double bond.
3. Alkenes are much more reactive than other functional groups.

B. Oxidation of alkenes (Sections 8.7–8.8).
1. In organic chemistry, oxidation decreases electron density on carbon either by forming C–O, C–N, or C–X bonds or by breaking C–H bonds.
2. Epoxidation (Section 8.7).
    a. Epoxides can be prepared by reaction of an alkene with a peroxyacid RCO_3H.
        i. The reaction occurs in one step with syn stereochemistry.
    b. Epoxides are also formed when halohydrins are treated with base.
    c. Acid-catalyzed reaction of an epoxide ring with water yields a 1,2-diol (glycol).
        i. Ring opening takes place by back-side attack of a nucleophile on the protonated epoxide ring.
        ii. A *trans*-1,2-diol is formed from an epoxycycloalkane.
3. Hydroxylation.
    a. OsO_4 causes the addition of two –OH groups to an alkene to form a diol.
        i. Hydroxylation occurs through a cyclic osmate intermediate.
    b. A safer reaction uses a catalytic amount of OsO_4 and the oxidant NMO.
    c. The reaction occurs with syn stereochemistry.
4. Cleavage to carbonyl compounds (Section 8.8).
    a. O_3 (ozone)causes cleavage of an alkene to produce aldehyde and/or ketone fragments.
        i. The reaction proceeds through a cyclic molozonide, which rearranges to an ozonide that is reduced by Zn.
    b. $KMnO_4$ in neutral or acidic solution cleaves alkenes to yield ketones, carboxylic acids or CO_2.
    c. Diols can be cleaved with HIO_4(periodic acid)to produce carbonyl compounds.

IV. Addition of carbenes (Section 8.9).
A. A carbene (R_2C:) adds to an alkene to give a cyclopropane.
B. The reaction occurs in a single step, without intermediates.
C. Treatment of $HCCl_3$ with KOH forms dichlorocarbene.
1. Addition of dichlorocarbene to a double bond is stereospecific, and only cisdichlorocyclopropanes are formed.
D. The Simmons-Smith reaction (CH_2I_2, Zn–Cu) produces a nonhalogenated cyclopropane via a carbenoid reagent.

V. Radical additions to alkenes: chain-growth polymers (Section 8.10).
   A. Many types of polymers can be formed by radical polymerization of alkene monomers.
      1. There are 3 steps in a chain-growth polymerization reaction.
         a. *Initiation* involves cleavage of a weak bond to form a radical
            i. The radical adds to an alkene to generate an alkyl radical.
         b. The alkyl radical adds to another alkene molecule (*propagation*) to yield a second radical.
            i. This step is repeated many, many times.
         c. *Termination* occurs when two radical fragments combine.
      2. Mechanisms of radical reactions are shown by using fishhook arrows.
      3. As in electrophilic addition reactions, the more stable radical (more substituted) is formed in preference to the less stable radical.
   B. Biological additions of radicals to alkenes (Section 8.11).
      1. Biochemical radical reactions are more controlled than laboratory radical reactions.

VI. Stereochemistry of reactions (Sections 8.12–8.13).
   A. Addition of H_2O to an achiral alkene (Section 8.12).
      1. When H_2O adds to an achiral alkene, a racemic mixture of products is formed.
      2. The achiral cationic intermediate can react from either side to produce a racemic mixture.
      3. Alternatively, the transition states for top side reaction and bottom side reaction are enantiomers and have the same energy.
      4. Enzyme-catalyzed reactions give a single enantiomer, even when the substrate is achiral.
   B. Addition of H_2O to a chiral alkene (Section 8.13).
      1. When H^+ adds to a chiral alkene, the intermediate carbocation is chiral.
      2. The original chirality center is unaffected by the reaction.
      3. Reaction of H_2O with the carbocation doesn't occur with equal probability from either side, and the resulting product is an optically active mixture of diastereomeric alcohols.
      4. Reaction of a chiral reactant with an achiral reactant leads to unequal amounts of diastereomeric products.

Review Unit 3: Organic Reactions, Alkenes

Major Topics Covered (with vocabulary):

Organic Reactions:
addition reaction elimination reaction substitution reaction rearrangement reaction reaction mechanism hemolytic heterolytic homogenic heterogenic radical reaction polar reaction initiation propagation termination electronegativity polarizability curved arrow electrophile nucleophile carbocation

Describing a Reaction:
K_{eq} $\Delta G°$ exergonic endergonic enthalpy entropy heat of reaction exothermic endothermic bond dissociation energy reaction energy diagram transition state activation energy reaction intermediate

Introduction to alkenes:
degree of unsaturation methylene group vinyl group allyl group cis–trans isomerism *E,Z* isomerism heat of hydrogenation hyperconjugation

Electrophilic addition reactions:
electrophilic addition reaction regiospecific Markovnikov's rule Hammond Postulate carbocation rearrangement hydride shift

Other reactions of alkenes:
dehydrohalogenation dehydration anti stereochemistry bromonium ion halohydrin hydration oxymercuration hydroboration syn stereochemistry carbine stereospecific Simmons–Smith reaction hydrogenation hydroxylation diol osmate molozonide ozonide

Polymerization reactions:
polymer monomer chain branching radical polymerization cationic polymerization

Types of Problems:

After studying these chapters, you should be able to:

- Identify reactions as polar, radical, substitution, elimination, addition, or rearrangement reactions.
- Understand the mechanism of radical reactions.
- Identify reagents as electrophiles or nucleophiles.
- Use curved arrows to draw reaction mechanisms.
- Understand the concepts of equilibrium and rate.
- Calculate K_{eq} and $\Delta G°$ of reactions, and use bond dissociation energies to calculate $\Delta H°$ of reactions.
- Draw reaction energy diagrams and label them properly.
- Calculate the degree of unsaturation of any compound, including those containing N, O, and halogen.
- Name acyclic and cyclic alkenes, and draw structures corresponding to names.
- Assign *E,Z* priorities to groups.
- Assign cis-trans and *E,Z* designations to double bonds.
- Predict the relative stability of alkene double bonds.
- Formulate mechanisms of electrophilic addition reactions.

- Predict the products of reactions involving alkenes.
- Choose the correct alkene starting material to yield a given product.
- Deduce the structure of an alkene from its molecular formula and products of cleavage.
- Carry out syntheses involving alkenes.

Points to Remember:

* In virtually all cases, a compound is of lower energy than the free elements of which it is composed. Thus, energy is released when a compound is formed from its component elements, and energy is required when bonds are broken. Entropy decreases when a compound is formed from its component elements (because decrease in freedom of motion). For two compounds of similar structure, less energy is required to break all bonds of the higher energy compound than is required to break all bonds of the lower energy compound.

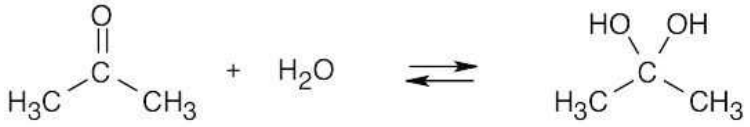
* Calculating the degree of unsaturation is an absolutely essential technique in the structure determination of all organic compounds. It is the starting point for deciding which functional groups are or aren't present in a given compound, and eliminates many possibilities. When a structure determination problem is given, always calculate the degree of unsaturation first.

* All cis–trans isomers can also be described by the *E,Z* designation, but not all *E,Z* isomers can be described by the cis–trans designation.

* Bond dissociation energies, described in Chapter 6, measure the energy required to homolytically break a bond. They are not the same as dissociation enthalpies. Bond dissociation energies can be used to calculate dissociation enthalpies in the gas phase if other quantities are also known.

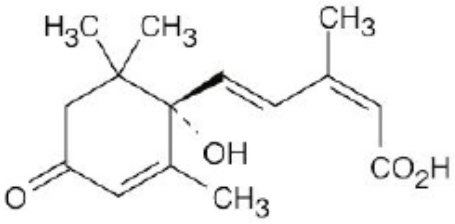
* Not all hydrogens bonded to carbons adjacent to a carbocation can take part in hyperconjugation at the same time. At any given instant, some of the hydrogens have C-H bonds that lie in the plane of the carbocation and are not suitably oriented for hyperconjugative overlap.

Self-Test:

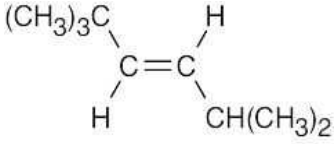


A

What type of reaction is occurring in **A**? Would you expect that the reaction occurs by a polar or a radical mechanism? If K_{eq} for the reaction at 298 K is 10^{-3}, what sign do you expect for $\Delta G°$? Would you expect $\Delta S°$ to be negative or positive? What about $\Delta H°$?



B Abscisic acid (a plant hormone)

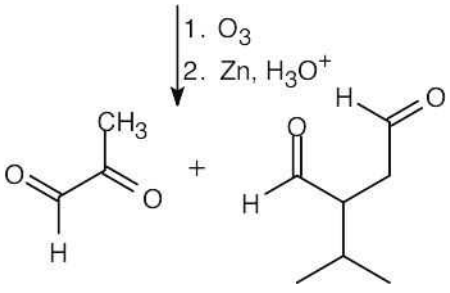


C

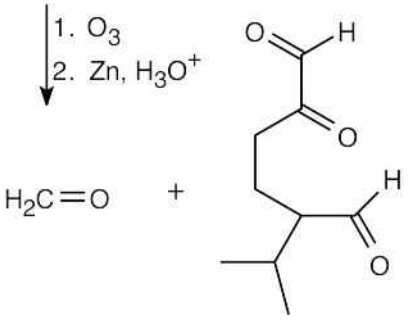
Give *E,Z* configurations for the double bonds in **B**. Provide a name for **C** (include bond stereochemistry). Predict the products of reaction of **C** with (a) 1 equiv HBr (b) H_2, Pd/C (c) BH_3, THF, then H_2O_2, HO^- (d) O_3, then Zn, H_3O^+.

Two isomeric compounds **D** and **E** have the formula $C_{10}H_{16}$. On hydrogenation, each compound reacts with two molar equivalents of H_2. Ozonolysis of each compound yields the following fragments:

D



E



How many rings/double bonds do **D** and **E** have? What are the structures of **D** and **E**?

Multiple Choice:

1. Which of the following molecules is not a nucleophile?
   (a) BH_3 (b) NH_3 (c) HO^- (d) $H_2C = CH_2$

2. Which of the following reactions probably has the greatest entropy increase?
   (a) addition reaction (b) elimination reaction (c) substitution reaction (d) rearrangement

3. At a specific temperature T, a reaction has negative $\Delta S°$ and $K_{eq} > 1$. What can you say about $\Delta G°$ and $\Delta H°$?
   (a) $\Delta G°$ is negative and $\Delta H°$ is positive
   (b) $\Delta G°$ and $\Delta H°$ are both positive
   (c) $\Delta G°$ and $\Delta H°$ are both negative
   (d) $\Delta G°$ is negative but you can't predict the sign of $\Delta H°$.

4. In which of the following situations is $\Delta G^‡$ likely to be smallest?
   (a) a slow exergonic reaction
   (b) a fast exergonic reaction
   (c) a fast endergonic reaction
   (d) a slow endergonic reaction

5. What is the degree of unsaturation of a compound whose molecular formula is $C_{11}H_{13}N$?
   (a) 4 (b) 5 (c) 6 (d) 7

6. Two equivalents of H_2 are needed to hydrogenate a hydrocarbon. It is also known that the compound contains two rings and has 15 carbons. What is its molecular formula?
   (a) $C_{15}H_{22}$ (b) $C_{15}H_{24}$ (c) $C_{15}H_{28}$ (d) $C_{15}H_{32}$

7. What is the usual relationship between the heats of hydrogenation of a pair of cis/trans alkene isomers?
   (a) Both have positive heats of hydrogenation
   (b) Both have negative heats of hydrogenation, and ΔH_{hydrog} for the cis isomer has a greater negative value
   (c) Both have negative heats of hydrogenation, and ΔH_{hydrog} for the trans isomer has a greater negative value
   (d) Both have negative heats of hydrogenation, but the relationship between the two values of ΔH_{hydrog} can't be predicted.

8. In a two-step exergonic reaction, what is the relationship of the two transition states?
   (a) both resemble the intermediate
   (b) the first resembles the starting material, and the second resembles the product
   (c) the first resembles the intermediate and the second resembles the product
   (d) there is no predictable relationship between the two transition states

9. For synthesis of an alcohol, acid-catalyzed hydration of an alkene is useful in all of the following instances except:
   (a) when an alkene has no acid-sensitive groups
   (b) when an alkene is symmetrical
   (c) when a large amount of the alcohol is needed
   (d) when two possible carbocation intermediates are of similar stability.

10. A reaction that produces a diol from an alcohol is a:
    (a) hydration (b) hydrogenation (c) hydroboration (d) hydroxylation

Chapter 9 – Alkynes: An Introduction to Organic Synthesis

Chapter Outline

I. Introduction to alkynes (Section 9.1–9.2).
   A. Naming alkynes (Section 9.1).
      1. The rules for naming alkynes are like the rules for alkenes (Sec. 7.3), with a few exceptions.
         a. The suffix *-yne* is used for an alkyne.
         b. Compounds with both double bonds and triple bonds are *enynes*.
         c. When there is a choice in numbering, double bonds receive lower numbers than triple bonds.
         d. Compounds can also contain alkynyl groups.
   B. Preparation of alkynes (Section 9.2).
      1. Alkynes can be prepared by elimination reactions of 1,2-dihalides, using a strong base.
      2. The dihalides are formed by addition of X_2 to alkenes.
      3. Vinylic halides give alkynes when treated with a strong base.

II. Reactions of alkynes (Sections 9.3–9.6).
   A. General principles (Section 9.3).
      1. Alkyne triple bonds result from the overlap of two *sp*-hybridized carbon atoms.
         a. One σ bond and two π bonds are formed.
      2. The length (120 pm) and strength (965 kJ/mol) of a –C≡C– bond make it the strongest carbon–carbon bond.
      3. Alkynes are somewhat less reactive than alkenes in electrophilic addition reactions.
   B. Addition of X_2 and HX.
      1. HX adds to alkynes by an electrophilic addition mechanism.
         a. Addition of two equivalents of HX occurs if the acid is in excess.
         b. Addition occurs with Markovnikov regiochemistry and with trans stereochemistry.
      2. X_2 also adds in the same manner, and trans stereochemistry is observed.
      3. The intermediate in addition reactions is a vinylic carbocation, which forms less readily than an alkyl carbocation.
      4. Mechanisms of some alkyne addition reactions are complex.
   C. Hydration reactions of alkynes (Section 9.4).
      1. Hg(II)-catalyzed additions.
         a. The –OH group adds to the more substituted carbon to give the Markovnikov product.
         b. The intermediate enol product tautomerizes to a ketone.
         c. The mechanism is similar to that of addition to alkenes, but no $NaBH_4$ is necessary for removal of Hg.
         d. A mixture of products is formed from an internal alkyne, but a terminal alkyne yields a methyl ketone.
      2. Hydroboration/oxidation of alkynes.

a. Hydroboration/oxidation of alkynes gives an intermediate enol product that tautomerizes to a carbonyl product.
    i. Hydroboration of a terminal alkyne gives an aldehyde.
    ii. Hydroboration of an internal alkyne gives a ketone.
b. Hydroboration/ oxidation is complementary to Hg(II)-catalyzed hydration.

D. Reduction of alkynes (Section 9.5).
1. Complete reduction to an alkane occurs when H_2/Pd is used.
2. Partial reduction to a cis alkene occurs with H_2 and a Lindlar catalyst.
3. Partial reduction with Li in NH_3 produces a trans alkene.
    a. The reaction proceeds through an anion radical → vinylic radical → vinylic anion.
    b. The more stable trans vinylic anion is formed.

E. Oxidative cleavage of alkynes (Section 9.6).
1. O_3 or $KMnO_4$ cleave alkyne bonds to produce carboxylic acids or CO_2 (terminal alkyne).
2. Oxidative cleavage reactions were formerly used for structure determinations.

III. Alkyne acidity (Sections 9.7–9.8).

A. Formation of acetylide anions (Section 9.7).
1. Terminal alkynes are weakly acidic ($pK_a = 25$).
2. Very strong bases ($^-NH_2$) can deprotonate a terminal alkyne, yielding an acetylide anion.
3. Acetylide anions are stabilized by the large amount of "*s* character" of the orbital that holds the electron.

B. Alkylation of acetylide anions (Section 9.8).
1. Acetylide anions are strongly nucleophilic.
2. Acetylide anions can react with haloalkanes to form substitution products.
    a. The nucleophilic acetylide anion attacks the electrophilic carbon of a haloalkane to produce a new alkyne.
    b. This reaction is called an alkylation reaction.
    c. Any terminal alkyne can form an alkylation product.
3. Acetylide alkylations are limited to primary alkyl bromides and iodides.
    a. Acetylide ions cause dehydrohalogenation reactions with secondary and tertiary halides.

IV. Organic synthesis (Section 9.9).

A. Reasons for the study of organic synthesis.
1. In the pharmaceutical and chemical industries, synthesis produces new molecules, or better routes to important molecules.
2. In academic laboratories, synthesis is done for the training of future organic chemists and in the development of improve reaction transformations.
3. In the classroom, synthesis is a tool for teaching the logic of organic chemistry.

B. Strategies for organic synthesis.
1. Work backward from the structure of the product, but –
2. Keep the structure of the starting material in mind.

Chapter 10 – Organohalides

Chapter Outline

I. Names and properties of alkyl halides (Section 10.1).
   A. Naming alkyl halides.
      1. Rules for naming alkyl halides:
         a. Find the longest chain and name it as the parent.
            i. If a double or triple bond is present, the parent chain must contain it.
         b. Number the carbon atoms of the parent chain, beginning at the end nearer the first substituent, whether alkyl or halo.
         c. Number each substituent.
            i. If more than one of the same kind of substituent is present, number each, and use the prefixes *di-, tri-, tetra-* and so on.
            ii. If different halogens are present, number all and list them in alphabetical order.
         d. If the parent chain can be numbered from either end, start at the end nearer the substituent that has alphabetical priority.
      2. Some alkyl halides are named by first citing the name of the alkyl group and then citing the halogen.
   B. Structure of alkyl halides.
      1. Alkyl halides have approximately tetrahedral geometry.
      2. Bond lengths increase with increasing size of the halogen bonded to carbon.
      3. Bond strengths decrease with increasing size of the halogen bonded to carbon.
      4. Carbon–halogen bonds are polar, and many halomethanes have dipole moments.
      5. Alkyl halides behave as electrophiles in polar reactions.

II. Preparation of alkyl halides (Sections 10.2–10.5).
   A. Radical halogenation of alkanes (Section 10.2).
      1. The sequence of steps: initiation, propagation, termination.
      2. Complications of radical halogenation.
         a. The reaction continues on to produce di- and polysubstituted products.
         b. If more than one type of hydrogen is present, more than one type of monosubstituted product is formed.
         c. The reactivity order of different types of hydrogen towards chlorination is: primary < secondary < tertiary.
            i. This reactivity order is due to the bond dissociation energies for formation of the alkyl radicals.
            ii. The stability order of alkyl radicals: primary < secondary < tertiary.
   B. Allylic bromination of alkenes (Sections 10.3).
      1. Reaction of an alkene with NBS causes bromination at the position allylic to the double bond.
      2. This reaction occurs by a radical chain mechanism.
         a. Br· abstracts an allylic hydrogen.
         b. The allylic radical reacts with Br_2 to form an allylic bromide, plus Br·.

3. Reaction occurs at the allylic position because an allylic C–H bond is weaker than most other C–H bonds, and an allylic radical is more stable.

C. Reasons for stability of an allylic radical (Section 10.4).
1. The carbon with the unpaired electron is sp^2-hybridized, and its *p* orbital can overlap with the *p* orbitals of the double-bond carbons.
2. The radical intermediate is thus stabilized by resonance.
   a. This stability is due to delocalization (spreading out) of the unpaired electron over an extended π network.
3. Reaction of the allylic radical with Br_2 can occur at either end of the π orbital system.
   a. A mixture of products may be formed if the alkene is unsymmetrical.
   b. These products aren't usually formed in equal quantities: reaction to form the more substituted double bond is favored.
4. Products of allylic bromination can be dehydrohalogenated to form dienes.

D. Alkyl halides from alcohols (Section 10.5).
1. Tertiary alkyl chlorides, bromides or iodides can be prepared by the reaction of a tertiary alcohol with HCl, HBr or HI.
   a. Reaction of secondary or primary alcohols occurs under more drastic conditions, which may destroy other acid-sensitive functional groups.
2. Primary and secondary alkyl chlorides and bromides can be formed by treatment of the corresponding alcohols with $SOCl_2$ or PBr_3, respectively.
   a. Reaction conditions are mild, less acidic, and are less likely to cause acid-catalyzed rearrangements.
3. Alkyl fluorides can be prepared using either $(CH_3CH_2)_2NSF_3$ or HF in pyridine.

III. Reactions of alkyl halides (Sections 10.6–10.7).

A. Grignard reagents (Section 10.6).
1. Organohalides react with Mg to produce organomagnesium halides, RMgX.
   a. These compounds are known as Grignard reagents.
2. Grignard reagents can be formed from alkyl, alkenyl and aryl halides.
   a. Steric hindrance is no barrier to formation of Grignard reagents.
3. The carbon bonded to Mg is negatively polarized and is nucleophilic.
4. Grignard reagents react with weak acids to form hydrocarbons.

B. Organometallic coupling reagents (Section 10.7).
1. Alkyl halides can react with Li to form alkyllithiums.
2. These alkyllithiums can combine with CuI to form lithium diorganocopper compounds (R_2CuLi), which are known as Gilman reagents.
3. R_2CuLi compounds can react with alkyl halides (except for fluorides) to form hydrocarbon products.
4. Organometallic coupling reactions are useful for forming large molecules from small pieces.
   a. The reaction can be carried out on alkyl, vinyl and aryl halides.
   b. The mechanism is not a typical polar nucleophilic substitution.

5. A related reaction is the Suzuki-Miyaura reaction – a palladium-catalyzed coupling of aryl or vinyl organotin reagents with organohalides.

IV. Oxidation and reduction in organic chemistry (Section 10.8).

A. In organic chemistry, an oxidation is a reaction that results in a loss in electron density by carbon.
   1. This loss may be due to two kinds of reactions:
      a. Bond formation between carbon and a more electronegative atom (usually O, N or halogen).
      b. Bond breaking between carbon and a less electronegative atom (usually H).
   2. Examples include chlorination of alkanes and reaction of alkenes with Br_2.

B. A reduction is a reaction that results in a gain of electron density by carbon.
   1. This gain may be due to two kinds of reactions:
      a. Bond formation between carbon and a less electronegative atom.
      b. Bond breaking between carbon and a more electronegative atom.
   2. Examples include conversion of a Grignard reagent to an alkane, and reduction of an alkene with H_2.

C. Alkanes are at the lowest oxidation level, and CO_2 is at the highest level.

D. A reaction that converts a compound from a lower oxidation level to a higher oxidation level is an oxidation.

E. A reaction that converts a compound from a higher oxidation level to a lower oxidation level is a reduction.

F. When comparing oxidation levels, compounds that have the same number of carbon atoms can be compared by adding the number of C−O, C−N, and C−X bonds in each, and then subtracting the number of C−H bonds. The larger the resultant value, the higher the oxidation level.

Chapter 11 – Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations

Chapter Outline

I. Substitution Reactions (Sections 11.1–11.6).
   A. S_N2 reactions (Sections 11.1–11.3).
      1. The discovery of S_N2 reactions (Section 11.1).
         a. Walden discovered that (+) malic acid and (–) malic acid could be interconverted (Section 11.1).
         b. This discovery meant that one or more reactions must have occurred with inversion of configuration at the chirality center.
         c. Nucleophilic substitution of tosylate ion by acetate ion occurs with inversion of configuration.
            i. Nucleophilic substitution reactions of primary and secondary alkyl halides always proceed with inversion of configuration.
      2. The S_N2 reaction (Section 11.2).
         a. Kinetics.
            i. The kinetics of a reaction measure the relationship between reactant concentrations and product concentrations and the rate of reaction.
            ii. In an S_N2 reaction, reaction rate depends on the concentration of both alkyl halide and nucleophile (bimolecular reaction).
               (a). This type of reaction is a second-order reaction.
            iii. In a second-order reaction, rate = $k \times [RX] \times [Nu]$.
               (a). The constant, *k,* is the rate constant.
         b. Mechanism.
            i. The reaction takes place in a single step, without intermediates.
            ii. The nucleophile attacks the substrate from a direction directly opposite to the leaving group.
               (a). This type of attack accounts for inversion of configuration.
            iii. In the transition state, the new bond forms at the same time as the old bond breaks.
            iv. Negative charge is shared between the attacking nucleophile and the leaving group.
            v. In the transition state, the three remaining bonds to carbon are in a planar arrangement.
            vi. Both substrate and nucleophile are involved in the step whose rate is measured.
      3. Characteristics of the S_N2 reaction (Section 11.3).
         a. Changes in the energy levels of reactants or of the transition state affect the reaction rate.
         b. Changes in the substrate.
            i. Reaction rate is decreased if the substrate is bulky.
            ii. Substrates, in order of increasing reactivity: tertiary, neopentyl, secondary, primary, methyl.

iii. S_N2 reactions can occur only at relatively unhindered sites.
iv. Vinylic and aryl halides are unreactive to S_N2 substitutions.

c. Changes in the nucleophile.
i. Any species can act as a nucleophile if it has an unshared electron pair.
(a). If the nucleophile has a negative charge, the product is neutral.
(b). If the nucleophile is neutral, the product is positively charged.
ii. The reactivity of a nucleophile is dependent on reaction conditions.
iii. In general, nucleophilicity parallels basicity.
iv. Nucleophilicity increases going down a column of the periodic table.
v. Negatively charged nucleophiles are usually more reactive than neutral nucleophiles.

d. Changes in the leaving group.
i. In general, the best leaving groups are those that best stabilize negative charge.
ii. Usually, the best leaving groups are the weakest bases.
iii. Good leaving groups lower the energy of the transition state.
iv. Poor leaving groups include F^-, HO^-, RO^-, and H_2N^-.
(a). Poor leaving groups can be converted to better leaving groups.

e. Changes in the solvent.
i. Polar, protic solvents slow S_N2 reactions by lowering the reactivity of the nucleophile.
ii. Polar, aprotic solvents raise the ground-state energy of the nucleophile and make it more reactive.

f. A summary:
i. Steric hindrance in the substrate raises the energy of the transition state, increasing $\Delta G^{\ddagger}$, and decreasing the reaction rate.
ii. More reactive nucleophiles have a higher ground-state energy, decreasing $\Delta G^{\ddagger}$, and increasing the reaction rate.
iii. Good leaving groups decrease the energy of the transition state, decreasing $\Delta G^{\ddagger}$, and increasing the reaction rate.
iv. Polar protic solvents solvate the nucleophile, lowering the ground-state energy, increasing $\Delta G^{\ddagger}$, and decreasing the reaction rate. Polar aprotic solvents do not solvate the nucleophile, raising the ground-state energy, decreasing $\Delta G^{\ddagger}$, and increasing the reaction rate.

B. S_N1 Reactions (Sections 11.4–11.5).
1. The S_N1 reaction (Section 11.4).
a. Under certain reaction conditions, tertiary halides are much more reactive than primary and methyl halides.
i. These reactions must be occurring by a mechanism other than S_N2.
b. Kinetics of the S_N1 reaction.
i. The rate of reaction of a tertiary alkyl halide with water depends only on the concentration of the alkyl halide (unimolecular reaction).

ii. The reaction is a first order process, with reaction rate = $k \times$ [RX].
iii. The rate expression shows that only RX is involved in the slowest, or rate-limiting, step, and the nucleophile is involved in a different, faster step.
iv. The rate expression also shows that there must be at least two steps in the reaction.
v. In an S_N1 reaction, slow dissociation of the substrate is followed by rapid reaction with the nucleophile.

c. Stereochemistry of S_N1 reactions.
i. An S_N1 reaction of an enantiomer produces racemic product because an S_N1 reaction proceeds through a planar, achiral intermediate.
ii. Few S_N1 reactions proceed with complete racemization.
iii. The ion pair formed by the leaving group and the carbocation sometimes shields one side of the carbocation from attack before the leaving group can diffuse away.

2. Characteristics of the S_N1 reaction (Section 11.5).
a. As in S_N2 reactions, factors that lower $\Delta G^{\ddagger}$ favor faster reactions.
b. Changes in the substrate.
i. The more stable the carbocation intermediate, the faster the S_N1 reaction.
ii. Substrates, in order of increasing reactivity: methyl, primary, secondary and allyl and benzyl, tertiary.
iii. Allylic and benzylic substrates are also reactive in S_N2 reactions.
c. Changes in the leaving group.
i. The best leaving groups are the conjugate bases of strong acids.
ii. In S_N1 reactions, water can act as a leaving group.
d. Changes in the nucleophile have no effect on S_N1 reactions.
e. Changes in the solvent.
i. Polar solvents (high dielectric constant) increase the rates of S_N1 reactions.
ii. Polar solvents stabilize the carbocation intermediate more than the reactants and lower $\Delta G^{\ddagger}$.
iii. Polar solvents stabilize by orienting themselves around the carbocation, with electron-rich ends facing the positive charge.
f. A summary:
i. The best substrates are those that form stable carbocations.
ii. Good leaving groups lower the energy of the transition state leading to carbocation formation and increase the reaction rate.
iii. The nucleophile does not affect the reaction rate, but it must be nonbasic.
iv. Polar solvents stabilize the carbocation intermediate and increase the reaction rate.

C. Biological substitution reactions (Section 11.6).
1. Both S_N1 and S_N2 reactions occur often in biochemical pathways.
2. In S_N1 reactions, the leaving group is often an organodiphosphate.
3. S_N2 reactions are involved in biological methylations.

II. Elimination reactions (Sections 11.7–11.11).
  A. Introduction (Section 11.7).
    1. In addition to bringing about substitution, a basic nucleophile can also cause elimination of HX from an alkyl halide to form a carbon–carbon double bond.
    2. A mixture of double-bond products is usually formed, but the product with the more substituted double bond is the major product.
      a. This observation is the basis of Zaitsev's rule.
    3. Double-bond formation can occur by several mechanistic routes, but at this point, we will study only three mechanisms.
  B. The E2 reaction (Sections 11.8–11.9).
    1. General features (Section 11.8).
      a. An E2 reaction occurs when an alkyl halide is treated with a strong base.
      b. The reaction occurs in one step, without intermediates.
      c. E2 reactions follow second-order kinetics.
      d. E2 reactions show the deuterium isotope effect.
        i. In a reaction in which a C–H bond is cleaved in the rate-limiting step, substitution of –D for –H results in a decrease in rate.
        ii. Because this effect is observed in E2 reactions, these reactions must involve C–H bond breaking in the rate-limiting step.
      e. E2 reactions always occur with periplanar geometry.
        i. Periplanar geometry is required because of the need for overlap of the sp^3 orbitals of the reactant as they become π orbitals in the product.
        ii. Anti periplanar geometry is preferred because it allows the substituents of the two carbons to assume a staggered relationship.
        iii. Syn periplanar geometry occurs only when anti periplanar geometry is not possible.
      f. The preference for anti-periplanar geometry results in the formation of double bonds with specific *E, Z* configurations.
    2. Elimination reactions and cyclohexane conformations (Section 11.9).
      a. The chemistry of substituted cyclohexanes is controlled by their conformations.
      b. The preference for anti-periplanar geometry for E2 reactions can be met only if the atoms to be eliminated have a trans-diaxial relationship.
      c. Neomenthyl chloride reacts 200x faster than menthyl chloride because the groups to be eliminated are trans diaxial in the most favorable conformation, and the Zaitsev product is formed.
      d. For menthyl chloride, reaction must proceed through a higher energy conformation, and non-Zaitsev product is formed.
  C. The E1 and E1cB reactions (Sections 11.10–11.11).
    1. An E1 reaction occurs when the intermediate carbocation of an S_N1 loses H^+ to form a C=C bond.
    2. E1 reactions usually occur in competition with S_N1 reactions.
    3. E1 reactions show first-order kinetics.

4. There is no geometric requirement for the groups to be eliminated, and the most stable (Zaitsev) product is formed.

D. The E1cB reaction (cB = conjugate base).
1. The E1cB reaction takes place through a carbanion intermediate.
2. The rate-limiting step involves base-induced abstraction of a proton.
3. Often the leaving group is poor.
4. A carbonyl group stabilizes the anion.
5. The E1cB is fairly common in biochemical pathways (Section 11.11).

III. Summary of reactivity (Section 11.12).

A. Primary halides.
1. S_N2 reaction is usually observed.
2. E1 reaction occurs if a strong, bulky base is used.
3. E1cB reaction occurs if the leaving group is two carbons away from a carbonyl group.

B. Secondary halides.
1. S_N2 and E2 reactions occur in competition.
2. Strong bases promote E2 elimination.
3. Secondary halides (especially allylic and benzylic halides) can react by S_N1 and E1 routes if weakly basic nucleophiles and protic solvents are used.
4. E1cB reaction occurs if the leaving group is two carbons away from a carbonyl group.

C. Tertiary halides.
1. Under basic conditions, E2 elimination is favored.
2. S_N1 and E1 products are formed under nonbasic conditions.
3. E1cB reaction occurs if the leaving group is two carbons away from a carbonyl group.

Review Unit 4: Alkynes; Alkyl Halides; Substitutions and Eliminations

Major Topics Covered (with vocabulary):

Alkynes:
alkyne enyne vicinal tautomer Lindlar catalyst acetylide anion alkylation

Organic Synthesis.

Alkyl halides:
allylic position delocalization Grignard reagent Gilman reagent Suzuki –Miyaura reaction

Oxidation and reduction in organic chemistry.

Substitution reactions:
nucleophilic substitution reaction Walden inversion reaction rate kinetics second-order reaction rate constant S_N2 reaction bimolecular nucleophilicity leaving group solvation S_N1 reaction first-order reaction rate-limiting step ion pair dielectric polarization

Elimination reactions:
Zaitsev's rule E2 reaction syn periplanar geometry anti periplanar geometry deuterium isotope effect E1 reaction E1cB reaction

Types of Problems:

After studying these chapters, you should be able to:

- Predict the products of reactions involving alkynes.
- Choose the correct alkyne starting material to yield a given product.
- Deduce the structure of an alkyne from its molecular formula and products of cleavage.
- Carry out syntheses involving alkynes.
- Draw, name, and synthesize alkyl halides.
- Understand the mechanism of radical halogenation and the stability order of radicals.
- Prepare Grignard reagents and dialkylcopper reagents and use them in synthesis.
- Predict the oxidation level of a compound.
- Formulate the mechanisms of S_N2, S_N1 and elimination reactions.
- Predict the effect of substrate, nucleophile, leaving group and solvent on substitution and elimination reactions.
- Predict the products of substitution and elimination reactions.
- Classify substitution and elimination reactions by type.

Points to Remember:

* Although it is very important to work backwards when planning an organic synthesis, don't forget to pay attention to the starting material, also. Planning a synthesis is like solving a maze from the middle outward: keeping your eye on the starting material can keep you from running into a dead end.

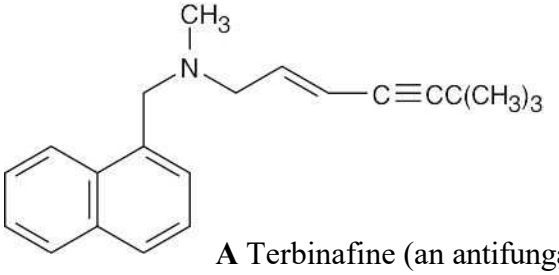
* The reagent Li/NH_3 is used to reduce an alkyne to a trans alkene; the reagent $NaNH_2/NH_3$ is used to form an acetylide anion. It is easy to confuse the two reagents.

* In naming alkyl halides by the IUPAC system, remember that a halogen is named as a substituent on an alkane. When numbering the alkyl halide, the halogens are numbered in the same way as alkyl groups and are cited alphabetically.

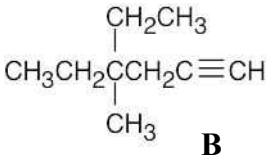
* The definition of oxidation and reduction given in Chapter 10 expands the concept to reactions that you might not have considered to be oxidations or reductions. As you learn new reactions, try to classify them as oxidations, reductions, or neither.

* Predicting the outcome of substitutions and eliminations is only straightforward in certain cases. For primary halides, S_N2 and E2 reactions are predicted. For tertiary halides, S_N1, E2, and E1(to a certain extent) are the choices. The possibilities for secondary halides are more complicated. In addition, many reactions yield both substitution and elimination products, and both inversion and retention of configuration may occur in the same reaction.

Self-Test:



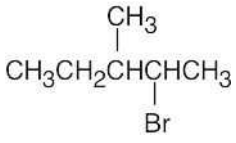
A Terbinafine (an antifungal)



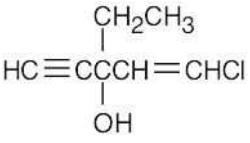
B

What is the configuration of the double bond in the side chain of **A**? What products result from treatment of **A** with $KMnO_4$, H_3O^+ (neither the aromatic ring nor the amine are affected)? How might the triple bond have been introduced?

Provide a name for **B.** Predict the products of reaction of **B** with (a) 1 equiv HBr (b) H_2, Pd/C (c) BH_3, THF, then H_2O_2, HO^- (d) O_3, then Zn, H_3O^+.

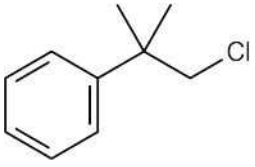


C



D

Ethchlorvynol
(a sedative)



E

Name **C**. Draw all stereoisomers of **C**, label them, and describe their relationship. Predict the products of reaction of **C** with: (a) NaOH; (b) Mg, then H_2O; (c) product of (b) + Br_2, *hν* (show the major product); (d) $(CH_3CH_2)_2CuLi$.

Draw the *R* enantiomer of **D**. Predict the products of reaction of **D** with: (a) HBr; (b) product of (a) + aqueous ethanol. Describe the reactivity of the Cl^- atom in substitution and elimination reactions.

How might **E** be synthesized from the appropriate alkylbenzene? From the appropriate alcohol? Predict the reactivity of **E** in substitution and elimination reactions.

Multiple Choice:

1. An enol is a tautomer of an:
   (a) alcohol (b) alkyne (c) alkene (d) ketone

2. Which reaction proceeds through a vinylic radical?
   (a) Hg-catalyzed hydration of an alkyne (b) Li/NH_3 reduction of an alkyne
   (c) catalytic hydrogenation of an alkyne (d) treatment of an alkyne with a strong base

3. Which of the following reagents is not used in a Suzuki–Miyaura reaction?
   (a) aromatic boronic acid (b) lithium (c) Pd catalyst (d) potassium carbonate

4. Monochlorination of 2,3-dimethylbutane yields what percent of 2-chloro-2, 3-dimethylbutane?
   (a) 16% (b) 35% (c) 45% (d) 55%

5. How many monobromination products can be formed by NBS bromination of 2-ethyl-1-pentene? Include double-bond isomers.
   (a) 3 (b) 4 (c) 5 (d) 6

6. Which of the following reactions is an oxidation?
   (a) hydroxylation (b) hydration (c) hydrogenation (d) addition of HBr

7. All of the following are true of S_N2 reactions except:
   (a) The rate varies with the concentration of nucleophile.
   (b) The rate varies with the type of nucleophile.
   (c) The nucleophile is involved in the rate-determining step.
   (d) The rate of the S_N2 reaction of a substrate and a nucleophile is the same as the rate of the E2 reaction of the same two compounds.

8. Which of the following is true of S_N1 reactions?
   (a) The rate varies with the concentration of nucleophile.
   (b) The rate varies with the type of nucleophile.
   (c) The rate is increased by use of a polar solvent.
   (d) The nucleophile is involved in the rate-determining step.

9. Which base is best for converting 1-bromohexane to 1-hexene?
   (a) $(CH_3)_3CO^-$ (b) ^-CN (c) ^-OH (d) $^-C{\equiv}CH$

10. Which of the following is both a good nucleophile and a good leaving group?
    (a) ^-OH (b) ^-CN (c) Cl^- (d) I^-

11. In the reaction of (2*R*,3*S*)-3-methyl-2-pentanol with tosyl chloride, what is the configuration of the product?
    (a) a mixture of all four possible stereoisomers
    (b) (2*R*,3*S*) and (2*S*,3*S*)
    (c) (2*R*,3*S*)
    (d) (2*S*,3*S*)

Chapter 12 – Structure Determination: Mass Spectroscopy and Infrared Spectroscopy

Chapter Outline

I. Mass Spectrometry (Sections 12.1–12.4).
  A. General features of mass spectrometry (Section 12.1).
    1. Purpose of mass spectrometry.
      a. Mass spectrometry is used to measure the molecular weight of a compound.
      b. Mass spectrometry can also provide information on the structure of an unknown compound.
    2. Technique of mass spectrometry.
      a. A small amount of sample is vaporized into the *ionization source* and is bombarded by a stream of high-energy electrons.
      b. An electron is dislodged from a molecule, producing a cation radical.
      c. Most of the cation radicals fragment; the fragments may be positively charged or a neutral radical.
      d. In the *deflector*, a strong magnetic field deflects the positively charged fragments, which are separated by *m/z* ratio.
      e. A *detector* records the fragments as peaks on a graphic display.
    3. Important terms.
      a. The mass spectrum is presented as a bar graph, with masses (*m/z)* on the *x* axis and intensity (relative abundance) on the *y* axis.
      b. The base peak is the tallest peak and is assigned an intensity of 100%.
      c. The parent peak, or molecular ion (M^+), corresponds to the unfragmented cation radical.
      d. In large molecules, the base peak is often not the molecular ion.
  B. Interpreting mass spectra (Sections 12.2–12.4).
    1. Molecular weight (Section 12.2).
      a. Mass spectra can frequently provide the molecular weight of a sample.
        i. Double-focusing mass spectrometers can provide mass measurements accurate to 0.0005 amu.
        ii. Some samples fragment so easily that M^+ is not seen.
      b. If you know the molecular weight of the sample, you can often deduce its molecular formula.
      c. There is often a peak at M+1 that is due to contributions from ^{13}C and ^{2}H.
    2. Fragmentation patterns of hydrocarbons.
      a. Fragmentation patterns can be used to identify a known compound, because a given compound has a unique fragmentation "fingerprint."
      b. Fragmentation patterns can also provide structural information.
        i. Most hydrocarbons fragment into carbocations and radicals.
        ii. The positive charge remains with the fragment most able to stabilize it.
        iii. It is often difficult to assign structures to fragments.
        iv. For hexane, major fragments correspond to the loss of methyl, ethyl, propyl, and butyl radicals.

3. Fragmentation patterns of common functional groups (Section 12.3).
    a. Alcohols.
        i. Alcohols can fragment by alpha cleavage, in which a C–C bond next to the –OH group is broken.
            (a). The products are a cation and a radical.
        ii. Alcohols can also dehydrate, leaving an alkene cation radical with a mass 18 units less than M^+.
    b. Amines also undergo alpha cleavage, forming a cation and a radical.
    c. Carbonyl compounds.
        i. Aldehydes and ketones with a hydrogen 3 carbons from the carbonyl group can undergo the McLafferty rearrangement.
            (a). The products are a cation radical and a neutral alkene.
        ii. Aldehydes and ketones also undergo alpha cleavage, which breaks a bond between the carbonyl group and a neighboring carbon.
            (a). The products are a cation and a radical.

C. Mass spectrometry in biological systems: TOF instruments (Section 12.4).
    1. Time-of-flight (TOF) instruments are used to produce charged molecules with little fragmentation.
    2. The ionizer can be either ESI or MALDI.
        a. In an ESI source, the sample is dissolved in a polar solvent and sprayed through a steel capillary tube.
            i. As the sample exits, it is subjected to a high voltage, which protonates the sample.
            ii. The solvent is evaporated, yielding protonated sample molecules.
        b. In a MALDI source, the sample is absorbed onto a matrix compound.
            i. The matrix compound is ionized by a burst of laser light.
            ii. The matrix compound transfers energy to the sample, protonating it.
    3. The samples are focused into a small packet and given a burst of energy.
        a. Each molecule moves at a velocity that depends on the square root of its mass.
    4. The analyzer is an electrically grounded tube that detects the charged molecules by velocity.

II. Spectroscopy and the electromagnetic spectrum (Section 12.5).
A. The nature of radiant energy.
    1. Different types of electromagnetic radiation make up the electromagnetic spectrum.
    2. Electromagnetic radiation behaves both as a particle and as a wave.
    3. Electromagnetic radiation can be characterized by three variables.
        a. The wavelength (λ) measures the distance from one maximum to the next.
        b. The frequency (ν) measures the number of wave maxima that pass a fixed point per unit time.
        c. The amplitude is the height measured from the midpoint to the maximum.
    4. Wavelength times frequency equals the speed of light.
    5. Electromagnetic energy is transmitted in discrete energy bundles called quanta.

a. $\varepsilon = h\nu$, where ε is energy per photon.
b. Energy varies directly with frequency but inversely with wavelength.
c. $E = 1.20 \times 10^{-2}$ (kJ/mol) × 1/λ (m) for a "mole" of photons.

