Chapter 1

Remembering General Chemistry:

Electronic Structure and Bonding

Organic Chemistry

Carbon-containing compounds were once considered "organ compounds" available only from living organisms.

The synthesis of the simple organic compound urea in 1828 showed that organic compounds can be prepared in the laboratory from non-living material.

Today, organic natural products are routinely synthesized in the laboratory.

Why Carbon?

Carbon neither gives up nor accepts electrons because it is in the center of the second periodic row.

Consequently, carbon forms bonds with other carbons and other atoms by sharing electrons.

The capacity of carbon to form bonds in this fashion makes it the building block of all living organisms.

Why Study Organic Chemistry?

Since carbon is the building block of all living organisms, a knowledge of Organic Chemistry is a prerequisite to understanding Biochemistry, Medicinal Chemistry, Chemical Engineering, Polymer, and Pharmacology.

Indeed, Organic Chemistry is a required course for studying Chemical Engineering, Pharmacy, Medicine, and Dentistry.

Admission into these professional programs is highly dependent on your performance in Organic Chemistry.

1.1 The Structure of an Atom

An atom consists of electrons, positively charged protons, and neutral neutrons.
Electrons form chemical bonds.
Atomic number: numbers of protons in its nucleus.
Mass number: the sum of the protons and neutrons of an atom.
Isotopes have the same atomic number but different mass numbers.
The atomic weight: the average weighted mass of its atoms.
Molecular weight: the sum of the atomic weights of all the atoms in the molecule.

1.2 The Distribution of Electrons in an Atom

Quantum mechanics uses the mathematical equation of wave motions to characterize the motion of an electron around a nucleus.
Wave functions or orbitals tell us the energy of the electron and the volume of space around the nucleus where an electron is most likely to be found.
The atomic orbital closer to the nucleus has the lowest energy.
Degenerate orbitals have the same energy.

1.3 IONIC AND COVALENT BONDS

Lewis's theory: an atom will give up, accept, or share electrons in order to achieve a filled outer shell or an outer shell that contains eight electrons → octet rule

Ionic Bonds : Formed by the Transfer of Electrons

Covalent Bonds : Formed by Sharing Electrons

1.4 HOW THE STRUCTURE OF A COMPOUND IS REPRESENTED: Lewis Structure

Formal charge = number of valence electrons –
(number of lone pair electrons +1/2 number of bonding electrons)

Nitrogen has five valence electrons

Carbon has four valence electrons

Hydrogen has one valence electron and halogen has seven

1.5 ATOMIC ORBITALS

An orbital tells us the volume of space around the nucleus where an electron is most likely to be found

1.6 Molecular Orbitals

Molecular orbitals belong to the whole molecule.

s bond: formed by overlapping of two *s* orbitals.

Bond strength/bond dissociation: energy required to break a bond or energy released to form a bond.

1.7 HOW SINGLE BONDS ARE FORMED IN ORGANIC COMPOUNDS

Bonding in Methane

Hybridization of One *s* and Three *p* Orbitals

The Bonds in Ethane

Hybridization of One *s* and Three *p* Orbitals : SP3

1.8 Bonding in Ethene: A Double Bond

Hybridization of One *s* and Two *p* Orbitals : SP2

1.9 Bonding in Ethyne: A Triple Bond

Hybridization of One *s* and One *p* Orbitals : SP

1.10 THE BONDS IN THE METHYL CATION, THE METHYL RADICAL, AND THE METHYL ANION

Bonding in the Methyl Cation

Bonding in the Methyl Radical

Bonding in the Methyl Anion

1.11 THE BONDS IN AMMONIA AND IN THE AMMONIUM ION

Hybridization of One *s* and Three *p* Orbitals : SP3

1.12 THE BONDS IN WATER: SP3

1.13 THE BOND IN A HYDROGEN HALIDE

1.14 HYBRIDIZATION AND MOLECULAR GEOMETRY

orbitals used in bond formation determine the bond angle

1.15 SUMMARY

The shorter the bond, the stronger it is

The greater the electron density in the region of orbital overlap, the stronger is the bond

The more *s* character, the shorter and stronger is the bond

The more *s* character, the larger is the bond angle

1.16 THE DIPOLE MOMENTS OF MOLECULES

The vector sum of the magnitude and the direction of the individual bond dipole determines the overall dipole moment of a molecule

Chapter 2

Acids and Bases: Central to Understanding Organic Chemistry

2.1 AN INTRODUCTION TO ACIDS AND BASES

Brønsted–Lowry Acids and Bases;

Acid: loses a proton Base: gains a proton

2.2 pH

The concentration of protons in a solution is indicated by pH. This concentration can be written as either [H^+] or, because a proton in water is solvated, as [H_3O^+].

2.3 ORGANIC ACIDS AND BASES

Protonated alcohols and protonated carboxylic acids are very strong acids.

2.4 HOW TO PREDICT THE OUTCOME OF AN ACID-BASE REACTION

Proton doner is the acid

2.5 HOW TO DETERMINE THE POSITION OF EQUILIBRIUM

- **Strong reacts to give weak**
- **The weaker the base, the stronger is its conjugate acid**
- **Stable bases are weak bases**

2.6 HOW THE STRUCTURE OF AN ACID AFFECTS ITS pK_a VALUE

Electronegativity

Hybridization

Size

2.7 HOW SUBSTITUENTS AFFECT THE STRENGTH OF AN ACID

Inductive electron withdrawal increases the acidity of a conjugate acid

2.8 AN INTRODUCTION TO DELOCALIZED ELECTRONS

Acetic acid is more acidic than ethanol

The delocalized electrons in acetic acid are shared by more than two atoms, thereby stabilizing the conjugated base

2.9 A SUMMARY OF THE FACTORS THAT DETERMINE ACID STRENGTH

1. Size: As the atom attached to the hydrogen increases in size, the strength of the acid increases
2. Electronegativity
3. Hybridization
4. Inductive effect
5. Electron delocalization

2.10 HOW pH AFFECTS THE STRUCTURE OF AN ORGANIC COMPOUND

Compounds exist primarily in their acidic forms in solutions that are more acidic than their pK_a values and primarily in their basic forms in solutions that are more basic than their pK_a values.

2.12 LEWIS ACIDS AND BASES

Lewis acid: non-proton-donating acid; will accept two electrons

Lewis base: electron pair donors

Chapter 3

An Introduction to Organic Compounds

Nomenclature, Physical Properties, and Representation of Structure

Alkanes are hydrocarbons containing only single bonds

General formula: C_nH_{2n+2}

Constitutional isomers have the same molecular formula, but their atoms are linked differently

five constitutional isomers with molecular formula C_6H_{14}

nine alkanes with molecular formula C_7H_{16}

3.1 HOW ALKYL SUBSTITUENTS ARE NAMED

Removing a hydrogen from an alkane results in an alkyl substituent

If a hydrogen is replaced by an OH: alcohol
by an NH_2 : an amine, by a halogen :alkyl halide by an OR, : an ether

straight-chain alkyl groups : the prefix "*n*" (for "normal") to
If a name does not have a prefix such as "*n*" or "iso," we assume that the carbons are in an unbranched chain.

