CHEM 124 – Freshman Organic Chemistry I – Fall 2014

Based on Lectures by Prof. Jonathan Ellman and "Organic Chemistry 5th Edition" by Marc Loudon

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Chapter 1 – Chemical Bonding and Chemical Structure

1.1 Introduction

A. Orgo deals with compounds of carbon
B. Emergence of Orgo: from the death of vitalism, esp after synthesis of urea, acetic acid.
C. Why Study Orgo?
    a. Appliances, Apparel, Materials, etc.
    b. Pharmaceuticals: Truvada (HIV), Isentress (integrase, HIV), Crestor (CVD), Humira (autoimmune).

1.2 Structure and Bonding

A. **Electropositive** (left, wants to lose e- & become positive) and Electronegative create polar bonds.
B. Lewis Structure: (a) only valence e-, (b) sum of e- is 2 or 8 or 6 or whatever, (c) Assign formal charges
C. **Formal Charge**: Subtract 1 for each bonding e- pair and 2 for each lone e- pair from the valence number.
D. Polar bonds: have a dipole moment $\mu=qr$, with units of debyes (D). r is a vector; positive → negative.
The dipole moment of a molecule is the sum of the vectors.

1.3 Structures of Covalent Compounds

A. Structure comes from atomic connectivity (what's bonded with what) and molecular geometry (how far apart and how situated, described by bond length and angle)
    a. Bond Length: increases toward **higher periods** (atomic size), **decreasing bond order**, and **lower groups** (atomic size, but less significant); in order of importance.
    b. Bond Angle: VSEPR – valence-shell electron-pair repulsion theory; bonds around a central atom are situated to be as far apart as possible.
    c. **Dihedral Angle** or Torsion Angle: describes the angle between bonds: measured as the angle between planes that lie on those bonds.
B. Methods for Determining Molecular Geometry:
    a. X-ray Crystallography: reveals arrangement in solid crystalline state, uses high speed computers.
    b. Electron Diffraction: reveals arrangement in gaseous state
    c. Microwave Spectroscopy: also gaseous, absorption reveals arrangement.
    d. Most data comes from gaseous methods. No methods for solutions.

1.4 Resonance Structures

A. Resonance hybrid (←→) is a single resonance-stabilized molecule represented by two unstable representations.
B. Dashed curved lines designate partial bonds. So do lines with short, perpendicular lines drawn underneath.
C. Structures (bonds and charges) are described by a weighted average.
Preference is given to structures with complete octets and formal charges that follow electronegativity.

1.5 Wave Nature of the Electron

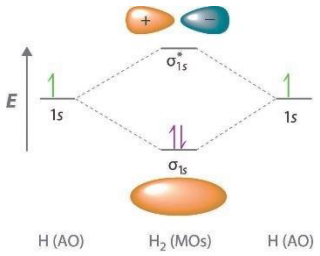
A. Heisenberg uncertainty principle: accuracy of position and velocity is limited → fuzzy e- clouds

1.6 Electronic Structure of the Hydrogen Atom

A. Orbitals: an allowed state or wave motion of an e-
B. Wavefunction: describes an atomic orbital in 3 dimensions.
C. **Quantum Numbers**: (3) describe orbitals.
    a. Principal Quantum Number (n) – [1, 2, 3…] SIZE AND ENERGY
    b. Angular Momentum (Azimuthal) Quantum Number (ℓ) – [0, 1, 2… n-1] SHAPE
    c. Magnetic Quantum Number ($m\ell$) – [-ℓ... -1, 0, 1… ℓ] also [x, y, z] ORIENTATION
    d. Spin Quantum Number (ms) – [$\pm\frac{1}{2}$]

D. Spatial Characteristics of Orbitals
   a. The 90% probability level measures approximate size.
   b. **Nodes** are points or surfaces where the wave is zero. Electrons can cross because nodes are a part of the wave motion, not the medium. **Nodes = n – 1.** There are ℓ angular nodes, and n – ℓ – 1 radial nodes. It's possible to draw the shape of an orbital by cutting X-angles and circles.
   c. The wavefunction draws the orbital, but electron density is proportional to the SQUARE of this function.

1.7 Electronic Structures of More Complex Atoms
A. Different atoms have different energy orbitals; the gaps between energy levels decreases as n increases.
B. Aufbau Principle: electrons are first placed into the lowest energy orbitals.
C. Pauli Exclusion Principle: no electron can share all four quantum numbers.
D. Hund's Rule: electrons don't pair unless they have to, in order to minimize repulsion.



1.8 Molecular Orbitals
A. Atomic orbitals don't describe e- in molecules because they're not localized.
B. **Determining electronic configuration for MOs**
   STEP 1: Start with the isolated atoms of the molecule and bring them together to their respective positions.
   STEP 2: Allow the overlapping valence atomic orbitals to interact
      RULE 1: The combination of two atomic orbitals gives two MOs.
      RULE 2: Two MOs are derived from the addition and subtraction of atomic orbitals in the overlap region. Constructive interference → bonding MOs; destructive interference → antibonding MOs.
   STEP 3: Arrange the MOs in order of increasing energy in an orbital interaction diagram.
      RULE 1: The two MOs have different energies: the bonding MO has a lower energy and the antibonding MO has a higher energy, compared to the isolated orbitals.
      RULE 2: Orbital energy increases with more nodes.
   STEP 4: Redistribute the electrons from constituent atoms into the MOs in order of increasing MO energy.
      RULE: Use the Aufbau principle and Hund's rule.
C. Sigma bounds have cylindrical symmetry (looks the same when rotated around a single axis)
D. Electrons are usually directly between nuclei, but not always. A chemical bond need not be an e- pair (although pairs tend to be stronger), and sharing of e- doesn't always contribute to bonding.