B. Electromagnetic radiation and organic molecules.
1. When an organic compound is struck by a beam of electromagnetic radiation, it absorbs radiation of certain wavelengths, and transmits radiation of other wavelengths.
2. If we determine which wavelengths are absorbed and which are transmitted, we can obtain an absorption spectrum of the compound.
a. For an infrared spectrum:
i. The horizontal axis records wavelength.
ii. The vertical axis records percent transmittance.
iii. The baseline runs across the top of the spectrum.
iv. Energy absorption is a downward spike (low percent transmittance).
3. The energy a molecule absorbs is distributed over the molecule.
4. There are many types of spectroscopies that differ in the region of the electromagnetic spectrum that is being used.

III. Infrared Spectroscopy (Sections 12.6–12.8).

A. Infrared radiation (Section 12.6).
1. The infrared (IR) region of the electromagnetic spectrum extends from 7.8×10^{-7} m to 10^{-4} m.
a. Organic chemists use the region from 2.5×10^{-6} m to 2.5×10^{-5} m.
b. Wavelengths are usually given in μm, and frequencies are expressed in wavenumbers, which are the reciprocal of wavelength.
c. The useful range of IR radiation is 4000 cm^{-1} to 400 cm^{-1}; this corresponds to energies of 48.0 kJ/mol to 4.80 kJ/mol.
2. IR radiation causes bonds to stretch and bend and causes other molecular vibrations.
3. Energy is absorbed at a specific frequency that corresponds to the frequency of the vibrational motion of a bond.
4. If we measure the frequencies at which IR energy is absorbed, we can find out the kinds of bonds a compound contains and identify functional groups.

B. Interpreting IR spectra (Sections 12.7–12.8).
1. General principles (Section 12.7).
a. Most molecules have very complex IR spectra.
i. This complexity means that each molecule has a unique fingerprint that allows it to be identified by IR spectroscopy.
ii. Complexity also means that not all absorptions can be identified.
b. Most functional groups have characteristic IR absorption bands that change very little from one compound to another.
c. The significant regions of IR absorptions:

i. 4000 cm^{-1} – 2500 cm^{-1} corresponds to absorptions by C–H, O–H, and N–H bonds.
ii. 2500 cm^{-1} – 2000 cm^{-1} corresponds to triple-bond stretches.
iii. 2000 cm^{-1} – 1500 cm^{-1} corresponds to double bond stretches.
iv. The region below 1500 cm^{-1} is the fingerprint region, where many complex bond vibrations occur that are unique to a molecule.

d. The frequency of absorption of different bonds depends on two factors:
i. The strength of the bond.
ii. The difference in mass between the two atoms in the bond.

2. IR spectra of some common functional groups (Section 12.8).
a. Alkanes.
i. C–C absorbs at 800–1300 cm^{-1}.
ii. C–H absorbs at 2850–2960 cm^{-1}.
b. Alkenes.
i. =C–H absorbs at 3020–3100 cm^{-1}.
ii. C=C absorbs at 1650–1670 cm^{-1}.
iii. $RCH=CH_2$ absorbs at 910 and 990 cm^{-1}.
iv. $R_2C=CH_2$ absorbs at 890 cm^{-1}.
c. Alkynes.
i. –C≡C– absorbs at 2100–2260 cm^{-1}.
ii. ≡C–H absorbs at 3300 cm^{-1}.
d. Aromatic compounds.
i. =C–H absorbs at 3030 cm^{-1}.
ii. Ring absorptions occur at 1660–2000 cm^{-1} and at 1450–1600 cm^{-1}.
e. The alcohol O–H bond absorbs at 3400–3650 cm^{-1}.
f. The N–H bond of amines absorbs at 3300–3500 cm^{-1}.
g. Carbonyl compounds.
i. Saturated aldehydes absorb at 1730 cm^{-1}; unsaturated aldehydes absorb at 1705 cm^{-1}.
ii. Saturated ketones absorb at 1715 cm^{-1}; unsaturated ketones absorb at 1690 cm^{-1}.
iii. Saturated esters absorb at 1735 cm^{-1}; unsaturated esters absorb at 1715 cm^{-1}.

Chapter 13 – Structure Determination: Nuclear Magnetic Resonance Spectroscopy

Chapter Outline

I. Principles of Nuclear Magnetic Resonance Spectroscopy (Sections 13.1–13.3).
   A. Theory of NMR Spectroscopy (Section 13.1).
      1. Many nuclei behave as if they were spinning about an axis.
         a. The positively charged nuclei produce a magnetic field that can interact with an externally applied magnetic field.
         b. The ^{13}C nucleus and the ^{1}H nucleus behave in this manner.
         c. In the absence of an external magnetic field, the spins of magnetic nuclei are randomly oriented.
      2. When a sample containing these nuclei is placed between the poles of a strong magnet, the nuclei align themselves either with (parallel to) the applied field or against (antiparallel to) the applied field, measured in Tesla (T).
         a. The parallel orientation is slightly lower in energy and is slightly favored.
      3. If the sample is irradiated with radiofrequency energy of the correct frequency, the nuclei of lower energy absorb energy and "spin-flip" to the higher energy state.
         a. The magnetic nuclei are in resonance with the applied radiation.
         b. The frequency of the rf radiation needed for resonance depends on the applied magnetic field strength and on the identity of the magnetic nuclei.
            i. In a strong magnetic field, higher frequency rf energy is needed.
            ii. At a magnetic field strength of 4.7 T, rf energy of 200 MHz is needed to bring a ^{1}H nucleus into resonance, and energy of 50 MHz for ^{13}C.
      4. Nuclei with an odd number of protons and nuclei with an odd number of neutrons show magnetic properties.
   B. The nature of NMR absorptions (Section 13.2).
      1. Not all ^{13}C nuclei and not all ^{1}H nuclei absorb at the same frequency.
         a. Each magnetic nucleus is surrounded by electrons that set up their own magnetic fields.
         b. These small fields oppose the applied field and shield the magnetic nuclei.
            i. $\boldsymbol{B}_{\text{effective}} = \boldsymbol{B}_{\text{applied}} - \boldsymbol{B}_{\text{local}}$.
            ii. This expression shows that the magnetic field felt by a nucleus is less than the applied field.
         c. These shielded nuclei absorb at slightly different values of magnetic field strength.
         d. A sensitive NMR spectrometer can detect these small differences.
         e. Thus, NMR spectra can be used to map the carbon–hydrogen framework of a molecule.
      2. NMR spectra.
         a. The horizontal axis shows effective field strength, and the vertical axis shows intensity of absorption.
         b. Each peak corresponds to a chemically distinct nucleus.
         c. Zero absorption is at the bottom.

   d. Absorptions due to both ^{13}C and ^{1}H can't both be observed at the same time and are displayed on separate spectra.
3. Operation of an NMR spectrometer
   a. A solution of a sample is placed in a thin glass tube between the poles of a magnet.
   b. The strong magnetic field causes the nuclei to align in either of the two possible orientations.
   c. The strength of the applied magnetic field is varied, holding the rf frequency constant.
   d. Chemically distinct nuclei come into resonance at slightly different values of ***B***.
   e. A detector monitors the absorption of rf energy.
   f. The signal is amplified and recorded as a peak.
4. Time scale of NMR absorptions.
   a. The time scale (10^{-3} s) of NMR spectra is much slower than that of most other spectra.
   b. If a process occurs faster than the time scale of NMR, absorptions are observed as "time-averaged" processes.
      i. NMR records only a single spectrum of the time-averaged process.
   c. NMR can be used to measure rates and activation energies of fast processes.
      i. Because cyclohexane ring-flips are very fast at room temperature, only a single peak is observed for equatorial and axial hydrogens at room temperature.
      ii. At –90°C, both axial and equatorial hydrogens can be identified.

C. Chemical Shifts (Section 13.3).
1. On NMR spectra, field strength increases from left (downfield) to right (upfield).
   a. Nuclei that absorb downfield require a lower field strength for resonance and are deshielded.
   b. Nuclei that absorb upfield require a higher field strength and are shielded.
2. TMS is used as a reference point in both ^{13}C NMR and ^{1}H NMR.
   a. The TMS (tetramethylsilane) absorption occurs upfield of most other absorptions, and is set as the zero point.
3. The chemical shift is the position along the x-axis where a nucleus absorbs energy.
4. NMR charts are calibrated by using an arbitrary scale – the delta (δ) scale.
   a. One δ equals 1 ppm of the spectrometer operating frequency.
   b. By using this system, all chemical shifts occur at the same value of δ, regardless of the spectrometer operating frequency.
5. NMR absorptions occur over a narrow range.
   a. ^{1}H absorptions occur 0–10 δ downfield from TMS.
   b. ^{13}C absorptions occur 1–220 δ downfield from TMS.
   c. The chances of accidental overlap can be reduced by using an instrument with a higher field strength.

II. ^{1}H NMR Spectroscopy (Sections 13.4–13.9).
   A. Chemical shifts in ^{1}H NMR spectroscopy (Section 13.4).
      1. Chemical shifts are determined by the local magnetic fields surrounding magnetic nuclei.
         a. More strongly shielded nuclei absorb upfield.
         b. Less shielded nuclei absorb downfield.
      2. Most ^{1}H NMR chemical shifts are in the range 0–10 δ.
         a. Protons that are sp^3-hybridized absorb at higher field strength.
         b. Protons that are sp^2-hybridized absorb at lower field strength.
         c. Protons on carbons that are bonded to electronegative atoms absorb at lower field strength.
      3. The ^{1}H NMR spectrum can be divided into 5 regions:
         a. Saturated (0–1.5 δ).
         b. Allylic (1.5–2.5 δ).
         c. H bonded to C next to an electronegative atom (2.5–4.5 δ).
         d. Vinylic (4.5–6.5 δ).
         e. Aromatic (6.5–8.0 δ).
         f. Aldehyde and carboxylic acid protons absorb even farther downfield.
   B. Integration of ^{1}H NMR signals: proton counting (Section 13.5).
      1. The area of a peak is proportional to the number of protons causing the peak.
      2. Modern NMR instruments provide a digital readout of relative peak areas, although older instruments showed a stair-step line.
   C. Spin–spin splitting (Section 13.6).
      1. The tiny magnetic field produced by one nucleus can affect the magnetic field felt by a neighboring nucleus.
      2. Protons that have n equivalent neighboring protons show a peak in their ^{1}H NMR spectrum that is split into $n + 1$ smaller peaks (a multiplet).
      3. This splitting is caused by the coupling of spins of neighboring nuclei.
      4. The distance between peaks in a multiplet is called the coupling constant (J).
         a. The value of J is determined by the geometry of the molecule and is independent of the spectrometer operating frequency.
         b. The value of J is shared between both groups of hydrogens whose spins are coupled.
         c. By comparing values of J, it is possible to know the atoms whose spins are coupled.
      5. Three rules for spin–spin splitting in ^{1}H NMR:
         a. Chemically identical protons do not show spin–spin splitting.
         b. The signal of a proton with n equivalent neighboring protons is split into a multiplet of $n + 1$ peaks with coupling constant J.
         c. Two groups of coupled protons have the same value of J.
      6. Spin–spin splitting is not seen in ^{13}C NMR.
         a. Although spin–spin splitting can occur between carbon and other magnetic nuclei, the spectrometer operating conditions suppress it.
         b. Coupling between the spins of two ^{13}C nuclei is not seen because

of the low probability that two ^{13}C nuclei might be adjacent.

D. Proton equivalence (Section 13.7).
   1. ^{1}H NMR can be used to determine the number of nonequivalent protons in a molecule.
   2. If it is not possible to decide quickly if two protons are equivalent, replace each proton by –X.
      a. If the protons are unrelated, the products formed by replacement are constitutional isomers.
      b. If the protons are chemically identical, the same product will form, regardless which proton is replaced, and the protons are homotopic.
      c. If the replacement products are enantiomers, the protons are enantiotopic.
      d. If the molecule contains a chirality center, the replacement products are diastereomers, and the protons are diastereotopic

E. Complex spin–spin splitting (Section 13.8).
   1. At times the signals in a ^{1}H NMR absorption overlap accidentally.
   2. Also, signals may be split by two or more nonequivalent kinds of protons.
      a. To understand the effect of multiple coupling, it helps to draw a tree diagram.
      b. In this type of multiplet, the peaks on one side of the multiplet may be larger than those on the other side.
         i. The larger peaks are on the side nearer to the coupled partner.
         ii. This helps identify the nuclei whose spins are coupled.

F. Uses of ^{1}H NMR Spectroscopy (Section 13.9).
   1. NMR is used to help identify the product of nearly every reaction run in the laboratory.

III. ^{13}C NMR spectroscopy (Sections 13.10–13.13).

A. Signal averaging and FT (Fourier-transform)-NMR (Section 13.10).
   1. The low natural abundance of ^{13}C (1.1%) makes it difficult to observe ^{13}C peaks because of background noise.
   2. If hundreds of individual runs are averaged, the background noise cancels.
      a. This technique takes a long time.
   3. In FT-NMR, all signals are recorded simultaneously.
      a. The sample is irradiated with a pulse of rf energy that covers all useful frequencies.
      b. The resulting complex signal must be mathematically manipulated before display.
      c. FT-NMR takes only a few seconds per spectrum.
   4. FT-NMR and signal averaging provide increased speed and sensitivity.
      a. Only a few mg of sample are needed for ^{13}C NMR spectra.
      b. Only a few *m*g of sample are needed for ^{1}H NMR spectra.

B. Characteristics of ^{13}C NMR spectroscopy (Section 13.11).
   1. Each distinct carbon shows a single line.
   2. The chemical shift depends on the electronic environment within a molecule.
      a. Carbons bonded to electronegative atoms absorb downfield.
      b. Carbons with sp^3 hybridization absorb in the range 0–90 δ.
      c. Carbons with sp^2 hybridization absorb in the range 110–220 δ.

i. Carbonyl carbons absorb in the range 160–220 δ.

3. Molecular symmetry reduces the number of absorptions.
4. Peaks are not uniform in size and are not integrated.

C. DEPT ^{13}C NMR spectra (Section 13.12).
1. With DEPT experiments, the number of hydrogens bonded to each carbon can be determined.
2. DEPT experiments are run in three stages.
   a. A broadband decoupled spectrum gives the chemical shifts of all carbons.
   b. A DEPT-90 spectrum shows signals due only to CH carbons.
   c. A DEPT-135 spectrum shows CH_3 and CH resonances as positive signals, and CH_2 resonances as negative signals.
3. Interpretation of DEPT spectra.
   a. Subtract all peaks in the DEPT-135 spectrum from the broadband-decoupled spectrum to find C.
   b. Use DEPT-90 spectrum to identify CH.
   c. Use negative DEPT-135 peaks to identify CH_2.
   d. Subtract DEPT-90 peaks from positive DEPT–135 peaks to identify CH_3.

D. Uses of ^{13}C NMR spectroscopy (Section 13.13).
   a. ^{13}C NMR spectroscopy can show the number of nonequivalent carbons in a molecule and can identify symmetry in a molecule.

Review Unit 5: Spectroscopy

Major Topics Covered (with vocabulary):

Mass Spectrometry:
cation radical mass spectrum base peak double-focusing mass spectrometer molecular ion alpha cleavage McLafferty rearrangement dehydration MALDI ESI TOF mass analyzer

The Electromagnetic Spectrum:
electromagnetic radiation wavelength frequency hertz amplitude quanta absorption spectrum

Infrared Spectroscopy:
wavenumber fingerprint region

Nuclear Magnetic Resonance Spectroscopy:
nuclear magnetic resonance rf energy effective magnetic field shielding downfield upfield chemical shift delta scale FT-NMR DEPT ^{13}C NMR homotopic enantiotopic diastereotopic integration multiplet spin-spin splitting coupling $n + 1$ rule coupling constant tree diagram

Types of Problems:

After studying these chapters, you should be able to:

- Write molecular formulas corresponding to a given molecular ion.
- Use mass spectra to determine molecular weights and base peaks, to distinguish between hydrocarbons, and to identify selected functional groups by their fragmentation patterns.
- Calculate the energy of electromagnetic radiation, and convert from wavelength to wavenumber and *vice versa*.
- Identify functional groups by their infrared absorptions.
- Use IR and MS to monitor reaction progress.
- Calculate the relationship between delta value, chemical shift, and spectrometer operating frequency.
- Identify nonequivalent carbons and hydrogens, and predict the number of signals appearing in the ^{1}H NMR and ^{13}C NMR spectra of compounds.
- Assign resonances to specific carbons or hydrogens of a given structure.
- Propose structures for compounds, given their NMR spectra.
- Predict splitting patterns, using tree diagrams if necessary.
- Use NMR to distinguish between isomers and to identify reaction products.

Points to Remember:

* In mass spectrometry, the molecular ion is a cation radical. Further fragmentations of the molecular ion can be of two types – those that produce a cation plus a radical, and those that produce a different cation radical plus a neutral atom. In all cases, the fragment bearing the charge – whether cation or cation radical – is the one that is detected.

* Although mass spectrometry has many uses in research, we are interested in it for only a limited amount of data. The most important piece of information it provides for us is the molecular weight of an unknown. A mass spectrum can also show if an unknown is branched or straight-chain (branched hydrocarbons have more complex spectra than their straight-chain isomers). Finally, if we know if certain groups are present, we can obtain structural information about an unknown compound. For example if we know that a ketone is present, we can look for peaks that correspond to alpha cleavage and/or McLafferty rearrangement fragments.

* The position of an IR absorption is related to both the strength of the bond and to the nature of the two atoms that form the bond. For example, a carbon-carbon triple bond absorbs a higher frequency than a carbon-carbon double bond, which absorbs at a higher frequency than a carbon-carbon single bond. Bonds between two atoms of significantly different mass absorb at higher frequencies than bonds between two atoms of similar mass.

* Not all IR absorptions are due to bond stretches. Many of the absorptions in the fingerprint region of an IR spectrum are due to bending and out-of-plane motions.

* It is confusing, but true, that larger δ values in an NMR spectrum are associated with nuclei that are less shielded, and that these nuclei require a lower field strength for resonance. Nuclei with small values of δ are more shielded and require a higher field strength for resonance.

* Both ^{13}C NMR and ^{1}H NMR are indispensable for establishing the structure of an organic compound. ^{13}C NMR indicates if a molecule is symmetrical and shows the types of carbons in a molecule (by DEPT NMR). ^{1}H NMR shows how the carbons are connected (by spin-spin splitting) and how many protons are in the molecule (by integration). Both types of spectra show (by chemical shift) the electronic environment of the magnetic nuclei.

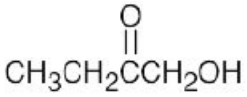
Self-Test:

Compound **A** is a hydrocarbon with $M^+ = 78$. What is its molecular formula? What is its degree of unsaturation? Draw three possible formulas for **A**. The ^{13}C NMR spectrum of **A** shows 3 peaks – at 18.5 δ, 69.4 δ and 82.4 δ, and the ^{1}H NMR spectrum shows two peaks. What is the structure of **A**? What significant absorptions would you see in the IR spectrum of **A**?

Compound **B** has the molecular formula C_8H_{14}, and shows 3 peaks in its ^{1}H NMR spectrum – at 1.7 δ (6H), 2.1 δ (4H) and 4.7 δ (4H). All 3 peaks are singlets. **B** also shows

an IR absorption at 890 cm^{-1}. What is a possible structure for **B**? If you're still not sure, the following peaks were observed in the ^{13}C NMR spectrum of **B**: 22 δ, 36 δ, 110 δ, 146 δ. The peaks at 36 δ and 110 δ were negative signals in the DEPT-135 spectrum, and the peak at 22 δ was a positive signal.

Compound **C** is a hydrocarbon with $M^+ = 112$. What are possible molecular formulas for **C**? The five peaks in the ^1H NMR spectrum of **C** are all singlets and occur at the following δ values: 0.9 δ (9 H), 1.8 δ (3 H), 1.9 δ (2 H), 4.6 δ (1 H) and 4.8 δ (1 H). An IR absorption at 890 cm^{-1} is also present What is the structure of **C**?



D

Describe the ^{13}C NMR and ^1H NMR spectra of **D**. For the ^1H NMR spectrum, include the spin-spin splitting patterns, peak areas, and positions of the chemical shifts. Give two significant absorptions that you might see in the IR spectrum. Would you expect to see products of McLafferty rearrangement in the mass spectrum of **D**? Of alpha cleavage?

Multiple Choice:

1. Which of the following formulas could not arise from a compound with $M^+ = 142$ that contains C, H, and possibly O?
   (a) $C_{11}H_{10}$ (b) $C_{10}H_8O$ (c) $C_9H_{18}O$ (d) $C_8H_{14}O_2$

2. Which of the following mass spectrum fragments is a cation, rather than a cation radical?
   (a) molecular ion
   (b) product of alpha cleavage
   (c) product of McLafferty rearrangement
   (d) product of dehydration of an alcohol

3. Which element contributes significantly to $(M+1)^+$?
   (a) N (b) H (c) C (d) O

4. In which type of spectroscopy is the wavelength of absorption the longest?
   (a) NMR spectroscopy (b) infrared spectroscopy
   (c) ultraviolet spectroscopy (d) X-ray spectroscopy

5. Which functional group is hard to detect in an IR spectrum?
   (a) aldehyde (b) –C≡CH (c) alcohol (d) ether

6. IR spectroscopy is especially useful for:
   (a) determining if an alkyne triple bond is at the end of a carbon chain or is in the middle
   (b) predicting the type of carbonyl group that is present in a compound
   (c) deciding if a double bond is monosubstituted or disubstituted
   (d) all of these situations

7. If a nucleus is strongly shielded:
   (a) The effective field is smaller than the applied field, and the absorption is shifted downfield.
   (b) The effective field is larger than the applied field, and the absorption is shifted upfield.
   (c) The effective field is smaller than the applied field, and the absorption is shifted upfield.
   (d) The effective field is larger than the applied field, and the absorption is shifted downfield.

8. When the operating frequency of an ^1H NMR spectrometer is changed:
   (a) The value of chemical shift in δ and of the coupling constant remain the same.
   (b) The values of chemical shift in Hz and of the coupling constant change.
   (c) The value of chemical shift in Hz remains the same, but the coupling constant changes.
   (d) The values of chemical shift in δ and of the coupling constant change.

9. ^{13}C NMR can provide all of the following data except:
   (a) the presence or absence of symmetry in a molecule
   (b) the connectivity of the carbons in a molecule
   (c) the chemical environment of a carbon
   (d) the number of hydrogens bonded to a carbon

10. Which kind of carbon is detected in DEPT-90 ^{13}C NMR spectroscopy?
    (a) primary carbon (b) secondary carbon (c) tertiary carbon (d) quaternary carbon

11. The protons on carbon 3 of (*R*)-2-bromobutane are:
    (a) homotopic (b) enantiotopic (c) diastereotopic (d) unrelated

Chapter 14 – Conjugated Compounds and Ultraviolet Spectroscopy

Chapter Outline

I. Conjugated Dienes (Sections 14.1–14.6).
   A. Preparation and stability of conjugated dienes (Section 14.1).
      1. Base-induced elimination of allylic halides is the most common method.
      2. The C2–C3 bond length of 1,3-butadiene is 6 pm shorter than a C–C single bond.
      3. Stability of conjugated dienes.
         a. Heats of hydrogenation show that conjugated dienes are somewhat more stable than nonconjugated dienes.
         b. Because conjugated dienes are more stable and contain less energy, they release less heat on hydrogenation.
      4. Molecular orbital description of 1,3-butadiene.
         a. The stability of 1,3-butadiene may be due to the greater amount of *s* character of the C–C single bond between the double bonds.
         b. Molecular orbital theory offers another explanation.
            i. If we combine 4 adjacent *p* orbitals, we generate a set of 4 molecular orbitals.
            ii. Bonding electrons go into the lower two MOs.
            iii. The lowest MO has a bonding interaction between C2 and C3 that gives that bond partial double-bond character.
            iv. The π electrons of butadiene are delocalized over this entire π framework.
   B. Reactions of conjugated dienes (Sections 14.2–14.6).
      1. Electrophilic addition to conjugated dienes (Sections 14.2–14.3).
         a. Conjugated dienes react in electrophilic addition reactions to give products of both 1,2-addition and 1,4-addition (Section 14.2).
            i. Addition of an electrophile gives an allylic carbocation intermediate that is resonance-stabilized.
            ii. Addition of the nucleophile in the second step of the reaction can occur at either end of the allylic carbocation to yield two products.
         b. The ratio of products can vary if the reaction is carried out under conditions of kinetic control or of thermodynamic control (Section 14.3).
            i. Under conditions of kinetic control (lower temperature), the product whose formation has the lower energy of activation forms in greater amounts.
            ii. Under conditions of thermodynamic control (high temperature), the more stable product (the product whose formation has a larger negative value of $\Delta G°$) forms in greater amounts.
            iii. In electrophilic addition reactions of conjugated dienes, the 1,2 (kinetic) adduct forms preferentially at low T, and the 1,4 (thermodynamic) adduct forms preferentially at high temperature.
      2. The Diels–Alder cycloaddition reaction (Sections 14.4–14.5).
         a. How the reaction occurs (Section 14.4).
            i. A diene can react with certain alkenes to form a cyclic product.
            ii. This reaction, the Diels–Alder reaction, forms two new C–C bonds in a single step.

iii. The reaction occurs by a pericyclic mechanism, which takes place in a step by a cyclic redistribution of electrons.
iv. In the reaction, σ overlap occurs between the two alkene *p* orbitals and the two *p* orbitals on carbons 1 and 4 of the diene.
v. The two alkene carbons and C1 and C4 of the diene rehybridize from sp^2 to sp^3, and C2 and C3 of the diene remain sp^2 hybridized.

b. The dienophile (Section 14.5).
i. The dienophile must have an electron-withdrawing group and may contain a triple bond.
ii. The stereochemistry of the dienophile is maintained during the reaction.
iii. Only endo product is formed because orbital overlap is greater in the transition state than for exo product.
(a) A substituent in a bicyclic ring system is endo if it is syn to the larger of the other two bridges.

c. The diene.
i. A diene must adopt an *s*-cis ("cis-like") conformation in order to undergo the Diels–Alder reaction.
ii. Some dienes can rotate to achieve an *s*-cis conformation; those that are rigid can't react.
iii. Dienes that have fixed *s*-cis geometry are very reactive.

3. Diene polymers (Section 14.6).
a. Like simple alkenes, conjugated dienes can polymerize.
i. Because double bonds remain in the polymer, cis–trans isomerism is possible.
ii. Polymerization can be initiated by either a radical or by acid.
iii. Polymerization occurs by 1,4-addition.

b. Natural rubber is a polymer of isoprene with *Z* double-bond stereochemistry, and *gutta-percha* is a polymer of isoprene with *E* double-bond stereochemistry.
c. Synthetic rubber and neoprene (a polymer of chloroprene) are also diene polymers.
d. Rubber needs to be hardened by vulcanization.
i. Heating rubber with sulfur forms cross-links that lock the chains together.

e. Rubber's ability to stretch and contract is due to the irregular shapes of the polymer chains.

II. Ultraviolet spectroscopy (Sections 14.7–14.9).
A. Principles of ultraviolet spectroscopy (Section 14.7).
1. The ultraviolet region of interest is between the wavelengths 200 nm and 400 nm.
2. The energy absorbed is used to promote a π electron in a conjugated system from a lower-energy orbital to a higher energy orbital.

B. Ultraviolet spectrum of 1,3-butadiene.
1. When 1,3-butadiene is irradiated with ultraviolet light, a π electron is promoted from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO).

2. UV radiation of 217 nm is necessary to promote this transition.
3. This transition is known as a $\pi \rightarrow \pi^*$ transition.

C. The ultraviolet spectrum.
1. A UV spectrum is a plot of absorbance (A) vs. wavelength in nanometers.
   a. The absorbance is $A = \log [I_0/I]$.
   b. I_0= intensity of incident light.
   c. I = intensity of transmitted light.
   d. The baseline is zero absorbance.
2. For a specific substance, A is related to the molar absorptivity (ε).
   a. Molar absorptivity, characteristic of a specific compound, is the absorbance of a sample whose concentration is 1 mol/L with a path length of 1 cm.
   b. $A = \varepsilon \times c \times l$.
   c. The range of ε is 10,000 – 25,000 L/mol·cm.
3. UV spectra usually consist of a single broad peak, whose maximum is λ_{max}.

D. Interpreting UV spectra (Section 14.8).
1. The wavelength necessary for a $\pi \rightarrow \pi^*$ transition depends on the energy difference between HOMO and LUMO.
2. By measuring this difference, it is possible to learn about the extent of conjugation in a molecule.
3. As the extent of conjugation increases, λ_{max} increases.
4. Different types of conjugated systems have characteristic values of λ_{max}.

E. Conjugation, color, and the chemistry of vision (Section 14.9).
1. Compounds with extensive systems of conjugated bonds absorb in the visible range of the electromagnetic spectrum (400 – 800 nm).
2. When “white light” strikes a conjugated molecule, the wavelength needed for excitation is absorbed, and all other light is transmitted.

Chapter 15 – Benzene and Aromaticity

Chapter Outline

I. Introduction to aromatic compounds (Sections 15.1–15.2).
  A. Sources of aromatic hydrocarbons (Section 15.1).
    1. Some aromatic hydrocarbons are obtained from distillation of coal tar.
    2. Other aromatic hydrocarbons are formed when petroleum is passed over a catalyst during refining.
  B. Naming aromatic compounds.
    1. Many aromatic compounds have nonsystematic names.
    2. Monosubstituted benzenes are named in the same way as other hydrocarbons, with -benzene as the parent name.
      a. Alkyl-substituted benzenes are named in two ways:
        i. If the alkyl substituent has six or fewer carbons, the hydrocarbon is named as an alkyl-substituted benzene.
        ii. If the alkyl substituent has more than six carbons, the compound is named as a phenyl-substituted alkane.
      b. The $C_6H_5CH_2$– group is a benzyl group, and the C_6H_5– group is a phenyl group.
    3. Disubstituted benzenes are named by the ortho(*o*), meta(*m*), para(*p*) system.
      a. A benzene ring with two substituents in a 1,2 relationship is *o*-disubstituted.
      b. A benzene ring with two substituents in a 1,3 relationship is *m*-disubstituted.
      c. A benzene ring with two substituents in a 1,4 relationship is *p*-disubstituted.
      d. The *o, m, p*–system of nomenclature is also used in describing reactions.
    4. Benzenes with more than two substituents are named by numbering the position of each substituent.
      a. Number so that the lowest possible combination of numbers is used.
      b. Substituents are listed alphabetically.
    5. Any of the nonsystematic names in Table 15.1 can be used as a parent name.
  C. Structure and stability of benzene (Section 15.2).
    1. Stability of benzene.
      a. Benzene doesn't undergo typical alkene reactions.
      b. Benzene reacts slowly with Br_2 to give substitution, not addition, products.
      c. $\Delta H°_{hydrog}$ of benzene is 150 kJ/mol less than that predicted for $3 \times \Delta H°_{hydrog}$ of cyclohexene, indicating that benzene has extra stability.
    2. Structure of benzene.
      a. All carbon–carbon bonds of benzene have the same length.
      b. The electron density in all bonds is identical.
      c. Benzene is planar, with all bond angles 120°.
      d. All carbons are sp^2-hybridized and identical, and each carbon has one electron in a *p* orbital perpendicular to the plane of the ring.
      e. Resonance theory explains that benzene is a resonance hybrid of two forms.
      f. Benzene is represented in this book as one line-bond structure, rather than as a hexagon with a circle to represent the double bonds.

3. Molecular orbital picture of benzene.
    a. It is impossible to define 3 localized π bonds; the electrons are delocalized over the ring.
    b. Six molecular orbitals (MOs) can be constructed for benzene.
        i. The 3 lower-energy MOs are bonding MOs.
        ii. The 3 higher energy MOs are antibonding.
        iii. One pair of bonding orbitals is degenerate, as is one pair of antibonding orbitals.
        iv. The 6 bonding electrons of benzene occupy the 3 bonding orbitals and are delocalized over the ring.

II. Aromaticity (Sections 15.3–15.6).
  A. The Hückel $4n + 2$ rule (Section 15.3).
    1. For a compound to be aromatic, it must possess the qualities we have already mentioned and, in addition, must fulfill Hückel's Rule.
    2. Hückel's Rule: A molecule is aromatic only if it has a planar, monocyclic system of conjugation with a total of $4n + 2$ π electrons (where n is an integer).
    3. Molecules with (4, 8, 12 ...) π electrons are antiaromatic.
    4. Examples:
        a. Cyclobutadiene ($n = 4$) is antiaromatic.
        b. Benzene ($n = 6$) is aromatic.
        c. Planar cyclooctatetraene ($n = 8$) is antiaromatic.
            i. Cyclooctatetraene is stable, but its chemical behavior is like an alkene, rather than an aromatic compound.
            ii. Cyclooctatetraene is tub-shaped, and its bonds have two different lengths.
    5. Why $4n + 2$?
        a. For aromatic compounds, there is a single lowest-energy MO that can accept two π electrons.
        b. The next highest levels occur in degenerate pairs that can accept 4 π electrons.
        c. For all aromatic compounds and ions, a stable species occurs only when $(4n + 2)$ π electrons are available to completely fill the bonding MOs.
  B. Aromatic ions (Section 15.4).
    1. Any cyclic conjugated molecule with $4n$ +2 electrons can be aromatic, even if it is an ion.
    2. The cyclopentadienyl anion.
        a. Although cyclopentadiene isn't aromatic, removal of H^+ produces a six-π-electron cyclic anion that is aromatic.
        b. Cyclopentadiene has a $pK_a = 16$, indicating that a stable anion is formed on removal of H^+.
        c. Both the cyclopentadienyl cation (4 π electrons) and the cyclopentadienyl radical (5 π electrons) are unstable.
    3. The cycloheptatrienyl cation.

a. Removal of H^- from cycloheptatriene produces the cycloheptatrienyl cation, which has 6 π electrons and is stable.
b. The cycloheptatrienyl radical and anion are unstable.

C. Aromatic heterocycles (Section 15.5).
1. A heterocycle (a cyclic compound containing one or more elements in addition to carbon in the ring) can also be aromatic.
2. Pyridine.
a. The nitrogen atom of pyridine contributes one π electron to the π system of the ring, making pyridine aromatic.
b. The nitrogen lone pair is not involved with the ring π system.
3. Pyrrole.
a. The nitrogen of pyrrole contributes both lone-pair electrons to the ring π system, making pyrrole aromatic.
b. The nitrogen atom makes a different contribution to the π ring system in and in pyridine.
4. Pyrimidine and imidazole rings are important in biological chemistry.

D. Polycyclic aromatic compounds (Section 15.6).
1. Although Hückel's Rule strictly applies only to monocyclic compounds, some polycyclic compounds show aromatic behavior.
2. Naphthalene has a Hückel number of π electrons and shows chemical and physical properties common to aromatic compounds.
3. There are many heterocyclic analogs of naphthalene.
i. Tryptophan, adenine, and guanine are biologically important polycyclic aromatic compounds.

III. Spectroscopy of aromatic compounds (Section 15.7).

A. IR spectroscopy.
1. A C–H stretch occurs at 3030 cm^{-1}.
2. As many as 4 absorptions occur in the region 1450–1600 cm^{-1}.
3. Weak absorptions are visible in the range 1660–2000 cm^{-1}.
4. Strong absorptions in the region 690–900 cm^{-1}, due to C–H out-of-plane bending, can be used to determine the substitution pattern of an aromatic ring.

B. UV spectroscopy.
1. The conjugated π system of an aromatic ring gives rise to an intense absorption at 205 nm and weaker absorptions in the range 255–275 nm.

C. NMR spectroscopy.
1. ^1H NMR.
a. Hydrogens directly bonded to an aromatic ring absorb in the region 6.5–8.0 δ.
i. Spin–spin coupling can give information about the substitution pattern.
ii. Aromatic protons are deshielded because the applied magnetic field sets up a ring-current, which produces a small magnetic field that reinforces the applied field outside of the ring and deshields the aromatic protons.

iii. If protons reside on the inside of an aromatic ring system, they are strongly shielded and absorb far upfield.
iv. The presence of a ring-current, evidenced by chemical shift, is a test of aromaticity.

b. Benzylic protons absorb at 2.3–3.0 δ.

2. ^{13}C NMR.
   a. Aromatic carbons absorb in the range 110–140 δ.
   b. Since alkene carbons also absorb in this region, ^{13}C NMR is not uniquely useful in identifying an aromatic ring.

Chapter 16 – Chemistry of Benzene: Electrophilic Aromatic Substitution

Chapter Outline

I. Electrophilic aromatic substitution reactions (Sections 16.1–16.3).
  A. Bromination of aromatic rings (Section 16.1).
    1. Characteristics of electrophilic aromatic substitution reactions.
      a. The accessibility of the π electrons of an aromatic ring make it a nucleophile.
      b. Aromatic rings are less reactive to electrophiles than are alkenes.
        i. A catalyst is needed to make the reacting molecule more electrophilic.
    2. Mechanism of bromination.
      a. Br_2 complexes with $FeBr_3$ to produce a positively polarized bromine.
      b. The polarized electrophile is attacked by the π electrons of the ring in a slow, rate-limiting step.
      c. The cation intermediate is doubly allylic but is much less stable than the starting aromatic compound.
      d. The carbocation intermediate loses H^+ from the bromine-bearing carbon in a fast step to regenerate an aromatic ring.
  B. Other aromatic substitution reactions (Section 16.2).
    1. Fluorination, chlorination and iodination.
      a. Fluorination is achieved by using the reagent F-TEDA-BF_4.
      b. Chlorine reacts in the presence of $FeCl_3$ to yield chlorinated rings.
      c. Iodination occurs only in the presence of an oxidizing agent.
    2. Nitration.
      a. A mixture of HNO_3 and H_2SO_4 is used for nitration.
      b. The reactive electrophile is NO_2^+.
      c. Products of nitration can be reduced with Fe or $SnCl_2$ to yield an arylamine.
    3. Sulfonation.
      a. Rings can be sulfonated by a mixture of SO_3 and H_2SO_4 to yield sulfonic acids.
      b. The reactive electrophile is either SO_3 or HSO_3^+.
      c. Sulfonation is reversible.
    4. Hydroxylation.
      a. Direct hydroxylation of an arylamine is rarely done in the laboratory.
      b. In enzyme-catalyzed biological hydroxylations, the reactive species is an "OH^+" equivalent.
  C. Alkylation of aromatic rings (Section 16.3).
    1. The Friedel–Crafts alkylation introduces an alkyl group onto an aromatic ring.
    2. An alkyl chloride, plus an $AlCl_3$ catalyst, produces an electrophilic carbocation.
    3. There are several limitations to using the Friedel–Crafts reaction.
      a. Only alkyl halides – not aryl or vinylic halides – can be used.
      b. Friedel–Crafts reactions don't succeed on rings that have amino substituents or deactivating groups.
      c. Polyalkylation is often seen.
      d. Rearrangements of the alkyl carbocation often occur.
        i. Rearrangements may occur by hydride shifts or by alkyl shifts.

D. Acylation of aromatic rings.
   1. Friedel–Crafts acylation occurs when an aromatic ring reacts with a carboxylic acid chloride (ROCl).
   2. The reactive electrophile is an acyl cation, which doesn't rearrange.
   3. Polyacylation never occurs in acylation reactions.

II. Substituent effects in substituted aromatic rings (Sections 16.4–16.5).
   A. Types of substituent effects (Section 16.4).
      1. Substituents affect the reactivity of an aromatic ring.
      2. Substituents affect the orientation of further substitution.
      3. Substituents can be classified into three groups:
         a. Ortho- and para-directing activators.
         b. Ortho- and para-directing deactivators.
         c. Meta-directing deactivators.
   B. Explanation of substituent effects (Section 16.4).
      1. All activating groups donate electrons to an aromatic ring.
      2. All deactivating groups withdraw electrons from a ring.
      3. Two kinds of effects are responsible for reactivity and orientation.
         a. Inductive effects are due to differences in bond polarity.
         b. Resonance effects are due to overlap of a *p* orbital of a substituent with a *p* orbital on an aromatic ring.
            i. Carbonyl, cyano and nitro substituents withdraw electrons.
               (a) These substituents have the structure –Y=Z.
            ii. Halogen, hydroxyl, alkoxyl and amino substituents donate electrons.
               (a) These substituents have the structure –Y**:**.
            iii. Resonance effects are greatest at the ortho and para positions.
         c. Resonance and inductive effects don't always act in the same direction.
      4. Alkyl groups – ortho- and para-directing activators.
         a. Alkyl groups inductively donate electrons to a ring.
         b. Alkyl groups are *o,p*-directors because the carbocation intermediates are best stabilized when attack occurs at the ortho and para positions.
      5. –OH, $–NH_2$ groups – ortho- and para-directing activators.
         a. –OH, $–NH_2$ donate electrons by resonance involving the ring and the group.
         b. The intermediates of ortho- and para-attack are more stabilized by resonance than are intermediates of meta attack.
      6. Halogens – ortho- and para-directing deactivators.
         a. The electron-withdrawing inductive effect of halogen outweighs its electron-donating resonance effect.
         b. The resonance effect orients substitution to the *o,p* positions.
         c. The inductive effect deactivates the ring.
      7. Meta-directing deactivators.

a. Meta-directing deactivators act through both inductive and resonance effects.
b. Because resonance effects destabilize ortho and para positions the most, substitution ion occurs at the meta position.

C. Trisubstituted benzenes: additivity of effects (Section 16.5).
1. If the effects of both groups are additive, the product of substitution is easy to predict.
2. If the directing effects of the groups are opposed, the more powerful activating group determines the product, although mixtures sometimes result.
3. For steric reasons, substitution rarely occurs between two groups that are meta to each other.

III. Other reactions of aromatic rings (Sections 16.6–16.10).
A. Nucleophilic aromatic substitution (Section 16.6).
1. An aryl halide with electron-withdrawing groups can undergo nucleophilic aromatic substitution.
2. This reaction occurs through an addition/elimination mechanism.
3. Addition of the nucleophile proceeds through an intermediate Meisenheimer complex that is stabilized by *o, p* electron-withdrawing substituents on the ring.
4. The halide is eliminated to yield product.

B. Benzyne (Section 16.7).
1. At high temperatures and with strong base, halobenzenes without electron-withdrawing substituents can be converted to phenols.
2. This reaction occurs by an elimination/addition reaction that involves a benzyne intermediate.
a. Strong base causes elimination of HX from the aryl halide to generate benzyne.
b. A nucleophile adds to benzyne to give the product.
3. The benzyne intermediate can be trapped in a Diels–Alder reaction.
4. Benzyne has the electronic structure of a distorted alkyne and has one very weak π bond.

C. Oxidation of aromatic compounds (Section 16.8).
1. Oxidation of alkylbenzene side chains.
a. Strong oxidizing agents cause the oxidation of alkyl side chains with benzylic hydrogens.
b. The products of side-chain oxidation are benzoic acids.
c. Reaction proceeds by a complex radical mechanism.
2. Bromination of alkylbenzene side chains.
a. NBS brominates alkylbenzene side chains at the benzylic position.
b. Bromination occurs by the mechanism described for allylic bromination and requires a radical initiator.
c. The intermediate benzylic radical is stabilized by resonance.

D. Reduction of aromatic compounds (Section 16.9).
1. Catalytic hydrogenation of aromatic rings.
a. It is possible to selectively reduce alkene bonds in the presence of aromatic rings because rings are relatively inert to catalytic hydrogenation.

   b. With a stronger catalyst, aromatic rings can be reduced to cyclohexanes.
2. Reduction of aryl alkyl ketones.
   a. Aryl alkyl ketones can undergo catalytic hydrogenation to form alkylbenzenes.
   b. Acylation plus reduction is a route to alkyl substitution without rearrangement.
   c. This reaction only occurs with aryl alkyl ketones and also reduces nitro groups to amino groups.

IV. Synthesis of polysubstituted benzenes (Section 16.10).

A. To synthesize substituted benzenes, it is important to introduce groups so that they have the proper orienting effects.
B. It is best to use retrosynthetic analysis (work backward from the product) to plan a synthesis.

Review Unit 6: Conjugation and Aromaticity

Major Topics Covered (with vocabulary):

Conjugated dienes:
delocalization 1,4-addition allylic position thermodynamic control kinetic control vulcanization Diels–Alder cycloaddition dienophile *endo* product *exo* product *s*-cis conformation

Ultraviolet spectroscopy:
highest occupied molecular orbital (HOMO) lowest unoccupied molecular orbital (LUMO) molar absorptivity

Aromaticity:
aromatic arene phenyl group benzyl group ortho, meta, para substitution degenerate Hückel $4n + 2$ rule antiaromatic heterocycle polycyclic aromatic compound ring current

Chemistry of aromatic compounds:
electrophilic aromatic substitution sulfonation F-TEDA-BF_4 Friedel–Crafts alkylation polyalkylation Friedel–Crafts acylation ortho- and para-directing activator ortho- and para-directing deactivator meta-directing deactivator inductive effect resonance effect nucleophilic aromatic substitution Meisenheimer complex benzyne benzylic position

Types of Problems:

After studying these chapters, you should be able to:

- Predict the products of electrophilic addition to conjugated molecules.
- Understand the concept of kinetic *vs*. thermodynamic control of reactions.
- Recognize diene polymers, and draw a representative segment of a diene polymer.
- Predict the products of Diels–Alder reactions, and identify compounds that are good dienophiles and good dienes.
- Calculate the energy required for UV absorption, and use molar absorptivity to calculate concentration.
- Predict if and where a compound absorbs in the ultraviolet region.
- Name and draw substituted benzenes.
- Draw resonance structures and molecular orbital diagrams for benzene and other cyclic conjugated molecules.
- Use Hückel's rule to predict aromaticity.
- Draw orbital pictures of cyclic conjugated molecules.
- Use NMR, IR and UV data to deduce the structures of aromatic compounds.
- Predict the products of electrophilic aromatic substitution reactions.
- Formulate the mechanisms of electrophilic aromatic substitution reactions.
- Understand the activating and directing effects of substituents on aromatic rings, and use inductive and resonance arguments to predict orientation and reactivity.
- Predict the products of other reactions of aromatic compounds.
- Synthesize substituted benzenes.