A compound can have more than one name, but a name must specify only one compound

A compound can have more than one name, but a name must specify only one compound

The use of an "iso" prefix:

3.2 THE NOMENCLATURE OF ALKANES

1. Determine the number of carbons in the longest continuous chain

2. Number the chain so that the substituent gets the lowest number

3. Number the substituents to yield the lowest possible number in the number of the compound

4. Assign the lowest possible numbers to all of the substituents

5. If the same substituent numbers are obtained in both directions, the first group cited receives the lower number

6. The carbon attached to the parent hydrocarbon is always the number 1
If di is the part of the branch name, it is included in the alphabetization

7. If a compound has two or more chains of the same length, the parent hydrocarbon is the chain with the greatest number of substituents

Systematic Naming of Substituents

Determine longest chain starting with the point of attachment.
Name longest chain as alkyl.
Number and name substituents and add to alkyl as prefix.
Name the substituent as (#-alkylalkyl). The parentheses distinguish substituent numbering from the numbering of the longest chain.

3.3 THE NOMENCLATURE OF CYCLOALKANES·SKELETAL STRUCTURES

Cycloalkanes are alkanes with their carbon atoms arranged in a ring.

General molecular formula for a cycloalkane : C_nH_{2n}

named by adding the prefix "cyclo"

1. **No number is needed for a single substituent on a ring**
2. **Name the two substituents in alphabetical order**
3. **If there are more than two substituents, they are cited in alphabetical order**

3.4 THE NOMENCLATURE OF ALKYL HALIDES

In the IUPAC system, alkyl halides are named as substituted alkanes

3.5 THE NOMENCLATURE OF ETHERS

a compound in which an oxygen is bonded to two alkyl substituents

a symmetrical ether : the alkyl substituents are identical, the ether is.
an unsymmetrical ether : the substituents are different

The common name of an ether

the names of the two alkyl substituents (in alphabetical order), followed by the word ether.

Iso, neo, cyclo are included in the alphabetization

The IUPAC system names an ether as an alkane with an RO substituent: The substituents by replacing the yl ending in the name of the alkyl substituent with oxy.

3.6 THE NOMENCLATURE OF ALCOHOLS

In an alcohol, the OH is a functional group

The common name : the name of the alkyl group followed by the word alcohol.

IUPAC system name : replacing the “e” with the suffix “ol.”

1. Determine the longest hydrocarbon containing the functional group:
2. The functional group suffix should get the lowest number:
3. If there are two OH groups, the suffix “diol” is added to the name of the parent hydrocarbon:
4. When there is both a functional group suffix and a substituent, the functional group suffix gets the lowest number:

3.7 THE NOMENCLATURE OF AMINES

The common name : the names of the alkyl groups bonded to the nitrogen, in alphabetical order, followed by “amine.”
written as one word (the common names of alcohols, ethers, and alkyl halides, in which “alcohol,” “ether,” and “halide” are separate words)

The IUPAC system name: the “e” at the end of the name of the parent hydrocarbon is replaced by “amine”

The substituents are listed in alphabetical order and a number or an “*N*” is assigned to each one:

Naming Quaternary Ammonium Salts

- the alkyl groups in alphabetical order, followed by “ammonium, then the name of the accompanying anion as a separate word.

3.9 THE PHYSICAL PROPERTIES OF ALKANES, ALKYL HALIDES, ALCOHOLS, ETHERS, AND AMINES

Attractive Forces: van der Waals force, Dipole–dipole interaction,
Hydrogen bonds

The greater the attractive forces between molecules, the higher is the boiling point of the compound.

van der Waals Forces: The boiling point of a compound increases with the increase in van der Waals force

Dipole–Dipole Interaction: stronger than van der Waals force but weaker than ionic or covalent bonds

A hydrogen bond : a special kind of dipole–dipole interaction between a hydrogen that is bonded to an oxygen, nitrogen, or fluorine and the lone-pair electrons of an oxygen, nitrogen, or fluorine in another molecule.

3.10 ROTATION OCCURS ABOUT CARBON—CARBON SINGLE BONDS

Conformations of Alkanes: Rotation about Carbon–Carbon Bonds

Most molecules : staggered conformations
more anti conformation than in a gauche conformation.
→ zigzag arrangements, as seen in the ball-and-stick model of decane.

3.11 SOME CYCLOALKANES HAVE ANGLE STRAIN

Angle strain results when bond angles deviate from the ideal 109.5° bond angle

cyclobutane and cyclo pentanes are not planar.
If planar, all pairs of eclipsed hydrogens.

3.12 CONFORMERS OF CYCLOHEXANE

The chair conformation of cyclohexane is free of strain

All the bond angles in a chair conformer are 111° , which is very close to the ideal tetrahedral bond angle of 109.5° and all the adjacent bonds are staggered

cyclohexane is completely free of strain

the heat of formation of cyclohexane) and dividing by 6 for its six CH2 groups gives us a value of -4.92 kcal/mol for a “strainless” CH2 group (-29.5/6=- 4.92).

cyclopentane has a “strainless” heat of formation of (5)(-4.92) = -24.6 kcal/mol
and an actual heat of formation of 18.4 kcal/mol. Therefore, cyclopentane has a total strainenergy of - 6.2 kcal/mol, because [- 18.4- (-24.6) = 6.2].

Drawing Cyclohexane

1. Draw two parallel lines of the same length.

2. Connect the tops of the lines with a V

3. The axial bonds (red lines) are vertical

4. The equatorial bonds (red lines with blue balls) point outward from the ring.

Systematic Method for Drawing Chair Conformations of Cis and Trans Substituted Cyclohexanes

1. Label the chair conformer axial and equatorial bonds with either up (U) or down (D) based on the flat cyclohexane ring.
2. Consider Cis substituents as either UU or DD and Trans substituents as either UD or DU.
3. Example, Draw the more stable conformation of cis-1,3-dimethylcyclohexane:

Chapter 4

Isomers: The Arrangement of Atoms in Space

Isomers: Compounds that have the same molecular formula but different structures.

Constitutional isomers differ in the way the atoms are connected.

4.1 Cis-Trans Isomers Result From Restricted Rotation

Cis: The substituents are on the same side of the ring.

Trans: The substituents are on opposite sides of the ring.

Cis–trans isomers have different physical properties.

Compounds with different conformations (conformers) cannot be separa

4.3 An Asymmetric (Chiral) Center Is a Cause of Chirality in a Molecule

Using the σ-Plane to Determine if a Molecule is Chiral or Achiral

1. The σ-plane is an internal plane of symmetry passing through a molecule.
2. If there is one or more σ-planes, the molecule is achiral.
3. If there are no σ-planes, the molecule is chiral.

The presence of asymmetric centers does not imply chirality!

Enantiomers

The two isomers are called enantiomers.

Enantiomers are different compounds: they can be separated.

Enantiomers have the same physical and chemical properties.