Points to Remember:

* It's not always easy to recognize Diels–Alder products, especially if the carbon-carbon double bond of the initial product has been hydrogenated. If no hydrogenation has taken place, look for a double bond in a six-membered ring and at least one electron-withdrawing group across the ring from the double bond. When a bicyclic product has been formed, it has probably resulted from a Diels-Alder reaction in which the diene is cyclic.

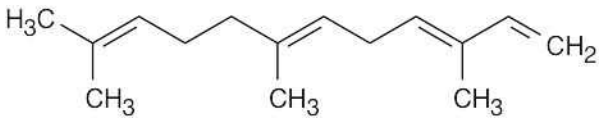
* To be aromatic, a molecule must be planar, cyclic, conjugated, and it must have $4n + 2$ electrons in its π system.

* The carbocation intermediate of electrophilic aromatic substitution loses a proton to yield the aromatic product. In all cases, a base is involved with proton removal, but the nature of the base varies with the type of substitution reaction. Although this book shows the loss of the proton, it often doesn't show the base responsible for proton removal. This doesn't imply that the proton flies off, unassisted; it just means that the base involved has not been identified in the problem.

* Nucleophilic aromatic substitution reactions and substitution reactions proceeding through benzyne intermediates take place by different routes. In the first reaction, the substitution takes place by an addition, followed by an elimination. In the second case, the substitution involves an elimination, followed by an addition. Virtually all substitutions are equivalent to an addition and an elimination (in either order).

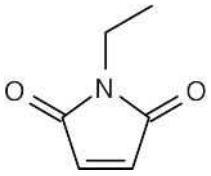
* Activating groups achieve their effects by making an aromatic ring more electron-rich and reactive toward electrophiles. Ortho and para directing groups achieve their effects by stabilizing the positive charge that results from ortho or para addition of an electrophile to the aromatic ring. The intermediate resulting from addition to a ring with an ortho or para director usually has one resonance form that is especially stable. The intermediate resulting from addition to a ring with a meta director usually has a resonance form that is especially unfavorable when addition occurs ortho or para to the functional group. Meta substitution results because it is less unfavorable than ortho or para substitution.

Self-Test:

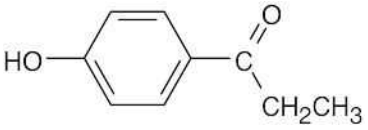


A α-Farnesene

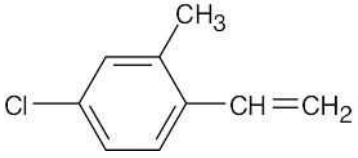
α-Farnesene (**A**), an important biological intermediate in the synthesis of many natural products, has double bonds that are both conjugated and unconjugated. Show the products you would expect from conjugate addition of HBr; of Br_2. What products would you expect from ozonolysis of **A**? Give one or more distinctive absorptions that you might see in the IR spectrum of **A** and distinguishing features of the ^1H NMR of **A**. Would you expect **A** to be UV-active?



B



C
Paroxypropione



D

Describe the π orbitals in the ring of **B**. Might this ring be described as aromatic?

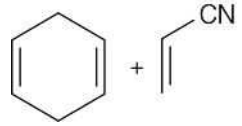
Paroxypropione (**C**) is a hormone inhibitor. Predict the products of reaction of **C** with: (a) Br_2, $FeBr_3$; (b) CH_3Cl, $AlCl_3$; (c) $KMnO_4$, H_3O^+; (d) H_2, Pd/C. If the product of (d) is treated with the reagents in (a) or (b), does the orientation of substitution change? What significant information can you obtain from the IR spectrum of **C**?

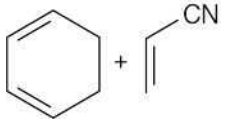
Name **D**. Plan a synthesis of **D** from benzene. Describe the ^1H NMR of **D** (include spin-spin splitting). Where might **D** show an absorption in a UV spectrum?

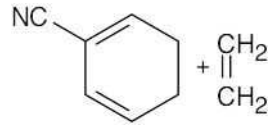
Multiple Choice:

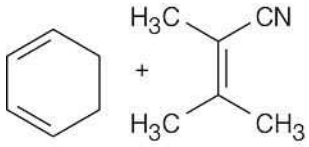
1. What are the hybridizations of the carbons in 1,2-butadiene, starting with C1?
(a) sp^2, sp^2, sp^2, sp^2 (b) sp^2, sp^2, sp^2, sp^3 (c) sp^2, sp, sp^2, sp^3 (d) sp, sp, sp^2, sp^3

2. In a reaction in which the less stable (ls) product is formed at lower temperature, and the more stable product (ms) is formed at higher temperature:
(a) $\Delta G_{ms}° > \Delta G_{ls}°$ and $\Delta G_{ms}^{‡} > \Delta G_{ls}^{‡}$
(b) $\Delta G_{ms}° > \Delta G_{ls}°$ and $\Delta G_{ls}^{‡} > \Delta G_{ms}^{‡}$
(c) $\Delta G_{ms}° < \Delta G_{ls}°$ and $\Delta G_{ms}^{‡} > \Delta G_{ls}^{‡}$
(d) $\Delta G_{ms}° < \Delta G_{ls}°$ and $\Delta G_{ls}^{‡} > \Delta G_{ms}^{‡}$
Note: In this problem, a large value for $\Delta G°$ means a large negative value.

3. Which of the following combinations is most likely to undergo a successful Diels–Alder reaction?
(a) 

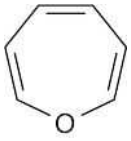
(b) 

(c) 

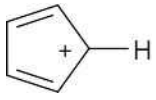
(d) 

4. Which of the following groups, when bonded to the terminal carbon of a conjugated π system, probably affects the value of λ_{max} the least?
(a) $–NH_2$ (b) –Cl (c) –OH (d) $–CH_3$

5. If the value of λ_{max} for an unsubstituted diene is approximately 220 nm, and each additional double bond increases the value of λ_{max} by 30 nm, what is the minimum number of double bonds present in a compound that absorbs in the visible range of the electromagnetic spectrum?
(a) 6 (b) 7 (c) 8 (d) 9

6. Which of the following compounds is aromatic?
(a) 
(b) 

(c) 

(d) 

7. How many benzene isomers of $C_7H_6Br_2$ can be drawn?
(a) 10 (b) 11 (c) 12 (d) 14

8. Which of the following functional groups isn't a meta-directing deactivator?
(a) $–NO_2$ (b) $–CONHCH_3$ (c) $–N(CH_3)_3^+$ (d) $–NHCOCH_3$

9. Which of the following compounds can't be synthesized by an electrophilic aromatic substitution reaction that we have studied?
(a) *m*-Cresol (b) *p*-Chloroaniline (c) 2,4-Toluenedisulfonic acid (d) *m*-Bromotoluene

10. In only one of the following compounds can you reduce the aromatic ring without also reducing the side chain. Which compound is it?
(a) *p*-Bromoanisole
(b) Acetophenone (methyl phenyl ketone)
(c) Styrene
(d) Phenylacetylene

Chapter 17 – Alcohols and Phenols

Chapter Outline

I. Naming alcohols and phenols (Section 17.1).
   A. Alcohols are classified as primary, secondary or tertiary, depending on the number of organic groups bonded to the –OH carbon.
   B. Rules for naming simple alcohols.
      1. The longest chain containing the –OH group is the parent chain, and the parent name replaces *-e* with *-ol*.
      2. Numbering begins at the end of the chain nearer the –OH group.
      3. The substituents are numbered according to their position on the chain and cited in alphabetical order.
   C. Phenols are named according to rules discussed in Section 15.1 for aromatic compounds.

II. Properties of alcohols and phenols (Section 17.2).
   A. Hydrogen-bonding of alcohols and phenols.
      1. Alcohols have sp^3 hybridization and a nearly tetrahedral bond angle.
      2. Alcohols and phenols have elevated boiling points, relative to hydrocarbons, due to hydrogen-bonding.
         a. In hydrogen-bonding, an –OH hydrogen is attracted to a lone pair of electrons on another molecule, resulting in a weak electrostatic force that holds the molecules together.
         b. These weak forces must be overcome in boiling.
   B. Acidity and basicity of alcohols and phenols.
      1. Alcohols and phenols are weakly acidic as well as weakly basic.
      2. Alcohols and phenols can be reversibly protonated to form oxonium ions.
      3. Alcohols and phenols dissociate to a slight extent to form alkoxide ions and phenoxide ions.
      4. Acidity of alcohols.
         a. Alcohols are similar in acidity to water.
         b. Alkyl substituents decrease acidity by preventing solvation of the alkoxide ion.
         c. Electron-withdrawing substituents increase acidity by delocalizing negative charge.
         d. Alcohols don’t react with weak bases, but they do react with alkali metals and strong bases.
      5. Acidity of phenols.
         a. Phenols are a million times more acidic than alcohols and are soluble in dilute NaOH.
         b. Phenol acidity is due to resonance stabilization of the phenoxide anion.
         c. Electron-withdrawing substituents increase phenol acidity, and electron-donating substituents decrease phenol acidity.

III. Alcohols (Sections 17.3–17.8).
   A. Preparation of alcohols (Sections 17.3–17.5).
      1. Familiar methods (Section 17.3).

a. Hydration of alkenes.
    i. Hydroboration/oxidation yields non-Markovnikov products.
    ii. Oxymercuration/reduction yields Markovnikov products.
b. 1,2-diols can be prepared by O_sO_4 hydroxylation, followed by reduction.
    i. This reaction occurs with syn stereochemistry.
    ii. Ring-opening of epoxides produces 1,2-diols with anti stereochemistry.

2. Reduction of carbonyl compounds (Section 17.4).
    a. Aldehydes are reduced to primary alcohols.
    b. Ketones are reduced to secondary alcohols.
        i. Either $NaBH_4$(milder) or $LiAlH_4$(more reactive) can be used to reduce aldehydes and ketones.
    c. Carboxylic acids and esters are reduced to primary alcohols with $LiAlH_4$.
        i. These reactions occur by addition of hydride to the positively polarized carbon of a carbonyl group.
        ii. Water adds to the alkoxide intermediate during workup to yield an alcohol product.
3. Reaction of carbonyl compounds with Grignard reagents (Section 17.5).
    a. RMgX adds to carbonyl compounds to give alcohol products.
        i. Reaction of RMgX with formaldehyde yields primary alcohols.
        ii. Reaction of RMgX with aldehydes yields secondary alcohols.
        iii. Reaction of RMgX with ketones yields tertiary alcohols.
        iv. Reaction of RMgX with esters yields tertiary alcohols with at least two identical R groups bonded to the alcohol carbon.
        v. No reaction occurs with carboxylic acids because the acidic hydrogen quenches the Grignard reagent.
    b. Limitations of the Grignard reaction.
        i. Grignard reagents can't be prepared from reagents containing other reactive functional groups.
        ii. Grignard reagents can't be prepared from compounds having acidic hydrogens.
    c. Grignard reagents behave as carbon anions and add to the carbonyl carbon.
        i. A proton from water is added to the alkoxide intermediate to produce the alcohol.

B. Reactions of alcohols (Sections 17.6–17.8).
1. Conversion to alkyl halides (Section 17.6).
    a. Tertiary alcohols (ROH) are converted to RX by treatment with HX.
        i. The reaction occurs by an S_N1 mechanism.
    b. Primary alcohols are converted by the reagents PBr_3 and $SOCl_2$.
        i. The reaction occurs by an S_N2 mechanism.
2. Conversion into tosylates.
    a. Reaction with *p*-toluenesulfonyl chloride converts alcohols to tosylates.
    b. Only the O–H bond is broken.

c. Tosylates behave as halides in substitution reactions.
d. S_N2 reactions involving tosylates proceed with inversion of configuration.

3. Dehydration to yield alkenes.
   a. Tertiary alcohols can undergo acid-catalyzed dehydration with warm aqueous H_2SO_4.
      i. Zaitsev products are usually formed.
      ii. The severe conditions needed for dehydration of secondary and primary alcohols restrict this method to tertiary alcohols.
      iii. Tertiary alcohols react fastest because the intermediate carbocation formed in this E1 reaction is more stable.
   b. Secondary alcohols are dehydrated with $POCl_3$ in pyridine.
      i. This reaction occurs by an E2 mechanism.
      ii. Pyridine serves both as a base and as a solvent.
4. Conversion into esters.
5. Oxidation of alcohols (Section 17.7).
   a. Primary alcohols can be oxidized to aldehydes or carboxylic acids.
   b. Secondary alcohols can be oxidized to ketones.
   c. Tertiary alcohols aren't oxidized.
   d. Oxidation to ketones and carboxylic acids can be carried out with $KMnO_4$, CrO_3, or $Na_2Cr_2O_7$.
   e. Oxidation of a primary alcohol to an aldehyde is achieved with the Dess–Martin periodinane.
      i. The Dess–Martin periodinane is also used on sensitive alcohols.
   f. Oxidation occurs by a mechanism closely related to an E2 mechanism.
6. Protection of alcohols (Section 17.8).
   a. It is sometimes necessary to protect an alcohol when it interferes with a reaction involving a functional group in another part of a molecule.
   b. The following reaction sequence may be applied:
      i. Protect the alcohol.
      ii. Carry out the reaction.
      iii. Remove the protecting group.
   c. A trimethylsilyl (TMS) ether can be used for protection.
      i. TMS ether formation occurs by an S_N2 route.
      ii. TMS ethers are quite unreactive.
      iii. TMS ethers can be cleaved by aqueous acid or by F^- to regenerate the alcohol.

IV. Phenols (Sections 17.9–17.10).

A. Preparation and uses of phenols (Section 17.9).
   1. Phenols can be prepared by treating chlorobenzene with NaOH.
   2. Phenols can also be prepared from isopropylbenzene (cumene).
      a. Cumene reacts with O_2 by a radical mechanism to form cumene hydroperoxide.
      b. Treatment of the hydroperoxide with acid gives phenol and acetone.

i. The mechanism involves protonation, rearrangement, loss of water, of water to form a hemiacetal, and breakdown to acetone and phenol.

3. Chlorinated phenols, such as 2,4-D, are formed by chlorinating phenol.
4. BHT is prepared by Friedel–Crafts alkylation of *p*-cresol with 2-methylpropene.

B. Reactions of phenols (Section 17.10).
1. Phenols undergo electrophilic aromatic substitution reactions (Chapter 16).
a. The –OH group is an *o,p*-director.
2. Strong oxidizing agents convert phenols to quinones.
a. Reaction with Fremy's salt to form a quinone occurs by a radical mechanism.
b. The redox reaction quinone → hydroquinone occurs readily.
c. Ubiquinones are an important class of biochemical oxidizing agents that function as a quinone/hydroquinone redox system.

V. Spectroscopy of alcohols and phenols (Section 17.11).
A. IR spectroscopy.
1. Both alcohols and phenols show –OH stretches in the region 3300–3600 cm^{-1}.
a. Unassociated alcohols show a peak at 3600 cm^{-1}.
b. Associated alcohols show a broader peak at 3300–3400 cm^{-1}.
2. Alcohols show a C–O stretch near 1050 cm^{-1}.
3. Phenols show aromatic bands at 1500–1600 cm^{-1}.
4. Phenol shows monosubstituted aromatic bands at 690 and 760 cm^{-1}.

B. NMR spectroscopy.
1. In ^{13}C NMR spectroscopy, carbons bonded to –OH groups absorb in the range 50–80 δ.
2. ^{1}H NMR.
a. Hydrogens on carbons bearing –OH groups absorb in the range 3.5–4.5 δ.
i. The hydroxyl hydrogen doesn't split these signals.
b. D_2O exchange can be used to locate the O–H signal.
c. Spin–spin splitting occurs between protons on the oxygen-bearing carbon and neighboring –H.
d. Phenols show aromatic ring absorptions, as well as an O–H absorption in the range 3–8 δ.

C. Mass Spectrometry.
1. Alcohols undergo alpha cleavage to give a neutral radical and an oxygen-containing cation.
2. Alcohols also undergo dehydration to give an alkene radical cation.

Chapter 18 – Ethers and Epoxides; Thiols and Sulfides

Chapter Outline

I. Acyclic ethers (Sections 18.1–18.4).
  A. Naming ethers (Section 18.1).
    1. Ethers with no other functional groups are named by citing the two organic substituents and adding the word "ether".
    2. When other functional groups are present, the ether is an alkoxy substituent.
  B. Properties of ethers.
    1. Ethers have the same geometry as water and alcohols.
    2. Ethers have a small dipole moment that causes a slight boiling point elevation.
    3. Ethers can react slowly with oxygen to give explosive peroxides.
  C. Synthesis of ethers (Section 18.2).
    1. Symmetrical ethers can be synthesized by acid-catalyzed dehydration of alcohols.
      a. This method is used only with primary alcohols.
    2. Williamson ether synthesis.
      a. Metal alkoxides react with primary alkyl halides and tosylates to form ethers.
      b. The alkoxides are prepared by reacting an alcohol with a strong base, such as NaH.
        i. Reaction of the free alcohol with the halide can also be achieved with Ag_2O.
      c. The reaction occurs via an S_N2 mechanism.
        i. The halide component must be primary.
        ii. In cases where one ether component is hindered, the ether should be synthesized from the alkoxide of the more hindered reagent and the halide of the less hindered reagent.
    3. Alkoxymercuration of alkenes.
      a. Ethers can be formed from the reaction of alcohols with alkenes.
      b. The reaction is carried out in the presence of mercuric trifluoroacetate.
      c. The mechanism is similar to that for hydration of alkenes.
        i. $NaBH_4$ is used for demercuration of the intermediate.
      d. Many different types of ethers can be prepared by this method.
  D. Reactions of ethers (Sections 18.3–18.4).
    1. Ethers are relatively unreactive and often used as solvents.
    2. Acidic cleavage (Section 18.3).
      a. Strong acids can be used to cleave ethers.
      b. Cleavage can occur by S_N2 or S_N1 routes.
        i. Primary and secondary alcohols react by an S_N2 mechanism, in which the halide attacks the ether at the less hindered site.
          (a) This route selectively produces one halide and one alcohol.
        ii. Tertiary, benzylic, and allylic ethers react by either an S_N1 or an E1 route.
    3. Claisen rearrangement (Section 18.4).
      a. The Claisen rearrangement is specific to allyl aryl ethers or aryl vinyl ethers.
      b. The result of Claisen rearrangement is an *o*-allyl phenol.
      c. The reaction takes place in a single step by a pericyclic mechanism.
        i. Inversion of the allyl group is evidence for this mechanism.

II. Cyclic ethers (Sections 18.5–18.7).
  A. Epoxides (oxiranes) (Sections 18.5–18.6).
    1. The three-membered ring of epoxides gives them unique chemical reactivity (Section 18.5).
    2. The nonsystematic name *–ene oxide* describes the method of formation.
    3. The systematic prefix *epoxy-* describes the location of the epoxide ring.
    4. Preparation of epoxides.
      a. Epoxides can be prepared by reaction of an alkene with a peroxyacid RCO_3H.
        i. The reaction occurs in one step with syn stereochemistry.
      b. Epoxides are formed when halohydrins are treated with base.
        i. This reaction is an intramolecular Williamson ether synthesis.
    5. Ring-opening reactions of epoxides (Section 18.6).
      a. Acid-catalyzed ring opening.
        i. Acid-catalyzed ring opening produces 1,2 diols.
        ii Ring opening takes place by back-side attack of a nucleophile on the protonated epoxide ring.
          (a) A trans-1,2-diol is formed from an epoxycycloalkane.
          (b) If HX is used, the product is a trans halohydrin.
        iii. When both epoxide carbons are primary or secondary, attack occurs primarily at the less hindered site.
        iv. When one epoxide carbon is tertiary, attack occurs at the more highly substituted site.
        v. The mechanism is midway between S_N2 and S_N1 routes.
          (a) The reaction occurs by back-side attack (S_N2), but positive charge is stabilized by a tertiary carbocation-like transition state (S_N1).
      b. Base-catalyzed ring-opening.
        i. Base-catalyzed ring opening occurs because of the reactivity of the strained epoxide ring.
        ii. Ring-opening takes place by an S_N2 mechanism, in which the nucleophile attacks the less hindered epoxide carbon.
        iii. Other nucleophiles can bring about ring opening.
          (a) Epoxides react with Grignard reagents to form a product with two more carbons than the starting alkyl halide.
          (b) Epoxide rings also react with amines in a ring-opening reaction.
  B. Crown ethers (Section 18.7).
    1. Crown ethers are large cyclic ethers.
    2. Crown ethers are named as *x*-crown-*y*, where *x* = the ring size and *y* = # of oxygens.
    3. Crown ethers are able to solvate metal cations.
      a. Different sized crown ethers solvate different cations.
      b. Complexes of crown ethers with ionic salts are soluble in organic solvents.
      c. This solubility allows many reactions to be carried out under aprotic conditions.
      d. The reactivity of many anions in S_N2 reactions is enhanced by crown ethers.

III. Thiols and sulfides (Section 18.8).
  A. Naming thiols and sulfides.
    1. Thiols (sulfur analogs of alcohols) are named by the same system as alcohols, with the suffix *-thiol* replacing *-ol.*
      a. The –SH group is a mercapto- group.
    2. Sulfides (sulfur analogs of ethers) are named by the same system as ethers, with *sulfide* replacing *ether*.
      a. The –SR group is an alkylthio- group.
  B. Thiols.
    1. Thiols stink!
    2. Thiols may be prepared by S_N2 displacement with a sulfur nucleophile.
      a. The reaction may proceed to form sulfides.
      b. Better yields occur when thiourea is used.
    3. Thiols can be oxidized by Br_2 or I_2 to yield disulfides, RSSR.
      a. The reaction can be reversed by treatment with zinc and acid.
      b. The thiol-disulfide interconversion is an important biochemical interconversion.
  C. Sulfides.
    1. Treatment of a thiol with base yields a thiolate anion, which can react with an alkyl halide to form a sulfide.
    2. Thiolate anions are excellent nucleophiles.
    3. Dialkyl sulfides can react with alkyl halides to form trialkylsulfonium salts, which are also good alkylating agents.
      a. Many biochemical reactions use trialkylsulfonium groups as alkylating agents.
    4. Sulfides are easily oxidized to sulfoxides (R_2SO) and sulfones (R_2SO_2).
      a. Dimethyl sulfoxide is used as a polar aprotic solvent.

IV. Spectroscopy of ethers (Section 18.9).
  A. IR spectroscopy.
    1. Ethers are difficult to identify by IR spectroscopy because many other absorptions occur at 1050–1150 cm^{-1}, where ethers absorb.
  B. NMR spectroscopy.
    1. ^1H NMR spectroscopy.
      a. Hydrogens on a carbon next to an ether oxygen absorb downfield (3.4–4.5 δ).
      b. Hydrogens on a carbon next to an epoxide oxygen absorb at a slightly higher field (2.5–3.5 δ).
    2. ^{13}C NMR spectroscopy.
      a. Ether carbons absorb downfield (50–80 δ).

Preview of Carbonyl Chemistry

Chapter Outline

I. The carbonyl group.
   A. Kinds of carbonyl compounds.
      1. All carbonyl compounds contain an acyl group (R–CO–X).
      2. The groups bonded to the acyl group can be of two types:
         a. Groups (R, X) that can't act as leaving groups.
            i. Examples: aldehydes and ketones.
         b. Groups (X) that can act as leaving groups.
            ii. Examples: carboxylic acids, esters, amides, acid halides, lactones, acid anhydrides, lactams.
   B. Nature of the carbonyl group.
      1. The carbonyl carbon is sp^2-hybridized.
         a. A π bond is formed between carbon and oxygen.
         b. Carbonyl compounds are planar about the double bond.
      2. The carbon-oxygen bond is polar.
         a. The carbonyl carbon acts as an electrophile.
         b. The carbonyl oxygen acts as a nucleophile.

II. Reactions of carbonyl compounds.
   A. Nucleophilic addition reactions of aldehydes and ketones.
      1. A nucleophile adds to the carbonyl carbon.
      2. The resulting tetrahedral intermediate has two fates:
         a. The negatively charged oxygen can be protonated to form an alcohol.
         b. Loss of water leads to formation of a C=Nu double bond.
   B. Nucleophilic acyl substitution reactions.
      1. A nucleophile adds to the carbonyl carbon.
      2. The resulting tetrahedral intermediate expels a leaving group to form a new carbonyl compound.
      3. This type of reaction takes place with carbonyl compounds other than aldehydes and ketones.
   C. Alpha substitution reactions.
      1. Reaction can occur at the position next to the carbonyl carbon (α position).
         a. This type of reaction is possible because of the acidity of alpha hydrogens.
         b. Reaction with a strong base forms an enolate anion, which behaves as a nucleophile.
      2. All carbonyl compounds can undergo α substitution reactions.
   D. Carbonyl condensation reactions.
      1. Carbonyl condensation reactions occur when two carbonyl compounds react with each other.
      2. The enolate of one carbonyl compound adds to the carbonyl group of a second compound.

Review Unit 7: Alcohols, Ethers, and Related Compounds

Major Topics Covered (with vocabulary):

The –OH group:
alcohol phenol glycol wood alcohol hydrogen bonding alkoxide ion phenoxide ion acidity constant

Alcohols:
Grignard Reagent Dess–Martin periodinane tosylate protecting group TMS ether

Phenols:
cumene hydroperoxide quinone hydroquinone ubiquinone

Acyclic ethers:
Williamson ether synthesis Claisen rearrangement

Cyclic ethers:
Epoxide oxirane vicinal glycol peroxyacid crown ether 18-crown-6

Thiols and sulfides:
Thiol sulfide mercapto group alkylthio group disulfide thiolate ion trialkylsulfonium salt sulfoxide sulfone

Types of Problems:

After studying these chapters, you should be able to:

– Name and draw structures of alcohols, phenols, ethers, thiols and sulfides.
– Explain the properties and acidity of alcohols and phenols.
– Prepare all of the types of compounds studied.
– Predict the products of reactions involving alcohols, phenols and ethers.
– Formulate mechanisms of reactions involving alcohols, phenols and ethers.
– Identify alcohols, phenols and ethers by spectroscopic techniques.

Points to Remember:

* The great biochemical importance of hydroxyl groups is due to two factors: (1) Hydroxyl groups make biomolecules more soluble because they can hydrogen-bond with water. (2) Hydroxyl groups can be oxidized to aldehydes, ketones and carboxylic acids. The presence of a hydroxyl group in a biological molecule means that all functional groups derived from alcohols can be easily introduced.

* Carbon–carbon bond-forming reactions are always more difficult to learn than functional group transformations because it is often difficult to recognize the components that form a carbon skeleton. The product of a Grignard reaction contains a hydroxyl group bonded to at least one alkyl group (usually two or three). When looking at a product that might have been formed by a Grignard reaction, remember that a tertiary alcohol results from the addition of a Grignard reagent to either a ketone or an ester (the alcohol formed from the ester has two identical –R groups), a secondary alcohol results from addition of a Grignard reagent to an aldehyde, and a primary alcohol results from addition of a Grignard reagent to

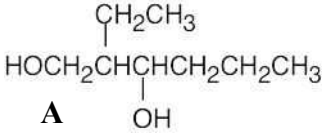
formaldehyde or to ethylene oxide. Remember that any molecule taking part in a Grignard reaction must not contain functional groups that might also react with the Grignard reagent.

* Ethers are quite unreactive, relative to many other functional groups we study, and are often used as solvents for that reason. Concentrated halogen acids can cleave ethers to alcohols and halides. Remember that the halide bonds to the less substituted alkyl group when the ethers are primary or secondary alkyl ethers.

* Epoxide rings can be opened by both acid and base. In basic ring-opening of an unsymmetrical epoxide (and in ring-opening using a Grignard reagent), attack occurs at the less substituted carbon of the epoxide ring. In acidic ring opening, the position of attack depends on the substitution pattern of the epoxide. When one of the epoxide carbons is tertiary, attack occurs at the more substituted carbon, but when the epoxide carbons are both primary or secondary, attack occurs at the less substituted carbon.

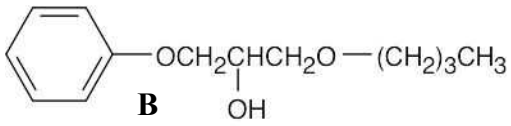
* The most useful spectroscopic data for these compounds: (1) A broad IR absorption in the range 3300 cm^{-1}–3600 cm^{-1} shows the presence of the –OH group of an alcohol or a phenol. (2) Hydrogens bonded to the –O–C– carbon of an alcohol or ether absorb in the range 3.5–4.5 δ in an ^{1}H NMR spectrum or in the range 50–80 δ in a ^{13}C NMR spectrum.

Self- Test:



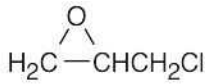
A

an insecticide



B

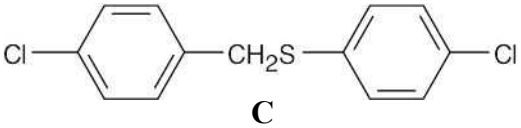
Febuprol (increases bile flow)



Epichlorohydrin

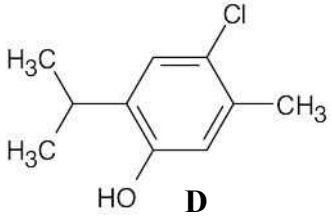
Provide an IUPAC name for **A** and identify chiral carbons. Would you expect **A** to be water-soluble? Label the hydroxyl groups of **A** as primary, secondary or tertiary. What products are formed when **A** reacts with: (a) CrO_3, H_3O^+ ; (b) PBr_3; (c) $(CH_3)_3SiCl$, Et_3N.

Name **B** by IUPAC rules. Show the three components that comprise **B**. The synthesis of **B** involves a ring-opening reaction of the epoxide epichlorohydrin. Use this information to propose a synthesis of **B** from epichlorohydrin and any alcohol or phenol.



C

Chlorbenside (larvicide)



D

Chlorothymol

What type of compound is **C**? Name **C**. Synthesize **C** from benzenethiol and benzene. What products are formed when **C** is treated with: (a) CH_3I; (b) H_2O_2, H_2O; (c) product o (b) + CH_3CO_3H.

Synthesize **D** from *m*-cresol; assume that isomeric product mixtures can be separated. Describe the IR and ^{1}H NMR spectrum of **D.**

Multiple Choice:

1. Hydrogen bonding affects all of the following except:
   (a) boiling point (b) solubility (c) position of –OH absorption in IR spectrum
   (d) chemical shift of –C–O– carbon in ^{13}C NMR

2. Which of the following alcohols can't be synthesized by a Grignard reaction?
   (a) Benzyl alcohol (b) Triphenylmethanol (c) 3-Bromo-1-hexanol (d) 1-Hexanol

3. Which of the following reactions of a chiral alcohol occurs with inversion of configuration?
   (a) reaction with NaH (b) reaction with PBr_3 (c) reaction with tosyl chloride
   (d) reaction with $(CH_3)_3SiCl$

4. How many diols of the formula $C_4H_{10}O_2$ are chiral?
   (a) 2 (b) 3 (c) 4 (d) 5

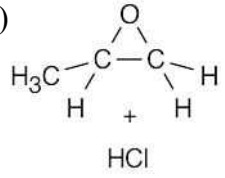
5. Which alcohol is the least acidic?
   (a) 2-Propanol (b) Methanol (c) Ethanol (d) 2-Chloroethanol

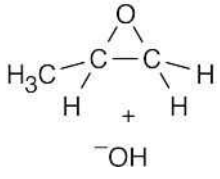
6. Which of the following compounds can't be reduced to form $C_6H_5CH_2OH$?
   (a) $C_6H_5CO_2H$ (b) C_6H_5CHO (c) $C_6H_5CO_2CH_3$ (d) $C_6H_5OCH_3$

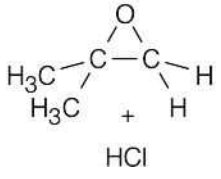
7. The reagent used for dehydration of an alcohol is:
   (a) PCl_3 (b) $POCl_3$ (c) $SOCl_2$ (d) PCC

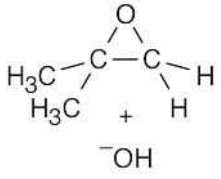
8. All of the following are products of oxidation of a thiol except:
   (a) a sulfide (b) a disulfide (c) a sulfoxide (d) a sulfone

9. In which of the following epoxide ring-opening reactions does attack of the nucleophile occur at the more substituted carbon of the epoxide ring?

   (a) 

   (b) 

   (c) 

   (d) 

10. Ethers are stable to all of the following reagents except:
    (a) nucleophiles (b) bases (c) strong acids (d) dilute acids

Chapter 19 - Aldehydes and Ketones: Nucleophilic Addition Reactions

Chapter Outline

I. General information about aldehydes and ketones (Sections 19.1–19.3).
  A. Naming aldehydes and ketones (Section 19.1).
    1. Naming aldehydes.
      a. Aldehydes are named by replacing the –e of the corresponding alkane with -al.
      b. The parent chain must contain the –CHO group.
      c. The aldehyde carbon is always carbon 1.
      d. When the –CHO group is attached to a ring, the suffix -carbaldehyde is used.
    2. Naming ketones.
      a. Ketones are named by replacing the –ane of the corresponding alkane with -one.
      b. Numbering starts at the end of the carbon chain nearer to the carbonyl carbon.
      c. The word *acyl* is used when a RCO– group is a substituent.
  B. Preparation of aldehydes and ketones (Section 19.2).
    1. Preparation of aldehydes.
      a. Oxidation of primary alcohols with Dess-Martin periodinane.
      b. Partial reduction of carboxylic acid derivatives.
    2. Preparation of ketones.
      a. Oxidation of secondary alcohols.
      b. Ozonolysis of alkenes with at least one disubstituted unsaturated carbon.
      c. Friedel–Crafts acylation of aromatic compounds.
      d. Preparation from carboxylic acid derivatives.
  C. Oxidation of aldehydes and ketones (Section 19.3).
    1. Aldehydes can be oxidized to carboxylic acids by many reagents.
      a. CrO_3 is used for normal aldehydes.
      b. Oxidation occurs through intermediate 1,1-diols.
    2. Ketones are generally inert to oxidation, but can be oxidized to carboxylic acids with strong oxidizing agents.

II. Nucleophilic addition reactions of aldehydes and ketones (Sections 19.4–19.13).
  A. Characteristics of nucleophilic addition reactions (Section 19.4).
    1. Mechanism of nucleophilic addition reactions.
      a. A nucleophile attacks the electrophilic carbonyl carbon from a direction 105° opposite to the carbonyl oxygen.
      b. The carbonyl group rehybridizes from sp^2 to sp^3, and a tetrahedral alkoxide intermediate is produced.
      c. The attacking nucleophile may be neutral or negatively charged.
        i. Neutral nucleophiles usually have a hydrogen atom that can be eliminated.
      d. The tetrahedral intermediate has two fates:
        i. The intermediate can be protonated to give an alcohol.
        ii. The carbonyl oxygen can be eliminated as –OH to give a product with a C=Nu double bond.

2. Relative reactivity of aldehydes and ketones.
    a. Aldehydes are usually more reactive than ketones in nucleophilic addition reactions for two reasons:
        i. A nucleophile can approach the carbonyl group of an aldehyde more readily because only one alkyl group is in the way.
        ii. Aldehyde carbonyl groups are more strongly polarized and electrophilic because they are less stabilized by the inductive effect of alkyl groups.
    b. Aromatic aldehydes are less reactive than aliphatic aldehydes because the electron-donating aromatic ring makes the carbonyl carbon less electrophilic.

B. Nucleophilic addition reactions (Section 19.5–19.13).
1. Hydration (Section 19.5).
    a. Water adds to aldehydes and ketones to give 1,1-diols (often referred to as gem diols or hydrates).
    b. The reaction is reversible, but generally the equilibrium favors the carbonyl compound.
    c. Reaction is slow in pure water, but is catalyzed by both aqueous acid and base.
        i. The base-catalyzed reaction is an addition of –OH, followed by protonation of the tetrahedral intermediate by water.
        ii. In the acid-catalyzed reaction, the carbonyl oxygen is protonated, and neutral water adds to the carbonyl carbon.
    d. The catalysts have different effects.
        i. Base catalysis converts water to a better nucleophile.
        ii. Acid catalysis makes the carbonyl carbon a better electrophile.
    e. Reactions of carbonyl groups with H-Y, where Y is electronegative, are reversible; the equilibrium favors the aldehyde or ketone.
2. Cyanohydrin formation (Section 19.6).
    a. HCN adds to aldehydes and ketones to give cyanohydrins.
        i. The reaction is base-catalyzed and proceeds through a tetrahedral intermediate.
        ii. Equilibrium favors the cyanohydrin adduct.
    b. HCN is one of the very few protic acids that add to a carbonyl group.
    c. Cyanohydrin formation is useful for the transformations that the –CN group can undergo.
        i. The –CN group can be reduced, to form an amine.
        ii. The –CN group can be hydrolyzed, to produce a carboxylic acid.
3. Addition of hydride and Grignard reagents (Section 19.7).
    a. Hydride addition.
        i. $LiAlH_4$ and $NaBH_4$ act as if they are $H:^-$ donors and add to carbonyl compounds to form tetrahedral alkoxide intermediates.
        ii. In a separate step, water is added to protonate the intermediate, yielding an alcohol.

   b. Addition of Grignard reagents.
      i. Mg^{2+} complexes with oxygen, making the carbonyl group more electrophilic.
      ii. $R:^-$ adds to the carbonyl carbon to form a tetrahedral intermediate.
      iii. Water is added in a separate step to protonate the intermediate, yielding an alcohol.
      iv. Grignard reactions are irreversible because $R:^-$ is not a leaving group.
4. Addition of Amines: Imine and Enamine Formation (Section 19.8).
   a. Amines add to aldehydes and ketones to form imines and enamines.
   b. An imine ($R_2C{=}NR$) is formed when a primary amine adds to an aldehyde or ketone.
      i. The process is acid-catalyzed.
      ii. A proton transfer converts the initial adduct to a carbinolamine.
      iii. Acid-catalyzed elimination of water yields an imine.
      iv. The reaction rate maximum occurs at pH = 4.5. At this pH, $[H^+]$ is high enough to catalyze elimination of water, but low enough so that the amine is nucleophilic.
      v. Some imine derivatives are useful for characterizing aldehydes and ketones.
   c. Enamines ($R_2N{=}CR{-}CR_2$) are produced when aldehydes and ketones react with secondary amines.
      i. The mechanism is similar to that of imine formation, except a proton from the α carbon is lost in the dehydration step.
5. Addition of hydrazine: the Wolff-Kishner reaction (Section 19.9).
   a. Hydrazine reacts with aldehydes and ketones in the presence of KOH to form alkanes.
      i. The intermediate hydrazone undergoes base-catalyzed bond migration, loss of N_2 and protonation to form the alkane.
   b. The Wolff-Kishner reduction can also be used to convert an acylbenzene to an alkylbenzene.
6. Addition of alcohols: acetal formation (Section 19.10).
   a. In the presence of an acid catalyst, two equivalents of an alcohol can add to an aldehyde or ketone to produce an acetal.
      i. The initial intermediate, a hemiacetal (hydroxy ether), is formed when the first equivalent of alcohol is added.
      ii. Protonation of –OH, loss of water, with formation of an oxonium ion, and addition of a second molecule of ROH yields the acetal.
   b. Since the reaction is reversible, changing the reaction conditions can drive the reaction in either direction.
   c. Because acetals are inert to many reagents, they can be used as protecting groups in syntheses.
      i. Diols are often used as protecting groups, forming cyclic acetals.
7. The Wittig reaction (Section 19.11).
   a. The Wittig reaction converts an aldehyde or ketone to an alkene.

   b. Steps in the Wittig reaction:
      i. An alkyl halide reacts with triphenylphosphine to form an alkyltriphenylphosphonium salt.
      ii. Butyllithium converts the salt to an ylide (phosphorane).
      iii. The ylide adds to an aldehyde or ketone to form a dipolar betaine.
         (a) In some cases, the addition is a one-step cycloaddition.
      iv. The betaine forms a four-membered ring intermediate (oxaphosphatane), which decomposes to form the alkene and triphenylphosphine oxide.
   c. Uses of the Wittig reaction.
      i. The Wittig reaction can be used to produce mono-, di-, and trisubstituted alkenes, but steric hindrance keeps tetrasubstituted alkenes from forming.
      ii. The Wittig reaction produces pure alkenes of known stereochemistry (excluding E,Z isomers).
8. Biological reductions (Section 19.12).
   a. The Cannizzaro reaction is unique in that the tetrahedral intermediate of addition of a nucleophile to an aldehyde can expel a leaving group.
   b. Steps in the Cannizzaro reaction.
      i. HO^- adds to an aldehyde with no α hydrogens to form a tetrahedral intermediate.
      ii. H^- is expelled and adds to another molecule of aldehyde.
      iii. The result is a disproportionation reaction, in which one molecule of aldehyde is oxidized and a second molecule is reduced.
   c. The Cannizzaro reaction isn't synthetically useful, but it resembles the mode of action of the enzyme cofactor NADH.
9. Conjugate addition to α,*β*-unsaturated aldehydes and ketones (Section 19.13).
   a. Steps in conjugate addition.
      i. Because the double bond of an α,*β*-unsaturated aldehyde/ketone is conjugated with the carbonyl group, addition can occur at the *β* position, which is an electrophilic site.
      ii. Protonation of the α carbon of the enolate intermediate results in a product having a carbonyl group and a nucleophile with a 1,3 relationship.
   b. Conjugate addition of amines.
      i. Primary and secondary amines add to α,β-unsaturated aldehydes and ketones.
      ii. The conjugate addition product is often formed exclusively.
   c. Conjugate addition of water.
      i. Water can add to yield β-hydroxy aldehydes and ketones.
      ii. Conjugate addition of water also occurs in living systems.
   d. Conjugate addition of organocopper reagents.
      i. Conjugate addition of organocopper reagents (R_2CuLi) alkylates the double bond of α,β-unsaturated ketones.
      ii. This type of addition doesn't occur with other organometallic reagents.

iii. Primary, secondary, tertiary, aryl, and alkenyl groups can be added.
iv. The mechanism may involve conjugate addition of the diorganocopper anion, followed by transfer of an –R group.

III. Spectroscopy of aldehydes and ketones (Section 19.14).
A. IR spectroscopy.
1. The C=O absorption of aldehydes and ketones occurs in the range 1660–1770 cm^{-1}.
a. The exact position of absorption can be used to distinguish between an aldehyde and a ketone.
b. The position of absorption also gives information about other structural features, such as unsaturation and angle strain.
c. The absorption values are constant from one compound to another.
2. Aldehydes also show absorptions in the range 2720–2820 cm^{-1}.
B. NMR spectroscopy.
1. ^{1}H NMR spectroscopy.
a. Aldehyde protons absorb near 10 δ, and show spin-spin coupling with protons on the adjacent carbon.
b. Hydrogens on the carbon next to a carbonyl group absorb near 2.0–2.3 δ.
i. Methyl ketone protons absorb at 2.1 δ.
2. ^{13}C NMR spectroscopy.
a. The carbonyl-group carbons absorb in the range 190–215 δ.
b. These absorptions characterize aldehydes and ketones.
c. Unsaturation lowers the value of δ.
C. Mass spectrometry.
1. Some aliphatic aldehydes and ketones undergo McLafferty rearrangement.
a. A hydrogen on the γ carbon is transferred to the carbonyl oxygen, the bond between the α carbon and the β carbon is broken, and a neutral alkene fragment is produced.
b. The remaining cation radical is detected.
2. Alpha cleavage.
a. The bond between the carbonyl group and the α carbon is cleaved.
b. The products are a neutral radical and an acyl cation, which is detected.

Chapter 20 – Carboxylic Acids and Nitriles

Chapter Outline

I. General information about carboxylic acids and nitriles (Sections 20.1–20.4).
   A. Naming carboxylic acids (Section 20.1).
      1. Acyclic carboxylic acids are named by replacing the *-e* of the corresponding alkane by *-oic acid*. The $–CO_2H$ carbon is numbered C1.
      2. Compounds that have a carboxylic acid bonded to a ring are named by using the suffix *-carboxylic acid*. The $–CO_2H$ carbon is bonded to C1.
      3. Many carboxylic acids have historical, nonsystematic names.
   B. Naming nitriles.
      1. Simple nitriles are named by adding *-nitrile* to the alkane name.
         a. The nitrile carbon is C1.
      2. More complex nitriles are named as derivatives of carboxylic acids by replacing *-oic acid* by *-onitrile* or by replacing *-carboxylic acid* by *-carbonitrile*.
         a. The nitrile carbon is bonded to C1.
   C. Structure and properties of carboxylic acids (Section 20.2).
      1. The carbonyl group of carboxylic acids is sp^2-hybridized and planar.
      2. Carboxylic acids are strongly associated because of hydrogen bonding, and their boiling points are elevated.
   D. Carboxylic acid acidity (Sections 20.2–20.4).
      1. Dissociation of carboxylic acids (Section 20.2).
         a. Carboxylic acids react with bases to form salts that can be water-soluble.
         b. Carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ and carboxylate anions.
            i. The K_a values for carboxylic acids are near 10^{-5}, making them weaker than mineral acids but stronger than alcohols.
         c. The relative strength of carboxylic acids is due to resonance stabilization of the carboxylate anion.
            i. Both carbon–oxygen bonds of carboxylate anions are the same length.
            ii. The bond length is intermediate between single and double bonds.
      2. Biological acids: the Henderson–Hasselbalch equation (Section 20.3).
         a. The pH of biological fluids (7.3) determines the ratio of dissociated (A^-) to nondissociated (HA) forms of carboxylic acids.
         b. This ratio can be calculated by using the Henderson–Hasselbalch equation.

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

         c. At physiological pH, carboxylic acids are almost completely dissociated.
      3. Substituent effects on acidity (Section 20.4).
         a. Carboxylic acids differ in acid strength.
            i. Electron-withdrawing groups stabilize carboxylate anions and increase acidity.
            ii. Electron-donating groups decrease acidity.

b. These inductive effects decrease with increasing distance from the carboxyl group.
c. Substituent effects in substituted benzoic acids.
i. Groups that are deactivating in electrophilic aromatic substitution reactions increase the acidity of substituted benzoic acids.
ii. The acidity of benzoic acids can be used to predict electrophilic reactivity.

II. Carboxylic acids (Sections 20.5–20.6).
A. Preparation of carboxylic acids (Section 20.5).
1. Methods already studied.
a. Oxidation of substituted alkylbenzenes.
b. Oxidation of primary alcohols and aldehydes.
2. Nitrile hydrolysis.
a. Nitriles can be hydrolyzed by strong aqueous acids or bases to yield carboxylic acids.
b. The sequence nitrile formation → nitrile hydrolysis can be used to prepare a carboxylic acid from a halide.
c. This method is generally limited to compounds that can undergo S_N2 reactions.
3. Carboxylation of Grignard reagents.
a. A Grignard reagent can be treated with CO_2 and protonated to form a carboxylic acid.
b. This method is limited to compounds that don't have other functional groups that interfere with Grignard reagent formation.
B. Reactions of carboxylic acids (Section 20.6).
1. Carboxylic acids can undergo some reactions typical of alcohols and ketones.
2. Other types of reactions of carboxylic acids:
a. Alpha substitution.
b. Deprotonation.
c. Nucleophilic acyl substitution.
d. Reduction.

III. Chemistry of nitriles (Section 20.7).
A. Preparation of nitriles.
1. Nitriles can be prepared by S_N2 reaction of ^{-}CN with a primary alkyl halide.
2. They can also be prepared by $SOCl_2$ dehydration of primary amides.
B. Reactions of nitriles.
1. Nitriles can react with nucleophiles via sp^2-hybridized imine intermediates.
2. Aqueous base hydrolyzes nitriles to carboxylates, plus an amine/ammonia.
a. The reaction involves formation of a hydroxy imine that isomerizes to an amide, which is further hydrolyzed to the carboxylate.
b. Milder conditions allow isolation of the amide.
3. Nitriles can also be hydrolyzed to carboxylic acids under acidic conditions.
4. $LiAlH_4$ reduces nitriles to primary amines.
5. Reaction of a nitrile with Grignard reagents yields a ketone.

IV. Spectroscopy of carboxylic acids and nitriles (Section 20.8).
   A. Infrared spectroscopy.
      1. The O–H absorption occurs at 2500–3300 cm^{-1} that is broad and easy to identify.
      2. The C=O absorption occurs at 1710–1760 cm^{-1}.
         a. The position of this absorption depends on whether the acid is free (1760 cm^{-1}) or associated (1710 cm^{-1}).
      3. Nitriles have an intense absorption at 2250 cm^{-1} that readily identifies them.
   B. NMR spectroscopy.
      1. ^{13}C NMR spectroscopy.
         a. Carboxylic acids absorb between 165–185 δ.
         b. Saturated acids absorb downfield from *α*,*β*-unsaturated acids.
         c. Nitrile carbons absorb in the range 115–130 δ.
      2. ^{1}H NMR spectroscopy.
         a. The carboxylic acid proton absorbs as a singlet at around 12 δ.

Chapter 21 – Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution Reactions

Chapter Outline

I. Introduction to carboxylic acid derivatives (Sections 21.1–21.2).
  A. Naming carboxylic acid derivatives (Section 21.1).
    1. Acid halides.
      a. The acyl group is named first, followed by the halide.
      b. For acyclic compounds, the *-ic acid* or *-oic acid* of the carboxylic acid name is replaced by *-oyl,* followed by the name of the halide.
        i. There are eight exceptions, in which *-yl* is used
      c. For cyclic compounds, the *-carboxylic acid* ending is replaced by *-carbonyl,* followed by the name of the halide.
    2. Acid anhydrides.
      a. Symmetrical anhydrides are named by replacing *acid* by *anhydride.*
      b. Unsymmetrical anhydrides are named by citing the two acids alphabetically, followed by *anhydride*.
    3. Esters.
      a. Esters are named by first identifying the alkyl group and then the carboxylic acid group, replacing *-oic acid* by *-ate*.
    4. Amides.
      a. Amides with an unsubstituted –NH2 group are named by replacing *-oic acid* or *–ic acid* by *-amide* or by replacing *-carboxylic acid* with *-carboxamide*.
      b. If nitrogen is substituted, the nitrogen substituents are named in alphabetical order, and an *N*- is put before each.
    5. Thioesters.
      a. Thioesters are named like esters, using the prefix *thio*- before the name of the ester derivative of the carboxylic acid.
    6. Acyl phosphates.
      a. Acyl phosphates are named by citing the acyl group and adding the word *phosphate*.
  B. Nucleophilic acyl substitution reactions (Section 21.2).
    1. Mechanism of nucleophilic acyl substitution reactions.
      a. A nucleophile adds to the polar carbonyl group.
      b. The tetrahedral intermediate eliminates one of the two substituents originally bonded to it, resulting in a net substitution reaction.
      c. Reactions of carboxylic acid derivatives take this course because one of the groups bonded to the carbonyl carbon is a good leaving group.
      d. The addition step is usually rate-limiting.
    2. Relative reactivity of carboxylic acid derivatives.
      a. Both steric and electronic factors determine relative reactivity.
        i. Steric hindrance in the acyl group decreases reactivity.
        ii. More polarized acid derivatives are more reactive than less polarized derivatives.

iii. The effect of substituents on reactivity is similar to their effect on electrophilic aromatic substitution reactions.

b. It is possible to convert more reactive derivatives into less reactive derivatives.

i. In order of decreasing reactivity: acid chlorides > acid anhydrides > thioesters > esters > amides.

ii. Only esters, amides, and carboxylic acids are found in nature.

3. Kinds of reactions of carboxylic acid derivatives:

a. Hydrolysis: reaction with water to yield a carboxylic acid.

b. Alcoholysis: reaction with an alcohol to yield an ester.

c. Aminolysis: reaction with ammonia or an amine to yield an amide.

d. Reduction.

i. Reaction with a hydride reducing agent yields an aldehyde or an alcohol.

ii. Amides are reduced to yield amines.

e. Reaction with an organometallic reagent to yield a ketone or alcohol.

II. Reactions of carboxylic acids and their derivatives (Section 21.3–21.9).

A. Reactions of carboxylic acids (Section 21.3).

1. Carboxylic acids can be converted to acid chlorides by reaction with $SOCl_2$.

a. The reaction proceeds through a chlorosulfite intermediate.

2. Acid anhydrides are usually formed by heating the corresponding carboxylic acid to remove 1 equivalent of water.

3. Conversion to esters.

a. Conversion can be affected by the S_N2 reaction of a carboxylate and an alkyl halide.

b. Esters can be produced by the acid-catalyzed reaction of a carboxylic acid and an alcohol.

i. This reaction is known as a Fischer esterification.

ii. Mineral acid makes the acyl carbon more reactive toward the alcohol.

iii. All steps are reversible.

iv. The reaction can be driven to completion by removing water or by using a large excess of alcohol.

v. Isotopic labelling studies have confirmed the mechanism.

4. Conversion to amides.

a. Amides are difficult to form from carboxylic acids because amines convert carboxylic acids to carboxylate salts that no longer have electrophilic carbons.

b. The reagent DCC (dicyclohexylcarbodiimide) can be used; it is used in the laboratory to form peptide bonds.

5. Reduction of carboxylic acids.

a. Reduction to alcohols can be achieved by use of $LiAlH_4$.

b. BH_3 in THF easily reduces carboxylic acids to alcohols.

B. Chemistry of carboxylic acid halides (Section 21.4).

1. Carboxylic acid halides are prepared by reacting carboxylic acids with either $SOCl_2$ or PBr_3 to form the corresponding acyl halide.

2. Acyl halides are very reactive.
    a. Most reactions occur by nucleophilic acyl substitution mechanisms.
3. Hydrolysis.
    a. Acyl halides react with water to form carboxylic acids.
    b. The reaction mixture usually contains a base to scavenge the HCl produced.
4. Anhydride formation.
    a. Acid halides react with carboxylate ions to form anhydrides.
5. Alcoholysis.
    a. Acyl halides react with alcohols to form esters.
    b. Base is usually added to scavenge the HCl produced.
    c. Primary alcohols are more reactive than secondary or tertiary alcohols.
        i. It's often possible to esterify a less hindered alcohol selectively.
6. Aminolysis.
    a. Acid chlorides react with ammonia and amines to give amides.
    b. Either two equivalents of ammonia/amine must be used, or NaOH must be present, in order to scavenge HCl.
7. Reduction.
    a. $LiAlH_4$ reduces acid halides to alcohols.
        i. The reaction is a substitution of H^- for Cl^- that proceeds through an intermediate aldehyde, which is then reduced.
8. Reaction with organometallic reagents.
    a. Reaction with Grignard reagents yields tertiary alcohols and proceeds through an intermediate ketone.
    b. Reaction with diorganocopper (Gilman) reagents yields ketones.
        i. Reaction occurs by a radical mechanism.
        ii. This reaction doesn't occur with other carboxylic acid derivatives.

C. Chemistry of carboxylic acid anhydrides (Section 21.5).
1. Acid anhydrides can be prepared by reaction of carboxylate anions with acid chlorides.
    a. Both symmetrical and unsymmetrical anhydrides can be prepared by this route.
2. Acid anhydrides react more slowly than acid chlorides.
    a. Acid anhydrides undergo most of the same reactions as acid chlorides.
    b. Acetic anhydride is often used to prepare acetate esters.
    c. In reactions of acid anhydrides, half of the molecule is unused, making anhydrides inefficient to use.

D. Chemistry of esters (Section 21.6).
1. Esters can be prepared by:
    a. S_N2 reaction of a carboxylate anion with an alkyl halide.
    b. Fischer esterification.
    c. Reaction of an acid chloride with an alcohol, in the presence of base.

2. Esters are less reactive than acid halides and anhydrides but undergo the same types of reactions.
3. Hydrolysis.
    a. Basic hydrolysis (saponification) occurs through a nucleophilic acyl substitution mechanism.
        i. Loss of alkoxide ion yields a carboxylic acid which is deprotonated to give a carboxylate anion.
        ii. Isotope-labelling studies confirm this mechanism.
    b. Acidic hydrolysis can occur by more than one mechanism.
        i. The usual route is by the reverse of Fischer esterification.
4. Aminolysis.
    a. Esters can be converted to amides by heating with ammonia/amines, but it's easier to start with an acid chloride.
5. Reduction.
    a. $LiAlH_4$ reduces esters to primary alcohols by a route similar to that described for acid chlorides.
    b. If DIBAH at –78 °C is used, reduction yields an aldehyde.
6. Reaction with Grignard reagents.
    a. Esters react twice with Grignard reagents to produce tertiary alcohols containing two identical substituents.

E. Chemistry of amides (Section 21.7).
1. Amides are prepared by the reaction of acid chlorides with ammonia/amines.
2. Hydrolysis.
    a. Hydrolysis occurs under more severe conditions than needed for hydrolysis of other acid derivatives.
    b. Acid hydrolysis occurs by addition of water to a protonated amide, followed by loss of ammonia or an amine.
    c. Basic hydrolysis occurs by attack of HO^-, followed by loss of $^-NH_2$.
3. Reduction.
    a. $LiAlH_4$ reduces amides to amines.

F. Chemistry of thiol and acyl phosphates (Section 21.8).
1. Nature uses thiol esters and acyl phosphates in nucleophilic acyl substitution reactions because they are intermediate in reactivity between acid anhydrides and esters.
2. Acetyl CoA is used as an acylating agent.

III. Polyamides and polyesters (Section 21.9).

A. Formation of polyesters and polyamides.
1. When a diamine and a diacid chloride react, a polyamide is formed.
2. When a diacid and a diol react, a polyester is formed.
3. These polymers are called step-growth polymers because each bond is formed independently of the others.

B. Types of polymers.
   1. Nylons are the most common polyamides.
   2. The most common polyester, Dacron, is formed from dimethylterephthalate and ethylene glycol.
   3. Biodegradable polymers are usually polyesters of naturally-occurring hydroxycarboxylic acids.

IV. Spectroscopy of carboxylic acid derivatives and nitriles (Section 21.10).
   A. Infrared spectroscopy.
      1. All of these compounds have characteristic carbonyl absorptions that help identify them; these are listed in Table 21.3.
   B. NMR spectroscopy is of limited usefulness in distinguishing carboxylic acid derivatives.
      1. Hydrogens next to carbonyl groups absorb at around 2.1 δ in a ^{1}H NMR spectrum, but this absorption can't be used to distinguish among carboxylic acid derivatives.
      2. Carbonyl carbons absorb in the range 160–180 δ, but, again, this absorption can't be used to distinguish among carboxylic acid derivatives.

Review Unit 8: Carbonyl Compounds 1 - Reaction at the Carbonyl Group

Major Topics Covered (with vocabulary):

Aldehydes and ketones:
-carbaldehyde acyl group acetyl group formyl group benzoyl group hydrate

Reactions of aldehydes and ketones:
nucleophilic addition reaction gem diol cyanohydrin imine enamine carbinolamine 2,4-dinitrophenylhydrazone Wolff-Kishner reaction acetal hemiacetal Wittig reaction ylide betaine Cannizzaro reaction conjugate addition α,β-unsaturated carbonyl compound

Carboxylic acids and their derivatives:
carboxylation carboxylic acid derivative acid halide acid anhydride amide ester nitrile–carbonitrile

Reactions of carboxylic acids and their derivatives:
nucleophilic acyl substitution hydrolysis alcoholysis aminolysis lactone Fischer esterification reaction saponification DIBAH lactam thiol ester acyl phosphate polyamide polyester step-growth polymer chain-growth polymer nylon

Types of Problems:

After studying these chapters, you should be able to:

- Name and draw aldehydes, ketones, carboxylic acids and their derivatives.
- Prepare all of these compounds.
- Explain the reactivity difference between aldehydes and ketones and between carboxylic acids and all their derivatives.
- Calculate dissociation constants of carboxylic acids, and predict the relative acidities of substituted carboxylic acids.
- Formulate mechanisms for reactions related to the reactions we have studied.
- Predict the products of the reactions for all functional groups we have studied.
- Use spectroscopic techniques to identify these compounds.
- Draw representative segments of step-growth polymers.

Points to Remember:

* In all of these reactions, a nucleophile adds to a positively polarized carbonyl carbon to form a tetrahedral intermediate. There are three possible fates for the tetrahedral intermediate: (1) The intermediate can be protonated, as occurs in Grignard reactions, reductions, and cyanohydrin formation. (2) The intermediate can lose water (or $^{-}$OH), as happens in imine and enamine formation. (3) The intermediate can lose a leaving group, as occurs in most reactions of carboxylic acid derivatives.

* Many of the reactions in these three chapters require acid or base catalysis. An acid catalyst protonates the carbonyl oxygen, making the carbonyl carbon more reactive toward nucleophiles, and/or protonates the tetrahedral intermediate, making loss of a leaving group easier. A base catalyst deprotonates the nucleophile, making it more nucleophilic. The pH optimum for these reactions is a compromise between the two needs.

* Here are a few reminders for drawing the mechanisms of nucleophilic addition and substitution reactions. (1) When a reaction is acid-catalyzed, none of the intermediates are negatively charged, although, occasionally, a few may be neutral. Check your mechanisms for charge balance. (2) Make sure you have drawn arrows correctly. The point of the arrow shows the new location of the electron pair at the base of the arrow. (3) In a polar reaction, two arrows never point at each other. If you find two arrows pointing at each other, redraw the mechanism.

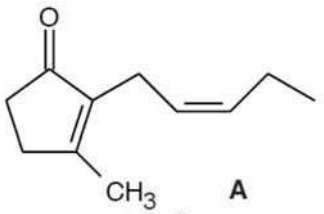
* Reactions of acyl halides are almost always carried out with an equivalent of base present. The base is used to scavenge the protons produced when a nucleophile adds to an acyl halide. If base were not present, hydrogen ions would protonate the nucleophile and make it unreactive.

* The products of acidic cleavage of an amide are a carboxylic acid and a protonated amine. The products of basic cleavage of an amide are a carboxylate anion and an amine.

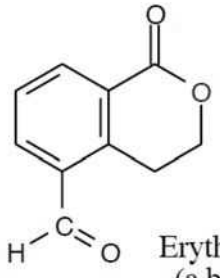
* In some of the mechanisms shown in the answers, a series of protonations and deprotonations occur. These steps convert the initial tetrahedral intermediate into an intermediate that more easily loses a leaving group. These deprotonations may be brought about by the solvent, by the conjugate base of the catalyst, by other molecules of the carbonyl compound, or may occur intramolecularly. When a "proton transfer" is shown as part of a mechanism, the base that removes the proton has often not been shown. However, it is implied that the proton transfer is assisted by a base: the proton doesn't fly off the intermediate unassisted.

* The most useful spectroscopic information for identifying carbonyl compounds comes from IR spectroscopy and ^{13}C NMR spectroscopy. Carbonyl groups have distinctive identifying absorptions in their infrared spectra. ^{13}C NMR is also useful for identifying aldehydes, ketones, and nitriles, although other groups are harder to distinguish. The ^{1}H NMR absorptions of aldehydes and carboxylic acids are also significant. Look at mass spectra for McLafferty rearrangements and alpha-cleavage reactions of aldehydes and ketones.

Self-Test:



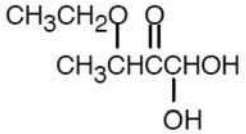
A
Jasmone
(used in perfumery)



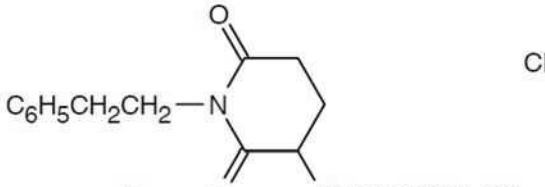
B
Erythrocentaurin
(a bitter tonic)

Predict the products of the reaction of **A** with: (a) $LiAlH_4$, then H_3O^+; (b) C_6H_5MgBr, then H_3O^+; (c) $(CH_3)_2NH$, H_3O^+; (d) CH_3OH, H^+ catalyst; (e) $(C_6H_5)_3P^+–CH_2–$; (f) 1 equiv. $CH_3CH_2NH_2$, H_3O^+. How would you reduce **A** to yield a saturated hydrocarbon? Where would you expect the carbonyl absorption of **A** to occur in its IR spectrum?

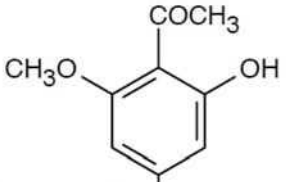
Predict the products of **B** with the reagents (a) – (d) above. What product(s) would be formed if **B** was treated with Br_2, $FeBr_3$? Where do the carbonyl absorptions occur in the IR spectrum of **B**? Describe the ^{13}C NMR spectrum of **B**.



C
Kethoxal
(antiviral)



D
Julocrotine



E
Xanthoxylin

Kethoxal (**C**) exists in solution as an equilibrium mixture. With what compound is it in equilibrium. Why does the equilibrium lie on the side of kethoxal?

Identify the carboxylic acid derivatives present in **D**. Show the products of treatment of **D** with (a) ^-OH, H_2O and (b) $LiAlH_4$, then H_2O.

Name **E**. Describe the IR spectrum and ^1H NMR spectrum of **E**.

Multiple Choice:

1. In which of the following nucleophilic addition reactions does the equilibrium lie on the side of the products?
   (a) Propanal + HCN
   (b) Acetone + H_2O
   (c) Acetaldehyde + HBr
   (d) 2,2,4,4-Tetramethyl-3-pentanone + HCN

2. Which alcohol can be formed by three different combinations of carbonyl compound + Grignard reagent?
   (a) 2-Butanol
   (b) 3-Methyl-3-hexanol
   (c) Triphenylmethanol
   (d) 1-Phenylethanol

3. A nitrile can be converted to all of the following except:
   (a) an aldehyde
   (b) an amide
   (c) an amine
   (d) A nitrile can be converted to all of the above compounds.

4. Which of the following *p*- substituted benzoic acids is the least acidic?
   (a) $CH_3COC_6H_5CO_2H$
   (b) $CH_3OC_6H_5CO_2H$
   (c) $BrC_6H_5CO_2H$
   (d) $NCC_6H_5CO_2H$

5. A carboxylic acid can be reduced by all of the following except:
   (a) $LiAlH_4$, then H_3O^+
   (b) BH_3, THF, then H_3O^+
   (c) $NaBH_4$, then H_3O^+
   (d) All of these reagents can reduce a carboxylic acid.

6. Which of the following carboxylic acids can be formed by both Grignard carboxylation and by nitrile hydrolysis?
   (a) Phenylacetic acid
   (b) Benzoic acid
   (c) Trimethylacetic acid
   (d) 3-Butynoic acid

7. Acid anhydrides are used mainly for:
   (a) synthesizing carboxylic acids
   (b) forming alcohols
   (c) introducing acetyl groups
   (d) forming aldehydes

8. A ketone is formed from an acid halide by reaction with:
   (a) DIBAH
   (b) $LiAlH_4$
   (c) RMgBr
   (d) $(CH_3CH_2)CuLi$

9. From which carboxylic acid derivative can you form a ketone as the product of a Grignard reaction?
   (a) acid chloride
   (b) ester
   (c) nitrile
   (d) amide

10. An infrared absorption at 1650 cm^{-1} indicates the presence of:
   (a) aromatic acid chloride
   (b) *N,N*-disubstituted amide
   (c) α,β-unsaturated ketone
   (d) aromatic ester

Chapter 22 – Carbonyl Alpha-Substitution Reactions

Chapter Outline

I. Keto–enol tautomerism (Section 22.1).
   A. Nature of tautomerism.
      1. Carbonyl compounds with hydrogens bonded to their α carbons equilibrate with their corresponding enols.
      2. This rapid equilibration is called tautomerism, and the individual isomers are tautomers.
      3. Unlike resonance forms, tautomers are isomers.
      4. Despite the fact that very little of the enol isomer is present at room temperature, enols are very important because they are reactive.
   B. Mechanism of tautomerism.
      1. In acid-catalyzed enolization, the carbonyl carbon is protonated to form an intermediate that can lose a hydrogen from its α carbon to yield a neutral enol.
      2. In base-catalyzed enol formation, an acid-base reaction occurs between a base and an α hydrogen.
         a. The resultant enolate ion is protonated to yield an enol.
         b. Protonation can occur either on carbon or on oxygen.
         c. Only hydrogens on the α positions of carbonyl compounds are acidic.

II. Enols (Sections 22.2–22.4).
   A. α-substitution reactions (Section 22.2).
      1. The electron-rich double bonds of enols cause them to behave as nucleophiles.
         a. The electron-donating enol –OH groups make enols more reactive than alkenes.
      2. When an enol reacts with an electrophile, the initial adduct loses –H from oxygen to give an α-substituted carbonyl compound.
   B. Reactions of enols (Sections 22.3–22.4).
      1. Alpha halogenation of aldehydes and ketones (Section 22.3).
         a. Aldehydes and ketones can be halogenated at their α positions by reaction of X_2 in acidic solution.
         b. The reaction proceeds by acid-catalyzed formation of an enol intermediate.
         c. Halogen isn't involved in the rate-limiting step: the rate doesn't depend on the identity of the halogen, but only on [carbonyl] and $[H^+]$.
         d. α-Bromo ketones are useful in syntheses because they can be dehydrobrominated by base treatment to form α,β-unsaturated ketones.
      2. Alpha-bromination of carboxylic acids (Section 22.4).
         a. In the Hell–Volhard–Zelinskii (HVZ) reaction, a mixture of Br_2 and PBr_3 can be used to brominate carboxylic acids in the α position.
         b. The initially formed acid bromide reacts with Br_2 to form an α-bromo acid bromide, which is hydrolyzed by water to give the α-bromo carboxylic acid.
         c. The reaction proceeds through an acid bromide enol.

III. Enolates (Sections 22.5–22.7).
   A. Enolate ion formation (Section 22.5).

1. Hydrogens alpha to a carbonyl group are weakly acidic.
    a. This acidity is due to overlap of a filled *p* orbital with the carbonyl group *p* orbitals, allowing the carbonyl group to stabilize the negative charge by resonance.
    b. The two resonance forms aren't equivalent: the form with the negative charge on oxygen is of lower energy.
2. Strong bases are needed for enolate ion formation.
    a. Alkoxide ions are often too weak to use in enolate formation.
    b. Lithium diisopropylamide can be used to form the enolates of many different carbonyl compounds.
3. When a hydrogen is flanked by two carbonyl groups, it is much more acidic.
    a. Both carbonyl groups can stabilize the negative charge.

B. Reactivity of enolate ions (Section 22.6).
1. Enolates are more useful than enols for two reasons:
    a. Unlike enols, stable solutions of enolates are easily prepared.
    b. Enolates are more reactive than enols because they are more nucleophilic.
2. Enolates can react either at carbon or at oxygen.
    a. Reaction at carbon yields an α-substituted carbonyl compound.
    b. Reaction at oxygen yields an enol derivative.

C. Reactions of enolate ions (Sections 22.6–22.7).
1. Base-promoted α-halogenation.
    a. Base-promoted halogenation of aldehydes and ketones proceeds readily because each halogen added makes the carbonyl compound more reactive.
    b. Consequently, polyhalogenated compounds are usually produced.
    c. This reaction is only useful with methyl ketones, which form HCX_3 when reacted with halogens.
    d. This reaction is known as the haloform reaction.
        i. The HCX_3 is a solid that can be identified.
        ii. The last step of the reaction involves a carbanion leaving group.
2. Alkylation reactions of enolates (Section 22.7).
    a. General features.
        i. Alkylations are useful because they form a new C–C bond.
        ii. Alkylations have the same limitations as S_N2 reactions; the alkyl groups must be methyl, primary, allylic or benzylic.
    b. The malonic ester synthesis.
        i. The malonic ester synthesis is used for preparing a carboxylic acid from a halide while lengthening the chain by two carbon atoms.
        ii. Diethyl malonate is useful because its enolate is easily prepared by a reaction with sodium ethoxide.
        iii. Since diethyl malonate has two acidic hydrogens, two alkylations can take place.

iv. Heating in aqueous HCl causes hydrolysis and decarboxylation of the alkylated malonate to yield a substituted monocarboxylic acid.
(a) Decarboxylations are common only to β-keto acids and malonic acids.
v. Cycloalkanecarboxylic acids can also be prepared.

c. The acetoacetic ester synthesis.
i. The acetoacetic ester synthesis is used for converting an alkyl halide to a methyl ketone, while lengthening the carbon chain by 3 atoms.
ii. As with malonic ester, acetoacetic ester has two acidic hydrogens which are flanked by a ketone and an ester, and two alkylations can take place.
iii. Heating in aqueous HCl hydrolyzes the ester and decarboxylates the acid to yield the ketone.
iv. Most β-keto esters can undergo this type of reaction.

d. Direct alkylation of ketones, esters, and nitriles.
i. LDA in a nonprotic solvent can be used to convert the above compounds to their enolates.
ii. Alkylation of an unsymmetrical ketone leads to a mixture of products, but the major product is alkylated at the less hindered position.

Chapter 23 – Carbonyl Condensation Reactions

Chapter Outline

I. The aldol reaction (Sections 23.1–23.6).
   A. Characteristics of the aldol reaction (Sections 23.1).
      1. The aldol condensation is a base-catalyzed dimerization of two aldehydes or ketones.
      2. The reaction can occur between two components that have α hydrogens.
      3. One component (the nucleophilic donor) is converted to its enolate and undergoes an α-substitution reaction.
      4. The other component (the electrophilic acceptor) undergoes nucleophilic addition.
      5. For simple aldehydes, the equilibrium favors the products, but for other aldehydes and ketones, the equilibrium favors the reactants.
      6. Carbonyl condensation reactions require only a catalytic amount of base (Section 23.2).
         a. Alpha-substitution reactions, on the other hand, use one equivalent of base.
   B. Dehydration of aldol products (Section 23.3).
      1. Aldol products are easily dehydrated to yield α,β-unsaturated aldehydes and ketones.
         a. Dehydration is catalyzed by both acid and base.
         b. Reaction conditions for dehydration are only slightly more severe than for condensation.
         c. Often, dehydration products are isolated directly from condensation reactions.
      2. Conjugated enones are more stable than nonconjugated enones.
      3. Removal of the water byproduct drives the aldol equilibrium towards product formation.
   C. Aldol products (Sections 23.4–23.5).
      1. Using aldol reactions in synthesis (Section 23.4).
         a. Obvious aldol products are:
            i. α,β-Unsaturated aldehydes/ketones.
            ii. β-Hydroxy aldehydes/ketones.
         b. Often, it's possible to work backwards from a compound that doesn't seem to resemble an aldol product and recognize aldol components.
      2. Mixed aldol reactions (Section 23.5).
         a. If two similar aldehydes/ketones react under aldol conditions, four products may be formed – two self-condensation products and two mixed products.
         b. A single product can be formed from two different components:
            i. If one carbonyl component has no α-hydrogens.
            ii. If one carbonyl compound is much more acidic than the other.
   D. Intramolecular aldol condensations (Section 23.6).
      1. Treatment of certain dicarbonyl compounds with base can lead to cyclic products.
      2. A mixture of cyclic products may result, but the more strain-free ring usually predominates.
II. The Claisen condensation (Sections 23.7–23.9).
   A. Features of the Claisen condensation (Section 23.7).

1. Treatment of an ester with one equivalent of base yields a β-keto ester.
2. The reaction is reversible and has a mechanism similar to that of the aldol reaction.
3. A major difference from the aldol condensation is the expulsion of an alkoxide ion from the tetrahedral intermediate of the initial Claisen adduct.
4. Because the product is often acidic, one equivalent of base is needed; addition of this amount of base drives the reaction to completion.
5. Addition of acid yields the final product.

B. Mixed Claisen condensations (Section 23.8).
1. Mixed Claisen condensations of two different esters can succeed if one component has no α hydrogens.
2. Mixed Claisen condensations between a ketone and an ester with no α hydrogens are also successful.

C. Intramolecular Claisen condensations: the Dieckmann cyclization (Section 23.9).
1. The Dieckmann cyclization is used to form cyclic β-keto esters.
   a. 1,6-Diesters form 5-membered rings.
   b. 1,7-Diesters form 6-membered rings.
2. The mechanism is similar to the Claisen condensation mechanism.
3. The product β-keto esters can be further alkylated.
   a. This is a good route to 2-substituted cyclopentanones and cyclohexanones.

III. Other carbonyl condensation reactions (Sections 23.10–23.13).

A. The Michael reaction (Section 23.10).
1. The Michael reaction is the conjugate addition of an enolate to an α,β-unsaturated carbonyl compound.
   a. The highest-yielding reactions occur between stable enolates and unhindered α,β-unsaturated carbonyl compounds.
2. Stable enolates are Michael donors, and α,β-unsaturated compounds are Michael acceptors.

B. The Stork reaction (Section 23.11).
1. A ketone that has been converted to an enamine can act as a Michael donor in a reaction known as the Stork reaction.
2. The sequence of reactions in the Stork reaction:
   a. Enamine formation from a ketone.
   b. Michael-type addition to an α,β-unsaturated carbonyl compound.
   c. Enamine hydrolysis back to a ketone.
3. This sequence is equivalent to the Michael addition of a ketone to an α,β-unsaturated carbonyl compound and yields a 1,5 diketone product.

C. The Robinson annulation reaction (Section 23.12).
1. The Robinson annulation reaction combines a Michael reaction with an intramolecular aldol condensation to synthesize substituted ring systems.
2. The components are a nucleophilic donor, such as a β-keto ester, and an α,β-unsaturated ketone acceptor.

3. The intermediate 1,5-diketone undergoes an intramolecular aldol condensation to yield a cyclohexenone.

D. Biological carbonyl condensation reactions (Section 23.13).
   1. Many biomolecules are synthesized by carbonyl condensation reactions.
   2. The enzyme aldolase catalyzes the addition of a ketone enolate to an aldehyde.
      a. This mixed aldol reaction is successful because of the selectivity of enzyme catalysis.
   3. Acetyl CoA is the major building block for the synthesis of biomolecules.
      a. Acetyl CoA can act as an electrophilic acceptor by being attacked at its carbonyl group.
      b. Acetyl CoA can act as a nucleophilic donor by loss of its acidic α hydrogen.

Chapter 24 – Amines and Heterocycles

Chapter Outline

I. Facts about amines (Section 24.1–24.5).
   A. Naming amines (Section 24.1).
      1. Amines are classified as primary (RNH_2), secondary (R_2NH), tertiary (R_3N) or quaternary ammonium salts (R_4N^+).
      2. Primary amines are named in several ways:
         a. For simple amines, the suffix *-amine* is added to the name of the alkyl substituent.
         b. The suffix *-amine* can replace the final *-ane* of the parent compound.
         c. For more complicated amines, the $–NH_2$ group is an amino substituent on the parent molecule.
      3. Secondary and tertiary amines:
         a. Symmetrical amines are named by using the prefixes *di-* and *tri-* before the name of the alkyl group.
         b. Unsymmetrical amines are named as *N*-substituted primary amines.
            i. The largest group is the parent.
      4. The simplest arylamine is aniline.
      5. Heterocyclic amines (nitrogen is part of a ring) have specific parent names.
         a. The nitrogens receive the lowest possible numbers.
   B. Structure and properties of amines (Section 24.2).
      1. The three amine bonds and the lone pair occupy the corners of a tetrahedron.
      2. An amine with three different substituents is chiral.
         a. The two amine enantiomers interconvert by pyramidal inversion.
         b. This process is rapid at room temperature.
      3. Amines with fewer than 5 carbons are water-soluble and form hydrogen bonds.
      4. Amines have higher boiling points than alkanes of similar molecular weight.
      5. Amines smell nasty!
   C. Basicity of amines (Sections 24.3–24.5).
      1. The lone pair of electrons makes amines both nucleophilic and basic (Section 24.3).
      2. The basicity constant K_b is the measure of the equilibrium of an amine with water.
         a. The larger the value of K_b (smaller pK_b), the stronger the base.
      3. More often, K_a is used to describe amine basicity.
         a. K_a is the dissociation constant of the conjugate acid of an amine.
         b. $pK_a + pK_b = 14$ (for aqueous media).
         c. The smaller the value of K_a (larger pK_a), the stronger the base.
      4. Base strength.
         a. Primary, secondary, and tertiary alkylamines have similar basicities.
         b. Arylamines and heterocyclic amines are less basic than alkylamines.
            i. The sp^2 electrons of the pyridine lone pair are less available for bonding.
            ii. The pyrrole lone pair electrons are part of the aromatic ring π system.
         c. Amides are nonbasic.

   d. Amine basicity can be used as a means of separating amines from a mixture.
      i. An amine can be converted to its salt, extracted from an organic solution with water, neutralized, and re-extracted with an organic solvent.
   e. Some amines are very weak acids.
      i. LDA is formed from diisopropylamine and acts as a strong base.
5. Basicity of substituted arylamines (Section 24.4).
   a. Arylamines are less basic than alkylamines for two reasons:
      i. Arylamine lone-pair electrons are delocalized over the aromatic ring and are less available for bonding.
      ii. Arylamines lose resonance stabilization when they are protonated.
   b. Electron-donating substituents increase arylamine basicity.
6. Biological amines and the Henderson–Hasselbalch equation (Section 24.5).
   a. The Henderson–Hasselbalch equation (Section 20.3) can be used to calculate the percent of protonated vs. unprotonated amines.
   b. At physiological pH (7.3), most amines exist in the protonated form.

II. Synthesis of amines (Section 24.6).

A. Reduction of amides, nitriles and nitro groups.
   1. S_N2 displacement with ^-CN, followed by reduction, turns a primary alkyl halide into an amine with one more carbon atom.
   2. Amide reduction converts an amide or nitrile into an amine with the same number of carbons.
   3. Arylamines can be prepared by reducing aromatic nitro compounds.
      a. Catalytic hydrogenation can be used if no other interfering groups are present.
      b. $SnCl_2$ can also be used.

B. S_N2 reactions of alkyl halides.
   1. It is possible to alkylate ammonia or an amine with RX.
      a. Unfortunately, it is difficult to avoid overalkylation.
   2. An alternative is displacement of ^-X by azide, followed by reduction.
   3. Also, reaction of an alkyl halide with phthalimide anion, followed by hydrolysis, gives a primary amine (Gabriel amine synthesis).

C. Reductive amination of aldehydes and ketones.
   1. Treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent yields an amine.
      a. The reaction proceeds through an imine, which is reduced.
      b. $NaBH_4$ or $NaBH(OAc)_3$ are the reducing agents most commonly used.
      c. Tertiary amines do not undergo reductive amination.

D. Rearrangements.
   1. Hofmann rearrangement.
      a. When a primary amide is treated with Br_2 and base, CO_2 is eliminated, and an amine with one less carbon is produced.
      b. The mechanism is lengthy and proceeds through an isocyanate intermediate.

c. In the rearrangement step, the –R group migrates at the same time as the Br^- ion leaves.

2. The Curtius rearrangement starts with an acyl azide and occurs by a mechanism very similar to that of the Hofmann rearrangement.

III. Reactions of amines (Sections 24.7–24.9).

A. Alkylation and acylation (Section 24.7).

1. Alkylation of primary and secondary amines occurs but is hard to control.
2. Primary and secondary amines can also be acylated.

B. Hofmann elimination.

1. Alkylamines can be converted to alkenes by the Hofmann elimination reaction.
   a. The amine is treated with an excess of methyl iodide to form a quaternary ammonium salt.
   b. Treatment of the quaternary salt with Ag_2O, followed by heat, gives the alkene.
2. The elimination is an E2 reaction.
3. The less substituted double bond is formed because of the bulk of the leaving group.
4. The reaction was formerly used for structure determination and is rarely used today.

C. Reactions of arylamines (Section 24.8).

1. Electrophilic aromatic substitution.
   a. Electrophilic aromatic substitutions are usually carried out on *N*-acetylated amines, rather than on unprotected amines.
      i. Amino groups are *o,p*-activators, and polysubstitution sometimes occurs.
      ii. Friedel–Crafts reactions don't take place with unprotected amines.
   b. Aromatic amines are acetylated by treatment with acetic anhydride.
   c. The *N*-acetylated amines are *o,p*-directing activators, but are less reactive than unprotected amines.
   d. Synthesis of sulfa drugs was achieved by electrophilic aromatic substitution reactions on *N*-protected aromatic amines.
2. The Sandmeyer reaction.
   a. When a primary arylamine is treated with HNO_2 (nitrous acid), an arenediazonium salt is formed.
   b. The diazonio group of arenediazonium salts can be replaced by many types of nucleophiles in radical substitution reactions.
      i. Aryl halides are formed by treatment with CuCl, CuBr or NaI.
      ii. Aryl nitriles are formed by treatment with CuCN.
      iii. Phenols are formed by treatment with Cu_2O and $Cu(NO_3)_2$.
      iv. H_3PO_2 (hypophosphorous acid) converts a diazonium salt to an arene, and is used when a substituent must be introduced and then removed.
      v. These reactions occur through radical, rather than polar, pathways.

3. Diazonium coupling reactions.
    a. Diazonium salts can react with activated aromatic rings to form colored azo compounds.
    b. The reaction is an electrophilic aromatic substitution that usually occurs at the *p*-position of the activated ring.
    c. The extended π system of the azo ring system makes these compounds brightly colored due to absorption in the visible region of the spectrum.

IV. Heterocyclic amines (Section 24.9).

A. Pyrrole, imidazole and other 5-membered ring unsaturated heterocycles.
    1. Structures of pyrrole, furan and thiophene.
        a. All are aromatic because they have six π electrons in a cyclic conjugated system.
        b. Pyrrole is nonbasic because all five nitrogen electrons are used in bonding.
        c. The carbon atoms in pyrrole are electron-rich and are reactive toward electrophiles.
    2. Electrophilic substitution reactions.
        a. All three compounds undergo electrophilic aromatic substitution reactions readily.
        b. Halogenation, nitration, sulfonation and Friedel–Crafts alkylation can take place if reaction conditions are modified.
        c. Reaction occurs at the 2-position because the reaction intermediate from attack at that position is more stable.
    3. Imidazole and thiazole.
        a. A nitrogen in each of these compounds is basic.

B. Pyridine and pyrimidine.
    1. Structure of pyridine.
        a. Pyridine is the nitrogen-containing analog of benzene.
        b. The nitrogen lone pair isn't part of the π electron system .
        c. Pyridine is a stronger base than pyrrole but a weaker base than alkylamines.
    2. Electrophilic substitution of pyridine.
        a. Electrophilic substitutions take place with great difficulty.
            i. The pyridine ring is electron-poor due to the electron-withdrawing inductive effect of nitrogen.
            ii. Acid-base complexation between nitrogen and an electrophile puts a positive charge on the ring.
    3. Pyrimidine has two nitrogens in the 1 and 3 positions of a six-membered ring.
        a. Pyrimidine is less basic than pyridine.

C. Polycyclic heterocycles.
    1. The reactivity of polycyclic heterocyclic compounds is related to the type of heteroatom and to the size of the ring.
    2. Indole has a pyrrole-like nitrogen and undergoes electrophilic aromatic substitutions in the heterocyclic ring.
    3. Purines have four nitrogens (three pyridine-like, and one pyrrole-like) in a fused-ring structure.

V. Spectroscopy of amines (Section 24.10).
   A. IR spectroscopy.
      1. Primary and secondary amines absorb in the region 3300–3500 cm^{-1}.
         a. Primary amines show a pair of bands at 3350 cm^{-1} and 3450 cm^{-1}.
         b. Secondary amines show a single band at 3350 cm^{-1}.
         c. These absorptions are sharper and less intense than alcohol absorptions, which also occur in this range.
   B. NMR spectroscopy.
      1. ^{1}H NMR.
         a. Amine protons are hard to identify because they appear as broad signals.
         b. Exchange with D_2O causes the amine signal to disappear and allows identification.
         c. Hydrogens on the carbon next to nitrogen are somewhat deshielded.
      2. ^{13}C NMR.
         a. Carbons next to nitrogen are slightly deshielded.
   C. Mass spectrometry.
      1. The nitrogen rule: A compound with an odd number of nitrogens has an odd-numbered molecular weight (and molecular ion).
      2. Alkylamines undergo α-cleavage and show peaks that correspond to both possible modes of cleavage.

Review Unit 9: Carbonyl Compounds II – Reaction at the α Carbon; Amines

Major Topics Covered (with vocabulary):

Carbonyl α-substitution reactions:
α-substitution reaction tautomerism tautomer enolate ion Hell-Volhard-Zelinskii reaction *β*-diketone *β*-keto eater malonic ester synthesis acetoacetic eater synthesis LDA

Carbonyl condensation reactions:
carbonyl condensation reactions aldol reaction enone mixed aldol reaction Claisen condensation reaction Dieckmann cyclization Michael reaction Michael acceptor Michael donor Stork enamine reaction Robinson annulation reaction

Amines:
primary, secondary, tertiary amine quaternary ammonium salt arylamine heterocyclic amine pyramidal inversion K_b azide synthesis Gabriel amine synthesis reductive amination Hofmann rearrangement Curtius rearrangement Hofmann elimination reaction arenediazonium salt diazotization Sandmeyer reaction azo compound diazonium coupling reaction pyrrole thiophene furan pyridine fused-ring heterocycle pyrimidine purine nitrogen rule

Types of Problems:

After studying these chapters, you should be able to:

- Draw keto-enol tautomers of carbonyl compounds, identify acidic hydrogens, and draw the resonance forms of enolates.
- Formulate the mechanisms of acid- and base-catalyzed enolization and of other *α*-substitution reactions.
- Predict the products of *α*-substitution reactions.
- Use *α*-substitution reactions in synthesis.
- Predict the products of carbonyl condensation reactions.
- Formulate the mechanisms of carbonyl condensation reactions.
- Use carbonyl condensation reactions in synthesis.
- Name and draw amines, and classify amines as primary, secondary, tertiary , quaternary, arylamines, or heterocyclic amines.
- Predict the basicity of alkylamines, arylamines and heterocyclic amines.
- Synthesize alkylamines and arylamines by several routes.
- Predict the products of reactions involving alkylamines and arylamines.
- Use diazonium salts in reactions involving arylamines, including diazo coupling reactions.
- Draw orbital pictures of heterocycles and explain their acid-base properties.
- Explain orientation and reactivity in heterocyclic reactions, and predict the products of reactions involving heterocycles.
- Propose mechanisms for reactions involving alkylamines, arylamines, and heterocycles.
- Identify amines by spectroscopic techniques.