4.5 ASYMMETRIC CENTERS AND STEREOCENTERS

Asymmetric center: an atom attached to four different groups

Stereocenter: an atom at which the interchange of two groups produces a stereoisomer

4.6 How to Draw Enantiomers

Perspective formulas

Fischer projections

Horizontal lines : the bonds project out of the plane of the paper toward the viewer

Vertical lines : the bonds that extend back from the plane of the paper away from the viewer.

4.7 Naming Enantiomers By the R,S System

Assign relative priorities to the four groups.

The *R,S* system of nomenclature

1. Consider the atomic number of the atoms bonded directly to the asymmetric carbon.
2. If there is a tie, consider the atoms attached to the tied atoms.
3. Multiple bonds are treated as attachment of multiple single bonds using divide-duplicate.
4. Rank the priorities by mass number in isotopes.

Same rules as for *E*/*Z* assignments

Orient the lowest priority (4) away from you:

Clockwise = *R* configuration
Counterclockwise = *S* configuration

Naming from the Perspective Formula

1. Rank the groups bonded to the asymmetric center with the lowest priority group in the back.

2. If the group (or atom) with the lowest priority is in the front, assign S or R and then switch your answer to R or S respectively.

3. Alternatively, atoms or groups can be switched so as to place the lowest priority group in the back. One switch: configuration opposite; two switches, configuration unchanged.

Configuration from the Fischer Projection

1. Consider the 3-dimensional equivalent to the Fischer Projection.

2. Rank the groups (or atoms) that are bonded to the asymmetric center and then draw an arrow from the highest priority (1) to the next highest priority (2).

3. If the lowest priority is on a horizontal bond, the configuration is opposite to the direction of the arrow.

4.8 Chiral compounds are optically active;
they rotate the plane of polarized light.

Achiral compounds do not rotate the plane of polarized light.
They are optically inactive.

Clockwise rotation : dextrorotatory, (+) , d.
Counterclockwise rotation : levorotatory, (-) , l.
Dextro and levo are Latin prefixes for “to the right” and “to the left,” respectively.
R and S are not related + and -

Some *R* enantiomers are (+) and some are (–).

Some *S* enantiomers are (+) and some are (–).

4.9 How Specific Rotation Is Measured

A polarizer measures the degree of optical rotation of a compound

The observed rotation (α): $$[\alpha]_\lambda^T = \frac{\alpha}{lc}$$

***T* is the temp in °C** $[\alpha]_\lambda^T =$ **Specific Rotation**

λ is the wavelength

α is the measured rotation in degrees

***l* is the path length in decimeters**

***c* is the concentration in grams per mL**

Each optically active compound has a characteristic specific rotation.

4.10 ENANTIOMERIC EXCESS

The enantiomeric excess (ee) tells us how much of an excess of one enantiomer is in a mixture.

4.11 Compounds with more than one asymmetric center

a maximum of 2^n stereoisomers can be obtained

4.12 Stereoisomers of Cyclic Compounds

Two asymmetric centers: four stereoisomers.
Enantiomers: cis isomer and trans isomer.
Each of the stereoisomers is a chiral molecule.

1-Bromo-4-methylcyclohexane has only one cis isomer and one trans isomer

These compounds possess an internal plane of symmetry (σ-plane) and are therefore achiral.

4.13 Meso Compounds Have Asymmetric Centers bu Are Optically Inactive

Meso compounds are optically inactive even though they have asymmetric centers.

Have two or more asymmetric centers and an internal plane of symmetry (σ-plane)

Meso compounds are achiral molecules with asymmetric centers !

As long as any one conformer of a compound has a plane of symmetry, the compound will be achiral

Is *cis*-1,2-dibromocyclohexane is a meso compound ? Yes!
If a molecule has an achiral conformer, the molecule is achiral, even if the achiral confomer is not the most stable conformer.

4.14 How to Name Isomers with More Than One Asymmetric Center

4.15 HOW ENANTIOMERS CAN BE SEPARATED

Enantiomers can have very different physiological properties.

4.16 NITROGEN AND PHOSPHORUS ATOMS CAN BE ASYMMETRIC CENTERS

Asymmetric Nitrogen Centers

Rapid lone pair inversion prevents resolution of amine enantiomers

Quaternary amine-based enantiomers can be resolved because there is no lone pair

Chapter 5

Alkenes:

Structures, Nomenclature, and an Introduction to Reactivity

Thermodynamics and Kinetics

Alkenes Are an Important Part of Our Lives

5.1 MOLECULAR FORMULAS AND THE DEGREE OF UNSATURATION

noncyclic alkane is C_nH_{2n+2}
cyclic alkane is C_nH_{2n}
acyclic alkene is also C_nH_{2n}

Noncyclic compounds are also called acyclic compounds

5.2 THE NOMENCLATURE OF ALKENES

1. **Longest continuous chain containing the functional group**
2. **The stereoisomers of an alkene are named using a *cis* or *trans* prefix (in italics).**
3. **When there are both a functional group and a substituent, the functional group gets the lowest number**
4. **Cite the substituents in alphabetical order:**
5. **Name with the lowest functional group number and then the lowest substituent numbers.**
6. **In a cyclic alkene, the alkene functional group is given the number 1, but the -1- is left out of the name:**

5.3 THE STRUCTURE OF ALKENES

Six carbon atoms are in the same plane.
p **orbitals overlap to form a π bond**

5.4 NAMING ALKENES USING THE *E,Z* SYSTEM

***Z*, Zusammen (together)** ***E*, Entgegen (opposite)**

Rule 1: Consider the atomic number of the atoms bonded directly to a specific *sp*^{2} carbon:

Higher atomic number has higher priority

Rule 2: If there is a tie, consider the atoms attached to the tied atoms:

Rule 3: Multiple bonds are treated as attachment of multiple single bonds using divide-duplicate.

Rule 4: Rank the priorities by mass number in isotopes:

5.5 HOW AN ORGANIC COMPOUND REACTS DEPENDS ON ITS FUNCTIONAL GROUP

The functional group determines the kinds of reactions a compound will undergo.

Organic compounds can be divided into families, and all the families in a group react in similar ways.

5.6 HOW ALKENES REACT

CURVED ARROWS SHOW THE FLOW OF ELECTRONS

Electron-deficient atoms or molecules (electrophiles) are attracted to electron-rich atoms or molecules (nucleophiles).

Addition of HBr to an Alkene

1st Step: Addition of a proton to the alkene. The proton is the electrophile.

2nd Step: Bromide traps the carbocation. Bromide is the nucleophile.

Rules on Using Curved Arrows

1. Full-headed arrows are drawn in the direction of two-electron flow.

2. Curved arrows are meant to indicate the movementof electrons.

3. The head of the curved arrow always points to the destination of the electrons.

4. The arrow must originate at the electron source.

5.7 THERMODYNAMICS AND KINETICS

Thermodynamics describes a reaction at equilibrium.
Kinetics explains the rates of chemical reactions.

A Reaction Coordinate Diagram Describes the Reaction Pathway

Transition states have partially formed bonds

Intermediates have fully formed bonds

Thermodynamics: How much product is formed?