Points to Remember:

* It is unusual to think of a carbonyl compound as an acid, but the protons α to a carbonyl group can be removed by a strong base. Protons α to two carbonyl groups are even more acidic: in some cases, acidity approaches that of phenols. This acidity is the basis for α-substitution reactions of compounds having carbonyl groups. Abstraction by base of an α proton produces a resonance-stabilized enolate anion that can be used in alkylations involving alkyl halides and tosylates.

* Alkylation of an unsymmetrical LDA-generated enolate generally occurs at the less hindered α carbon.

* When you need to synthesize a β-hydroxy ketone or aldehyde or an α,β-unsaturated ketone or aldehyde, use an aldol reaction. When you need to synthesize a β-diketone or β-keto ester, use a Claisen reaction. When you need to synthesize a 1,5-dicarbonyl compound, use a Michael reaction. The Robinson annulation is used to synthesize polycyclic molecules by a combination of a Michael reaction with an aldol condensation.

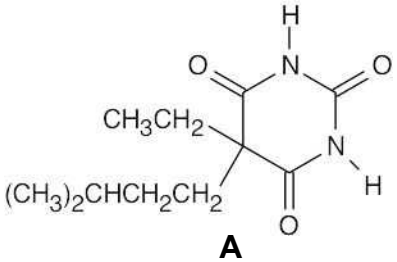
* In many of the mechanisms in this group of chapters, the steps involving proton transfer are not explicitly shown. The proton transfers occur between the proton and the conjugate base with the most favorable pK of those present in the solution. These steps have been omitted at times to simplify the mechanisms.

* In the Claisen condensation, the enolate of the β-dicarbonyl compound is treated with H_3O^+ to yield the neutral product.

* For an amine, the larger the value of pK_a of its ammonium ion, the stronger the base. The smaller the value of pK_b of the amine, the stronger the base.

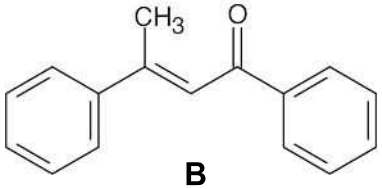
* The Sandmeyer reaction allows the synthesis of substituted benzenes that can't be formed by electrophilic aromatic substitution reactions. These reactions succeed because N_2 is a very good leaving group.

Self-Test:



A

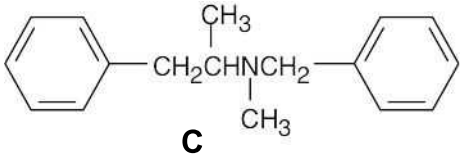
Pentymal
(a sedative)



B

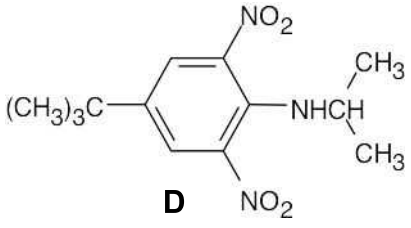
Dypnone
(sunscreen)

The six-membered ring in **A** is formed by the cyclization of two difunctional compounds. What are they? What type of reaction occurs to form the ring? The two alkyl groups are introduced into one of the difunctional compounds prior to cyclization. What type of reaction is occurring, and how is it carried out? What type of reaction occurs in the formation of Dypnone (**B**)? Why might **B** be effective as a sunscreen?



C

Benzphetamine
(an appetite suppressant)



D

Butralin
(an herbicide)

What type of amine is **C**? Do you expect it to be more or less basic than ammonia? Than aniline? What product do you expect from Hofmann elimination of **C**? What significant absorptions might be seen in the IR spectrum of **C**? What information can be obtained from the mass spectrum? Plan a synthesis of **D** from benzene.

Multiple Choice:

1. Which of the following compounds has four acidic hydrogens?
   (a) 2-Pentanone
   (b) 3-Pentanone
   (c) Acetophenone
   (d) Phenylacetone

2. In which of the following reactions is an enol, rather than an enolate, the reacting species?
   (a) acetoacetic acid synthesis
   (b) malonic ester synthesis
   (c) LDA alkylation
   (d) Hell–Volhard–Zelinskii reaction

3. Cyclobutanecarboxylic acid is probably the product of a:
   (a) malonic ester synthesis
   (b) acetoacetic ester synthesis
   (c) LDA alkylation
   (d) Hell–Volhard–Zelinskii reaction

4. An LDA alkylation can be used to alkylate all of the following, except:
   (a) aldehydes
   (b) ketones
   (c) esters
   (d) nitriles

5. If you want to carry out a carbonyl condensation, and you don't want to form α-substitution product, you should:
   (a) lower the temperature
   (b) use one equivalent of base
   (c) use a catalytic amount of base
   (d) use a polar aprotic solvent

6. Which reaction forms a cyclohexenone?
   (a) Dieckmann cyclization
   (b) Michael reaction
   (c) Claisen condensation
   (d) intramolecular aldol condensation

7. All of the following molecules are good Michael donors except:
   (a) Ethyl acetoacetate
   (b) Nitroethylene
   (c) Malonic ester
   (d) Ethyl 2-oxocyclohexanecarboxylate

8. The ammonium ion of which of the following amines has the smallest value of pK_a?
   (a) Methylamine
   (b) Trimethylamine
   (c) Aniline
   (d) *p*-Bromoaniline

9. All of the following methods of amine synthesis are limited to primary amines, except:
   (a) Curtius rearrangement
   (b) reductive amination
   (c) Hofmann rearrangement
   (d) azide synthesis

10. To form an azo compound, an aryldiazonium salt should react with:
   (a) CuCN
   (b) benzene
   (c) nitrobenzene
   (d) phenol

Chapter 25 – Biomolecules: Carbohydrates

Chapter Outline

I. Classification of carbohydrates (Section 25.1).
   A. Simple *vs*. complex:
      1. Simple carbohydrates (monosaccharides) can't be hydrolyzed to smaller units.
      2. Complex carbohydrates are made up of two or more simple sugars linked together.
         a. A disaccharide is composed of two monosaccharides.
         b. A polysaccharide is composed of three or more monosaccharides.
   B. Aldoses *vs.* ketoses:
      1. A monosaccharide with an aldehyde carbonyl group is an aldose.
      2. A monosaccharide with a ketone carbonyl group is a ketose.
   C. *Tri-, tetr-, pent-*, etc. indicate the number of carbons in the monosaccharide.

II. Monosaccharides (Sections 25.2–25.7).
   A. Configurations of monosaccharides (Section 25.2–25.4).
      1. Fischer projections (Section 25.2).
         a. Each chirality center of a monosaccharide is represented by a pair of crossed lines.
            i. The horizontal line represents bonds coming out of the page.
            ii. The vertical line represents bonds going into the page.
         b. Allowed manipulations of Fischer projections:
            i. A Fischer projection can be rotated on the page by 180°, but not by 90° or 270°.
            ii. Holding one group steady, the other three groups can be rotated clockwise or counterclockwise.
         c. Rules for assigning *R,S* configurations.
            i. Assign priorities to the substituents in the usual way (Section 5.5).
            ii. Perform one of the two allowed motions to place the lowest priority group at the top of the Fischer projection.
            iii. Determine the direction of rotation of the arrow that travels from group 1 to group 2 to group 3, and assign *R* or *S* configuration.
         d. Carbohydrates with more than one chirality center are shown by stacking the centers on top of each other.
            i. The carbonyl carbon is placed at or near the top of the Fischer projection.
      2. D,L sugars (Section 25.3).
         a. (*R*)-Glyceraldehyde is also known as D-glyceraldehyde.
         b. In D sugars, the –OH group farthest from the carbonyl group points to the right in a Fischer projection.
            i. Most naturally-occurring sugars are D sugars.
         c. In L sugars, the –OH group farthest from the carbonyl group points to the left in a Fischer projection.
         d. D,L designations refer only to the configuration farthest from the carbonyl carbon and are unrelated to the direction of rotation of plane-polarized light.

3. Configurations of aldoses (Section 25.4).
    a. There are 4 aldotetroses – D and L erythrose and threose.
    b. There are 4 D,L pairs of aldopentoses: ribose, arabinose, xylose and lyxose.
    c. There are 8 D,L pairs of aldohexoses : allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.
    d. A scheme for drawing and memorizing the D-aldohexoses:
        i. Draw all –OH groups at C5 pointing to the right.
        ii. Draw the first four –OH groups at C4 pointing to the right and the second four pointing to the left.
        iii. Alternate –OH groups at C3: two right, two left, two right, two left.
        iv. Alternate –OH groups at C2: right, left, etc.
        v. Use the mnemonic "All altruists gladly make gum in gallon tanks" to assign names.

B. Cyclic structures of monosaccharides (Section 25.5).
1. Hemiacetal formation.
    a. Monosaccharides are in equilibrium with their internal hemiacetals.
        i. Glucose exists primarily as a six-membered pyranose ring, formed between the –OH group at C5 and the aldehyde group at C1.
        ii. Fructose exists primarily as a five-membered furanose ring.
    b. Structure of pyranose rings.
        i. Pyranose rings have a chair-like geometry.
        ii. The hemiacetal oxygen is at the right rear for D-sugars.
        iii. An –OH group on the right in a Fischer projection is on the bottom face in a pyranose ring, and an –OH group on the left is on the top face.
        iv. For D sugars, the $–CH_2OH$ group is on the top.
2. Mutarotation.
    a. When a monosaccharide cyclizes, a new chirality center is generated.
        i. The two diastereomers are anomers.
        ii. The form with the anomeric –OH group trans to the $–CH_2OH$ group is the α anomer (minor anomer).
        iii. The form with the anomeric –OH group cis to the $–CH_2OH$ group is the β anomer (major anomer).
    b. When a solution of either pure anomer is dissolved in water, the optical rotation of the solution reaches a constant value.
        i. This process is called mutarotation.
        ii. Mutarotation is due to the reversible opening and recyclizing of the hemiacetal ring and is catalyzed by both acid and base.

C. Reactions of monosaccharides (Section 25.6).
1. Ester and ether formation.
    a. Esterification occurs by treatment with an acid anhydride or acid chloride.
    b. Ethers are formed by treatment with methyl iodide and Ag_2O.
    c. Ester and ether derivatives are crystalline and easy to purify.

2. Glycoside formation.
    a. Treatment of a hemiacetal with an alcohol and an acid catalyst yields an acetal.
        i. Acetals aren't in equilibrium with an open-chain form and do exhibit mutarotation.
        ii. Aqueous acid reconverts the acetal to a monosaccharide.
    b. These acetals, called glycosides, occur in nature.
    c. Glycosides are named by first citing the alkyl group and then replacing the *–ose* suffix of the sugar with *-oside*.
    d. The laboratory synthesis of glycosides is achieved by the Koenigs–Knorr reaction.
        i. Treatment of the acetylpyranose with HBr, followed by treatment with the appropriate alcohol and Ag_2O, gives the acetylglycoside.
        ii. Both anomers give the same product.
        iii. The reaction involves neighboring-group participation by acetate.
3. Phosphorylation.
    a. Monosaccharides can be phosphorylated by ATP to form a glycosyl monophosphate.
    b. The resulting glycosyl monophosphate can react with a second nucleoside triphosphate to produce a glycosyl diphosphate.
    c. This product can react with a lipid or a protein to form a glycoconjugate.
4. Reduction of monosaccharides.
    a. Reaction of a monosaccharide with $NaBH_4$ yields an alditol (a polyalcohol).
5. Oxidation of monosaccharides.
    a. Several mild reagents can oxidize the carbonyl group to a carboxylic acid (aldonic acid).
        i. In the laboratory, aqueous Br_2 is used to oxidize aldoses (not ketoses).
        ii. Historically, Tollens reagent, Fehling's reagent and Benedict's reagent have served as tests for reducing sugars.
        iii. All aldoses and some ketoses are reducing sugars, but glycosides are nonreducing.
    b. The more powerful oxidizing agent, dilute HNO_3, oxidizes aldoses to dicarboxylic acids (aldaric acids).
    c. Enzymes can oxidize the $–CH_2OH$ of a monosaccharide (with oxidizing the aldehyde) to form a uronic acid.
6. Chain-lengthening: the Kiliani–Fischer synthesis.
    a. In the Kiliani–Fischer synthesis, an aldehyde group becomes C2 of a chain-lengthened monosaccharide and the added carbon is the new C1.
    b. The reaction involves cyanohydrin formation, reduction and hydrolysis.
    c. The products are two diastereomeric aldoses that differ in configuration at C2.
7. Chain-shortening: the Wohl degradation.
    a. The Wohl degradation shortens an aldose by one carbon.

b. The reaction involves treatment of the aldose with hydroxylamine, dehydration and loss of HCN from the resulting cyanohydrin.

D. Eight essential monosaccharides (Section 25.7).
1. Glucose, galactose, mannose and xylose are aldoses.
2. Fucose is a deoxy sugar.
3. *N*-Acetylglucosamine and *N*-acetylgalactosamine are amino sugars.
4. *N*-Acetylneuraminic acid is the parent compound of the sialic acids.
5. All of the essential monosaccharides arise from glucose.

III. Other carbohydrates (Sections 25.8–25.11).

A. Disaccharides (Section 25.8).
1. Cellobiose and maltose.
a. Cellobiose and maltose contain a 1 → 4-glycosidic acetal bond between two glucose monosaccharide units.
b. Maltose consists of two glucopyranose units joined by a 1→ 4-α-glycosidic bond.
c. Cellobiose consists of two glucopyranose units joined by a 1→ 4-β-glycosidic bond.
d. Both maltose and cellobiose are reducing sugars and exhibit mutarotation.
e. Humans can't digest cellobiose but can digest maltose.
2. Lactose.
a. Lactose consists of a unit of galactose joined by a β-glycosidic bond between C1 and C4 of a glucose unit.
b. Lactose is a reducing sugar found in milk.
3. Sucrose.
a. Sucrose is a disaccharide that yields glucose and fructose on hydrolysis.
i. Sucrose is called "invert sugar" because the sign of rotation changes when sucrose is hydrolyzed.
ii. Sucrose is one of the most abundant pure organic chemicals in the world.
b. The two monosaccharides are joined by a glycosidic link between C1 of glucose and C2 of fructose.
c. Sucrose isn't a reducing sugar and doesn't exhibit mutarotation.

B. Polysaccharides and their synthesis (Section 25.9).
1. Polysaccharides have a reducing end and undergo mutarotation, but aren't considered to be reducing sugars because of their size.
2. Important polysaccharides.
a. Cellulose.
i. Cellulose consists of thousands of D-glucose units linked by 1→ 4-β-glycosidic bonds.
ii. In nature, cellulose is used as structural material.
b. Starch.
i. Starch consists of thousands of D-glucose units linked by 1→ 4-α-glycosidic bonds.

ii. Starch can be separated into amylose (water-soluble) and amylopectin (water-insoluble) fractions.
(a) Amylopectin contains 1→ 6-α-glycosidic branches.
iii. Starch is digested in the mouth by glycosidase enzymes, which only cleave α-glycosidic bonds.

c. Glycogen.
i. Glycogen is an energy-storage polysaccharide.
ii. Glycogen contains both 1→ 4- and 1→ 6-links.

3. An outline of the glycan assembly method of polysaccharide synthesis.
a. A glycal (a monosaccharide with a C1–C2 double bond) is protected at C6 by formation of a silyl ether and at C3–C4 by formation of a cyclic carbonate ester.
b. The protected glycal is epoxidized.
c. Treatment of the glycal epoxide (in the presence of $ZnCl_2$) with a second glycal having a free C6 hydroxyl group forms a disaccharide.
d. The process can be repeated.

C. Other important carbohydrates (Section 25.10).
1. Deoxy sugars have an –OH group missing and are components of nucleic acids.
2. In amino sugars, an –OH is replaced by a $–NH_2$.
a. Amino sugars are found in chitin and in antibiotics.

D. Cell surface carbohydrates and influenza viruses (Section 25.11).
1. Polysaccharides are involved in cell surface recognition.
a. Polysaccharide markers on the surface of influenza viruses are variants of two types of glycoproteins –hemagglutinin (H – Type 5 or Type 1), and neuraminidase (N – Type 1).
b. Infection occurs when a virus binds to a receptor on a target cell and is engulfed by the cell.
c. New viral particles are produced, pass out of the cell, and are held to surface receptors.
d. A neuraminidase enzyme cleaves the receptor–virus bond, allowing the virus to invade a new cell.
2. Antiviral vaccines block the neuraminidase enzyme, limiting the spread of the virus.

Chapter 26 – Biomolecules: Amino Acids, Peptides, and Proteins

Chapter Outline

I. Amino acids (Sections 26.1–26.3).
  A. Structure of amino acids (Section 26.1).
    1. Amino acids exist in solution as zwitterions.
      a. Zwitterions are internal salts and have many of the properties associated with salts.
        i. They have large dipole moments.
        ii. They are soluble in water.
        iii. They are crystalline and high-melting.
      b. Zwitterions can act either as acids or as bases.
        i. The $-CO_2^-$ group acts as a base.
        ii. The ammonium group acts an acid.
    2. All natural amino acids are α-amino acids: the amino group and the carboxylic acid group are bonded to the same carbon.
    3. All but one (proline) of the 20 common amino acids are primary amines.
    4. All of the amino acids are represented by both a three-letter code and a one-letter code. See Table 26.1.
    5. All amino acids except glycine are chiral.
      a. Only one enantiomer (L) of each pair is naturally-occurring.
      b. In Fischer projections, the carboxylic acid is at the top, and the amino group points to the left.
      c. α-Amino acids are referred to as L-amino acids.
    6. Side chains can be neutral, acidic, or basic.
      a. Fifteen of the 20 amino acids are neutral.
      b. Two (aspartic acid and glutamic acid) are acidic.
        i. At pH = 7.3, their side chains exist as carboxylate ions.
      c. Three (lysine, arginine and histidine) are basic.
        i. At pH = 7.3, the side chains of lysine and arginine exist as ammonium ions.
        ii. Histidine is not quite basic enough to be protonated at pH = 7.3.
        iii. The double-bonded nitrogen in the histidine ring is basic.
      d. Cysteine and tyrosine are weakly acidic but are classified as neutral.
    7. Humans are able to synthesize only 11 of the 20 amino acids.
      a. These are nonessential amino acids.
      b. The 9 essential amino acids must be supplied in the diet.
  B. The Henderson–Hasselbalch equation and isoelectric points (Section 26.2).
    1. The Henderson–Hasselbalch equation.
      a. If we know the values of pH and pK_a, we can calculate the percentages of protonated, neutral and deprotonated forms of an amino acid.
      b. If we do these calculations at several pH values, we can construct a titration curve for each amino acid.

2. The isoelectric point (p*I*) is the pH at which an amino acid exists as a neutral, dipolar zwitterion.
    a. p*I* is related to side chain structure.
        i. The 15 amino acids that are neutral have p*I* near neutrality.
        ii. The two acidic amino acids have p*I* at a lower pH.
        iii. The 3 basic amino acids have p*I* at a higher pH.
    b. For neutral amino acids, p*I* is the average of the two pK_a values.
    c. For acidic amino acids, p*I* is the average of the two lowest pK_a values.
    d. For basic amino acids, p*I* is the average of the two highest pK_a values.
    e. Proteins have an overall p*I*.
3. Electrophoresis allows the separation of amino acids by differences in their p*I*.
    a. A buffered solution of amino acids is placed on a paper or gel.
    b. Electrodes are connected to the solution, and current is applied.
    c. Negatively charged amino acids migrate to the positive electrode, and positively charged amino acids migrate to the negative electrode.
    d. Amino acids can be separated because the extent of migration depends on p*I*.

C. Synthesis of α-amino acids (Section 26.3).
1. The Hell–Volhard–Zelinskii method and the phthalimide method.
    a. An α-bromo acid is produced from a carboxylic acid by α-bromination.
    b. Displacement of –Br by ammonia gives the α-amino acid.
2. The amidomalonate synthesis.
    a. An alkyl halide reacts with the anion of diethyl amidomalonate.
    b. Hydrolysis of the adduct yields the α-amino acid.
3. Reductive amination.
    a. Reductive amination of an α-keto carboxylic acid gives an α-amino acid.
    b. This method is related to the biosynthetic pathway for synthesis of amino acids.
4. All of the methods listed above produce a racemic mixture of amino acids.

D. Enantioselective synthesis of amino acids.
1. Resolution of racemic mixtures:
    a. The mixture can react with a chiral reagent, followed by separation of the diastereomers and reconversion to amino acids.
    b. Enzymes selectively catalyze reactions that form one of the enantiomers, but not the other.
2. Enantioselective synthesis.
    a. Enantioselective hydrogenation of *Z*-enamido acids produces chiral α-amino acids.
    b. The most effective catalysts are complexes of rhodium (I), cyclooctadiene and a chiral diphosphine.

II. Peptides (Sections 26.4–26.8).
  A. Peptide structure (Section 26.4).
    1. Peptide bonds.
      a. A peptide is an amino acid polymer in which the amine group of one amino acid forms an amide bond with the carboxylic acid group of a second amino acid.
      b. The sequence of –N–CH–CO– is known as the backbone of the peptide or protein.
      c. Rotation about the amide bond is restricted.
    2. The N-terminal amino acid of the polypeptide is always drawn on the left.
    3. The C-terminal amino acid of the polypeptide is always drawn on the right.
    4. Peptide structure is described by using three-letter codes, or one-letter codes, for the individual amino acids, starting with the N-terminal amino acid on the left.
    5. Disulfide bonds.
      a. Two cysteines can form a disulfide bond (–S–S–).
      b. Disulfide bonds can link two polypeptides or introduce a loop within a polypeptide chain.
  B. Structure determination of peptides (Sections 26.5–26.6).
    1. Amino acid analysis (Section 26.5).
      a. Amino acid analysis provides the identity and amount of each amino acid present in a protein or peptide.
      b. First, all disulfide bonds are reduced and all peptide bonds are hydrolyzed.
      c. The mixture is placed on a chromatography column, and the residues are eluted.
        i. As each amino acid elutes, it undergoes reaction with ninhydrin, which produces a purple color that is detected and measured spectrophotometrically.
      d. Alternatively, the mixture can be analyzed by HPLC.
      e. Amino acid analysis is reproducible on properly maintained equipment; residues always elute at the same time, and only small sample sizes are needed.
    2. The Edman degradation (peptide sequencing) (Section 26.6).
      a. The Edman degradation removes one amino acid at a time from the $–NH_2$ end of a peptide.
        i. The peptide is treated with phenylisothiocyanate (PITC), which reacts with the amino-terminal residue.
        ii. The PITC derivative is split from the peptide.
        iii. The residue undergoes acid-catalyzed rearrangement to a PTH, which is identified chromatographically.
        iv. The shortened chain undergoes another round of Edman degradation.
      b. Since the Edman degradation can only be used on peptides containing fewer than 50 amino acids, a protein must be cleaved into smaller fragments.
        i. Partial acid hydrolysis is unselective and therefore is of limited usefulness.
        ii. The enzyme trypsin cleaves proteins at the carboxyl side of Arg and Lys residues.
        iii. The enzyme chymotrypsin cleaves proteins at the carboxyl side of Phe, Tyr and Trp residues.

c. The complete amino acid sequence of a protein results from determining the individual sequences of peptides and overlapping them.

C. Synthesis of peptides (Sections 26.7–26.8).
1. Laboratory synthesis of peptides (Section 26.7).
a. Groups that are not involved in peptide bond formation are protected.
i. Carboxyl groups are often protected as methyl or benzyl esters.
ii. Amino groups are protected as Boc or Fmoc derivatives.
b. The peptide bond is formed by coupling with DCC (dicyclohexylcarbodiimide).
c. The protecting groups are removed.
i. Boc groups are removed by brief treatment with trifluoroacetic acid.
ii. Fmoc groups are removed by treatment with base.
iii. Esters are removed by mild hydrolysis or by hydrogenolysis (benzyl).
2. Automated peptide synthesis – Merrifield solid-phase method (Section 26.8).
a. The carboxyl group of a Boc-protected amino acid is attached to a polystyrene resin by formation of an ester bond.
b. The resin is washed with trifluoroacetic acid, and the Boc group is removed.
c. A second Boc-protected amino acid is coupled to the first, and the resin is washed.
d. The cycle (deprotecting, coupling, washing) is repeated as many times as needed.
e. Finally, treatment with anhydrous HF removes the final Boc group and frees the polypeptide.
f. Robotic peptide synthesizers have improved yield and preparation time.

III. Proteins (Section 26.9).
A. Classification of proteins.
1. Fibrous proteins consist of long, filamentous polypeptide chains.
2. Globular proteins are compact and roughly spherical.
B. Protein structure.
1. Levels of protein structure.
a. Primary structure refers to the amino acid sequence of a protein.
b. Secondary structure refers to the organization of segments of the peptide backbone into a regular pattern, such as a helix or sheet.
c. Tertiary structure describes the overall three-dimensional shape of a protein.
d. Quaternary structure describes how protein subunits aggregate into a larger structure.
2. Examples of structural features.
a. α-Helix.
i. An α-helix is a right-handed coil; each turn of the coil contains 3.6 amino acids.
ii. The structure is stabilized by hydrogen bonds between amide N–H groups and C=O groups four residues away.

   b. *β*-Pleated sheet.
      i. In a *β*-pleated sheet, hydrogen bonds occur between residues in adjacent chains.
      ii. In a *β*-pleated sheet, the peptide chain is extended, rather than coiled.
   c. Tertiary structure.
      i. The nonpolar amino acid side chains congregate in the center of a protein to avoid water.
      ii. The polar side chain residues are on the surface, where they can take part in hydrogen bonding and salt bridge formation.
      iii. Other important features of tertiary structure are disulfide bridges and hydrogen bonds between amino acid side chains.
3. Denaturation of proteins.
   a. Modest changes in temperature and pH can disrupt a protein's tertiary structure.
      i. This process is known as denaturation.
      ii. Denaturation doesn't affect protein primary structure.
   b. Denaturation affects both physical and catalytic properties of proteins.
   c. Occasionally, spontaneous renaturation can occur.

C. Enzymes (Sections 26.10–26.11).
1. Description of enzymes and cofactors (Section 26.10).
   a. An enzyme is a substance (usually protein) that catalyzes a biochemical reaction.
   b. An enzyme is specific and usually catalyzes the reaction of only one substrate.
      i. Some enzymes, such as papain, can operate on a range of substrates.
   c. How enzymes function.
      i. Enzymes form an enzyme–substrate complex, within which the conversion to product takes place.
      ii. Enzymes accelerate the rate of reaction by lowering the energy of the transition state.
      iii. The rate constant for the conversion of E·S to E + P is the turnover number.
   d. Enzymes are grouped into 6 classes according to the reactions they catalyze.
      i. Oxidoreductases catalyze oxidations and reductions.
      ii. Transferases catalyze the transfer of a group from one substrate to another.
      iii. Hydrolases catalyze hydrolysis reactions.
      iv. Lyases catalyze the addition or loss of a small molecule to or from a substrate.
      v. Isomerases catalyze isomerizations.
      vi. Ligases catalyze bond formation between two molecules, often coupled with hydrolysis of ATP
   e. The name of an enzyme has two parts, ending with *-ase*.
      i. The first part identifies the substrate.
      ii. The second part identifies the enzyme's class.
   f. Most enzymes are globular proteins, and many consist of a protein portion (apoenzyme) and a cofactor.
      i. Cofactors may be small organic molecules (coenzymes) or inorganic ions.

   ii. Many coenzymes are derived from vitamins.
2. How enzymes work – citrate synthase (Section 26.11).
   a. Citrate synthase catalyzes the aldol-like addition of acetyl CoA to oxaloacetate to produce citrate.
   b. Functional groups in a cleft of the enzyme bind oxaloacetate.
   c. Functional groups in a second cleft bind acetyl CoA.
      i. The two reactants are now in close proximity.
   d. Two enzyme amino acid residues generate the enol of acetyl CoA.
   e. The enol undergoes nucleophilic addition to the ketone carbonyl group of oxaloacetate.
   f. Two enzyme amino acid residues deprotonate the enol and protonate the carbonyl oxygen.
   g. Water hydrolyzes the thiol ester, releasing citrate and CoA.

Review Unit 10: Biomolecules I – Carbohydrates, Amino Acids, Peptides

Major Topics Covered (with vocabulary):

Monosaccharides:
carbohydrate monosaccharide aldose ketose Fischer projection D, L sugars pyranose furanose anomer anomeric center α anomer β anomer mutarotation glycoside Koenigs- Knorr reaction aldonic acid alditol reducing sugar aldaric acid Kiliani-Fischer synthesis Wohl degradation fucose glucosamine galactosamine neuraminic acid

Other sugars:
disaccharide 1,4' link cellobiose maltose lactose sucrose polysaccharide cellulose amylose amylopectin glycogen glycal assembly method deoxy sugar amino sugar cell-surface carbohydrate hemagglutinin neuraminidase

Amino acids:
amino acid zwitterion amphoteric α-amino acid side chain isoelectric point (p*I*) electrophoresis Henderson-Hasselbalch equation amidomalonate synthesis reductive amination resolution enantioselective synthesis

Peptides:
residue backbone *N*-terminal amino acid C-terminal amino acid disulfide link amino acid analysis Edman degradation phenylthiohydantoin trypsin chymotrypsin peptide synthesis protection Boc derivative Fmoc derivative DCC Merrifield solid-phase technique

Proteins:
simple protein conjugated protein primary structure secondary structure tertiary structure quaternary structure α-helix β-pleated sheet salt bridge prosthetic group enzyme cofactor apoenzyme holoenzyme coenzyme vitamin isomerase hydrolase ligase lyase oxidoreductase transferase denaturation

Types of Problems:

After studying these chapters, you should be able to:

- Classify carbohydrates as aldoses, ketoses, D or L sugars, monosaccharides, or polysaccharides.
- Draw monosaccharides as Fischer projections or chair conformations.
- Predict the products of reactions of monosaccharides and disaccharides.
- Deduce the structures of monosaccharides and disaccharides.
- Formulate mechanisms for reactions involving carbohydrates.
- Identify the common amino acids and draw them with correct stereochemistry in dipolar form.
- Explain the acid-base behavior of amino acids.
- Synthesize amino acids.
- Draw the structure of simple peptides.
- Deduce the structure of peptides and proteins.
- Outline the synthesis of peptides.

– Explain the classification of proteins and the levels of structure of proteins.
– Draw structures of reaction products of amino acids and peptides.

Points to Remember:

* Aldohexoses, ketohexoses and aldopentoses can all exist in both pyranose forms and furanose forms.

* A reaction that produces the same functional group at both ends of a monosaccharide halves the number of possible stereoisomers of the monosaccharide.

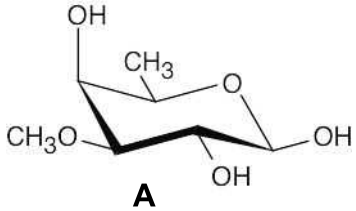
* The reaction conditions that form a glycoside are different from those that form a polyether, even though both reactions, technically, form –OR bonds.

* At physiological pH, the side chains of the amino acids aspartic acid and glutamic acid exist as anions, and the side chains of the amino acids lysine and arginine exist as cations. The imidazole ring of histidine exists as a mixture of protonated and neutral forms.

* Since the amide backbone of a protein is neutral and uncharged, the isoelectric point of a protein or peptide is determined by the relative numbers of acidic and basic amino acid residues present in the peptide.

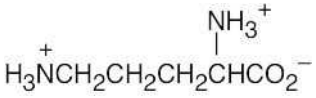
* In the Merrifield technique of protein synthesis, a protecting group isn't needed for the carboxyl group because it is attached to the polymer support.

Self-Test:



A

Digitalose
(hydrolysis product of digitoxigenin, a heart medication)



C

Ornithine

Digitalose (**A**) is related to which D-aldohexose? Provide a name for **A**, including the configuration at the anomeric carbon. Predict the products of the reaction of **A** with: (a) CH_3OH, H^+ catalyst; (b) CH_3I, Ag_2O.

Vicianose (**B**) is a disaccharide associated with a natural product found in seeds. Treatment of **B** with CH3I and Ag_2O, followed by hydrolysis, gives 2,3,4-tri-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-L-arabinose. What is the structure of **B**? Is **B** a reducing sugar?

Ornithine (**C**) is a nonstandard amino acid that occurs in metabolic processes. Which amino acid does it most closely resemble? Estimate pK_a values and p*I* for ornithine, and draw the

major form present at pH = 2, pH = 6, and pH = 11. If ornithine were a component of proteins, how would it affect the tertiary structure of a protein?

Tyr–Gly–Gly–Phe–Leu–Arg–Arg–Ile–Arg–Pro–Lys–Leu–Lys–Trp–Asp–Asn–Gln
Porcine Dynorphin (**D**)

Dynorphin (**D**) is a neuropeptide. Indicate the *N*-terminal end and the C-terminal end. Show the products of cleavage with: (a) trypsin; (b) chymotrypsin. Show the *N*-phenylthiohydantoin that results from treatment of **D** with phenyl isothiocyanate. Do you expect **D** to be an acidic, a neutral or a basic peptide? Kallidin (**E**) is a decapeptide that serves as a vasodilator. The composition of **E** is Arg_2 Gly Lys Phe_2 Pro_3 Ser. The C-terminal residue is Arg. Partial acid hydrolysis yields the following fragments: Pro–Gly–Phe, Lys–Arg–Pro, Pro–Phe–Arg, Pro–Pro–Gly, Phe–Ser–Pro What is the structure of **E**?

Multiple Choice:

1. The enantiomer of α-D-glucopyranose is:
   (a) β-D-Glucopyranose
   (b) α-L-Glucopyranose
   (c) β-L-Glucopyranose
   (d) none of these

2. All of the following reagents convert an aldose to an aldonic acid except:
   (a) dilute HNO_3
   (b) Fehling's reagent
   (c) Benedict's reagent
   (d) aqueous Br_2

3. Which two aldoses yield D-lyxose after Wohl degradation?
   (a) D-Glucose and D-Mannose
   (b) D-Erythrose and D-Threose
   (c) D-Galactose and D-Altrose
   (d) D-Galactose and D-Talose

4. All of the following disaccharides are reducing sugars except:
   (a) Cellobiose
   (b) Sucrose
   (c) Maltose
   (d) Lactose

5. Which of the following polysaccharides contains β-glycosidic bonds?
   (a) Amylose
   (b) Amylopectin
   (c) Cellulose
   (d) Glycogen

6. To find the p*I* of an acidic amino acid:
   (a) find the average of the two lowest pK_a values
   (b) find the average of the two highest pK_a values
   (c) find the average of all pK_a values
   (d) use the value of the pK_a of the side chain.

7. Which of the following techniques can synthesize a single enantiomer of an amino acid?
   (a) Hell–Volhard–Zelinskii reaction
   (b) reductive amination
   (c) amidomalonate synthesis
   (d) hydrogenation of a *Z* enamido acid

8. The purple product that results from the reaction of ninhydrin with an amino acid contains which group of the amino acid?
   (a) the amino group
   (b) the amino nitrogen
   (c) the carboxylic acid group
   (d) the side chain

9. Which of the following reagents is not used in peptide synthesis?
   (a) Phenylthiohydantoin
   (b) Di-*tert*-butyl dicarbonate
   (c) Benzyl alcohol
   (d) Dicyclohexylcarbodiimide

10. Which structural element is not present in myoglobin?
    (a) a prosthetic group
    (b) regions of α-helix
    (c) hydrophobic regions
    (d) quaternary structure

Chapter 27 – Biomolecules: Lipids

Chapter Outline

I. Esters (Sections 27.1–27.3).
  A. Waxes, fats and oils (Section 27.1).
    1. Waxes are esters of long-chain carboxylic acids with long-chain alcohols.
    2. Fats and oils are triacylglycerols.
      a. Hydrolysis of a fat yields glycerol and three fatty acids.
      b. The fatty acids need not be the same.
    3. Fatty acids.
      a. Fatty acids are even-numbered, unbranched long-chain (C_{12}–C_{20}) carboxylic acids.
      b. The most abundant saturated fatty acids are palmitic (C_{16}) and stearic (C_{18}) acids.
      c. The most abundant unsaturated fatty acids are oleic and linoleic acids (both C_{18}).
        i. Linoleic and arachidonic acids are polyunsaturated fatty acids.
      d. Unsaturated fatty acids are lower-melting than saturated fatty acids because the double bonds keep molecules from packing closely.
      e. The C=C bonds can be catalytically hydrogenated to produce higher-melting fats.
        i. Occasionally, cis–trans bond isomerization takes place.
  B. Soap (Section 27.2).
    1. Soap is a mixture of the sodium and potassium salts of fatty acids produced by hydrolysis (saponification) of animal fat.
    2. Soap acts as a cleanser because the two ends of a soap molecule are different.
      a. The hydrophilic carboxylate end dissolves in water.
      b. The hydrophobic hydrocarbon tails solubilize greasy dirt.
      c. In water, the hydrocarbon tails aggregate into spherical clusters (micelles), in which greasy dirt can accumulate in the interior.
    3. Soaps can form scum when a fatty acid anion encounters Mg^{2+} or Ca^{2+} cations.
      a. This problem is circumvented by detergents, which don't form insoluble metal salts.
  C. Phospholipids (Section 27.3).
    1. Glycerophospholipids.
      a. Glycerophospholipids consist of glycerol, two fatty acids (at C1 and C2 of glycerol), and a phosphate group bonded to an amino alcohol at C3 of glycerol.
    2. Sphingomyelins.
      a. Sphingomyelins have sphingosine or a related dihydroxyamine as their backbone.
      b. They are abundant in brain and nerve tissue.
    3. Phospholipids comprise the major lipids in cell membranes.
      a. The phospholipid molecules are organized into a lipid bilayer, which has polar groups on the inside and outside, and nonpolar tails in the middle.

II. Prostaglandins and other eicosanoids (Section 27.4).
  A. Prostaglandins.
    1. Prostaglandins are C_{20} lipids that contain a C_5 ring and two side chains.
    2. Prostaglandins are present in small amounts in all body tissues and fluids.
    3. Prostaglandins have many effects: they lower blood pressure, affect blood platelet aggregation, affect kidney function and stimulate uterine contractions.
  B. Eicosanoids.
    1. Prostaglandins, thromboxanes, and leukotrienes make up the eicosanoid class of compounds.
    2. Eicosanoids are named by their ring system, substitution pattern and number of double bonds.
    3. Eicosanoids are biosynthesized from arachidonic acid, which is synthesized from linoleic acid.
      a. The transformation from arachidonic acid is catalyzed by the cyclooxygenase (COX) enzyme.
      b. One form of the COX enzyme catalyzes the usual functions, and a second form produces additional prostaglandin as a result of inflammation.

III. Terpenoids (Section 27.5).
  A. Facts about terpenoids.
    1. Terpenoids occur as essential oils in lipid extractions of plants.
    2. Terpenoids are small organic molecules with diverse structures.
    3. All terpenoids are structurally related.
      a. Terpenoids arise from head-to-tail bonding of isopentenyl diphosphate units.
      b. Carbon 1 is the head, and carbon 4 is the tail.
    4. Terpenoids are classified by the number of five-carbon multiples they contain.
      a. Monoterpenoids are synthesized from two five-carbon units.
      b. Sesquiterpenoids are synthesized from three five-carbon units.
      c. Larger terpenoids occur in both animals and plants.
  B. Biosynthesis of terpenoids.
    1. Nature uses the isoprene equivalent isopentenyl diphosphate (IPP) to synthesize terpenoids.
      a. IPP is biosynthesized by two routes that depend on the organism and the structure of the terpenoid.
        i. The mevalonate pathway produces sesquiterpenoids and triterpenoids in most animals and plants.
        ii. The 1-deoxyxylulose 5-phosphate pathway gives monoterpenoids, diterpenoids, and tetraterpenoids.
    2. The mevalonate pathway.
      a. Acetyl CoA undergoes Claisen condensation to form acetoacetyl CoA.
      b. Another acetyl CoA undergoes an aldol-like addition to acetoacetyl CoA to give (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).

c. HMG CoA is reduced by NADPH, yielding (*R*)-mevalonate.
d. Phosphorylation and decarboxylation convert (*R*)-mevalonate to IPP.

3. Conversion of IPP to terpenoids.
a. IPP is isomerized to dimethylallyl diphosphate (DMAPP) by a carbocation pathway.
b. The C=C bond of IPP displaces the PPO^- group of dimethallyl diphosphate, to form geranyl diphosphate (GPP), the precursor to all monoterpenoids.
c. Geranyl diphosphate reacts with IPP to yield farnesyl diphosphate (FPP), the precursor to sesquiterpenoids.
d. GPP is isomerized and cyclizes on the way to yielding many monoterpenoids.

IV. Steroids (Sections 27.6–27.7).

A. Steroids are derived from the triterpenoid lanosterol.
1. Steroids have a tetracyclic fused ring system, whose rings are designated A, B, C, and D.
2. The three six-membered rings adopt chair geometry and do not undergo ring-flips.

B. Stereochemistry of steroids (Section 27.6).
1. Two cyclohexane rings can be joined either cis or trans.
a. In a trans-fused ring, the groups at the ring junction are trans.
b. In cis-fused rings, the groups at the ring junction are cis.
c. Cis ring fusions usually occur between rings A and B.
2. In both kinds of ring fusions, the angular methyl groups usually protrude above the rings.
3. Steroids with A–B trans fusions are more common.
4. Substituents can be either axial or equatorial.
a. Equatorial substituents are more favorable for steric reasons.

C. Types of steroid hormones.
1. Sex hormones.
a. Androgens (testosterone, androsterone) are male sex hormones.
b. Estrogens (estrone, estradiol) and progestins are female sex hormones.
2. Adrenocortical hormones.
a. Mineralocorticoids (aldosterone) regulate cellular Na^+ and K^+ balance.
b. Glucocorticoids (hydrocortisone) regulate glucose metabolism and control inflammation.
3. Synthetic steroids.
a. Oral contraceptives and anabolic steroids are examples of synthetic steroids.

D. Biosynthesis of steroids (Section 27.7).
1. All steroids are biosynthesized from lanosterol.
2. Lanosterol is formed from squalene, which is the product of dimerization of farnesyl diphosphate (FPP).
3. Squalene is first epoxidized to form 2,3-oxidosqualene.
4. Nine additional steps are needed to form lanosterol.
a. The first several steps are cyclization reactions.
b. The last steps are hydride and methyl shifts involving carbocations.

Chapter 28 – Biomolecules: Nucleic Acids

Chapter Outline

I. Nucleic acids (Sections 28.1–28.2).
   A. Nucleotides (Section 28.1).
      1. Nucleotides are composed of a heterocyclic purine or pyrimidine base, an aldopentose, and a phosphate group.
         a. In RNA, the purines are adenine and guanine, the pyrimidines are uracil and cytosine, and the sugar is ribose.
         b. In DNA, thymine replaces uracil, and the sugar is 2'-deoxyribose.
      2. Positions on the base receive non-prime superscripts, and positions on the sugar receive prime superscripts.
      3. The heterocyclic base is bonded to C1' of the sugar.
      4. DNA is vastly larger than RNA and is found in the cell nucleus.
   B. Nucleic acids.
      1. Nucleic acids are composed of nucleotides connected by a phosphodiester bond between the 5' ester of one nucleotide and the 3' hydroxyl group of another.
         a. One end of the nucleic acid polymer has a free hydroxyl group and is called the 3' end.
         b. The other end has a free phosphate group and is called the 5' end.
      2. The structure of a nucleic acid depends on the order of bases.
      3. The sequence of bases is described by starting at the 5' end and listing the bases by their one-letter abbreviations in order of occurrence.
   C. Base-pairing in DNA (Section 28.2).
      1. DNA consists of two polynucleotide strands coiled in a double helix.
         a. Adenine and thymine hydrogen-bond with each other, and cytosine and guanine hydrogen-bond with each other.
      2. Because the two DNA strands are complementary, the amount of A equals the amount of T, and the amount of C equals the amount of G.
      3. The double helix is 20 Å wide, there are 10 bases in each turn, and each turn is 34 Å in height.
      4. The double helix has a major groove and a minor groove into which polycyclic aromatic molecules can intercalate.
   D. The “central dogma” of molecular genetics.
      1. The function of DNA is to store genetic information and to pass it on to RNA, which, in turn, uses it to make proteins.
      2. Replication, transcription and translation are the three processes that are responsible for carrying out the central dogma.

II. The transfer of genetic information (Sections 28.3–28.5).
   A. Replication of DNA (Section 28.3).
      1. Replication is the enzyme-catalyzed process whereby DNA makes a copy of itself.
      2. Replication is semiconservative: each new strand of DNA consists of one old strand and one newly synthesized strand.