Thermodynamic Parameters

Gibbs standard free-energy change (ΔG^o)

Entropy (ΔS^o): a measure of freedom of motion

Enthalphy (ΔH^o): the heat given off or absorbed during a reaction

Exergonic Reaction $-\Delta G^o$ **Endergonic Reaction** $+\Delta G^o$

ΔH^o can be calculated from bond dissociation energies

Entropic Reactions

An entropic reaction results in a massive change in volume without heat evolution.
Air bag deployment is a common entropic reaction.
TATP is an entropic explosive used by terrorists.

5.8 THE RATE OF A CHEMICAL REACTION

1. **The number of collisions that take place between the reacting molecules in a given period of time. The rate of the reaction increases as the number of collisions increases.**

2. **The fraction of collisions that occur with sufficient energy to get the reacting molecules over the energy barrier. If the free energy of activation is small, then more collisions will lead to reaction than if the free energy of activation is large.**

3. **The fraction of collisions that occur with the proper orientation. For example, 2-butene and HBr will react only if the molecules collide with the hydrogen of HBr approaching the bond of 2-butene. If a collision occurs with the hydrogen approaching a methyl group of 2-butene, no reaction will take place, regardless of the energy of the collision.**

5.9 THE DIFFERENCE BETWEEN THE RATE OF A REACTION AND THE RATE CONSTANT FOR A REACTION

$k = Ae^{-E_a/RT}$ **Arrhenius Equation**

A is the frequency factor which represents the fraction of collisions that occurs with the proper orientation for reaction.

The term $e^{-(E_a/RT)}$ is the fraction of collisions with the minimum energy (E_a) needed for reaction. R is the gas constant, T (°K) is the temperature, and E_a is the experimental energy of activation.

If $E_a = 0$, the reaction is encounter controlled with $k = A$. The second order encounter-controlled k value in water is 10^{10} $M^{-1}sec^{-1}$.

The Arrhenius equation predicts that the rate of a reaction will double with each 10°K increase in temperature.

5.10 A REACTION COORDINATE DIAGRAM DESCRIBES THE ENERGY CHANGES THAT TAKE PLACE DURING A REACTION

Transition states have partially formed bonds

Intermediates have fully formed bonds

5.11 CATALYSIS

A catalyst provides a pathway with a lower energy barrier but it does not change the energy of the starting point (the reactants) or the end point (the products).

5.12 CATALYSIS BY ENZYMES

All reactions occurred in biological systems are reactions of organic compounds.

Most biological catalysts are proteins called enzymes.

Molecular recognition is the ability of one molecule to recognize another molecule as a result of intermolecular interactions.

Chapter 6

The Reactions of Alkenes
The Stereochemistry of Addition Reactions

Reaction of an alkene is an addition reaction

synthesis of an alkene is an elimination reaction

6.1 THE ADDITION OF A HYDROGEN HALIDE TO AN ALKENE

Carbocation Formation Is the Rate-Limiting Step

6.2 CARBOCATION STABILITY DEPENDS ON THE NUMBER OF ALKYL GROUPS ATTACHED TO THE POSITIVELY CHARGED CARBON

Alkyl groups decrease the concentration of positive charge in the carbocation

Species Stability Predicted by Hyperconjugation

6.3 WHAT DOES THE STRUCTURE OF THE TRANSITION STATE LOOK LIKE?

Hammond postulate: the transition state will be more similar to the species that it is closer to energetically

Exergonic reaction: early transition state

Endergonic reaction: late transition state

The transition state is more similar in structure to the species to which it is more similar in energy

In an electrophilic addition reaction, the more stable carbocation forms faster.

6.4 ELECTROPHILIC ADDITION REACTIONS ARE REGIOSELECTIVE

Markovnikov's Rule

The electrophile adds to the *sp*^{2} carbon that is bonded to the greater number of hydrogens:

In a regioselective reaction, one constitutional isomer is the major or the only product.

6.5 THE ADDITION OF WATER TO AN ALKENE

Mechanism

H^+ (an electrophile) adds to the *sp*^{2} carbon of the alkene (a nucleophile) that is bonded to the most hydrogens.

H_2O (a nucleophile) adds to the carbocation (an electrophile), forming a protonated alcohol.

The protonated alcohol loses a proton because the pH of the solution is greater than the pK_a of the protonated alcohol. (We have seen that protonated alcohols are very strong acids)

6.6 THE ADDITION OF AN ALCOHOL TO AN ALKENE

Varying the alkene and alcohol starting materials will afford structurally diverse ether products:

6.7 A CARBOCATION WILL REARRANGE IF IT CAN FORM A MORE STABLE CARBOCATION

The Fate of Carbocations:

They can trap nucleophiles:
They can rearrange:
They can trap alkene nucleophiles:
They can lose a proton to afford an alkene:

Rearrangement of Carbocations

1,2-hydride shift **1,2-methyl shift**

A carbocation does not always rearrange:

Why? Because rearrangement has not resulted in a more a stable carbocation.

6.8 THE ADDITION OF BORANE TO AN ALKENE: HYDROBORATION-OXIDATION

Hydroboration is a two-step process:

1. **Trialkylborane formation**
2. **Hydroperoxide and base treatment**

Borane (BH_3), a neutral molecule, is an electrophile because its boron atom does not have a complete octet.

Regioselectivity due to carbocation formation is the transition state and steric interaction between borane and the alkene substituents

6.9 THE ADDITION OF A HALOGEN TO AN ALKENE

Bromonium Ion Formation

Trapping of the Bromonium or Chloronium Ion by Nucleophilic Solvents Is Regioselective

Addition of halogens to an alkene in the presence of a primary alcohol affords a halo ether by the same mechanism.

6.10 THE ADDITION OF A PEROXYACID TO AN ALKENE

Oxidation decreases the number of C-H bonds or increases the number of C-O, C-N, or C-X bonds

Naming of Epoxide

There are three ways of naming an epoxide:

As an epoxy-substituted alkane.
As an alkene, just add the word oxide for an epoxy compound.
As an oxirane ring derivative.

6.11 THE ADDTION of OZONE TO AN ALKENE: OZONOLYSIS

Alkenes can be oxidized to 1,2-diols and 1,2-diols can be further oxidized to aldehydes and ketones. Alkenes can be directly oxidized to carbonyl compounds by ozone

The molozonide is unstable because it has two O—O bonds, but the ozonide is stable

Ozonides can be cleaved to carbonyl compounds:

6.12 THE ADDITION OF HYDROGEN TO AN ALKENE

The most stable alkene has the smallest heat of hydrogenation.

6.13 THE RELATIVE STABILITIES OF ALKENES

Alkyl substituents stabilize both alkenes and carbocations.

The most stable alkene has the greatest number of alkyl groups bonded to its *sp*^{2} carbon.