3. How replication occurs:
    a. The DNA helix partially unwinds.
        i. This process is catalyzed by the enzyme helicase.
    b. New nucleotides form base pairs with their complementary partners.
    c. Formation of new bonds is catalyzed by DNA polymerase and takes place in the 5' → 3' direction.
        i. Bond formation occurs by attack of the 3' hydroxyl group on the 5' triphosphate, with loss of a diphosphate leaving group.
    d. Both new chains are synthesized in the 5' →3' direction.
        i. One chain is synthesized continuously (the leading strand).
        ii. The other strand is synthesized in small pieces, which are later joined by DNA ligase enzymes (the lagging strand).

B. Transcription – synthesis of RNA (Section 28.4).
    1. There are 3 main types of RNA:
        a. Messenger RNA (mRNA) carries genetic information to ribosomes when protein synthesis takes place.
        b. Ribosomal RNA (rRNA), complexed with protein, comprises the physical makeup of the ribosomes.
        c. Transfer RNA (tRNA) brings amino acids to the ribosomes, where they are joined to make proteins.
        d. There are also small RNAs, which carry out a variety of cellular functions.
    2. DNA contains "promoter sites", which indicate where mRNA synthesis is to begin, and base sequences that indicate where mRNA synthesis stops.
        a. RNA polymerase binds to the promoter sequence.
    3. mRNA is synthesized in the nucleus by transcription of DNA.
        a. The DNA partially unwinds, forming a "bubble".
        b. Ribonucleotides form base pairs with their complementary DNA bases.
        c. Bond formation occurs in the 5' →3' direction.
        d. Only one strand of DNA (the antisense, or noncoding, strand) is transcribed.
        e. Thus, the synthesized mRNA is a copy of the sense (coding) strand with U replacing T.
    4. Synthesis of mRNA is not necessarily continuous.
        a. Often, synthesis begins in a region of DNA called an exon and is interrupted by a seemingly noncoding region of DNA called an intron.
        b. In the final mRNA, the noncoding sections have been removed and the remaining pieces have been spliced together by specific enzymes.

C. Translation (Section 28.5).
    1. Translation is the process in which proteins are synthesized at the ribosomes by using mRNA as a template.

2. The message delivered by mRNA is contained in "codons" – 3-base groupings that are specific for an amino acid.
    a. Amino acids are coded by 61 of the possible 64 codons.
    b. The other 3 codons are "stop" codons.
3. Each tRNA is responsible for bringing an amino acid to the growing protein chain.
    a. A tRNA has a cloverleaf-shaped secondary structure and consists of 70–100 ribonucleotides.
    b. Each tRNA contains an anticodon complementary to the mRNA codon.
4. The protein chain is synthesized by enzyme-catalyzed peptide bond formation.
5. A 3-base "stop" codon on mRNA signals when synthesis is complete.

III. DNA technology (Sections 28.6–28.8).

A. DNA sequencing (Section 28.6).
1. Before sequencing, the DNA chain is cleaved at specific sites by restriction endonucleases.
    a. The restriction endonuclease recognizes both a sequence on the sense strand and its complement on the antisense strand.
    b. The DNA strand is cleaved by several different restriction endonucleases, to produce fragments that overlap those from a different cleavage.
2. Maxam–Gilbert DNA sequencing.
    a. This method uses chemical techniques.
3. Sanger dideoxy DNA sequencing.
    a. The following mixture is assembled:
        i. The restriction fragment to be sequenced.
        ii. A primer (a small piece of DNA whose sequence is complementary to that on the 3' end of the fragment).
        iii. The 4 DNA nucleoside triphosphates.
        iv. Small amounts of the four dideoxynucleotide triphosphates, each of which is labeled with a different fluorescent dye.
    b. DNA polymerase is added to the mixture, and a strand begins to grow from the end of the primer.
    c. Whenever a dideoxynucleotide is incorporated, chain growth stops.
    d. When reaction is complete, the fragments are separated by gel electrophoresis.
    e. Because fragments of all possible lengths are represented, the sequence can be read by noting the color of fluorescence of each fragment.

B. DNA synthesis (Section 28.7).
1. DNA synthesis is based on principles similar to those for peptide synthesis.
2. The following steps are needed:
    a. The nucleosides are protected and bound to a silica support.
        i. Adenine and cytosine bases are protected by benzoyl groups.
        ii. Guanine is protected by an isobutyryl group.
        iii. Thymine isn't protected.
        iv. The 5' –OH group is protected as a DMT ether.

b. The DMT group is removed.
c. The polymer-bound nucleoside is coupled with a protected nucleoside containing a phosphoramidite group.
    i. One of the phosphoramidite oxygens is protected as a β-cyano ether.
    ii. Tetrazole catalyzes the coupling.
d. The phosphite is oxidized to a phosphate with I_2.
e. Steps b – d are repeated until the desired chain is synthesized.
f. All protecting groups are removed and the bond to the support is cleaved by treatment with aqueous ammonia.

C. The polymerase chain reaction (Section 28.8).
1. The polymerase chain reaction (PCR) can produce vast quantities of a DNA fragment.
2. The key to PCR is *Taq* DNA polymerase, a heat-stable enzyme.
    a. Newer heat-stable DNA polymerase enzymes have become available.
3. Steps in PCR:
    a. The following mixture is heated to 95 °C (a temperature at which DNA becomes single-stranded);
        i. *Taq* polymerase.
        ii. Mg^{2+} ion.
        iii. The 4 deoxynucleotide triphosphates.
        iv. A large excess of two oligonucleotide primers, each of which is complementary to the ends of the fragment to be synthesized.
    b. The temperature is lowered to 37 °C – 50 °C, causing the primers to hydrogen bond to the single-stranded DNA.
    c. After raising the temperature to 72 °C, *Taq* catalyzes the addition of further nucleotides, yielding two copies of the original DNA.
    d. The process is repeated until the desired quantity of DNA is produced.

Chapter 29 – The Organic Chemistry of Metabolic Pathways

Chapter Outline

I. Overview of metabolism and biochemical energy (Section 29.1).
   A. Metabolism.
      1. The reactions that take place in the cells of organisms are collectively called metabolism.
         a. The reactions that produce smaller molecules from larger molecules are called catabolism and produce energy.
         b. The reactions that build larger molecules from smaller molecules are called anabolism and consume energy.
      2. Catabolism can be divided into four stages:
         a. In digestion, bonds in food are hydrolyzed to yield monosaccharides, fats, and amino acids.
         b. These small molecules are degraded to acetyl CoA.
         c. In the citric acid cycle, acetyl CoA is catabolized to CO_2, and energy is produced.
         d. Energy from the citric acid cycle enters the electron transport chain, where ATP is synthesized.
   B. Biochemical energy.
      1. ATP, a phosphoric acid anhydride, is the storehouse for biochemical energy.
      2. The breaking of a P–O bond of ATP can be coupled with an energetically unfavorable reaction, so that the overall energy change is favorable.
      3. The resulting phosphates are much more reactive than the original compounds.

II. Lipid metabolism (Sections 29.2–29.4).
   A. Catabolism of fats (Section 29.2–29.3).
      1. Triacylglycerols are first hydrolyzed in the stomach and small intestine to yield glycerol plus fatty acids (Section 29.2).
         a. The reaction is catalyzed by a lipase.
            i. Aspartic acid, serine and histidine residues in the enzyme bring about reaction.
         b. Glycerol is phosphorylated and oxidized and enters glycolysis.
            i. The mechanism of oxidation involves a hydride transfer to NAD^+.
            ii. The addition to NAD^+ is stereospecific.
      2. β-Oxidation (in the mitochondria) (Section 29.3).
         a. Fatty acids are degraded by β-oxidation, a 4-step spiral that results in the cleavage of an n-carbon fatty acid into $n/2$ molecules of acetyl CoA.
         b. Before entering β-oxidation, a fatty acid is first converted to its fatty-acyl CoA.
      3. Steps of β oxidation.
         a. Introduction of a double bond conjugated with the carbonyl group.
            i. The reaction is catalyzed by acyl CoA dehydrogenase.
            ii. The enzyme cofactor FAD is also involved and is reduced.
            iii. The mechanism involves abstraction of the pro-*R* α and β hydrogens, resulting in formation of a trans double bond.

b. Conjugate addition of water to form an alcohol.
   i. The reaction is catalyzed by enoyl CoA hydratase.
c. Alcohol oxidation.
   i. The reaction is catalyzed by L-3-hydroxyacyl CoA dehydrogenase.
   ii. The cofactor NAD+ is reduced to $NADH/H^+$ at the same time.
   iii. Histidine deprotonates the hydroxyl group.
d. Cleavage of acetyl CoA from the chain.
   i. The reaction, which is catalyzed by *β*-keto thiolase, is a retro-Claisen reaction.
   ii. Nucleophilic addition of coenzyme A to the keto group is followed by loss of acetyl CoA enolate, leaving behind a chain-shortened fatty-acyl CoA.

4. An *n*-carbon fatty acid yields *n*/2 molecules of acetyl CoA after (*n*/2–1) passages of *β*-oxidation.
   a. Since most fatty acids have an even number of carbons, no carbons are left over after *β*-oxidation.
   b. Those with an odd number of carbons require further steps for degradation.

B. Biosynthesis of fatty acids (Section 29.4).
1. General principles.
   a. In most cases, the pathway of synthesis isn't the exact reverse of degradation.
      i. If $\Delta G°$ is negative for one route, it must be positive for the exact reverse, which is thus energetically unfavorable.
      ii. The metabolic strategy is for one pathway to be related to its reverse but not to be identical.
   b. All common fatty acids have an even number of carbons because they are synthesized from acetyl CoA.
   c. In vertebrates, a large multienzyme synthase complex catalyzes all steps in the pathway.
2. Synthetic pathway.
   a. Steps 1–2: Acyl transfers convert acetyl CoA to more reactive species.
      i. Acetyl CoA is converted to acetyl ACP.
      ii. The acetyl group of acetyl ACP is transferred to the synthase enzyme.
   b. Steps 3–4: Carboxylation and acyl transfer.
      i. Acetyl CoA reacts with bicarbonate to yield malonyl CoA and ADP.
         (a) The coenzyme biotin, a CO_2 carrier, transfers CO_2 in a nucleophilic acyl substitution reaction.
      ii. Malonyl CoA is converted to malonyl ACP.
      iii. At this point, both acetyl groups and malonyl groups are bound to the synthase enzyme.
   c. Step 5: Condensation.
      i. A Claisen condensation forms acetoacetyl CoA from acetyl synthase and malonyl ACP.
      ii. The reaction proceeds by an initial decarboxylation of malonyl ACP to give an enolate that adds to acetyl synthase to form acetoacetyl CoA.

d. Steps 6–8: Reduction and dehydrogenation.
    i. The ketone group of acetoacetyl CoA is reduced by NADPH.
    ii. The β-hydroxy thiol ester is dehydrated.
    iii. The resulting double bond is hydrogenated by NADPH to yield butyryl ACP.
e. The steps are repeated with butyryl synthase and malonyl ACP to give a six carbon unit.
f. Fatty acids up to palmitic acid (16 carbon atoms) are synthesized by this route.
    i. Elongation of palmitic acid and larger acids occurs with acetyl CoA units as the two-carbon donor, rather than ACP.

III. Carbohydrate metabolism (Sections 29.5–29.8).
A. Catabolism of carbohydrates (Sections 29.5–29.7).
1. Glycolysis (Section 29.5).
a. Glycolysis is a 10-step series of reactions that converts glucose to pyruvate.
b. Steps 1–2: Phosphorylation and isomerization.
    i. Glucose is phosphorylated at the 6-position by reaction with ATP.
        (a) The enzyme hexokinase is involved.
    ii. Glucose 6-P is isomerized to fructose 6-P by glucose-6-P isomerase.
c. Step 3: Fructose 6-P is phosphorylated to yield fructose 1,6-bisphosphate.
    i. ATP and phosphofructokinase are involved.
d. Step 4: Cleavage.
    i. Fructose 1,6-bisphosphate is cleaved to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate.
        (a) The reaction is a reverse aldol reaction catalyzed by aldolase.
e. Step 5: Isomerization.
    i. Dihydroxyacetone phosphate is isomerized to glyceraldehyde 3-phosphate.
    ii. The net result is production of two glyceraldehyde 3-phosphates, both of which pass through the rest of the pathway.
f. Steps 6–7: Oxidation, phosphorylation, and dephosphorylation.
    i. Glyceraldehyde 3-phosphate is both oxidized and phosphorylated to give 1,3-bisphosphoglycerate.
        (a) Oxidation by NAD^+ occurs via a hemithioacetal to yield a product that forms the mixed anhydride.
    ii. The mixed anhydride reacts with ADP to form ATP and 3-phosphoglycerate
        (a) The enzyme phosphoglycerate kinase is involved.
g. Step 8: Isomerization.
    i. 3-Phosphoglycerate is isomerized to 2-phosphoglycerate by phosphoglycerate mutase.
h. Steps 9–10: Dehydration and dephosphorylation.
    i. 2-Phosphoglycerate is dehydrated by enolase to give phosphoenolpyruvate.
    ii. Pyruvate kinase catalyzes the transfer of a phosphate group to ADP, with formation of pyruvate.

2. The conversion of pyruvate to acetyl CoA (Section 29.6).
    a. The conversion pyruvate → acetyl CoA is catalyzed by an enzyme complex called pyruvate dehydrogenase complex.
    b. Step 1: Addition of thiamin.
        i. A nucleophilic ylide group on thiamin diphosphate adds to the carbonyl group of pyruvate to yield a tetrahedral intermediate.
    c. Step 2: Decarboxylation.
    d. Step 3: Reaction with lipoamide.
        i. The enamine product of decarboxylation reacts with lipoamide, displacing sulfur and opening the lipoamide ring.
    e. Step 4: Elimination of thiamin diphosphate ylide.
    f. Step 5: Acyl transfer.
        i. Acetyl dihydrolipoamide reacts with coenzyme A to give acetyl CoA.
        ii. The resulting dihydrolipoamide is reoxidized to lipoamide by FAD.
        iii. $FADH_2$ is reoxidized to FAD by NAD^+.
    g. Other fates of pyruvate.
        i. In the absence of oxygen, pyruvate is reduced to lactate.
        ii. In bacteria, pyruvate is fermented to ethanol.
3. The citric acid cycle (conversion of acetyl CoA to CO_2) (Section 29.7).
    a. Characteristics of the citric acid cycle.
        i. The citric acid cycle is a closed loop of eight reactions.
        ii. The intermediates are constantly regenerated.
        iii. The cycle operates as long as NAD^+ and $FADH_2$ are available, which means that oxygen must also be available.
    b. Steps 1–2: Addition to oxaloacetate.
        i. Acetyl CoA adds to oxaloacetate to form citryl CoA, which is hydrolyzed to citrate.
            (a) The reaction is catalyzed by citrate synthase.
        ii. Citrate is isomerized to isocitrate by aconitase.
            (b) The reaction is an E1cb dehydration, followed by conjugate addition of water.
    c. Steps 3–4: Oxidative decarboxylations.
        i. Isocitrate is oxidized by isocitrate dehydrogenase to give a ketone that loses CO_2 to give α-ketoglutarate.
        ii. α-Ketoglutarate is transformed to succinyl CoA in a reaction catalyzed by a multienzyme dehydrogenase complex.
    d. Steps 5–6: Hydrolysis and dehydrogenation of succinyl CoA.
        i. Succinyl CoA is converted to an acyl phosphate, which transfers a phosphate group to GDP in a reaction catalyzed by succinyl CoA synthase.
        ii. Succinate is dehydrogenated by FAD and succinate dehydrogenase to give fumarate; the reaction is stereospecific.
    e. Steps 7–8: Regeneration of oxaloacetate.

i. Fumarase catalyzes the addition of water to fumarate to produce (*S*)-malate.
ii. (*S*)-malate is oxidized by NAD^+ and malate dehydrogenase to complete the cycle.

B. Carbohydrate biosynthesis: gluconeogenesis (Section 29.8).
1. Step 1: Carboxylation.
a. Pyruvate is carboxylated to yield oxaloacetate in a reaction that uses biotin and ATP.
2. Step 2: Decarboxylation and phosphorylation.
a. Concurrent decarboxylation and phosphorylation of oxaloacetate produce phosphoenolpyruvate.
3. Steps 3–4: Hydration and isomerization.
a. Conjugate addition of water gives 2-phosphoglycerate.
b. Isomerization produces 3-phosphoglycerate.
4. Steps 5–7: Phosphorylation, reduction and tautomerization.
a. Reaction of 3-phosphoglycerate with ATP yields an acyl phosphate.
b. The acyl phosphate is reduced by $NADPH/H^+$ to an aldehyde.
c. The aldehyde tautomerizes to dihydroxyacetone phosphate.
5. Step 8: Aldol reaction.
a. Dihydroxyacetone phosphate and glyceraldehyde 3-phosphate join to form fructose 1,6-bisphosphate.
b. This reaction involves the imine of dihydroxyacetone phosphate, which forms an enamine that takes part in the condensation.
6. Steps 9-11: Hydrolysis and isomerization.
a. Fructose 1,6-bisphosphate is hydrolyzed to fructose 6-phosphate.
b. Fructose 6-phosphate isomerizes to glucose 6-phosphate.
c. Glucose 6-phosphate is hydrolyzed to glucose.
7. Several of these steps are the reverse of steps of glycolysis.

IV. Protein metabolism (Section 29.9).
A. Catabolism of proteins: Deamination.
1. The pathway to amino acid catabolism:
a. The amino group is removed as ammonia by transamination.
b. The ammonia is converted to urea.
c. What remains is converted to a compound that enters the citric acid cycle.
i. Each carbon skeleton is degraded in a unique pathway.
2. Transamination.
a. The $-NH_2$ group of an amino acid adds to the aldehyde group of pyridoxal phosphate to form an imine (Schiff base).
b. The imine tautomerizes to a different imine.
c. The second imine is hydrolyzed to give an α-keto acid and an amino derivative of pyridoxal phosphate.
d. The pyridoxal derivative transfers its amino group to α-ketoglutarate, to regenerate pyridoxal phosphate and form glutamate.

3. Deamination.
    a. The glutamate from transamination undergoes oxidative deamination to yield ammonium ion and α-ketoglutarate.

V. Some conclusions about biological chemistry (Section 29.10).
   A. The mechanisms of biochemical reactions are almost identical to the mechanisms of laboratory reactions.
   B. Most metabolic pathways are linear.
      1. Linear pathways make sense when a multifunctional molecule is undergoing transformation.
      2. Cyclic pathways may be more energetically feasible when a molecule is small.

Review Unit 11: Biomolecules II – Lipids, Nucleic Acids, Metabolic Pathways

Major Topics Covered (with vocabulary):

Lipids:
wax fat oil triacylglycerol fatty acid polyunsaturated fatty acid soap saponification micelle phosphoglyceride sphingolipid lipid bilayer sphingosine sphingomyelin prostaglandin terpenoid essential oil monoterpenoid sesquiterpenoid isopentenyl diphosphate steroid hormone sex hormone adrenocortical hormone androgen estrogen mineralocorticoid glucocorticoid squalene lanosterol

Nucleic acids and nucleotides:
nucleoside nucleotide deoxyribonucleic acid (DNA) ribonucleic acid (RNA) adenine guanine thymine cytosine 3' end 5' end base pairing double helix complementary pairing major groove minor groove intercalation

Nucleic acids and heredity:
replication semiconservative DNA polymerase replication fork DNA ligase transcription mRNA rRNA tRNA sense (coding) strand antisense (noncoding) strand promoter sites exon intron translation codon anticodon

DNA technology:
DNA sequencing Maxam-Gilbert method restriction endonuclease restriction fragment palindrome Sanger dideoxy method DNA synthesis DMT ether phosphoramidite phosphite polymerase chain reaction (PCR)

Metabolic pathways:
metabolism anabolism catabolism digestion phosphoric acid anhydride ATP NAD^+ $NADH/H^+$ β-oxidation pathway glycolysis Schiff base pyruvate acetyl CoA pyruvate dehydrogenase complex thiamine lipoamide citric acid cycle electron-transport chain transamination oxidative deamination gluconeogenesis biotin

Types of Problems:

After studying these chapters, you should be able to:

- Draw the structures of fats, oils, steroids and other lipids.
- Determine the structure of a fat.
- Predict the products of reactions of fats and steroids.
- Locate the five-carbon units in terpenoids.
- Understand the mechanism of terpenoid and steroid biosynthesis.
- Draw the structures and conformations of steroids and other fused-ring systems.
- Draw purines, pyrimidines, nucleosides, nucleotides, and representative segments of DNA and their complements.
- List the base sequence that codes for a given amino acid or peptide.
- Deduce an amino acid sequence from a given mRNA sequence (and *vice versa*).
- Draw the anticodon sequence of tRNA, given the mRNA sequence.
- Outline the process of DNA sequencing, and deduce a DNA sequence from an electrophoresis pattern.
- Outline the method of DNA synthesis, and formulate the mechanisms of synthetic steps.

- Explain the basic concepts of metabolism, and understand the energy relationships of biochemical reactions.
- Answer questions relating to the metabolic pathways of carbohydrates, fatty acids and amino acids.
- Formulate mechanisms for metabolic pathways similar to those in the text.

Points to Remember:

* When trying to locate the five-carbon units in a terpenoid, look for an isopropyl group first; at least one should be apparent. After finding it, count 5 carbons, and locate the second five-carbon unit. If there are two possibilities for the second unit, choose the one that has the double bond in the correct location.

* In general, the reactions of steroids that are presented in this book are familiar and uncomplicated. Keeping track of the stereochemistry of the tetracyclic ring system is somewhat more complicated.

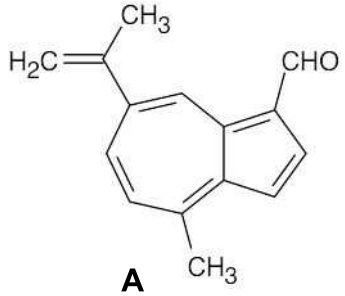
* In situations where base-pairing occurs, such as replication, transcription or translation, a polynucleotide chain (written with the 5' end on the left and the 3' end on the right) pairs with a second chain (written with the 3' end on the left and the 5' end on the right). Base pairing is complementary, and the two chains are always read in opposite directions.

* Note the difference between transamination and oxidative deamination. Transamination is a reaction in which an amino group of an α-amino acid is transferred to α-ketoglutarate, yielding an α-keto acid and glutamate. In oxidative deamination, glutamate loses its amino group in an NAD^+-dependent reaction that regenerates α-ketoglutarate and produces NH_4^+.

* Look at the steps of glycolysis, and then look at the steps of gluconeogenesis. Several steps in one pathway are the exact reverse of steps in the other pathway because the energy required for these steps is small. Other, high-energy transformations must occur by steps that are not the exact reverse and that require different enzymes. Gluconeogenesis is a metabolic pathway that takes place mainly during fasting and strenuous exercise because dietary sources of carbohydrates are usually available.

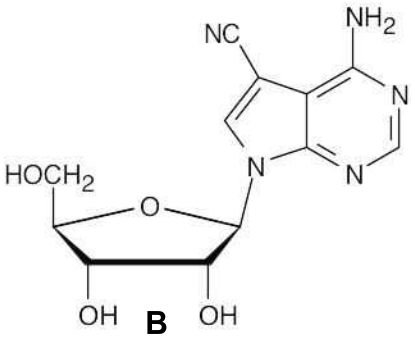
* The conversion pyruvate → acetyl CoA is catalyzed by pyruvate dehydrogenase complex. The conversion acetyl CoA → carbohydrates doesn't occur in animals because they can obtain carbohydrates from food and don't usually need to synthesize carbohydrates. Only plants can, at times, use acetyl CoA to synthesize carbohydrates.

Self-Test:



A

Lactaroviolin
(an antibiotic)



B

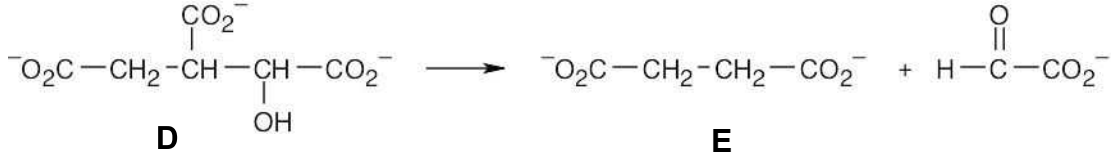
Toyocyamycin
(an antibiotic)

What type of terpenoid is **A**? Show the location of the five-carbon units.
Toyocamycin (**B**) is related to which nucleoside? What are the differences between **B** and the nucleoside?

3' 5'
–ACG–CCT–TAG–GGC–TTA–GGA–

C

C represents a segment of the antisense strand of a molecule of DNA. Draw: (a) the sense strand; (b) the mRNA that is synthesized from **C** during transcription; (c) the tRNA anticodons that are complementary to the mRNA codons; and (d) the amino acids (use one-letter codes) that form the peptide that **C** codes for.



D **E**

The above reaction is part of a metabolic pathway that occurs in plants. Identify **D** and **E**. What type of reaction is taking place? Do think that NAD^+, FAD, or ATP are needed for this reaction to occur?

Multiple Choice:

1. Which type of molecule is most likely to be found in a lipid bilayer?
   (a) triacylglycerol
   (b) prostaglandin
   (c) sphingomyelin
   (d) triterpene

2. Which of the following terpenoids might have been formed by a tail-to-tail coupling?
   (a) monoterpenoid
   (b) sesquiterpenoid
   (c) diterpenoid
   (d) triterpenoid

3. Prostaglandins and related compounds have all of the following structural features in common except:
   (a) cis double bonds
   (b) a carboxylic acid group
   (c) a C_{20} chain
   (d) hydroxyl groups

4. Which of the following steps doesn't occur in the synthesis of isopentenyl diphosphate?
   (a) Claisen condensation
   (b) oxidation
   (c) aldol condensation
   (d) decarboxylation

5. Which nucleic acid has nonstandard bases, in addition to the usual bases?
   (a) DNA
   (b) mRNA
   (c) rRNA
   (d) tRNA

6. Which base doesn't need a protecting group in DNA synthesis?
   (a) Thymine
   (b) Cytosine
   (c) Adenine
   (d) Guanine

7. Which amino acid has only one codon?
   (a) Tyrosine
   (b) Arginine
   (c) Lysine
   (d) Tryptophan

8. Which of the following enzyme cofactors is not involved in the conversion of pyruvate to acetyl CoA?
   (a) Thiamine pyrophosphate
   (b) Pyridoxal phosphate
   (c) Lipoamide
   (d) NAD^+

9. Which of the following steps of the citric acid cycle doesn't produce reduced coenzymes?
   (a) Isocitrate →α-Ketoglutarate
   (b) α-Ketoglutarate →Succinyl CoA
   (c) Fumarate →Malate
   (d) Succinate →Fumarate

10. The amino acid aspartate can be metabolized as what citric acid cycle intermediate after transamination?
   (a) Oxaloacetate
   (b) Malate
   (c) α-Ketoglutarate
   (d) Succinate

Chapter 30 – Orbitals and Organic Chemistry: Pericyclic Reactions

Chapter Outline

I. Molecular orbitals and pericyclic reactions of conjugated pi systems (Section 30.1).
   A. Molecular orbitals of conjugated π systems.
      1. The *p* orbitals of the sp^2-hybridized carbons of a polyene interact to form a set of π molecular orbitals.
      2. The energies of these orbitals depend on the number of nodes they have.
         a. The molecular orbitals with fewer nodes are bonding MOs.
         b. The molecular orbitals with more nodes are antibonding MOs.
      3. A molecular orbital description can be used for any conjugated π system.
         a. In the ground state, only the bonding orbitals are used.
         b. On irradiation with UV light, an electron is promoted to an antibonding orbital.
            i. This is known as an excited state.
   B. Molecular orbitals and pericyclic reactions.
      1. The mechanisms of pericyclic reactions can be explained by molecular orbital theory.
         a. A pericyclic reaction can take place only if the lobes of the reactant MOs have the correct algebraic sign in the transition state.
         b. If the symmetries of both reactant and product orbitals correlate, the reaction is symmetry-allowed.
         c. If the symmetries don't correlate, the reaction is symmetry-disallowed.
            i. The reaction may still take place, but only by a nonconcerted, high-energy pathway.
      2. A modification of MO theory states that only two MOs need be considered (frontier orbitals):
         a. The highest occupied molecular orbital (HOMO).
         b. The lowest unoccupied molecular orbital (LUMO).

II. Electrocyclic reactions (Sections 30.2–30.4).
   A. General description of electrocyclic reactions Section 30.2).
      1. Nature of electrocyclic reactions.
         a. An electrocyclic reaction involves the cyclization of a conjugated polyene.
            i. One π bond is broken, a new σ bond is formed and a cyclic compound results.
         b. Electrocyclic reactions are reversible.
            i. The triene–cyclohexadiene equilibrium favors the ring-closed product.
            ii. The diene–cyclobutene equilibrium favors the ring-opened product.
      2. Stereochemistry of electrocyclic reactions.
         a. A specific *E,Z* bond isomer yields a specific cyclic stereoisomer under thermal conditions.
         b. The stereochemical results are opposite when the reactions are carried out under photochemical conditions.

3. Orbital explanation for outcomes of electrocyclic reactions.
    a. The signs of the outermost lobes of the interacting orbitals explain these results.
        i. For a bond to form, the lobes must be of the same sign.
    b. The outermost π lobes of the polyene must rotate so that the lobes that form the bonds are of the same sign.
        i. If the lobes are on the same side of the molecule, the lobes must rotate in opposite directions – disrotatory motion.
        ii. If the lobes of the same sign are on opposite sides of the polyene, both lobes must rotate in the same direction – conrotatory motion.

B. Stereochemistry of thermal electrocyclic reactions (Section 30.3).
    1. The stereochemistry of an electrocyclic reaction is determined by the symmetry of the polyene HOMO.
    2. The ground-state electronic configuration is used to identify the HOMO for thermal reactions.
        a. For trienes, the HOMO has lobes of like sign on the same side of the molecule, and ring-closure is disrotatory.
        b. For dienes, ring closing is conrotatory.
    3. In general, polyenes with odd numbers of double bonds undergo disrotatory thermal electrocyclic reactions, and polyenes with even numbers of double bonds undergo conrotatory thermal electrocyclic reactions.

C. Stereochemistry of photochemical electrocyclic reactions (Section 30.4).
    1. UV irradiation of a polyene causes excitation of one electron from the ground-state HOMO to the ground-state LUMO.
    2. UV irradiation changes the symmetry of HOMO and LUMO and also changes the reaction stereochemistry.
        a. Photochemical electrocyclic reactions of trienes occur with conrotatory motion.
        b. Photochemical electrocyclic reactions of dienes occur with disrotatory motion.
    3. Thermal and photochemical electrocyclic reactions always take place with opposite stereochemistry.

III. Cycloaddition reactions (Sections 30.5–30.6).

A. General description of cycloaddition reactions (Section 30.5).
    1. A cycloaddition reaction is a reaction in which two unsaturated molecules add to give a cyclic product.
    2. Cycloadditions are controlled by the orbital symmetry of the reactants.
        a. Reactions that are symmetry-disallowed either don’t take place or occur by a higher-energy nonconcerted pathway.
    3. The Diels–Alder cycloaddition is an example.
        a. Reaction occurs between a diene and a dienophile to yield a cyclic product.
        b. The products have a specific stereochemistry.
        c. The reaction is known as a [4 + 2] cycloaddition.
    4. Cycloadditions can only occur if the terminal π lobes have the correct stereochemistry.

a. In suprafacial cycloadditions, a bonding interaction takes place between lobes on the same face of one reactant and lobes on the same face of the other reactant.
b. Antarafacial cycloadditions occur between lobes on the same face of one reactant and lobes on opposite faces of the other reactant.
c. Often, antarafacial cycloadditions are symmetry-allowed but geometrically constrained.

B. Stereochemistry of cycloadditions (Section 30.6).
1. A cycloaddition reaction takes place when a bonding interaction occurs between the HOMO of one reactant and the LUMO of the other reactant.
2. The symmetries of the terminal lobes of the HOMO and LUMO of the reactants in a [4 + 2] thermal cycloaddition allow the reaction to proceed with suprafacial geometry.
3. For [2 + 2] cycloadditions:
a. Orbital symmetry shows that thermal cyclization must occur by an antarafacial pathway.
b. Because of geometrical constraints, thermal [2 + 2] cycloadditions aren't seen.
c. Photochemical [2 + 2] cycloadditions take place because the addition can occur by a suprafacial pathway.
4. Thermal and photochemical cycloadditions always take place by opposite stereochemical pathways.

IV. Sigmatropic rearrangements (Sections 30.7–30.8).
A. General description of sigmatropic rearrangements (Section 30.7).
1. In a sigmatropic rearrangement, a σ-bonded atom or group migrates across a π electron system.
a. A σ bond is broken, the π bonds move, and a new σ bond is formed in the product.
b. The σ bonded group can be either at the end or in the middle of the π system.
c. The notation [3,3] indicates the positions in the groups to which migration occurs.
2. Sigmatropic rearrangements are controlled by orbital symmetry.
a. Migration of a group across the same face of the π system is suprafacial rearrangement.
b. Migration from one face to the other face is antarafacial rearrangement.
c. Both types of rearrangements are symmetry-allowed, but suprafacial rearrangements are geometrically easier.

B. Examples of sigmatropic rearrangements (Section 30.8).
1. The [1,5] migration of a hydrogen atom across two double bonds of a π system is very common.
a. Thermal [1,3] hydrogen shifts are unknown.
2. The Cope rearrangement and the Claisen rearrangement involve reorganization of an odd number of electron pairs and proceed by suprafacial geometry.

V. A summary of rules for pericyclic reactions (Section 30.9).
A. Thermal reactions with an even number of electron pairs are either conrotatory or antarafacial.
B. A change from thermal to photochemical, or from even to odd, changes the outcome to disrotatory/suprafacial.
C. A change of both thermal and even causes no change.

Chapter 31 – Synthetic Polymers

Chapter Outline

I. Chain-growth polymers (Sections 31.1–31.3).
  A. General features of chain-growth polymerization reactions (Section 31.1).
    1. How polymerization occurs.
      a. An initiator adds to a carbon–carbon double bond of a vinyl monomer.
      b. The reactive intermediate adds to a second molecule of monomer.
      c. The process is repeated.
    2. Types of polymerization.
      a. A radical initiator leads to radical polymerization.
      b. An acid causes cationic polymerization.
        i. Acid-catalyzed polymerization is effective only if the vinyl monomers contain electron-donating groups.
      c. Anionic polymerization can be brought about by anionic catalysts.
        i. Vinyl monomers in anionic catalysis must have electron-withdrawing groups.
        ii. Polymerization occurs by conjugate nucleophilic addition to the monomer.
        iii. Acrylonitrile, styrene and methyl methacrylate can be polymerized anionically.
        iv. "Super glue" is an example of an anionic polymer.
  B. Stereochemistry of polymerization: Ziegler-Natta catalysts (Section 31.2).
    1. There are three possible stereochemical outcomes of polymerization of a substituted vinyl monomer.
      a. If the substituents all lie on the same side of the polymer backbone, the polymer is isotactic.
      b. If the substituents alternate along the backbone, the polymer is syndiotactic.
      c. If the substituents are randomly oriented, the polymer is atactic.
    2. The three types of polymers have different properties.
    3. Although polymerization using radical initiators can't be control stereochemically, Ziegler–Natta catalysts can yield polymers of desired stereochemical orientation.
      a. Ziegler–Natta catalysts are organometallic-transition metal complexes.
        i. They are usually formed by treatment of an alkylaluminum with titanium tetrachloride.
      b. Ziegler–Natta polymers have very little chain-branching.
      c. Ziegler–Natta catalysts are stereochemically controllable.
      d. Polymerization occurs by coordination of the alkene monomer to the complex, followed by insertion into the polymer chain.
    4. Common Ziegler–Natta polymers.
      a. Polyethylene produced by the Ziegler–Natta process (high-density polyethylene) is linear, dense, strong, and heat-resistant.
      b. Other high-molecular-weight polyethylenes have specialty uses.

C. Copolymers (Section 31.3).
    1. Copolymers are formed when two different monomers polymerize together.
    2. The properties of copolymers are different from those of the corresponding monomers.
    3. Types of copolymers.
        a. Random copolymers.
        b. Alternating copolymers.
        c. Block copolymers.
            i. Block copolymers are formed when an excess of a second monomer is added to a still-active mix.
        d. Graft copolymers.
            i. Graft copolymers are made by gamma irradiation of a completed homopolymer to generate a new radical initiation site for further growth of a chain.

II. Step-growth polymers (Section 31.4).
    A. Step-growth polymer are formed by reactions in which each bond is formed independently of the others.
    B. Most step-growth polymers result from reaction of two difunctional compounds.
        1. Step-growth polymers can also result from polymerization of a single difunctional compound.
    C. Types of step-growth polymers.
        1. Polyamides and polyesters.
        2. Polycarbonates (formed from carbonates and alcohols or phenols).
        3. Polyurethanes.
            a. A urethane has a carbonyl group bonded to both an $–NR_2$ group and an –OR group.
            b. Most polyurethanes are formed from the reaction of a diisocyanate and a diol.
            c. Polyurethanes are used as spandex fibers and insulating foam.
                i. Foaming occurs when a small amount of water is added during polymerization, producing bubbles of CO_2.
                ii. Polyurethane foams often use a polyol, to increase the amount of crosslinking.

III. Olefin metathesis polymerization (Section 31.5).
    A. General features.
        1. In an olefin metathesis reaction, two olefins (alkenes) exchange substituents.
        2. The catalysts contain a carbon–metal (usually ruthenium) double bond.
            a. They react reversibly with an alkene to form a 4-membered metallacyte.
            b. The metallacyte opens to give a different catalyst and a different alkene.
        3. The reaction is compatible with many olefin functional groups.
        4. The double bonds allow for further manipulations.
    B. Ring-opening metathesis polymerization (ROMP).
        1. The monomer is a moderately strained cycloalkene.
        2. The resulting polymer has double bonds spaced regularly along the chain.

C. Acyclic diene metathesis (ADMET).
   1. The monomer is a long-chain dialkene with double bonds at the end of the chain.
   2. As the reaction progresses, gaseous ethylene escapes, driving the reaction toward product.

IV. Intramolecular olefin metathesis (Section 31.6).

A. Physical properties of polymers.
   1. Because of their large size, polymers experience large van der Waals forces.
      a. These forces are strongest in linear polymers.
   2. Many polymers have regions held together by van der Waals forces; these regions are known as crystallites.
      a. Polymer crystallinity is affected by the substituents on the chains.
      b. T_m is the temperature at which the crystalline regions of a polymer melt.
   3. Some polymers have little ordering but are hard at room temperature.
      a. These polymers become soft at a temperature T_g (glass transition temperature).

V. Polymer structure and physical properties

A. Thermoplastics.
   1. Thermoplastics have a high T_g and are hard at room temperature.
   2. Because they become soft at higher temperatures, they can be molded.
   3. Plasticizers such as dialkyl phthalates are often added to thermoplastics to keep them from becoming brittle at room temperature.

B. Fibers.
   1. Fibers are produced by extrusion of a molten polymer.
   2. On cooling and drawing out, the crystallite regions orient along the axis of the fiber to add tensile strength.

C. Elastomers.
   1. Elastomers are amorphous polymers that can stretch and return to their original shape.
   2. These polymers have a low T_g and a small amount of cross-linking.
   3. The randomly coiled chains straighten out in the direction of the pull, but they return to their random orientation when stretching is done.
   4. Natural rubber is an elastomer, but Gutta-percha is highly crystalline.

D. Thermosetting resins.
   1. Thermosetting resins become highly cross-linked and solidify when heated.
   2. Bakelite, a phenolic resin formed from phenol and formaldehyde, is the most familiar example.

Review Unit 12: Pericyclic Reactions, Synthetic Polymers

Major Topics Covered (with vocabulary):

Pericyclic reactions:
pericyclic reaction concerted reaction symmetry-allowed symmetry-disallowed frontier orbitals HOMO LUMO electrocyclic reaction disrotatory motion conrotatory motion cycloaddition reaction suprafacial cycloaddition antarafacial cycloaddition sigmatropic rearrangement suprafacial rearrangement antarafacial rearrangement Cope rearrangement Claisen rearrangement

Synthetic polymers:
chain-growth polymer Ziegler–Natta catalyst isotactic syndiotactic atactic homopolymer copolymer block copolymer graft copolymer step-growth polymer polycarbonate polyurethane olefin metathesis Grubbs catalyst ADMET ROMP crystallite melt transition temperature glass transition thermoplastic fiber elastomer thermosetting resin plasticizer

Types of Problems:

After studying these chapters, you should be able to:

- Understand the principles of molecular orbitals, and locate the HOMO and LUMO of conjugated π systems.
- Predict the stereochemistry of thermal and photochemical electrocyclic reactions.
- Know the stereochemical requirements for cycloaddition reactions, and predict the products of cycloadditions.
- Classify sigmatropic reactions by order and predict their products.
- Know the selection rules for pericyclic reactions.
- Locate the monomer units of a polymer; predict the structure of a polymer, given its monomer units.
- Formulate the mechanisms of radical, cationic, anionic, and step-growth polymerizations.
- Understand the stereochemistry of polymerization, and draw structures of atactic, isotactic, and syndiotactic polymers.
- Understand copolymerization, graft polymerization and block polymerization.
- Select monomers to form products by olefin metathesis.

Points to Remember:

* Just because a reaction is symmetry-disallowed doesn't mean that it can't occur. Reactions that are symmetry-allowed occur by relatively low-energy, concerted pathways. Reactions that are symmetry-disallowed must take place by higher energy, nonconcerted routes.

* To predict if a reaction is symmetry-allowed, it is only necessary to be concerned with the signs of the outermost lobes.

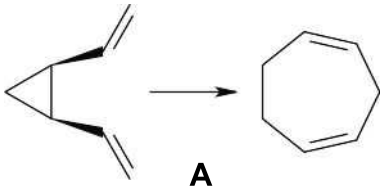
* The notations in brackets in a sigmatropic rearrangement refer to the positions in the migrating groups to which migration occurs.

* The stereochemical outcome of a concerted reaction run under thermal conditions is always opposite to the stereochemical outcome of the same reaction run under photochemical conditions.

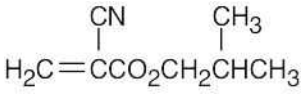
* To show the monomer unit of a chain-growth polymer, find the smallest repeating unit, break the polymer bonds, and draw the monomer with its original double bond in place. To show the monomer unit of a step-growth polymer, find the smallest repeating unit, break the polymer bonds, and draw the monomer unit or units with the small molecules that were displaced by polymerization added to the monomer units.

* Fishhook arrows are used to show movement of single electrons.

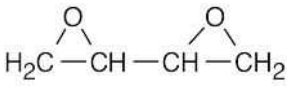
Self-Test:



A



B



C

What type of reaction is occurring in **A**? Describe it by order and type. If the reaction of the stereoisomer shown proceeds readily, is the reaction being carried out under thermal or photochemical conditions?

Under what conditions would you expect monomer **B** to polymerize? (Actually it polymerizes well under all conditions). Is the polymer a chain-growth or a step-growth polymer? Draw a representative segment of the polymer.

Suggest a use for **C** in polymerizations.

Multiple Choice:

1. In which orbitals do the outermost lobes have opposite signs on the same side of the π system?
   (a) HOMO in the ground state of a 2 π electron system
   (b) HOMO in the excited state of a 4 π electron system
   (c) LUMO in the excited state of a 6 π electron system
   (d) HOMO in the ground state of a 4 π electron system

2. Which reaction is symmetry-disallowed?
   (a) conrotatory photochemical ring-opening of a 6 π electron system
   (b) suprafacial thermal cycloaddition of a 6 π electron system
   (c) antarafacial thermal sigmatropic rearrangement of a 4 π electron system
   (d) antarafacial photochemical cycloaddition of a 6 π electron system

3. Which of the following reactions is symmetry-allowed but geometrically constrained?
   (a) thermal electrocyclic reaction of a 4 π electron system
   (b) photochemical cycloaddition of a 4 π electron system
   (c) thermal sigmatropic rearrangement of a 4 π electron system
   (d) photochemical electrocyclic reaction of a 4 π electron system

4. All of the following sigmatropic rearrangements involve 6 π electrons except:
   (a) rearrangement of allyl phenyl ether to *o*-allyl phenol
   (b) rearrangement of 1,5-heptadiene to 3-methyl-1,5-hexadiene
   (c) rearrangement of 1,3,5-heptatriene in which a hydrogen atom migrates across the π system
   (d) rearrangement of homotropilidene

5. Consider the 4 π electron thermal electrocyclic reactions of two double-bond stereoisomers. All of the following are true except:
   (a) one reaction is concerted and one isn't
   (b) the equilibrium lies on the side of the ring-opened product
   (c) the reaction proceeds with conrotatory motion
   (d) The ring-closed products are stereoisomers

6. Which of the following monomers is most likely to undergo cationic polymerization?
   (a) $H_2C{=}CF_2$
   (b) $H_2C{=}CH_2$
   (c) formaldehyde
   (d) $H_2C{=}C(CH_3)_2$

7. Which of the following is not a copolymer?
   (a) Saran
   (b) Nylon 6
   (c) Dacron
   (d) Lexan

8. In which step-growth polymer is an alcohol the by product?
   (a) polyester
   (b) polyamide
   (c) polyurethane
   (d) polycarbonate

9. Which type of polymer has large regions of oriented crystallites and little or no crosslinking?
   (a) a thermoplastic
   (b) a fiber
   (c) an elastomer
   (d) a thermosetting resin

10. A copolymer formed by irradiating a homopolymer in the presence of a second monomer is called a:
   (a) random copolymer
   (b) alternating copolymer
   (c) graft copolymer
   (d) block copolymer

Appendix A: Functional-Group Synthesis

The following table summarizes the synthetic methods by which important functional groups can be prepared. The functional groups are listed alphabetically, followed by reference to the appropriate text section and a brief description of each synthetic method.

Acetals, $R_2C(OR')_2$

(Sec. 19.10)	from ketones and aldehydes by acid-catalyzed reaction with alcohols

Acid anhydrides, RCO_2COR'

(Sec. 21.3)	from dicarboxylic acids by heating
(Sec. 21.5)	from acid chlorides by reaction with carboxylate salts

Acid bromides, RCOBr

(Sec. 21.4)	from carboxylic acids by reaction with PBr_3

Acid chlorides, RCOCl

(Sec. 21.3)	from carboxylic acids by reaction with $SOCl_2$

Alcohols, ROH

(Sec. 8.4)	from alkenes by oxymercuration/demercuration
(Sec. 8.5)	from alkenes by hydroboration/oxidation
(Sec. 8.7)	from alkenes by hydroxylation with OsO_4
(Sec. 11.2, 11.3)	from alkyl halides and tosylates by S_N2 reaction with hydroxide ion
(Sec. 18.3)	from ethers by acid-induced cleavage
(Sec. 18.5)	from epoxides by acid-catalyzed ring opening with either H_2O or HX
(Sec. 18.5)	from epoxides by base-induced ring opening
(Sec. 17.4, 19.7)	from ketones and aldehydes by reduction with $NaBH_4$ or $LiAlH_4$
(Sec. 17.5, 19.7)	from ketones and aldehydes by addition of Grignard reagents
(Sec. 21.3)	from carboxylic acids by reduction with either $LiAlH_4$ or BH_3
(Sec. 21.4)	from acid chlorides by reduction with $LiAlH_4$
(Sec. 21.4)	from acid chlorides by reaction with Grignard reagents
(Sec. 21.5)	from acid anhydrides by reduction with $LiAlH_4$
(Sec. 17.4, 21.6)	from esters by reduction with $LiAlH_4$
(Sec. 17.5, 21.6)	from esters by reaction with Grignard reagents

Aldehydes, RCHO

(Sec. 8.8)	from disubstituted alkenes by ozonolysis
(Sec. 8.8)	from 1,2-diols by cleavage with sodium periodate
(Sec. 9.4)	from terminal alkynes by hydroboration followed by oxidation
(Sec. 17.7, 19.2)	from primary alcohols by oxidation
(Sec. 19.2, 21.6)	from esters by reduction with DIBAH [$HAl(i\text{-}Bu)_2$]

Alkanes, RH

(Sec. 8.6)	from alkenes by catalytic hydrogenation
(Sec. 10.6)	from alkyl halides by protonolysis of Grignard reagents
(Sec. 10.7)	from alkyl halides by coupling with Gilman reagents
(Sec. 19.9)	from ketones and aldehydes by Wolff–Kishner reaction

Alkenes, $R_2C{=}CR_2$

(Sec. 8.1, 11.8)	from alkyl halides by treatment with strong base (E2 reaction)
(Sec. 8.1, 17.6)	from alcohols by dehydration
(Sec. 9.5)	from alkynes by catalytic hydrogenation using the Lindlar catalyst
(Sec. 9.5)	from alkynes by reduction with lithium in liquid ammonia
(Sec. 19.11)	from ketones and aldehydes by treatment with alkylidenetriphenylphosphoranes (Wittig reaction)
(Sec. 22.3)	from α-bromo ketones by heating with pyridine
(Sec. 24.7)	from amines by methylation and Hofmann elimination

Alkynes, RC≡CR

(Sec. 9.2)	from dihalides by base-induced double dehydrohalogenation
(Sec. 9.8)	from terminal alkynes by alkylation of acetylide anions

Amides, $RCONH_2$

(Sec. 21.4)	from acid chlorides by treatment with an amine or ammonia
(Sec. 21.5)	from acid anhydrides by treatment with an amine or ammonia
(Sec. 21.6)	from esters by treatment with an amine or ammonia
(Sec. 20.7)	from nitriles by partial hydrolysis with either acid or base
(Sec. 21.3, 26.7)	from a carboxylic acid and an amine by treatment with dicyclohexylcarbodiimide (DCC)

Amines, RNH_2

(Sec. 19.13)	from conjugated enones by addition of primary or secondary amines
(Sec. 21.7, 24.6)	from amides by reduction with $LiAlH_4$
(Sec. 20.7, 24.6)	from nitriles by reduction with $LiAlH_4$
(Sec. 24.6)	from primary alkyl halides by treatment with ammonia
(Sec. 24.6)	from primary alkyl halides by Gabriel synthesis
(Sec. 24.6)	from primary alkyl azides by reduction with $LiAlH_4$
(Sec. 24.6)	from acid chlorides by Curtius rearrangement of acyl azides
(Sec. 24.6)	from primary amides by Hofmann rearrangement
(Sec. 24.6)	from ketones and aldehydes by reductive amination with an amine and $NaBH_3CN$

Amino Acids, $RCH(NH_2)CO_2H$

(Sec. 26.3)	from α-bromo acids by S_N2 reaction with ammonia
(Sec. 26.3)	from α-keto acids by reductive amination
(Sec. 26.3)	from primary alkyl halides by alkylation with diethyl acetamidomalonate
(Sec. 26.3)	from *(Z)*-amido acids by enantioselective hydrogenation

Arenes, Ar–R

(Sec. 16.3)	from arenes by Friedel–Crafts alkylation with an alkyl halide
(Sec. 16.9)	from aryl alkyl ketones by catalytic reduction of the keto group
(Sec. 24.8)	from arenediazonium salts by treatment with hypophosphorous acid

Arylamines, Ar–NH_2

(Sec. 16.2, 24.6) from nitroarenes by reduction with either Fe, Sn, or H_2/Pd

Arenediazonium salts, Ar–$N_2^+ X^-$

(Sec. 24.8) from arylamines by reaction with nitrous acid

Arenesulfonic acids Ar–SO_3H

(Sec. 16.2) from arenes by electrophilic aromatic substitution with SO_3/H_2SO_4

Azides, R–N_3

(Sec. 24.6) from primary alkyl halides by S_N2 reaction with azide ion

Carboxylic acids, RCO_2H

(Sec. 8.8) from mono- and 1,2-disubstituted alkenes by ozonolysis
(Sec. 16.8) from arenes by side-chain oxidation with $Na_2Cr_2O_7$ or $KMnO_4$
(Sec. 19.3) from aldehydes by oxidation
(Sec. 20.5) from alkyl halides by conversion into Grignard reagents followed by reaction with CO_2
(Sec. 20.5, 20.7) from nitriles by acid or base hydrolysis
(Sec. 21.4) from acid chlorides by reaction with aqueous base
(Sec. 21.5) from acid anhydrides by reaction with aqueous base
(Sec. 21.6) from esters by hydrolysis with aqueous base
(Sec. 21.7) from amides by hydrolysis with aqueous base

Cyanohydrins, RCH(OH)CN

(Sec. 19.6) from aldehydes and ketones by reaction with HCN

Cycloalkanes

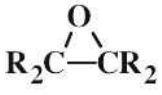
(Sec. 8.9) from alkenes by addition of dichlorocarbene
(Sec. 8.9) from alkenes by reaction with CH_2I_2 and Zn/Cu (Simmons–Smith reaction)
(Sec. 16.10) from arenes by hydrogenation

Disulfides, RS–SR'

(Sec. 18.7) from thiols by oxidation with Br_2 or I_2

Enamines, $RCH{=}CRNR_2$

(Sec. 19.8) from ketones or aldehydes by reaction with secondary amines

Epoxides , 

(Sec. 18.4) from alkenes by treatment with a peroxyacid
(Sec. 18.4) from halohydrins by treatment with base

Esters, RCO_2R'

(Sec. 21.3) from carboxylic acid salts by S_N2 reaction with primary alkyl halides
(Sec. 21.3) from carboxylic acids by acid-catalyzed reaction with an alcohol (Fischer esterification)
(Sec. 21.4) from acid chlorides by base-induced reaction with an alcohol
(Sec. 21.5) from acid anhydrides by base-induced reaction with an alcohol
(Sec. 22.7) from alkyl halides by alkylation with diethyl malonate
(Sec. 22.7) from esters by treatment of their enolate ions with alkyl halides

Ethers, R–O–R'

(Sec. 16.6) from activated haloarenes by reaction with alkoxide ions
(Sec. 18.7) from unactivated haloarenes by reaction with alkoxide ions via benzyne intermediates
(Sec. 18.2) from primary alkyl halides by S_N2 reaction with alkoxide ions (Williamson ether synthesis)
(Sec. 18.2) from alkenes by alkoxymercuration/demercuration
(Sec. 18.5) from alkenes by epoxidation with peroxyacids

Halides, alkyl, $R_3C–X$

(Sec. 7.7) from alkenes by electrophilic addition of HX
(Sec. 8.2) from alkenes by addition of halogen
(Sec. 8.3) from alkenes by electrophilic addition of hypohalous acid (HOX) to yield halohydrins
(Sec. 9.3) from alkynes by addition of halogen
(Sec. 9.3) from alkynes by addition of HX
(Sec. 10.3) from alkenes by allylic bromination with *N*-bromosuccinimide (NBS)
(Sec. 10.5) from alcohols by reaction with HX
(Sec. 10.5) from alcohols by reaction with $SOCl_2$
(Sec. 10.5) from alcohols by reaction with PBr_3
(Sec. 11.3) from alkyl tosylates by S_N2 reaction with halide ions
(Sec. 16.8) from arenes by benzylic bromination with *N*-bromosuccinimide (NBS)
(Sec. 18.3) from ethers by cleavage with either HX
(Sec. 22.3) from ketones by α-halogenation with bromine
(Sec. 22.4) from carboxylic acids by α-halogenation with phosphorus and PBr_3 (Hell– Volhard–Zelinskii reaction)

Halides, aryl, Ar–X

(Sec. 16.1, 16.2) from arenes by electrophilic aromatic substitution with halogen
(Sec. 24.8) from arenediazonium salts by reaction with cuprous halides (Sandmeyer reaction)

Halohydrins, $R_2CXC(OH)R_2$

(Sec. 8.3) from alkenes by electrophilic addition of hypohalous acid (HOX)
(Sec. 18.5) from epoxides by acid-induced ring opening with HX

Imines. $R_2C{=}NR'$

(Sec. 19.8) from ketones or aldehydes by reaction with primary amines

Ketones, $R_2C{=}O$

(Sec. 8.8) from alkenes by ozonolysis
(Sec. 8.8) from 1,2-diols by cleavage reaction with sodium periodate
(Sec. 9.4) from alkynes by mercuric-ion-catalyzed hydration
(Sec. 9.4) from alkynes by hydroboration/oxidation
(Sec. 16.3) from arenes by Friedel–Crafts acylation reaction with an acid chloride
(Sec. 17.7) from secondary alcohols by oxidation
(Sec. 19.2, 21.4) from acid chlorides by reaction with lithium diorganocopper (Gilman) reagents
(Sec. 19.13) from conjugated enones by addition of lithium diorganocopper reagents
(Sec. 20.7) from nitriles by reaction with Grignard reagents
(Sec. 22.7) from primary alkyl halides by alkylation with ethyl acetoacetate
(Sec. 22.7) from ketones by alkylation of their enolate ions with primary alkyl halides

Nitriles, $R{-}C{\equiv}N$

(Sec. 11.3, 20.7) from primary alkyl halides by S_N2 reaction with cyanide ion
(Sec. 20.7) from primary amides by dehydration with $SOCl_2$
(Sec. 22.7) from nitriles by alkylation of their α-anions with primary alkyl halides
(Sec. 24.8) from arenediazonium ions by treatment with CuCN

Nitroarenes, $Ar{-}NO_2$

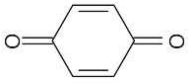
(Sec. 16.2) from arenes by electrophilic aromatic substitution with nitric/sulfuric acids

Organometallics, R–M

(Sec. 10.6) formation of Grignard reagents from organohalides by treatment with magnesium
(Sec. 10.7) formation of organolithium reagents from organohalides by treatment with lithium
(Sec. 10.7) formation of lithium diorganocopper reagents (Gilman reagents) from organolithium reagents by treatment with cuprous halides

Phenols, Ar–OH

(Sec. 16.6) from aryl halides by nucleophilic aromatic substitution with hydroxide ion
(Sec. 24.8) from arenediazonium salts by reaction with Cu_2O and $Cu(NO_3)_2$

Quinones, 

(Sec. 17.10) from phenols by oxidation with Fremy's salt $[(KSO_3)_2NO]$

Sulfides, R–S–R'

(Sec. 18.7) from thiols by S_N2 reaction of thiolate ions with primary alkyl halides

Sulfones, R–SO_2–R'

(Sec. 18.7) from sulfides or sulfoxides by oxidation with peroxyacids

Sulfoxides, R–SO–R'

(Sec. 18.7) from sulfides by oxidation with H_2O_2

Thiols, R–SH

(Sec. 11.3) from primary alkyl halides by S_N2 reaction with hydrosulfide anion

(Sec. 18.7) from primary alkyl halides by S_N2 reaction with thiourea, followed by hydrolysis

Appendix B: Functional-Group Reactions

The following table summarizes the reactions of important functional groups. The functional groups are listed alphabetically, followed by a reference to the appropriate text section.

Acetal

1. Hydrolysis to yield a ketone or aldehyde plus alcohol (Section 19.10)

Acid anhydride

1. Hydrolysis to yield a carboxylic acid (Section 21.5)
2. Alcoholysis to yield an ester (Section 21.5)
3. Aminolysis to yield an amide (Section 21.5)
4. Reduction to yield a primary alcohol (Section 21.5)

Acid chloride

1. Friedel–Crafts reaction with an aromatic compound to yield an aryl ketone (Section 16.3)
2. Hydrolysis to yield a carboxylic acid (Section 21.4)
3. Alcoholysis to yield an ester (Section 21.4)
4. Aminolysis to yield an amide (Section 21.4)
5. Reduction to yield a primary alcohol (Section 21.4)
6. Grignard reaction to yield a tertiary alcohol (Section 21.4)
7. Reaction with a lithium diorganocopper reagent to yield a ketone (Section 21.4)

Alcohol

1. Acidity (Section 17.2)
2. Oxidation (Section 17.7)
    a. Reaction of a primary alcohol to yield an aldehyde or acid
    b. Reaction of a secondary alcohol to yield a ketone
3. Reaction with a carboxylic acid to yield an ester (Section 21.3)
4. Reaction with an acid chloride to yield an ester (Section 21.4)
5. Reaction with an acid anhydride to yield an ester (Section 21.5)
6. Dehydration to yield an alkene (Section 17.6)
7. Reaction with a primary alkyl halide to yield an ether (Section 18.2)
8. Conversion into an alkyl halide (Section 17.6)
    a. Reaction of a tertiary alcohol with HX
    b. Reaction of a primary or secondary alcohol with $SOCl_2$
    c. Reaction of a primary or secondary alcohol with PBr_3

Aldehyde

1. Oxidation to yield a carboxylic acid (Section 19.3)
2. Nucleophilic addition reactions
    a. Reduction to yield a primary alcohol (Sections 17.4 and 19.7)
    b. Reaction with a Grignard reagent to yield a secondary alcohol (Sections 17.5 and 19.7)
    c. Grignard reaction of formaldehyde to yield a primary alcohol (Section 17.5)
    d. Reaction with HCN to yield a cyanohydrin (Section 19.6)
    e. Wolff–Kishner reaction with hydrazine to yield an alkane (Section 19.9)
    f. Reaction with an alcohol to yield an acetal (Section 19.10)
    g. Wittig reaction to yield an alkene (Section 19.11)

   h. Reaction with an amine to yield an imine or enamine (Section 19.8)
3. Aldol reaction to yield a β-hydroxy aldehyde (Section 23.1)
4. Alpha bromination of an aldehyde (Section 22.3)

Alkane

1. Radical halogenation to yield an alkyl halide (Sections 10.3)

Alkene

1. Electrophilic addition of HX to yield an alkyl halide (Sections 7.7 through 7.11)
   Markovnikov regiochemistry is observed.
2. Electrophilic addition of halogen to yield a 1,2-dihalide (Section 8.2)
3. Oxymercuration/demercuration to yield an alcohol (Section 8.4)
   Markovnikov regiochemistry is observed, yielding the more highly substituted alcohol.
4. Hydroboration/oxidation to yield an alcohol (Section 8.5)
5. Hydrogenation to yield an alkane (Section 8.6)
6. Hydroxylation to yield a 1,2-diol (Section 8.7)
7. Oxidative cleavage to yield carbonyl compounds (Section 8.8)
8. Simmons–Smith reaction with CH_2I_2 to yield a cyclopropane (Section 8.9)
9. Reaction with dichlorocarbene to yield a dichlorocyclopropane (Section 8.9)
10. Allylic bromination with NBS (Section 10.4)
11. Alkoxymercuration to yield an ether (Section 18.2)
12. Reaction with a peroxyacid to yield an epoxide (Sections 8.7 and 18.5)

Alkyne

1. Electrophilic addition of HX to yield a vinylic halide (Section 9.3)
2. Electrophilic addition of halogen to yield a dihalide (Section 9.3)
3. Mercuric-sulfate-catalyzed hydration to yield a methyl ketone (Section 9.4)
4. Hydroboration/oxidation to yield an aldehyde (Section 9.4)
5. Alkylation of an alkyne anion (Section 9.8)
6. Reduction (Section 9.5)
   a. Hydrogenation over Lindlar catalyst to yield a cis alkene
   b. Reduction with Li/NH_3 to yield a trans alkene

Amide

1. Hydrolysis to yield a carboxylic acid (Section 21.7)
2. Reduction with $LiAlH_4$ to yield an amine (Section 21.7)
3. Dehydration to yield a nitrile (Section 20.7)

Amine

1. Basicity (Section 24.3)
2. S_N2 alkylation of an alkyl halide to yield an amine (Section 24.6)
3. Nucleophilic acyl substitution reactions
   a. Reaction with an acid chloride to yield an amide (Section 21.4)
   b. Reaction with an acid anhydride to yield an amide (Section 21.5)
4. Hofmann elimination to yield an alkene (Section 24.7)
5. Formation of an arenediazonium salt (Section 24.8)

Arene

1. Oxidation of an alkylbenzene side chain to yield a benzoic acid (Section 16.8)
2. Catalytic reduction to yield a cyclohexane (Section 16.9)
3. Reduction of an aryl alkyl ketone to yield an arene (Section 16.10)
4. Electrophilic aromatic substitution (Sections 16.1 through 16.3)
   a. Halogenation (Sections 16.1 and 16.2)
   b. Nitration (Section 16.2)
   c. Sulfonation (Section 16.2)
   d. Friedel–Crafts alkylation (Section 16.3)
      Aromatic ring must be at least as reactive as a halobenzene.
   e. Friedel–Crafts acylation (Section 16.3)

Arenediazonium salt

1. Conversion into an aryl chloride (Section 24.8)
2. Conversion into an aryl bromide (Section 24.8)
3. Conversion into an aryl iodide (Section 24.8)
4. Conversion into an aryl cyanide (Section 24.8)
5. Conversion into a phenol (Section 24.8)
6. Conversion into a substitution benzene (Section 24.8)

Carboxylic acid

1. Acidity (Sections 20.2 through 20.4)
2. Reduction to yield a primary alcohol (Sections 17.4 and 21.3)
   a. Reduction with $LiAlH_4$
   b. Reduction with BH_3
3. Nucleophilic acyl substitution reactions (Sections 21.2 and 21.3)
   a. Conversion into an acid chloride
   b. Conversion into an acid anhydride
   c. Conversion into an ester
      (1) Fischer esterification
      (2) S_N2 reaction with an alkyl halide
4. Alpha bromination (Hell–Volhard–Zelinskii reaction) (Section 22.4)

Diene

1. Conjugate addition of HX and X_2 (Section 14.2)
2. Diels–Alder reaction (Sections 14.4, 14.5, and 30.5)

Epoxide

1. Acid-catalyzed ring opening with HX to yield a halohydrin (Section 18.5)
2. Ring opening with aqueous acid to yield a 1,2-diol (Section 18.5)

Ester

1. Hydrolysis to yield a carboxylic acid (Section 21.6)
2. Aminolysis to yield an amide (Section 21.6)
3. Reduction to yield a primary alcohol (Sections 17.4 and 21.6)
4. Partial reduction with DIBAH to yield an aldehyde (Section. 21.6)

5. Grignard reaction to yield a tertiary alcohol (Sections 17.5 and 21.6)
6. Claisen condensation to yield a β-keto ester (Section 23.7)

Ether

1. Acid-induced cleavage to yield an alcohol and an alkyl halide (Section 18.3)
2. Claisen rearrangement of an allyl aryl ether to yield an *o*-allyl phenol (Section 30.8)

Halide, alkyl

1. Reaction with magnesium to form a Grignard reagent (Section 10.6)
2. Reduction to yield an alkane (Section 10.6)
3. Coupling with a diorganocopper reagent to yield an alkane (Section 10.7)
4. Reaction with an alcohol to yield an ether (Section 18.2)
5. Nucleophilic substitution (S_N1 or S_N2) (Sections 11.1 through 11.5)
6. Dehydrohalogenation to yield an alkene (E1 or E2) (Sections 11.7 through 11.10)

Halohydrin

1. Conversion into an epoxide (Section 18.5)

Ketone

1. Nucleophilic addition reactions
    a. Reduction to yield a secondary alcohol (Sections 17.4 and 19.7)
    b. Reaction with a Grignard reagent to yield a tertiary alcohol (Sections 17.5 and 19.7)
    c. Wolff–Kishner reaction with hydrazine to yield an alkane (Section 19.9)
    d. Reaction with HCN to yield a cyanohydrin (Section 19.6)
    e. Reaction with an alcohol to yield an acetal (Section 19.10)
    f. Wittig reaction to yield an alkene (Section 19.11)
    g. Reaction with an amine to yield an imine or enamine (Section 19.8)
2. Aldol reaction to yield a β-hydroxy ketone (Section 23.1)
3. Alpha bromination (Section 22.3)

Nitrile

1. Hydrolysis to yield a carboxylic acid (Sections 20.5 and 20.7)
2. Reduction to yield a primary amine (Section 20.7)
3. Reaction with a Grignard reagent to yield a ketone (Section 20.7)

Nitroarene

1. Reduction to yield an arylamine (Sections 16.2 and 24.6)

Organometallic reagent

1. Reduction by treatment with acid to yield an alkane (Section 10.6)
2. Nucleophilic addition to a carbonyl compound to yield an alcohol (Sections 17.5 and 9.7)
3. Conjugate addition of a lithium diorganocopper to an α,β-unsaturated ketone (Section 19.13)
4. Coupling reaction of a lithium diorganocopper reagent with an alkyl halide to yield analkane (Section 10.7)

5. Coupling reaction of a lithium diorganocopper with an acid chloride to yield a ketone (Section 21.4)
6. Reaction with carbon dioxide to yield a carboxylic acid (Section 20.5)

Phenol

1. Acidity (Section 17.2)
2. Reaction with an acid chloride to yield an ester (Section 21.4)
3. Reaction with an alkyl halide to yield an ether (Section 18.2)
4. Oxidation to yield a quinone (Section 17.10)

Quinone

1. Reduction to yield a hydroquinone (Section 17.10)

Sulfide

1 Reaction with an alkyl halide to yield a sulfonium salt (Section 18.7)
2. Oxidation to yield a sulfoxide (Section 18.7)
3. Oxidation to yield a sulfone (Section 18.7)

Thiol

1. Reaction with an alkyl halide to yield a sulfide (Section 18.7)
2. Oxidation to yield a disulfide (Section 18.7)

Appendix C: Reagents in Organic Chemistry

The following list summarizes the uses of some important reagents in organic chemistry. The reagents are listed alphabetically, followed by a brief description of the uses of each and references to the appropriate text sections.

Acetic acid, CH_3CO_2H: Used as a solvent for the reduction of ozonides with zinc (Section 8.8) and the α-bromination of ketones and aldehydes with Br_2 (Section 22.3).

Acetic anhydride, $(CH_3CO)_2O$: Reacts with alcohols to yield acetate esters (Sections 21.5 and 25.6) and with amines to yield acetamides (Section 21.5).

Aluminum chloride, $AlCl_3$: Acts as a Lewis acid catalyst in Friedel–Crafts alkylation and acylation reactions of aromatic compounds (Section 16.3).

Ammonia, NH_3: Used as a solvent for the reduction of alkynes by lithium metal to yield trans alkenes (Section 9.5).
– Reacts with acid chlorides and acid anhydrides to yield amides (Sections 21.4 and 21.5).

Borane, BH_3: Adds to alkenes, giving alkylboranes that can be oxidized with alkaline H_2O_2 to yield alcohols (Section 8.5).
– Adds to alkynes, giving vinylic organoboranes that can be oxidized with H_2O_2 to yield aldehydes (Section 9.4).
– Reduces carboxylic acids to yield primary alcohols (Section 21.3).

Bromine, Br_2: Adds to alkenes, yielding 1,2-dibromides (Sections 8.2, 14.2).
– Adds to alkynes yielding either 1,2-dibromoalkenes or 1,1,2,2-tetrabromoalkanes (Section 9.3).
– Reacts with arenes in the presence of $FeBr_3$ catalyst to yield bromoarenes (Section 16.1).
– Reacts with ketones in acetic acid solvent to yield α-bromo ketones (Section 22.3).
– Reacts with carboxylic acids in the presence of PBr_3 to yield α-bromo carboxylic acids (Hell–Volhard–Zelinskii reaction) (Section 22.4).
– Oxidizes aldoses to yield aldonic acids (Section 25.6).

***N*-Bromosuccinimide (NBS), $(CH_2CO)_2NBr$:** Reacts with alkenes in the presence of aqueous dimethylsulfoxide to yield bromohydrins (Section 8.3).
– Reacts with alkenes in the presence of light to yield allylic bromides (Section 10.3).
– Reacts with alkylbenzenes in the presence of light to yield benzylic bromides (Section 16.8).

Di-*tert*-butoxy dicarbonate, $(t\text{-}BuOCO)_2O$: Reacts with amino acids to give *t*-Boc protected amino acids suitable for use in peptide synthesis (Section 26.7).

Butyllithium, $CH_3CH_2CH_2CH_2Li$: Reacts with dialkylamines to yield lithium dialkylamide bases such as LDA [lithium diisopropylamide] (Section 22.5).
– Reacts with alkyltriphenylphosphonium salts to yield alkylidenephosphoranes (Wittig reagents) (Section 19.11).

Carbon dioxide, CO_2: Reacts with Grignard reagents to yield carboxylic acids (Section 20.5).

Chlorine, Cl_2: Adds to alkenes to yield 1,2-dichlorides (Section 8.2).
– Reacts with alkanes in the presence of light to yield chloroalkanes by a radical chain reaction pathway (Section 10.2).
– Reacts with arenes in the presence of $FeCl_3$ catalyst to yield chloroarenes (Section 16.2).

***m*-Chloroperoxybenzoic acid, *m*-$ClC_6H_4CO_3H$:** Reacts with alkenes to yield epoxides (Section 8.7).

Chlorotrimethylsilane, $(CH_3)_3SiCl$: Reacts with alcohols to add the trimethylsilyl protecting group (Section 17.8).

Chromium trioxide, CrO_3: Oxidizes alcohols in aqueous acid to yield carbonyl-containing products. Primary alcohols yield carboxylic acids, and secondary alcohols yield ketones (Section 17.7).

Cuprous bromide, CuBr: Reacts with arenediazonium salts to yield bromoarenes (Sandmeyer reaction; Section 24.8).

Cuprous chloride, CuCl: Reacts with arenediazonium salts to yield chloroarenes (Sandmeyer reaction; Section 24.8).

Cuprous cyanide, CuCN: Reacts with arenediazonium salts to yield substituted benzonitriles (Sandmeyer reaction; Section 24.8).

Cuprous iodide, CuI: Reacts with organolithiums to yield lithium diorganocopper reagents (Gilman reagents; Section 10.7).

Cuprous oxide, Cu_2O: Reacts with arenediazonium salts to yield phenols (Section 24.8).

Dess–Martin periodinane, $C_7H_4IO_2(OAc)_4$: Oxidizes primary alcohols to aldehydes (Sections 17.7 and 19.2).

Dichloroacetic acid, Cl_2CHCO_2H: Cleaves DMT protecting groups in DNA synthesis (Section 28.7).

Dicyclohexylcarbodiimide (DCC), $C_6H_{11}–N=C=N–C_6H_{11}$: Couples an amine with a carboxylic acid to yield an amide. DCC is often used in peptide synthesis (Section 26.7).

Diethyl acetamidomalonate, $CH_3CONHCH(CO_2Et)_2$: Reacts with alkyl halides in a common method of α-amino acid synthesis (Section 26.3).

Diiodomethane, CH_2I_2: Reacts with alkenes in the presence of zinc–copper couple to yield cyclopropanes (Simmons–Smith reaction) (Section 8.9).

Diisobutylaluminum hydride (DIBAH), $(i\text{-Bu})_2AlH$: Reduces esters to yield aldehydes (Sections 19.2 and 21.6).

2,4-Dinitrophenylhydrazine, $2,4\text{-}(NO_2)_2C_6H_3NHNH_2$: Reacts with aldehydes and ketones to yield 2,4-DNPs that serve as useful crystalline derivatives (Section 19.8).

Ethylene glycol, $HOCH_2CH_2OH$: Reacts with ketones or aldehydes in the presence of an acid catalyst to yield acetals that serve as useful carbonyl protecting groups (Section 19.10).

F-TEDA-BF_4, $C_7H_{14}B_2ClF_9N_2$: Fluorinates an aromatic ring (Section 16.2).

Ferric bromide, $FeBr_3$: Acts as a catalyst for the reaction of arenes with Br_2 to yield bromoarenes (Section 16.1).

Ferric chloride, $FeCl_3$: Acts as a catalyst for the reaction of arenes with Cl_2 to yield chloroarenes (Section 16.2).

Grignard reagent, RMgX: Reacts with acids to yield alkanes (Section 10.6).
- Adds to carbonyl-containing compounds (ketones, aldehydes, esters) to yield alcohols (Section 19.7).
- Adds to nitriles to yield ketones (Section 19.9).

Hydrazine, H_2NNH_2: Reacts with ketones or aldehydes in the presence of KOH to yield the corresponding alkanes (Wolff–Kishner reaction) (Section 19.19).

Hydrogen bromide, HBr: Adds to alkenes with Markovnikov regiochemistry to yield alkyl bromides (Sections 7.7 and 14.2).
- Adds to alkynes to yield either bromoalkenes or 1,1-dibromoalkanes (Section 9.3).
- Reacts with alcohols to yield alkyl bromides (Sections 10.5 and 17.6).
- Cleaves ethers to yield alcohols and alkyl bromides (Section 18.3).

Hydrogen chloride, HCl: Adds to alkenes with Markovnikov regiochemistry to yield alkyl chlorides (Section 14.2).
- Adds to alkynes to yield either chloroalkenes or 1,1-dichloroalkanes (Section 8.3).
- Reacts with alcohols to yield alkyl chlorides (Section 17.6).

Hydrogen cyanide, HCN: Adds to ketones and aldehydes to yield cyanohydrins (Section 19.6).

Hydrogen iodide, HI: Cleaves ethers to yield alcohols and alkyl iodides (Section 18.3).

Hydrogen peroxide, H_2O_2: Oxidizes organoboranes to yield alcohols. Used in conjunction with addition of borane to alkenes, the overall transformation effects syn Markovnikov addition of water to an alkene (Section 8.5).
– Oxidizes vinylic boranes to yield aldehydes (Section 9.4).
– Oxidizes sulfides to yield sulfoxides (Section 18.8).

Hydroxylamine, NH_2OH: Reacts with ketones and aldehydes to yield oximes (Section 19.8).
– Reacts with aldoses to yield oximes as the first step in the Wohl degradation of aldoses (Section 25.6).

Hypophosphorous acid, H_3PO_2: Reacts with arenediazonium salts to yield arenes (Section 24.8).

Iodine, I_2: Reacts with arenes in the presence of CuCl or H_2O_2 to yield iodoarenes (Section 16.2).

Iodomethane, CH_3I: Reacts with alkoxide anions to yield methyl ethers (Section 18.2).
– Reacts with carboxylate anions to yield methyl esters (Section 21.6).
– Reacts with enolate ions to yield α-methylated carbonyl compounds (Section 22.7).
– Reacts with amines to yield methylated amines (Section 24.6).

Iron, Fe: Reacts with nitroarenes in the presence of aqueous acid to yield anilines (Section 24.6).

Lindlar catalyst: Acts as a catalyst for the partial hydrogenation of alkynes to yield cis alkenes (Section 9.5).

Lithium, Li: Reduces alkynes in liquid ammonia solvent to yield trans alkenes (Section 9.5).
– Reacts with organohalides to yield organolithium compounds (Section 10.7).

Lithium aluminum hydride, $LiAlH_4$: Reduces ketones, aldehydes, esters, and carboxylic acids to yield alcohols (Sections 17.4, 19.7, and 20.6).
– Reduces amides to yield amines (Section 21.7).
– Reduces alkyl azides to yield amines (Section 24.6).
– Reduces nitriles to yield amines (Sections 20.7 and 24.6).

Lithium diisopropylamide (LDA), $LiN(i\text{-}Pr)_2$: Reacts with carbonyl compounds (aldehydes, ketones, esters) to yield enolate ions (Sections 22.5 and 22.7).

Lithium diorganocopper reagent (Gilman reagent), LiR_2Cu: Couples with alkyl halides to yield alkanes (Section 10.7).
- Adds to α,β-unsaturated ketones to give 1,4-addition products (Section 19.13).
- Reacts with acid chlorides to give ketones (Section 21.4).

Magnesium, Mg: Reacts with organohalides to yield Grignard reagents (Section 10.6).

Mercuric acetate, $Hg(O_2CCH_3)_2$: Adds to alkenes in the presence of water, giving α-hydroxy organomercury compounds that can be reduced with $NaBH_4$ to yield alcohols. The overall effect is the Markovnikov hydration of an alkene (Section 8.4).

Mercuric sulfate, $HgSO_4$: Acts as a catalyst for the addition of water to alkynes in the presence of aqueous sulfuric acid, yielding ketones (Section 9.4).

Mercuric trifluoroacetate, $Hg(O_2CCF_3)_2$: Adds to alkenes in the presence of alcohol, giving α-alkoxy organomercury compounds that can be reduced with $NaBH_4$ to yield ethers. The overall reaction effects a net addition of an alcohol to an alkene (Section 18.2).

Nitric acid, HNO_3: Reacts with arenes in the presence of sulfuric acid to yield nitroarenes (Section 16.2).
- Oxidizes aldoses to yield aldaric acids (Section 25.6).

Nitrous acid, HNO_2: Reacts with amines to yield diazonium salts (Section 24.8).

Osmium tetroxide, OsO_4: Adds to alkenes to yield 1,2-diols (Section 8.7).

Ozone, O_3: Adds to alkenes to cleave the carbon–carbon double bond and give ozonides, which can be reduced with zinc in acetic acid to yield carbonyl compounds (Section 8.8).

Palladium on carbon, Pd/C: Acts as a hydrogenation catalyst for reducing carbon–carbon multiple bonds. Alkenes and alkynes are reduced to yield alkanes (Sections 8.6 and 9.5).
- Acts as a hydrogenation catalyst for reducing aryl ketones to yield alkylbenzenes (Sections 16.10 and 24.6).

Periodic acid, HIO_4: Reacts with 1,2-diols to yield carbonyl-containing cleavage products (Section 8.8).

Peroxyacetic acid, CH_3CO_3H: Oxidizes sulfoxides to yield sulfones (Section 18.7).

Phenylisothiocyanate, $C_6H_5–N=C=S$: Used in the Edman degradation of peptides to identify N-terminal amino acids (Section 26.6).

Phosphorus oxychloride, $POCl_3$: Reacts with secondary and tertiary alcohols to yield alkene dehydration products (Section 17.6).

Phosphorus tribromide, PBr_3: Reacts with alcohols to yield alkyl bromides (Section 10.5).
– Reacts with carboxylic acids to yield acid bromides (Section 21.4).
– Reacts with carboxylic acids in the presence of bromine to yield α-bromo carboxylic acids (Hell–Volhard–Zelinskii reaction) (Section 22.4).

Platinum oxide (Adams catalyst), PtO_2: Acts as a hydrogenation catalyst in the reduction of alkenes and alkynes to yield alkanes (Section 9.5).

Potassium hydroxide, KOH: Reacts with alkyl halides to yield alkenes by an elimination reaction (Section 11.7).
– Reacts with 1,1- or 1,2-dihaloalkanes to yield alkynes by a twofold elimination reaction (Section 9.2).

Potassium nitrosodisulfonate (Fremy's salt), $K(SO_3)_2NO$: Oxidizes phenols to yield quinones (Section 17.10).

Potassium permanganate, $KMnO_4$: Oxidizes alkynes to give carboxylic acid triple-bond cleavage products (Section 9.6).
– Oxidizes aromatic side chains to yield benzoic acids (Section 16.8).

Potassium phthalimide, $C_6H_4(CO)_2NK$: Reacts with alkyl halides to yield *N*-alkylphthalimides, which are hydrolyzed by aqueous sodium hydroxide to yield amines (Gabriel amine synthesis) (Section 24.6).

Potassium *tert*-butoxide, KO-*t*-Bu: Reacts with allylic halides to yield conjugated dienes (Section 14.1).

Pyridine, C_5H_5N: Acts as a basic catalyst for the reaction of alcohols with acid chlorides to yield esters (Section 21.4).
– Reacts with α-bromo ketones to yield α,β-unsaturated ketones (Section 22.3).

Pyrrolidine, C_4H_8N: Reacts with ketones to yield enamines for use in the Stork enamine reaction (Section 23.11).

Rhodium on carbon, Rh/C: Acts as a hydrogenation catalyst in the reduction of benzene rings to yield cyclohexanes (Section 16.9).

Silver oxide, Ag_2O: Catalyzes the reaction of monosaccharides with alkyl halides to yield ethers (Section 25.6).
– Reacts with tetraalkylammonium salts to yield alkenes (Hofmann elimination) (Section 24.7).

Sodium amide, $NaNH_2$: Reacts with terminal alkynes to yield acetylide anions (Section 9.7).
– Reacts with 1,1- or 1,2-dihalides to yield alkynes by a twofold elimination reaction (Section 9.2).
– Reacts with aryl halides to yield anilines by a benzyne aromatic substitution mechanism (Section 16.7).

Sodium azide, NaN_3: Reacts with alkyl halides to yield alkyl azides (Section 24.6).
– Reacts with acid chlorides to yield acyl azides. On heating in the presence of water, acyl azides yield amines and carbon dioxide (Section 24.6).

Sodium bisulfite, $NaHSO_3$: Reduces osmate esters, prepared by treatment of an alkene with osmium tetroxide, to yield 1,2-diols (Section 8.7).

Sodium borohydride, $NaBH_4$: Reduces organomercury compounds, prepared by oxymercuration of alkenes, to convert the C–Hg bond to C–H (Section 8.4).
– Reduces ketones and aldehydes to yield alcohols (Sections 17.4 and 19.7).
– Reduces quinones to yield hydroquinones (Section 17.10).

Sodium cyanide, NaCN: Reacts with alkyl halides to yield alkanenitriles (Section 20.5).

Sodium dichromate, $Na_2Cr_2O_7$: Oxidation of phenols to quinones (Section 17.10).

Sodium hydride, NaH: Reacts with alcohols to yield alkoxide anions (Section 17.2).

Sodium hydroxide, NaOH: Reacts with aryl halides to yield phenols by a benzyne aromatic substitution mechanism (Section 16.7).

Sodium iodide, NaI: Reacts with arenediazonium salts to yield aryl iodides (Section 24.8).

Stannous chloride, $SnCl_2$: Reduces nitroarenes to yield anilines (Sections 16.2 and 24.6).
– Reduces quinones to yield hydroquinones (Section 17.10).

Sulfur trioxide, SO_3: Reacts with arenes in sulfuric acid solution to yield arenesulfonic acids (Section 16.2).

Sulfuric acid, H_2SO_4: Reacts with alcohols and water to yield alkenes (Section 8.4).
- Reacts with alkynes in the presence of water and mercuric sulfate to yield ketones (Section 9.4).
- Catalyzes the reaction of nitric acid with aromatic rings to yield nitroarenes (Section 16.2).
- Catalyzes the reaction of SO_3 with aromatic rings to yield arenesulfonic acids (Section 16.2).

Tetrazole: Acts as a coupling catalyst for use in DNA synthesis (Section 28.7).

Thionyl chloride, $SOCl_2$: Reacts with primary and secondary alcohols to yield alkyl chlorides (Section 10.5).
- Reacts with carboxylic acids to yield acid chlorides (Section 21.4).

Thiourea, H_2NCSNH_2: Reacts with primary alkyl halides to yield thiols (Section 18.7).

***p*-Toluenesulfonyl chloride, *p*-$CH_3C_6H_4SO_2Cl$:** Reacts with alcohols to yield tosylates (Sections 11.1 and 17.6).

Trifluoroacetic acid, CF_3CO_2H: Acts as a catalyst for cleaving *tert*-butyl ethers, yielding alcohols and 2-methylpropene (Section 18.3).
- Acts as a catalyst for cleaving the *t*-Boc protecting group from amino acids in peptide synthesis (Section 26.7).

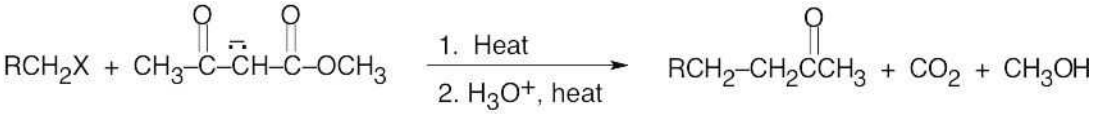
Triphenylphosphine, $(C_6H_5)_3P$: Reacts with primary alkyl halides to yield the alkyltriphenylphosphonium salts used in Wittig reactions (Section 19.11).

Zinc, Zn: Reduces ozonides, produced by addition of ozone to alkenes, to yield ketones and aldehydes (Section 8.8).
- Reduces disulfides to yield thiols (Section 18.7).

Zinc–copper couple, Zn–Cu: Reacts with diiodomethane in the presence of alkenes to yield cyclopropanes (Simmons–Smith reaction) (Section 8.9).

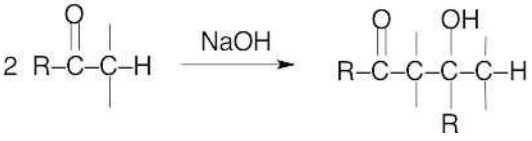
Appendix D: Name Reactions in Organic Chemistry

Acetoacetic ester synthesis (Section 22.7): a multistep reaction sequence for converting a primary alkyl halide into a methyl ketone having three more carbon atoms in the chain.

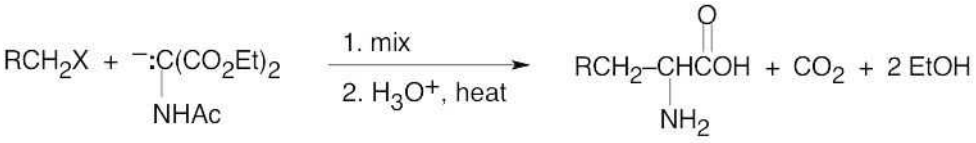


Adams' catalyst (Section 8.6): PtO_2, a catalyst used for the hydrogenation of carbon–carbon double bonds.

Aldol condensation reaction (Section 23.1): the nucleophilic addition of an enol or enolate ion to a ketone or aldehyde, yielding a β-hydroxy ketone.

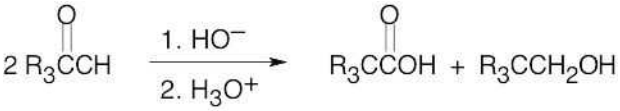


Amidomalonate amino acid synthesis (Section 26.3): a multistep reaction sequence, similar to the malonic ester synthesis, for converting a primary alkyl halide into an amino acid.

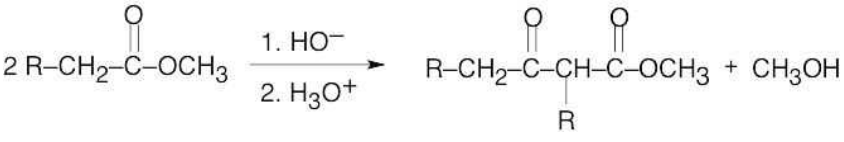


Benedict's test (Section 25.6): a chemical test for aldehydes, involving treatment with cupric ion in aqueous sodium citrate.