6.14 REGIOSELECTIVE, STEREOSELECTIVE, AND STEREOSPECIFIC REACTIONS

A regioselective reaction: preferential formation of one constitutional isomer

A stereoselective reaction: preferential formation of a stereoisomer

Enantioselectivity: selective formation of an enantiomer

Diastereoselectivity: selective formation of a diastereomer

A stereospecific reaction: each stereoisomeric reactant forms a different stereoisomeric product or a different set of stereoisomeric products

All stereospecific reactions are stereoselective

Not all stereoselective reactions are stereospecific

6.15 THE STEREOCHEMISTRY OF ELECTROPHILIC ADDITION REACTIONS OF ALKENES

Identical amounts of the *R* and *S* enantiomers are formed in the reaction !

Not stereoselective !
because it does not select for a particular stereoisomer

Addition reaction in a compound that already has an asymmetric center : a pair of diastereomers are formed.

The transition states are also diastereomeric and the two transition states will not have the same stability,
so different amounts of the two diastereomers will be formed.

Thus, the reaction is stereoselective !

Addition reactions that form products with two asymmetric centers

All four possible stereoisomers result:

not stereospecific !

Syn addition of H_2 to a *cis* alkene

Exclusive Formation of Meso Stereoisomer, If each of the two asymmetric centers in the product is bonded to the same four substituents,

Syn addition of H_2 to a *trans* alkene

Exclusive Formation of Threo Enantiomers!

The Stereochemistry of Peroxyacid Addition

Syn addition to a cis alkene forms the cis enantiomers.

Syn addition to a trans alkene forms the trans enantiomers.

Addition of a peroxyacid to *cis*-2-butene forms a meso compound

The addition of a peroxyacid to an alkene to form an epoxide is a concerted reaction. Orientation of alkyl substituents remain unchanged.

6.16 THE STEREOCHEMISTRY OF ENZYME-CATALYZED REACTIONS

Enzyme Catalyzed Reactions Are Enantioselective !

6.17 ENANTIOMERS CAN BE DISTINGUISHED BY BIOLOGICAL MOLECULES

enzyme : chiral reagent
it distinguish between cis–trans isomers, such as maleate and fumarate, it can also distinguish betweenenantiomers and catalyze the reaction of only one of them.

A **receptor** : a protein that binds a particular molecule.

receptors located on the exteriors of nerve cells in the nose are able to perceive and differentiate the estimated 10,000 smells to which the cells are exposed.

Chapter 7

The Reactions of Alkynes

An Introduction to Multistep Synthesis

Only a few alkynes are found in nature. Why?

An alkyne is a hydrocarbon that contains a carbon–carbon triple bond

General formula: C_nH_{2n-2} (acyclic); C_nH_{2n-4} (cyclic)

7.1 The nomenclature of alkynes

In common nomenclature, alkynes are named as substituted acetylenes

In IUPAC nomenclature:
The yne suffix is assigned the lowest number.
Then substituents are assigned the lowest possible set of numbers.

7.2 How to name a compound that has more than one functional group

Find the longest chain bearing both functional groups.
Assign ene and yne suffixes the lowest set of numbers.

If there is a tie between a double bond and a triple bond, the ene suffix is assigned the lower number:

A chain is numbered to give the lowest possible number to the functional group with the higher priority:

7.4 The Structure of Alkynes

A triple bond is composed of a σ bond and two π bonds

7.5 Alkynes are less reactive than alkenes

The transition state for the alkyne addition is less stable than for an alkene addition

Relative Stabilities of Carbocations

A vinylic cation (sp) is formed in the first step of the alkyne addition reaction whereas an alkyl cation (sp^2) is formed in the first step of the alkene addition reaction

7.6 The addition of hydrogen halides and the addition of halogens to an alkyne

The second hydrohalide addition affords a geminal dihalide

The initial addition of the proton can occur with equal ease to either of the *sp* carbons and the *geminal* regioisomer always results

Stereoselectivity of Alkyne Addition Reactions

Trans addition of hydrohalides HCl and HBr occur because of a π-complex intermediate:

Adding excess halide anion increases the yield of trans addition product.

7.7 Addition of water to an alkyne

One method of synthesizing ketones.

Hg^{2+} is added to increase the rate of water addition to terminal alkynes

Mechanism involves a prototropic shift

7.8 The addition of borane to an alkyne: hydroboration-oxidation

Hydroboration–Oxidation of Terminal Alkynes

Bulky borane required to distinguish terminal end from substituted end:

7.9 The addition of hydrogen to an alkyne

Catalytic reduction of an alkyne affords an alkane without buildup of the alkene intermediate

Use a poisoned catalyst developed by Lindlar to obtain the alkene

Lindlar Catalyst:
prepared by precipitating palladium on calcium carbonate
and treating it with lead(II) acetate and quinoline.

Reason for trans stereochemistry: electron repulsion and steric hindrance.

7.10 A hydrogen bonded to an *sp* carbon is acidic

relative base strength

The stronger the acid, the weaker its conjugate base:

An amide anion cannot remove a hydrogen bonded to an *sp*^{2} or *sp*^{3} carbon.

7.11 Synthesis using acetylide ions: Formation of C–C Bond

We can convert terminal alkynes to longer internal alkynes by addition of alkyl halides

Chapter 8

Delocalized Electrons and Their Effect on Stability, Reactivity, and pK_a *and the Products of a Reaction*

8.1 Delocalized Electrons Explain Benzene's Structure

8.2 The Bonding in Benzene

A planar molecule

Has six identical carbon–carbon bonds

Each π electron is shared by all six carbons

The π electrons are delocalized

8.3 Resonance Contributors and the Resonance Hybrid

Resonance contributors do not depict any real electron distribution

π electrons cannot delocalize in nonplanar molecules

8.4 How to Draw Resonance Contributions

Only electrons move.

Only π electrons and lone-pair electrons move.

The total number of electrons in the molecule does not change.

An sp^3 carbon cannot accept electrons; it already has an octet.

Do not break $sp^3(\sigma)$ bonds.

8.5 THE PREDICTED STABILITIES OF RESONANCE CONTRIBUTORS

the more it contributes to the structure of the resonance hybrid, the more similar the contributor is to the real molecule.

predicted stability of a resonance contributor

-an atom with an incomplete octet
-a negative charge that is not on the most electronegative atom or a positive charge that is not on the least electronegative (most electropositive) atom
-charge separation

8.6 DELOCALIZATION ENERGY IS THE ADDITIONAL STABILITY DELOCALIZED ELECTRONS GIVE TO A COMPOUND

Delocalized electrons stabilize a compound by the delocalization energy.

Electron delocalization is also called resonance.

the greater the number of relatively stable resonance contributors, the greater is the delocalization energy, therefore the delocalization energy of a carboxylate ion is greater than that of the compound in the following example

8.7 BENZENE IS AN AROMATIC COMPOUND

8.8 THE TWO CRITERIA FOR AROMATICITY

- **A compound must have an uninterrupted cyclic cloud of *p* electrons above and below the plane of the molecule**

- **The *p* cloud must contain an odd number of pairs of *p* electrons, or $4n + 2$ ($n = 0, 1, 2 \ldots$) total electrons.**

Therefore, benzene is an aromatic compound because it is cyclic and planar, every carbon in the ring has a *p* orbital, and the p cloud contains *three* pairs of p electrons

Hückel’s Rule

For a planar, cyclic compound to be aromatic, its uninterrupted *p* cloud must contain ($4n + 2$) *p* electrons, where n is any whole number

Why?

8.9 APPLYING THE CRITERIA FOR AROMATICITY

SOME CHEMICAL CONSEQUENCES OF AROMATICITY

The Effect of Aromaticity on the pK_a Values of Some Compounds

Why is the pK_a of cyclopentadiene so much lower than that of ethane?

Because the conjugate base is aromatic:

8.10 AROMATIC HETEROCYCLIC COMPOUNDS

The heteroatom donates either one or two electrons to the π system

The lone-pair electrons on the nitrogen atom of pyrrole are π electrons

Furan and thiophene are aromatic

8.11 ANTIAROMATICITY

A compound is antiaromatic if it is a planar, cyclic, continuous loop of *p* orbitals with an even number of pairs of *p* electrons:

Antiaromatic compounds are highly unstable, but the nonplanar versions are stable

8.12 A MOLECULAR ORBITAL DESCRIPTION OF AROMATICITY AND ANTIAROMATICITY

Aromatic compounds are stable because they have filled bonding π molecular orbitals:

8.13 MORE EXAMPLES THAT SHOW HOW DELOCALIZED ELECTRONS INCREASE STABILITY

that the most stable alkene has the smallest heat of hydrogenation

The hybridization of the orbitals forming the carbon-carbon single bonds also causes a conjugated diene to be more stable than an isolated diene:

Allenes

The central carbon is *sp* hybrdized. One of its *p* orbitals overlaps a *p* orbital of an adjacent *sp*2 carbon and the second *p* orbital overlaps a *p* orbital of the other *sp*2 carbon

8.14 A MOLECULAR ORBITAL DESCRIPTION OF STABILITY

The distribution of electrons in ethene.

Bonding MO: constructive (in-phase) overlap
Antibonding MO: destructive (out-of-phase) overlap

1,3-Butadiene and 1,4-Pentadiene

1,3-butadiene are delocalized over four carbons

Symmetry in Molecular Orbitals

y_1 and y_3 in 1,3-butadiene are symmetrical molecular orbitals
y_2 and y_4 in 1,3-butadiene are fully asymmetrical orbitals

The highest-energy molecular orbital of 1,3-butadiene that contains electrons is y_2 (HOMO)

The lowest-energy molecular orbital of 1,3-butadiene that does not contain electrons is y_3 (LUMO)

HOMO = the highest occupied molecular orbital
LUMO = the lowest unoccupied molecular orbital

8.15 HOW DELOCALIZED ELECTRONS AFFECT pK_a VALUES

The OH group of phenol is attached to an *sp*^{2} carbon, which is more electronegative than the *sp*^{3} carbon to which the OH group of cyclohexanol is attached.

aniline's nitrogen is attached to an *sp*^{2} carbon, whereas cyclohexylamine's nitrogen is attached to a less electronegative *sp*^{3} carbon.

when the nitrogen loses a proton, the lone pair that formerly held the proton can be delocalized. Loss of a proton can increase the delocalization energy.

8.16 DELOCALIZED ELECTRONS CAN AFFECT THE PRODUCT OF A REACTION

8.17 REACTIONS OF DIENES

In the presence of limiting electrophilic reagent, only the more reactive double bond reacts

Reactions of Conjugated Dienes

An isolated diene undergoes only 1,2-addition

A conjugated diene undergoes both 1,2- and 1,4-addition

8.18 Thermodynamic Versus Kinetic Control

The thermodynamic product is the most stable product

The thermodynamic product predominates when the reaction is reversible (thermodynamic control)

The kinetic product is the product that is formed most rapidly

The kinetic product predominates when the reaction is irreversible (kinetic control)

The Stereochemisty of the Diels–Alder Reaction

If a Diels–Alder reaction creates a product with an asymmetric center, identical amounts of the *R* and *S* enantiomers will be formed

Chapter 9

Substitution Reactions of Alkyl Halides

What is a substitution reaction?

The atom or group that is substituted or eliminated in these reactions is called a leaving group.

Alkyl halides have relatively good leaving groups

9.1 THE MECHANISM FOR AN S_N2 REACTION

S_N2 reaction:
S: substitution, N: nucleophilic, and 2: bimolecular.

Experimental Evidence for the S_N2 Reaction Mechanism

The rate of the reaction is dependent on the concentration of both the alky halide and the nucleophile.

The rate of the reaction with a given nucleophile decreases with increasing branching of the alkyl halide at the reacting center.

The configuration of the substituted product is inverted compared to the configuration of the reacting chiral alkyl halide.

Why Does Branching Lower the S_N2 Rate?

Because the nucleophile attacks the back side of the carbon that is bonded to the leaving group:

Inversion of configuration (Walden inversion) in an S_N2 reaction is due to back-side attack

9.2 FACTORS THAT AFFECT S_N2 REACTIONS

the Leaving Groups in S_N2 Reactions

Good leaving groups are the conjugate bases of strong acids, i.e., they are weak bases.

Nucleophiles in the S_N2 Reaction

Basicity is a measure of how well a compound (a base) shares its lone pair with a proton.

Nucleophilicity is a measure of how readily a compound (a nucleophile) is able to attack an electron-deficient atom.

Second-row nucleophiles:
- Are approximately the same size.
-The stronger the base, the better the nucleophile.

Nucleophiles with differences in size

Down a column of the periodic table: nucleophiles become larger and more polarizable, but less solvated and less basic.

The Influence of Solvent on Higher-Row Nucleophiles

In an aprotic medium, fluoride is the best nucleophile by virtue of its basicity and lack of solvation

In an protic medium, iodide is the best nucleophile by virtue of its polarizability and lack of solvation

Nucleophilicity Is Affected by the Solvent

Therefore water and alcohol solvents are not suitable for S_N2 reactions with second-row nucleophiles also.

S_N2 reactions with second-row nucleophiles are carried out in polar aprotic solvents such as DMSO, DMF, and acetonitrile (CH_3CN)

Consequently, the anionic nucleophile is unsolvated and reactive

Nucleophilicity Is Affected by Steric Effects

Bulk decreases nucleophilicity, but not basicity.

Why? Nucleophilic attack more sterically congested than proton abstraction.

9.3 THE MECHANISM FOR AN S_N1 REACTION

Experimental Evidence for an S_N1 Reaction

The rate of the reaction depends only on the concentration of the alkyl halide.

The rate of the reaction increases with branching of the alkyl halide at the reacting center.

An S_N1 reaction with an enantiomeric pure alkyl halide affords a racemic or partially racemic product.

The Stereochemistry of S_N1 Reactions

The carbocation reaction intermediate leads to the formation of a racemic mixture

The S_N1 reaction of an enantiomeric pure alkyl halide affords a racemic mixture:

If the halogen is bonded to an asymmetric center, the product will be a pair of enantiomers.