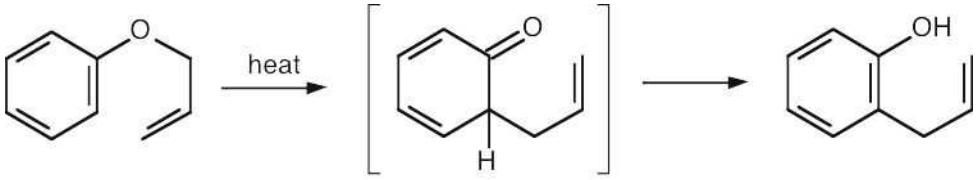
Cannizzaro reaction (Section 19.12): the disproportionation reaction that occurs when a nonenolizable aldehyde is treated with base.



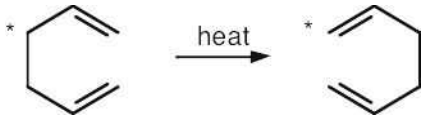
Claisen condensation reaction (Section 23.7): a nucleophilic acyl substitution reaction that occurs when an ester enolate ion attacks the carbonyl group of a second ester molecule. The product is a β-keto ester.



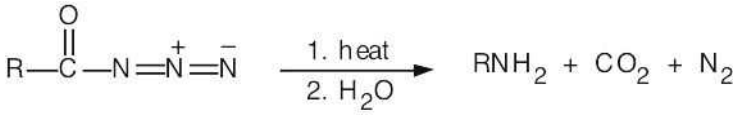
Claisen rearrangement (Section 30.8): the thermal [3.3] sigmatropic rearrangement of an allyl vinyl ether or an allyl phenyl ether.



Cope rearrangement (Section 30.8): the thermal [3.3] sigmatropic rearrangement of a 1,5-diene to a new 1,5-diene.

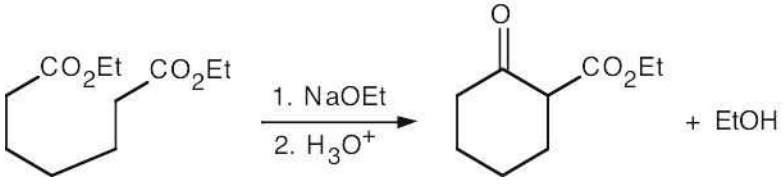


Curtius rearrangement (Section 24.6): the thermal rearrangement of an acyl azide to an isocyanate, followed by hydrolysis to yield an amine.

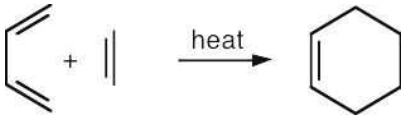


Diazonium coupling reaction (Section 24.8): the coupling reaction between an aromatic diazonium salt and a phenol or aniline.

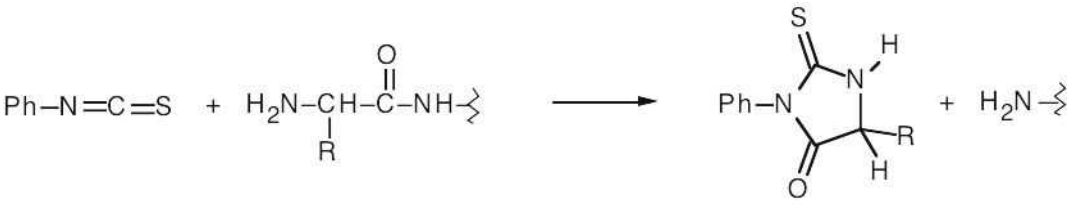
Dieckmann reaction (Section 23.9): the intramolecular Claisen condensation reaction of a 1,6- or 1,7-diester, yielding a cyclic β-keto ester.



Diels–Alder cycloaddition reaction (Sections 14.4–14.5 and 30.5): the reaction between a diene and a dienophile to yield a cyclohexene ring.

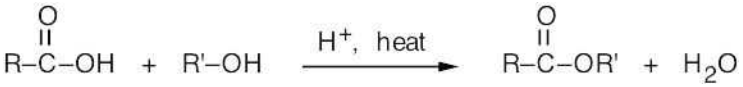


Edman degradation (Section 26.6): a method for cleaving the N-terminal amino acid from a peptide by treatment of the peptide with *N*-phenylisothiocyanate.

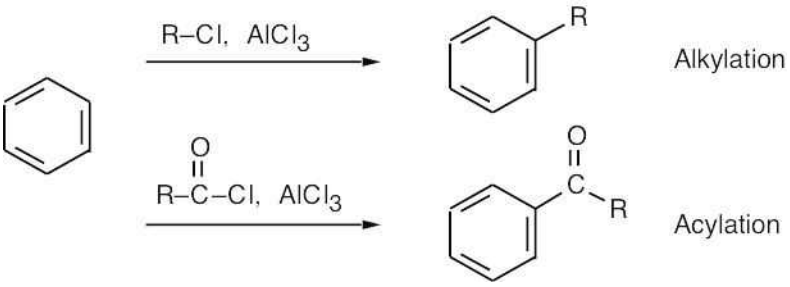


Fehling's test (Section 25.6): a chemical test for aldehydes, involving treatment with cupric ion in aqueous sodium tartrate.

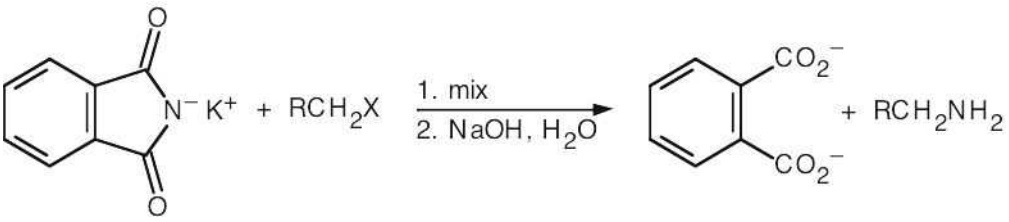
Fischer esterification reaction (Section 21.3): the acid-catalyzed reaction between a carboxylic acid and an alcohol, yielding the ester.



Friedel–Crafts reaction (Section 16.3): the alkylation or acylation of an aromatic ring by treatment with an alkyl- or acyl chloride in the presence of a Lewis-acid catalyst.

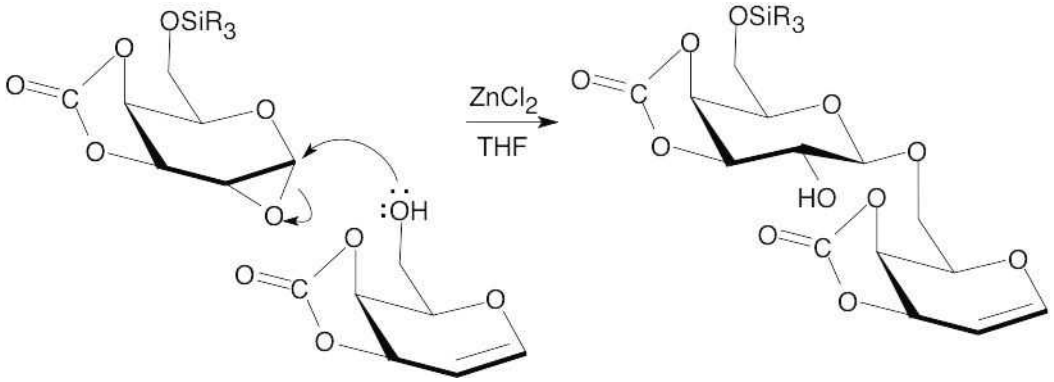


Gabriel amine synthesis (Section 24.6): a multistep sequence for converting a primary alkyl halide into a primary amine by alkylation with potassium phthalimide, followed by hydrolysis.

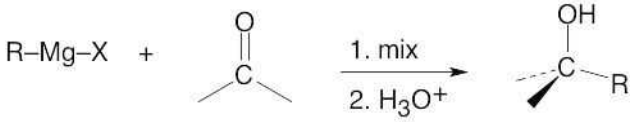


Gilman reagent (Section 10.7): a lithium dialkylcopper reagent, R_2CuLi, prepared by treatment of a cuprous salt with an alkyllithium. Gilman reagents undergo a coupling reaction with alkyl halides, a 1,4-addition reaction with α,β-unsaturated ketones, and a coupling reaction with acid chlorides to yield ketones.

Glycal assembly method (Section 25.9): a method of polysaccharide synthesis in which a glycal is converted into its epoxide, which is then opened by reaction with an alcohol.

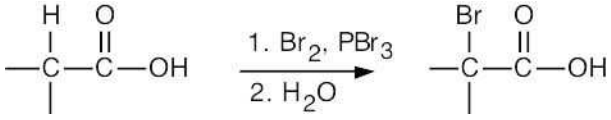


Grignard reaction (Section 19.7): the nucleophilic addition reaction of an alkylmagnesium halide to a ketone, aldehyde, or ester carbonyl group.

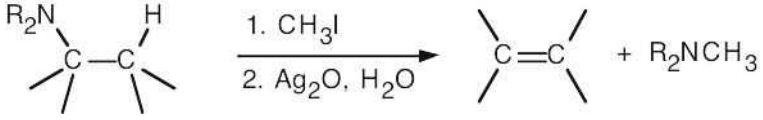


Grignard reagent (Section 10.6): an organomagnesium halide, RMgX, prepared by reaction between an organohalide and magnesium metal. Grignard reagents add to carbonyl compounds to yield alcohols.

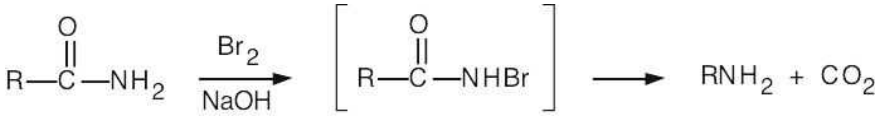
Hell–Volhard–Zelinskii reaction (Section 22.4): the α-bromination of a carboxylic acid by treatment with bromine and phosphorus tribromide.



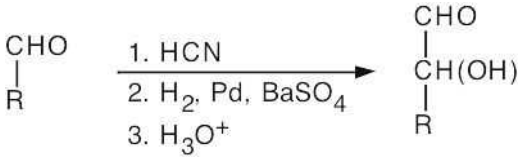
Hofmann elimination (Section 24.7): a method for effecting the elimination reaction of an amine to yield an alkene. The amine is first treated with excess iodomethane, and the resultant quaternary ammonium salt is heated with silver oxide.



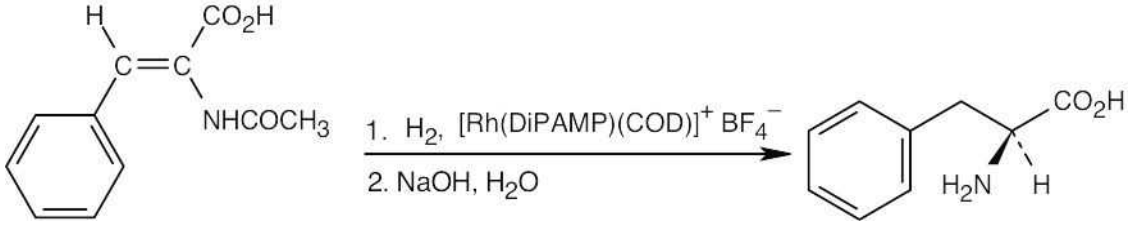
Hofmann rearrangement (Section 24.6): the rearrangement of an *N*-bromoamide to a primary amine by treatment with aqueous base.



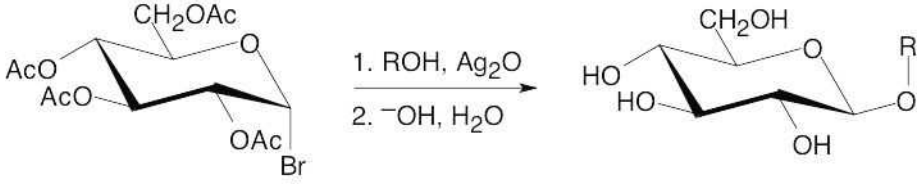
Kiliani–Fischer synthesis (Section 25.6): a multistep sequence for chain-lengthening an aldose into the next higher homolog.



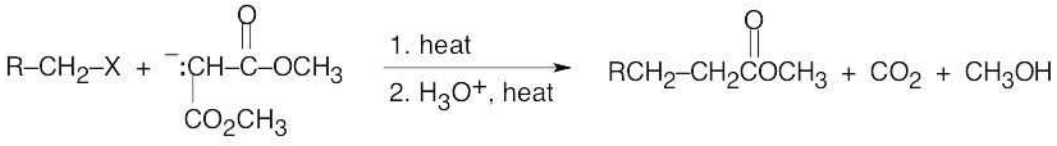
Knowles amino acid synthesis (Section 26.3): an enantioselective method of amino acid synthesis by hydrogenation of a Z enamido acid with a chiral hydrogenation catalyst.



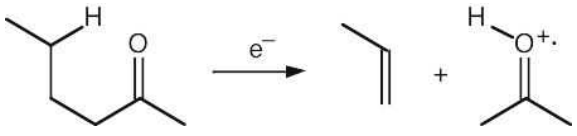
Koenigs–Knorr reaction (Section 25.6): a method for synthesizing a glycoside by reaction of a pyranosyl bromide with an alcohol and Ag_2O.



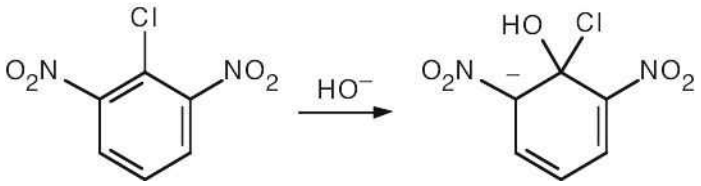
Malonic ester synthesis (Section 22.7): a multistep sequence for converting an alkyl halide into a carboxylic acid with the addition of two carbon atoms to the chain.



McLafferty rearrangement (Section 19.14): a mass spectral fragmentation pathway for carbonyl compounds having a hydrogen three carbon atoms away from the carbonyl carbon.

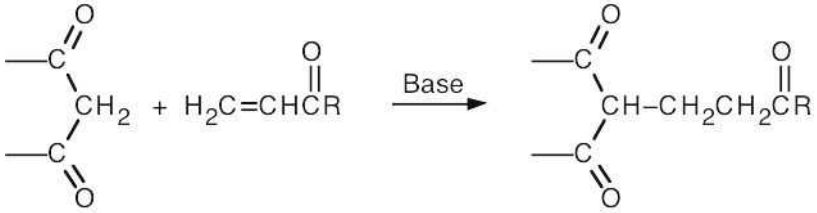


Meisenheimer complex (Section 16.6): an intermediate formed in the nucleophilic aryl substitution reaction of a base with a nitro-substituted aromatic ring.

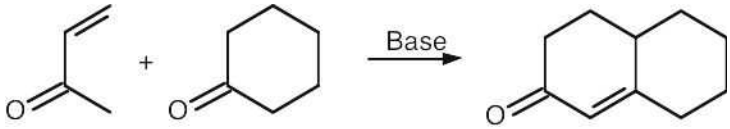


Merrifield solid-phase peptide synthesis (Section 26.8): a rapid and efficient means of peptide synthesis in which the growing peptide chain is attached to an insoluble polymer support.

Michael reaction (Section 23.10): the 1,4-addition reaction of a stabilized enolate anion such as that from a 1,3-diketone to an α,β-unsaturated carbonyl compound.



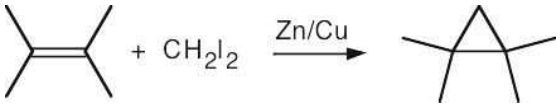
Robinson annulation reaction (Section 23.12): a multistep sequence for building a new cyclohexenone ring onto a ketone. The sequence involves an initial Michael reaction of the ketone followed by an internal aldol cyclization.



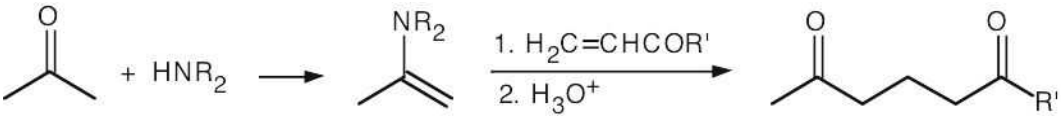
Sandmeyer reaction (Section 24.8): a method for converting an aryldiazonium salt into an aryl halide by treatment with a cuprous halide.

Sanger dideoxy method (Section 28.6): an enzymatic method for DNA sequencing.

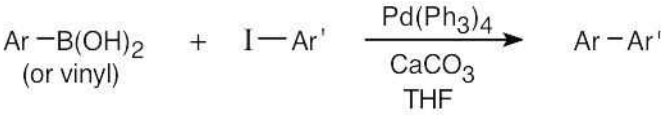
Simmons–Smith reaction (Section 8.9): a method for preparing a cyclopropane by treating an alkene with diiodomethane and zinc–copper.



Stork enamine reaction (Section 23.11): a multistep sequence whereby a ketone is converted into an enamine by treatment with a secondary amine, and the enamine is then used in Michael reactions.



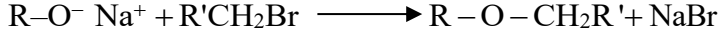
Suzuki–Miyaura reaction (Section 10.7): an organometallic coupling of an aromatic or vinyl substituted boronic acid with an aryl or vinyl substituted organohalide in the presence of a base and a palladium catalyst.



Tollens' test (Section 25.6): a chemical test for detecting aldehydes by treatment with ammoniacal silver nitrate. A positive test is signaled by formation of a silver mirror on the walls of the reaction vessel.

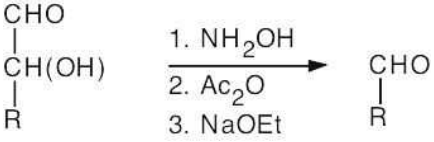
Walden inversion (Section 11.1): the inversion of stereochemistry at a chirality center during an S_N2 reaction.

Williamson ether synthesis (Section 18.2): a method for preparing an ether by treatment of a primary alkyl halide with an alkoxide ion.

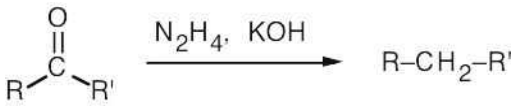


Wittig reaction (Section 19.11): a general method of alkene synthesis by treatment of a ketone or aldehyde with an alkylidenetriphenylphosphorane.

Wohl degradation (Section 25.6): a multistep reaction sequence for degrading an aldose into the next lower homolog.



Wolff–Kishner reaction (Section 19.9): a method for converting a ketone or aldehyde into the corresponding hydrocarbon by treatment with hydrazine and strong base.

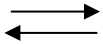


Woodward–Hoffmann orbital symmetry rules (Section 30.1): a series of rules for predicting the stereochemistry of pericyclic reactions. Even-electron species react thermally through either antarafacial or conrotatory pathways, whereas odd-electron species react thermally through either suprafacial or disrotatory pathways.

Appendix E: Abbreviations

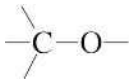
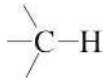
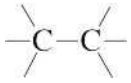
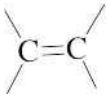
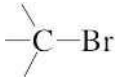
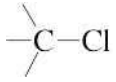
Å	symbol for Angstrom unit (10^{-8} cm = 10^{-10} m)
ADMET	acyclic diene metathesis, a method of polymerization
Ac–	acetyl group, 
Ar–	aryl group
at. no.	atomic number
at. wt.	atomic weight
$[\alpha]_D$	specific rotation
Boc	*tert*-butoxycarbonyl group, 
bp	boiling point
n-Bu	*n*-butyl group, $CH_3CH_2CH_2CH_2$–
sec-Bu	*sec*-butyl group, $CH_3CH_2CH(CH_3)$–
t-Bu	*tert*-butyl group, $(CH_3)_3C$–
cm	centimeter
cm^{-1}	wavenumber, or reciprocal centimeter
D	stereochemical designation of carbohydrates and amino acids
DCC	dicyclohexylcarbodiimide, C_6H_{11}–N=C=N–C_6H_{11}
δ	chemical shift in ppm downfield from TMS
Δ	symbol for heat; also symbol for change
Δ*H*	heat of reaction
dm	decimeter (0.1 m)
DMF	dimethylformamide, $(CH_3)_2NCHO$
DMSO	dimethyl sulfoxide, $(CH_3)_2SO$
DNA	deoxyribonucleic acid
DNP	dinitrophenyl group, as in 2,4-DNP (2,4-dinitrophenylhydrazone)
(E)	entgegen, stereochemical designation of trans-double bond geometry
E_{act}	activation energy
E1	unimolecular elimination reaction
E1cB	unimolecular elimination that takes place through a carbanion intermediate
E2	bimolecular elimination reaction
Et	ethyl group, CH_3CH_2–

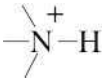
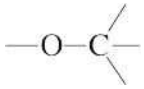
g	gram
hv	symbol for light
Hz	Hertz, or cycles per second (s^{-1})
i-	iso
IR	infrared
J	Joule
J	symbol for coupling constant
K	Kelvin temperature
K_a	acid dissociation constant
kJ	kilojoule
L	stereochemical designation of carbohydrates and amino acids
LAH	lithium aluminum hydride, $LiAlH_4$
Me	methyl group, CH_3–
mg	milligram (0.001 g)
MHz	megahertz (10^6 s^{-1})
mL	milliliter (0.001 L)
mm	millimeter (0.001 m)
mp	melting point
μg	microgram (10^{-6} g)
mμ	millimicron (nanometer, 10^{-9} m)
MW	molecular weight
n-	normal, straight-chain alkane or alkyl group
ng	nanogram (10^{-9} gram)
nm	nanometer (10^{-9} meter)
NMR	nuclear magnetic resonance
–OAc	acetate group, 
Ph	phenyl group, $–C_6H_5$
pH	measure of acidity of aqueous solution
pK_a	measure of acid strength (= –log K_a)
pm	picometer (10^{-12} m)
ppm	parts per million
n-Pr	*n*-propyl group, $CH_3CH_2CH_2$–

i-Pr	isopropyl group, $(CH_3)_2CH–$
pro-*R*	designation of a prochirality center
pro-*S*	designation of a prochirality center
R–	symbol for a generalized alkyl group
(R)	*rectus*, designation of chirality center
Re face	a face of a planar, sp^2-hybridized carbon atom
RNA	ribonucleic acid
ROMP	ring-opening metathesis polymerization
(S)	*sinister*, designation of chirality center
sec-	secondary
Si face	a face of a planar, sp^2-hybridized carbon atom
S_N1	unimolecular substitution reaction
S_N2	bimolecular substitution reaction
tert-	tertiary
THF	tetrahydrofuran
TMS	tetramethylsilane nmr standard, $(CH_3)_4Si$
Tos	tosylate group, 
UV	ultraviolet
X–	halogen group (–F, –Cl, –Br, –I)
(Z)	zusammen, stereochemical designation of cis-double bond geometry
	chemical reaction in direction indicated
	reversible chemical reaction
	resonance symbol
	curved arrow indicating direction of electron flow
≡	is equivalent to
>	greater than
<	less than
≈	approximately equal to
	indicates that the organic fragment shown is a part of a larger molecule
	single bond coming out of the plane of the paper

-----	single bond receding into the plane of the paper
……	partial bond
δ+, δ–	partial charge
‡	denoting the transition state

Appendix F: Infrared Absorption Frequencies

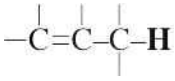
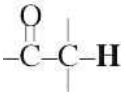
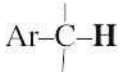
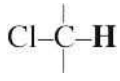
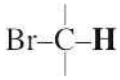
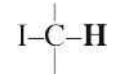
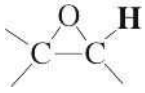
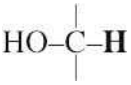
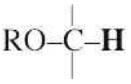
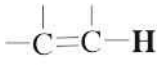
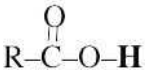
Functional Group		Frequency (cm^{-1})*	Text Section
Alcohol	–O–H	3300–3600 (s)	17.11
		1050 (s)	
Aldehyde	–CO–H	2720, 2820 (m)	19.14
aliphatic		1725 (s)	
aromatic		1705 (s)	
Alkane			12.8
		2850–2960 (s)	
		800–1300 (m)	
Alkene			12.8
		3020–3100 (s)	
		1650–1670 (m)	
	$RCH{=}CH_2$	910, 990 (m)	
	$R_2C{=}CH_2$	890 (m)	
Alkyne	≡C–H	3300 (s)	12.8
	–C≡C–	2100–2260 (m)	
Alkyl bromide			12.8
		500–600 (s)	
Alkyl chloride			12.8
		600–800 (s)	
Amine			
primary			24.10
		3400, 3500 (s)	
secondary			24.10
		3350 (s)	

Ammonium salt			24.10
		2200–3000 (broad)	
Aromatic ring	Ar–H	3030 (m)	15.7
monosubstituted	Ar–R	690–710 (s)	
		730–770 (s)	
o-disubstituted		735–770 (s)	
m-disubstituted		690–710 (s)	
		810–850 (s)	
p-disubstituted		810–840 (s)	
Carboxylic acid	–O–H	2500–3300 (broad)	20.8
associated		1710 (s)	
free		1760 (s)	
Acid anhydride			21.10
		1760, 1820 (s)	
Acid chloride			21.10
aliphatic		1810 (s)	
aromatic		1770 (s)	
Amide			21.10
aliphatic		1810 (s)	
aromatic		1770 (s)	
N-substituted		1680 (s)	
NN-disubstituted		1650 (s)	
Ester			21.10
aliphatic		1735 (s)	
aromatic		1720 (s)	
Ether			18.8
		1050–1150 (s)	

Ketone			19.14
aliphatic		1715 (s)	
aromatic		1690 (s)	
6-membered ring		1715 (s)	
5-membered ring		1750 (s)	
Nitrile			20.8
aliphatic	–C≡N	2250 (m)	
aromatic		2230 (m)	
Phenol	–O–H	3500 (s)	17.11

*(s) = strong; (m) = medium intensity

Appendix G: Proton NMR Chemical Shifts

Type of Proton		Chemical Shift (δ)	Text Section
Alkyl, primary	R–C**H**$_3$	0.7–1.3	13.4
Alkyl, secondary	R–C**H**$_2$–R	1.2–1.4	13.4
Alkyl tertiary	R$_3$C–**H**	1.4–1.7	13.4
Allylic		1.6–1.9	13.4
α to carbonyl		2.0–2.3	19.14
Benzylic		2.3–3.0	15.7
Acetylenic	R–C≡C–**H**	2.5–2.7	13.4
Alkyl chloride		3.0–4.0	13.4
Alkyl bromide		2.5–4.0	13.4
Alkyl iodide		2.0–4.0	13.4
Amine		2.2–2.6	24.10
Epoxide		2.5–3.5	18.8
Alcohol		3.5–4.5	17.11
Ether		3.5–4.5	18.8
Vinylic		5.0–6.0	13.4
Aromatic	Ar–**H**	6.5–8.0	15.7
Aldehyde		9.7–10.0	19.14
Carboxylic acid		11.0–12.0	20.8
Alcohol	R–O–**H**	3.5–4.5	17.11
Phenol	Ar–O–**H**	2.5–6.0	17.11

Appendix H: Nobel Prize Winners in Chemistry

1901 **Jacobus H. van't Hoff** (Germany)
"for the discovery of laws of chemical dynamics and osmotic pressure in solutions"

1902 **Emil Fischer** (Germany)
"for the extraordinary services he has rendered by his work on sugar and purine syntheses"

1903 **Svante Arrhenius** (Sweden)
"for his theory of electrolytic dissociation"

1904 **Sir William Ramsay** (United Kingdom)
"for the discovery of the inert gaseous elements in air, and his determination of their place in the periodic system"

1905 **Adolf von Baeyer** (Germany)
"in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds"

1906 **Henri Moissan** (France)
"for his investigation and isolation of the element fluorine, and for the adoption in the service of science of the electric furnace named after him"

1907 **Eduard Buchner** (Germany)
"for his biochemical researches and his discovery of cell-free fermentation"

1908 **Ernest Rutherford** (United Kingdom)
"for his investigation into the disintegration of the elements and the chemistry of radioactive substances"

1909 **Wilhelm Ostwald** (Germany)
"for his work on catalysis and for his investigations into the fundamental principles governing chemical equilibria and rates of reaction"

1910 **Otto Wallach** (Germany)
"for his services to organic chemistry and the chemical industry by his pioneer work in the field of alicyclic substances"

1911 **Marie Curie** (France)
"in recognition of her services to the advancement of chemistry by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element"

1912 **Victor Grignard** (France)
"for the discovery of the so-called Grignard reagent, which in recent years has greatly advanced the progress of organic chemistry"

Paul Sabatier (France)
"for his method of hydrogenating organic compounds in the presence of finely disintegrated metals whereby the progress of organic chemistry has been greatly advanced in recent years"

1913 **Alfred Werner** (Switzerland)
"in recognition of his work on the linkage of atoms in molecules by which he has thrown new light on earlier investigations and opened up new fields of research especially in inorganic chemistry"

1914 **Theodore W. Richards** (United States)
"in recognition of his accurate determinations of the atomic weight of a large number of chemical elements"

1915 **Richard Willstätter** (Germany)
"for his researches on plant pigments, especially chlorophyll"

1916–17 No award

1918 **Fritz Haber** (Germany)
"for the synthesis of ammonia from its elements"

1919 No award

1920 **Walther Nernst** (Germany)
"in recognition of his work in thermochemistry"

1921 **Frederick Soddy** (United Kingdom)
"for his contributions to our knowledge of the chemistry of radioactive substances, and his investigations into the origin and nature of isotopes"

1922 **Francis W. Aston** (United Kingdom)
"for his discovery, by means of his mass spectrograph, of isotopes, in a large number of non-radioactive elements, and for his enunciation of the whole-number rule"

1923 **Fritz Pregl** (Austria)
"for his invention of the method of microanalysis of organic substances"

1924 No award

1925 **Richard Zsigmondy** (Germany)
"for his demonstration of the heterogeneous nature of colloid solutions, and for the methods he used, which have since become fundamental in modern colloid chemistry"

1926 **The (Theodor) Svedberg** (Sweden)
"for his work on disperse systems"

1927 **Heinrich Wieland** (Germany)
"for his investigations of the constitution of the bile acids and related substances"

1928 **Adolf Windaus** (Germany)
"for his services rendered through his research into the constitution of the sterols and their connection with the vitamins"

1929 **Arthur Harden** (United Kingdom)
Hans von Euler-Chelpin (Sweden)
"for their investigations on the fermentation of sugar and fermentative enzymes"

1930 **Hans Fischer** (Germany)
"for his researches into the constitution of haemin and chlorophyll, and especially for his synthesis of haemin"

1931 **Frederich Bergius** (Germany)
Carl Bosch (Germany)
"in recognition of their contributions to the invention and development of chemical high-pressure methods"

1932 **Irving Langmuir** (United States)
"for his discoveries and investigations in surface chemistry"

1933 No award

1934 **Harold C. Urey** (United States)
"for his discovery of heavy hydrogen"

1935 **Frédéric Joliot** (France)
Iréne Joliot-Curie (France)
"in recognition of their synthesis of new radioactive elements"

1936 **Peter Debye** (Germany)
"for his contributions to our knowledge of molecular structure through his investigations on dipole moments and on the diffraction of X-rays and electrons in gases"

1937 **Norman Haworth** (United Kingdom)
"for his investigations on carbohydrates and vitamin C"

Paul Karrer (Switzerland)
"for his investigations on carotenoids, flavins, and vitamins A and B"

1938 **Richard Kuhn** (Germany)
"for his work on carotenoids and vitamins"

1939 **Adolf Butenandt** (Germany)
"for his work on sex hormones"

Leopold Ruzicka (Switzerland)
"for his work on polymethylenes and higher terpenes"

1940–42 No award

1943 **George de Hevesy** (Sweden)
"for his work on the use of isotopes as tracers in the study of chemical processes"

1944 **Otto Hahn** (Germany)
"for his discovery of the fission of heavy nuclei"

1945 **Artturi Virtanen** (Finland)
"for his researches and inventions in agricultural and nutrition chemistry, especially for his fodder preservation method"

1946 **James B. Sumner** (United States)
"for his discovery that enzymes can be crystallized"

John H. Northrop (United States)
Wendell M. Stanley (United States)
"for their preparation of enzymes and virus proteins in a pure form"

1947 **Sir Robert Robinson** (United Kingdom)
"for his investigations on plant products of biological importance, especially the alkaloids"

1948 **Arne Tiselius** (Sweden)
"for his research on electrophoresis and adsorption analysis, especially for his discoveries concerning the complex nature of the serum proteins"

1949 **William F. Giauque** (United States)
"for his contributions in the field of chemical thermodynamics, particularly concerning the behavior of substances at extremely low temperatures"

1950 **Kurt Alder** (Germany)
Otto Diels (West Germany, now Germany)
"for their discovery and development of the diene synthesis"

1951 **Edwin M. McMillan** (United States)
Glenn T. Seaborg (United States)
"for their discoveries in the chemistry of the transuranium elements"

1952 **Archer J. P. Martin** (United Kingdom)
Richard L. M. Synge (United Kingdom)
"for their invention of partition chromatography"

1953 **Hermann Staudinger** (Germany)
"for his discoveries in the field of macromolecular chemistry"

1954 **Linus C. Pauling** (United States)
"for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances"

1955 **Vincent du Vigneaud** (United States)
"for his work on biochemically important sulfur compounds, especially for the first synthesis of a polypeptide hormone"

1956 **Sir Cyril Hinshelwood** (United Kingdom)
Nikolay Semenov (U.S.S.R., now Russia)
"for their researches into the mechanism of chemical reactions"

1957 **Lord Todd** (United Kingdom)
"for his work on nucleotides and nucleotide co-enzymes"

1958 **Frederick Sanger** (United Kingdom)
"for his work on the structure of proteins, particularly that of insulin"

1959 **Jaroslav Heyrovsky** (Czechoslovakia, now Czech Republic)
"for his discovery and development of the polarographic methods of analysis"

1960 **Willard F. Libby** (United States)
"for his method to use carbon-14 for age determination in archaeology, geology, geophysics, and other branches of science"

1961 **Melvin Calvin** (United States)
"for his research on the carbon dioxide assimilation in plants"

1962 **John C. Kendrew** (United Kingdom)
Max F. Perutz (United Kingdom)
"for their studies of the structures of globular proteins"

1963 **Giulio Natta** (Italy)
Karl Ziegler (Germany)
"for their discoveries in the field of the chemistry and technology of high polymers"

1964 **Dorothy Crowfoot Hodgkin** (United Kingdom)
"for her determinations by X-ray techniques of the structures of important biochemical substances"

1965 **Robert B. Woodward** (United States)
"for his outstanding achievements in the art of organic synthesis"

1966 **Robert S. Mulliken** (United States)
"for his fundamental work concerning chemical bonds and the electronic structure of molecules by the molecular orbital method"

1967 **Manfred Eigen** (Germany)
Ronald G. W. Norrish (United Kingdom)
George Porter (United Kingdom)
"for their studies of extremely fast chemical reactions, effected by disturbing the equilibrium by means of very short pulses of energy"

1968 **Lars Onsager** (United States)
"for his discovery of the reciprocal relations bearing his name, which are fundamental for the thermodynamics of irreversible processes"

1969 **Derek H. R. Barton** (United Kingdom)
Odd Hassel (Norway)
"for their contributions to the development of the concept of conformation and its application in chemistry"

1970 **Luis F. Leloir** (Argentina)
"for his discovery of sugar nucleotides and their role in the biosynthesis of carbohydrates"

1971 **Gerhard Herzberg** (Canada)
"for his contributions to the knowledge of electronic structure and geometry of molecules, particularly free radicals"

1972 **Christian B. Anfinsen** (United States)
"for his work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation"

Stanford Moore (United States)
William H. Stein (United States)
"for their contribution to the understanding of the connection between chemical structure and catalytic activity of the active center of the ribonuclease molecule"

1973 **Ernst Otto Fischer** (Germany)
Geoffrey Wilkinson (United Kingdom)
"for their pioneering work, performed independently, on the chemistry of the organometallic, so called sandwich compounds"

1974 **Paul J. Flory** (United States)
"for his fundamental achievements, both theoretical and experimental, in the physical chemistry of macromolecules"

1975 **John Cornforth** (United Kingdom)
"for his work on the stereochemistry of enzyme-catalyzed reactions"

Vladimir Prelog (Switzerland)
"for his research on the stereochemistry of organic molecules and reactions"

1976 **William N. Lipscomb** (United States)
"for his studies on the structures of boranes illuminating problems of chemical bonding"

1977 **Ilya Prigogine** (Belgium and United States)
"for his contributions to non-equilibrium thermodynamics, particularly the theory of dissipative structures"

1978 **Peter Mitchell** (United Kingdom)
"for his contribution to the understanding of biological energy transfer through the formulation of the chemiosmotic theory"

1979 **Herbert C. Brown** (United States)
Georg Wittig (Germany)
"for their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis"

1980 **Paul Berg** (United States)
"for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant-DNA"

Walter Gilbert (United States)
Frederick Sanger (United Kingdom)
"for their contributions concerning the determination of base sequences in nucleic acids"

1981 **Kenichi Fukui** (Japan)
Roald Hoffmann (United States)
"for their theories, developed independently, concerning the course of chemical reactions"

1982 **Aaron Klug** (England)
"for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid – protein complexes"

1983 **Henry Taube** (United States)
"for his work on the mechanisms of electron transfer reactions, especially in metal complexes"

1984 **R. Bruce Merrifield** (United States)
"for his development of methodology for chemical synthesis on a solid matrix"

1985 **Herbert A. Hauptman** (United States)
Jerome Karle (United States)
"for their outstanding achievements in the development of direct methods for the determination of crystal structures"

1986 **Dudley R. Herschbach** (United States)
Yuan T. Lee (United States)
John C. Polanyi (Canada)
"for their contributions concerning the dynamics of chemical elementary processes"

1987 **Donald J. Cram** (United States)
Jean-Marie Lehn (France)
Charles J. Pedersen (United States)
"for their development and use of molecules with structure-specific interactions of high selectivity"

1988 **Johann Deisenhofer** (United States)
Robert Huber (Germany)
Hartmut Michel (Germany)
"for the determination of the three-dimensional structure of a photosynthetic reaction centre"

1989 **Sidney Altman** (United States)
Thomas R. Cech (United States)
"for their discovery of catalytic properties of RNA"

1990 **Elias James Corey** (United States)
"for his development of the theory and methodology of organic synthesis"

1991 **Richard R. Ernst** (Switzerland)
"for his contributions to the development of the methodology of high resolution magnetic resonance (NMR) spectroscopy"

1992 **Rudolph A. Marcus** (United States)
"for his contributions to the theory of electron transfer reactions in chemical systems"

1993 **Kary B. Mullis** (United States)
"for his invention of the polymerase chain reaction (PCR) method"

Michael Smith (Canada)
"for his fundamental contributions to the establishment of oligonucleotide-based, site-directed mutagenesis and its development for protein studies"

1994 **George A. Olah** (United States)
"for his contributions to carbocation chemistry"

1995 **Paul Crutzen** (Germany)
Mario Molina (United States)
F. Sherwood Rowland (United States)
"for their work in atmospheric chemistry, particularly concerning the formation and decomposition of ozone"

1996 **Robert F. Curl, Jr.** (United States)
Harold W. Kroto (United Kingdom)
Richard E. Smalley (United States)
"for their discovery of fullerenes"

1997 **Paul D. Boyer** (United States)
John E. Walker (United Kingdom)
"for their elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP)"

Jens C. Skou (Denmark)
"for the first discovery of an ion-transporting enzyme, Na + , K + -ATPase"

1998 **Walter Kohn** (United States)
John A. Pople (United States)
"to Walter Kohn for his development of the density-functional theory and to John Pople for his development of computational methods in quantum chemistry"

1999 **Ahmed H. Zewail** (United States)
"for his studies of the transition states of chemical reactions using femtosecond spectroscopy"

2000 **Alan J. Heeger** (United States)
Alan G. MacDiarmid (United States)
Hideki Shirakawa (Japan)
"for the discovery and development of electrically conductive polymers"

2001 **William S. Knowles** (United States)
Ryoji Noyori (Japan)
"for their work on chirally catalysed hydrogenation reactions"

K. Barry Sharpless (United States)
"for his work on chirally catalysed oxidation reactions"

2002 **John B. Fenn** (United States)
Koichi Tanaka (Japan)
"for their development of soft desorption ionisation methods for mass spectrometric analyses of biological macromolecules"

Kurt Wüthrich (Switzerland)
"for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution"

2003 **Peter Agre** (United States)
"for the discovery of water channels"

Roderick MacKinnon (United States)
"for structural and mechanistic studies of ion channels"

2004 **Aaron Ciechanover** (Israel)
Avram Hershko (Israel)
Irwin Rose (United States)
"for the discovery of ubiquitin-mediated protein degradation"

2005 **Yves Chauvin** (France)
Robert H. Grubbs (United States)
Richard R. Schrock (United States)
"for the development of the metathesis method in organic synthesis"

2006 **Roger D. Kornberg** (United States)
"for his studies of the molecular basis of eukaryotic transcription"

2007 **Gerhard Ertl** (Germany)
"for his studies of chemical processes on solid surfaces"

2008 **Osamu Shimomura** (United States)
Martin Chalfie (United States)
Roger Y. Tsien (United States)
"for the discovery and development of the green fluorescent protein, GFP"

2009 **Venkatraman Ramakrishnan** (United Kingdom)
Thomas A. Steitz (United States)
Ada E. Yonath (Israel)
"for studies of the structure and function of the ribosome"

2010 **Richard F. Heck** (United States)
Ei-ichi Negishi (United States)
Akira Suzuki (Japan)
"for palladium-catalyzed cross couplings in organic synthesis"

2011 **Dan Shechtman** (Israel)
"for the discovery of quasicrystals"

2012 **Robert J. Lefkowitz** (United States)
Brian K. Kobilka (United States)
"for studies of G-protein-coupled receptors"

2013 **Martin Karplus** (United States)
Michael Levitt (United States)
Arieh Warshel (United States)
"for the development of multiscale models for complex chemical systems"

2014 **Eric Betzig** (United States)
Stefan W. Hell (Germany)
William E. Moerner (United States)
"for the development of super-resolved fluorescence microscopy"

2015 **Tomas Lindahl** (United Kingdom)
Paul Modrich (United States)
Aziz Sancar (United States)
"for mechanistic studies of DNA repair"

2016 **Jean-Pierre Sauvage** (France)
Sir J. Fraser Stoddart (United States)
Bernard L. Feringa (Netherlands)
"for the design and synthesis of molecular machines"

2017 **Jacques Dubochet** (Switzerland)
Joachim Frank (United States)
Richard Henderson (United Kingdom)
"for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution"

2018 **Frances H. Arnold** (United States)
"for the directed evolution of enzymes"

George P. Smith (United States)
Sir Gregory P. Winter (United Kingdom)
"for the phage display of peptides and antibodies"

2019 **John B. Goodenough** (United States)
M. Stanley Whittingham (United States)
Akira Yoshino (Japan)
"for the development of lithium-ion batteries"

2020 **Emmanuelle Charpentier** (Germany)
Jennifer A. Doudna (United States)
"for the development of a method for genome editing"

2021 **Benjamin List** (Germany)
David W. C. MacMillan (United States)
"for the development of asymmetric organocatalysis"

2022 **Carolyn Bertozzi** (United States)
Morten Meldal (Denmark)
K. Barry Sharpless (United States)
"for the development of click chemistry and bioorthogonal chemistry"

2023 **Moungi Bawendi** (United States)
Louis Brus (United States)
Alexei Ekimov (United States)
"for the discovery and synthesis of quantum dots"

Appendix I: Answers to Multiple Choice Questions in Review Units 1–12

Review Unit 1:	1. d	2. b	3. a	4. c	5. d	6. b	7. a	8. d	9. a	10. c
Review Unit 2:	1. c	2. a	3. d	4. c	5. d	6. b	7. a	8. d	9. b	10. d
Review Unit 3:	1. a	2. b	3. c	4. b	5. c	6. b	7. b	8. a	9. d	10. d
Review Unit 4:	1. d 11. c	2. b	3. b	4. c	5. b	6. a	7. d	8. c	9. a	10. d
Review Unit 5:	1. b 11. c	2. b	3. c	4. a	5. d	6. d	7. c	8. a	9. b	10. c
Review Unit 6:	1. c	2. a	3. b	4. d	5. c	6. c	7. a	8. d	9. d	10. a
Review Unit 7:	1. d	2. c	3. b	4. b	5. a	6. d	7. b	8. a	9. c	10. c
Review Unit 8:	1. a	2. b	3. a	4. b	5. c	6. a	7. c	8. d	9. c	10. b
Review Unit 9:	1. b	2. d	3. a	4. a	5. c	6. d	7. b	8. c	9. b	10. d
Review Unit 10:	1. b	2. a	3. d	4. b	5. c	6. a	7. d	8. b	9. a	10. d
Review Unit 11:	1. c	2. d	3. a	4. b	5. d	6. a	7. d	8. b	9. c	10. a
Review Unit 12:	1. d	2. a	3. c	4. c	5. a	6. d	7. b	8. a	9. b	10. c