9.4 FACTORS THAT AFFECT S_N1 REACTIONS

The Leaving Group in S_N1 Reactions

The Nucleophile in S_N1 Reactions

The rate-determining step of an S_N1 reaction is formation of the carbocation.

Therefore the reactivity of the nucleophile has no effect on the rate of an S_N1 reaction

9.5 Benzylic, Allylic, Vinyl, and Aryl Halides

Benzylic and allylic halides can undergo S_N2 or S_N1 reactions:

S_N2 conditions: Aprotic solvent and good nucleophile.

Tertiary benzylic and tertiary allylic halides are unreactive in the S_N2 reaction because of steric hindrance.

Benzylic and allylic halides can undergo S_N1 reactions because benzylic and allylic carbocations are stable.

S_N1 conditions: Protic solvent and poor nucleophile.

More than one product may result from an S_N1 reaction of an allylic halide:

Vinyl and aryl halides do not undergo S_N2 because:

sp **carbons are more electronegative than the** ***sp***^{2} **carbons, so** ***sp*** **carbons are more resistant to becoming positively charged.**

sp^2 **carbons form stronger bonds than do** ***sp***^{3} **carbons**

9.6 COMPETITION BETWEEN S_N2 AND S_N1 REACTIONS

The rate law for the reaction of an alkyl halide that can undergo both S_N2 AND S_N1 reactions

9.7 THE ROLE OF THE SOLVENT IN S_N2 AND S_N1 REACTIONS

The dielectric constant of a solvent is a measure of how well the solvent can insulate opposite charges from one another.

The effect of a solvent on the rate of an S_N2 reaction:

S_N2 reactions of a neutral alkyl halide and a charged nucleophile

Increasing the polarity of the solvent will decrease the reaction rate, because a polar solvent stabilizes the nucleophile more.

S_N2 reaction of an alkyl halide and a neutral nucleophile

increasing the polarity of the solvent increases the reaction rate

9.8 Intermolecular Versus Intramolecular S_N2 Reactions

An intramolecular reaction is favored when a five- or six-membered ring product is formed:

Three-membered ring compounds are generally formed more easily than four membered ring compounds.

the intramolecular reaction becomes less favored as the ring size increases beyond six members

9.9 Methylating Agents Used by Chemists VS. Those Used by Cells

Methylation by a Chemist

Methylation by a Cell (SAM; Biological Methylating Agent)

Chapter 10

Elimination Reactions of Alkyl Halides, Competition Between Substitution and Elimination

An alkyl halide can undergo elimination reactions

10.1 THE E2 REACTION

Hydroxide cannot act as a nucleophile in this reaction because of the bulky tertiary halide. Rather, hydroxide acts as a base and abstracts a proton.

A biimolecular reaction:

The removal of a proton and a halide ion is called dehydrohalogenation

An E2 reaction is also called a b-elimination or a 1,2-elimination reaction:

The weaker the base, the better it is as a leaving group

10.2 AN E2 REACTION IS REGIOSELECTIVE

The major product of an E2 reaction is the most stable alkene

The Zaitsev Rule

The more substituted alkene product is obtained when a proton is removed from the b-carbon that is bonded to the fewest hydrogens

The most stable alkene is generally (but not always) the most substituted alkene

Conjugated alkene products are preferred over the more substituted alkene product :

Do not use Zaitsev's rule to predict the major product in these cases!

Bulky bases affect the product distribution resulting in the Hofmann product, the least substituted alkene:

However, it takes a lot of steric hindrance for the less stable product to be the major product:

The major product of an E2 elimination reaction is the more stable alkene except if the reactants are sterically hindered or the leaving group is poor

10.3 THE E1 REACTION

A unimolecular reaction:

The alkyl halide dissociates, forming a carboanion.
The base forms the elimination product by removing a proton from a β-carbon.

The E1 reaction, like the S_N1 reaction, involves a carbocation intermediate

How does a weak base like water remove a proton from an *sp*^{3} carbon?

- **The presence of a positive charge greatly reduces the pK_a**

- **Hyperconjugation weakens the C-H bond by electron density**

The major product in an E1 reaction is generally the more substituted alkene

The first step is the rate-determining step, the rate of an E1 reaction depends both on the ease with which the carbocation is formed and how readily the leaving group leaves

10.4 BENZYLIC AND ALLYLIC HALIDES

Benzylic and allylic halides readily undergo E2 reactions, because the new double bond in the product is relatively stable – conjugation with a benzene ring or with a double bond

Also benzylic/allylic halides undergo E1 reactions because they form relatively stable carbocations.

If the two resonance contributors are not mirror images, as they are in the preceding example, two dienes will be formed.

10.5 COMPETITION BETWEEN E2 AND E1 REACTIONS

An E2 is favored by a high concentration of strong base and an aprotic polar solvent (such as DMSO or DMF)

An E1 is favored by a weak base and a protic polar solvent*(such as H_2O or ROH)*

Ex) a tertiary alkyl halide with a strong base : E2 reaction
a tertiary alkyl halide with a weak base : E1 reaction

10.6 E2 AND E1 REACTIONS ARE STEREOSELECTIVE

Stereochemistry of the E2 Reaction

The bonds to the eliminated groups (H and X) must be in the same plane

The best overlap of the interacting orbitals is achieved through back-side attack

The anti elimination is favored over the syn elimination

Anti elimination avoids repulsion of the electron-rich base

When only one hydrogen is bonded to the β-carbon, the major product of an E2 reaction depends on the structure of the alkene

Anti elimination of HBr from (2S,3R)-2-bromo-3-phenylbutane forms the Z isomer.

Stereochemistry of the E1 Reaction

The major stereoisomer obtained from an E1 reaction is the alkene in which the bulkiest substituents are on opposite sides of the double bond

Both syn and anti elimination can occur in an E1 reaction

10.7 ELIMINATION FROM SUBSTITUTED CYCLOHEXANES

In an E2 reaction, groups to be eliminated must be in axial positions

Neomenthyl chloride undergoes the E2 200 time faster than menthyl chloride

Zaitsev’s rule?

No β proton with axial position !

E1 Reactions of Substituted Cyclohexanes

The two groups that are eliminated do not both have to be in axial positions because the elimination reaction is not concerted. In this case, *Zaitsev’s rule* is followed.

10.8 A KINETIC ISOTOPE EFFECT CAN HELP DETERMINE A MECHANISM

A carbon deuterium bond (C–D) is about 1.2 kcal/mol stronger than a carbon hydrogen bond (C–H).

The deuterium kinetic isotope effect is 7.1, indicating that a C–H (or C–D) bond must be broken in the rate-determining step.

10.9 COMPETITION BETWEEN SUBSTITUTION AND ELIMINATION

Alkyl halides can undergo S_N2, S_N1, E2, and E1

Decide whether the reaction conditions favor S_N2/E2 or S_N1/E1

S_N2/E2 reactions are favored by a high concentration of a good nucleophile/strong base

S_N1/E1 reactions are favored by a poor nucleophile/weak base

Decide how much of the product will be the substitution product and how much of the product will be the elimination product

In case : If either the primary alkyl halide or the nucleophile/base is sterically hindered - elimination win the competition

-A secondary alkyl halide forms both substitution and elimination products under S_N2/E2 conditions.

Bulky bases, DBN and DBU are commonly used to encourage elimination over substitution.

High temperature favors elimination over substitution:

Why? Because elimination is entropically favorable.

Tertiary alkyl halides undergo only elimination under S_N2/E2 conditions:

S_N1/E1 conditions:

The elimination reaction favored at higher temperatures.

Primary alkyl halides do not form carbocations; therefore they cannot undergo S_N1 and E1 reactions.

10.10 SUBSTITUTION AND ELIMINATION REACTIONS IN SYNTHESIS

Williams Synthesis

In synthesizing *tert*-butyl ehtyl ether, the hindered butoxide ion should be used -

In case of synthesis using tert-butyl halide and ethoxide ion, any ether would not be formed

Consecutive E2 Elimination Reactions

Requires a strong base $NaNH_2$. Reaction carried out in liquid ammonia. This is how alkynes are commonly synthesized.

If a weaker base, such as - OH is used at room temperature, the reaction will stop at the vinylic halide and no alkyne will be formed.

Chapter 11

Reactions of Alcohols,Ethers, Epoxides, Amines, and Thiols

11.1 NUCLEOPHILIC SUBSTITUTION REACTIONS OF ALCOHOLS: FORMING ALKYL HALIDES

Alcohols and ethers have to be activated before they can undergo a substitution or an elimination reaction:

Convert the strongly basic leaving group (OH^-) into the good leaving group, H_2O (a weaker base):

Only weakly basic nucleophiles can be used

Primary, secondary, and tertiary alcohols all undergo nucleophilic substitution reactions with HI, HBr, and HCl:

Secondary and tertiary alcohols undergo S_N1 reactions with hydrogen halides

Primary alcohols undergo S_N2 reactions with hydrogen halides

When HCl is used, the SN2 reaction is slower because Cl^- is a poorer nucleophile than Br^- or I^- in protic polar solvents (alcohol, water), The rate of the reaction can be increasedusing $ZnCl_2$ as a catalyst.

$ZnCl_2$ functions as a Lewis acid that complexes strongly with the lone-pair electrons on oxygen.

Rearrangement is possible in the S_N1 reaction of the secondary or tertiary alcohol.

11.2 Other Methods Used to Convert Alcohols into Alkyl Halides

Alcohols are inexpensive, so converted to reactive alkyl halides to be used as starting materials for the preparation of many organic compounds

Utilization of phosphorus tribromide.	**PBr_3, phosphorus tribromide**
	PCl_3, phosphorus trichloride
Other phosphorus reagents can be used.	**PCl_5, phosphorus pentachloride**
	$POCl_3$, phosphorus oxychloride

11.3 Converting An Alcohol into A Sulfonate Esters

Sulfonyl chlorides available to activate OH groups:

Sulfonate esters have excellent leaving groups because a sulfonic acid is a very strong acid

11.4 ELIMINATION REACTIONS OF ALCOHOLS: DEHYDRATION

Dehydration of Secondary and Tertiary Alcohols by an E1 Pathway

To prevent the rehydration of the alkene product, one needs to remove the product as it is formed

The major product is the most stable alkene product:

The rate of dehydration reflects the ease with which the carbocation is formed.

The most stable alkene product has the most stable transition state

Carbocation rearrangement.

The dehydration of a tertiary or a secondary alcohol is an E1 reaction, the dehydration of a primary alcohol is an E2 reaction competing with S_N2

Primary Alcohols Undergo Dehydration by an E2 Pathway

The product obtained from E2 in most cases is identical to the product obtained from E1 (carbocation and rearrangment).

The Stereochemical Outcome of the E1 Dehydration

Alcohols and ethers undergo S_N1/E1 reactions unless they would have to form a primary carbocation

11.5 Oxidation of Alcohols

Chromic acid (H_2CrO_4) is formed by dissolving chromium trioxide (CrO_3) or sodium dichromate ($Na_2Cr_2O_7$) in aqueous acid.

Oxidation by chromic acid.

Secondary alcohols are oxidized to ketones.

Primary alcohols are oxidized to aldehydes and eventually carboxylic acids.

A tertiary alcohol cannot be oxidized and is converted to a stable chromate ester instead.

The oxidation of aldehydes to acids requires the presence of water.

In the absence of water, the oxidation stops at the aldehyde.

PCC, a methylene chloride–soluble reagent: Mild oxidation reagent

11.6 Nucleophilic Substitution Reactions of Ethers

Ethers, like alcohols, can be activated by protonation.

Ether cleavage both by S_N1 and S_N2 reactions

Reagents such as $SOCl_2$ and PCl_3 can activate alcohols but not ethers

The oxygen atom does not have a proton that can dissociate, then the more stable starting materials are re-formed.
So Ethers are frequently used as solvents because only they react with hydrogen halides

11.7 Nucleophilic Substitution Reactions of Epoxides

Epoxides are more reactive than ethers in nucleophilic substitution reactions because of ring strain.

11.8 ARENE OXIDES

Mechanism for arene oxide rearrangement.

Naphtalene oxide rearrangement.

Arene oxides as a carcinogen.

11.9 AMINES DO NOT UNDERGO SUBSTITUTION OR ELIMINATION REACTIONS

The stronger the base, the poorer it is as a leaving group. Therefore amines do not undergo substitution reactions because NH_2^- is a very strong base (a very poor leaving group):

Unlike the leaving group of a protonated alcohol, the leaving group of a protonated amine cannot be replaced by a halide ion

Even the protonated amine moiety cannot be the living group

11.10 QUATERNARY AMMONIUM HYDROXIDES UNDERGO ELIMINATION REACTIONS

The reaction of a quaternary ammonium ion with hydroxide ion is Hofmann elimination reaction.

Quaternary ammonium *halides* cannot undergo Hofmann elimination reactions because halide ions are weak bases.

However, a quaternary ammonium *halide* can be converted into a quaternary ammonium *hydroxide* by treatment with silver oxide and water.

11.11 THIOLS, SULFIDES, AND SULFONIUM SALTS

Thiols are sulfur analogs of alcohols
used to form strong complexes with heavy metal cations such as arsenic and mercury:

named by adding the suffix "thiol" to the name of the parent hydrocarbon

Thiols are stronger acids (pK_a = 10) than alcohols

Thiols are not good at hydrogen bonding

In protic solvent, thiolate ions are better nucleophiles than alkoxide ions:

Sulfur is an excellent nucleophile because its electron cloud is polarized

Because sulfonium salt has a weakly basic leaving group, a sulfonium ion readily undergoes nucleophilic substitution reactions.

Mustard—A Chemical Warfare Agent

World War I: chemical agents as weapons
→blisters (물집) over the surface of the body

The blistering caused by the high local concentrations of HCl produced by the contact with water—or any other nucleophile—on skin or in lung tissue.

Mustard gas: alkylating agent

Mustard has a profound effect on rapidly dividing cells:
possibly effective antitumor agent, while it is too reactive.