1.9 Hybrid Orbitals
A. Bonding in Methane:
   a. Problem: $2s^1$ and $2p^3$ orbitals aren't directed tetrahedrally.
      Solution: The combination of the orbitals creates four bonding MOs and 4 antibonding MOs.
   b. Problem: The electron density pudding model seems to debunk individual bonding.
      Solution: Hybridization allows for mixing of orbitals with different shapes (s, p, d…)
B. Bonding in Ammonia:
   a. The same as methane, but with a lone electron pair.
   b. Problem: Hybridization costs energy
      Solution: Hybrid orbitals help minimize repulsion and give directional character.
   c. Problem: Angle of H – N – H is 107.3, not 109.5
      Solution: (VSEPR) e- pairs repel bonds more. (MO Theory) unshared e- pairs prefer lower energy s-orbitals and don't need directionality advantage. This means higher s-character, covering more space.

Chapter 2 – Alkanes

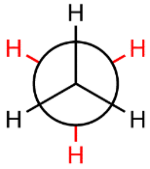
2.1 Hydrocarbons

A. The C=C bond in ethane is an $sp^3 – sp^3$ sigma bond. The C – H bonds are $sp^3 – s$ bonds like in CH_4.
B. **Aliphatic hydrocarbons**: alkanes, alkenes, and alkynes. Derived from aleiphatos "fat."
C. Aromatic hydrocarbons: ring-shaped ones, like benzene.
D. Alkanes (paraffins) have single bonds, alkenes (olefins) have double bonds, and alkynes (acetylenes) have triple bonds.

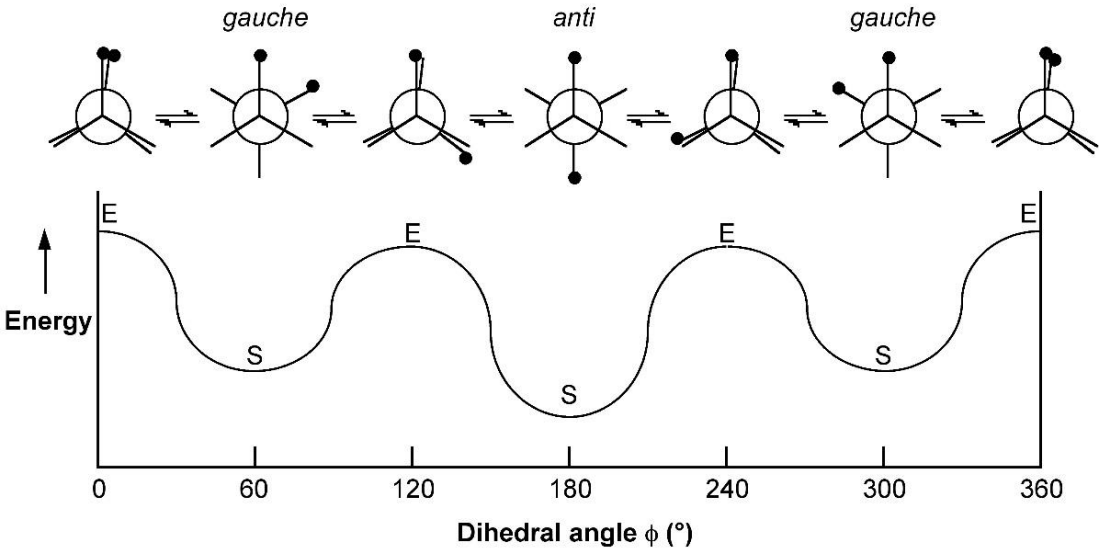
2.2 Unbranched Alkanes

A. Alkanes with unbranched carbon chains are called normal or n-alkanes.
B. Molecular: C_2H_6. Structural = everything. Condensed structural: $CH_3 – CH_3$
C. Homologous series: differ by the addition of methylene groups ($R – CH_2 – R$), and have regular variation in physical properties (density, boiling points, etc). Ex: unbranched alkanes

2.3 Conformations of Alkanes



A. Newman projection: planar projection along one projected bond; reveals dihedral angles.
B. Conformation: spatial arrangement of atoms.
    1. **Staggered** conformation: one bond bisects the angle of another, as shown.
    2. **Eclipsed** conformation: smallest dihedral angle is 0 degrees.
C. A conformation is preferred if it (a) minimizes torsional strain and repulsion (accounts for ~75%), or (b) there is a favorable interaction between the bonding and antibonding MOs.
D. Internal rotation: rapid conversion between stable forms through unstable forms, fueled by heat
E. Van der Waals Radius: energy is required to force two non-bonded atoms closer than the sum of their van der Waals radii. This destabilizes the gauche formation.
F. Conformational analysis: investigation of molecular conformations and relative energies.



2.4. Constitutional Isomers and Nomenclature

A. Isomers: different compounds, same molecular formula
    1. Constitutional (structural) isomers differ in connectivity.
    2. Geometric isomers differ in orientation about double bonds.
    3. Enantiomers differ in their left-right orientation.
B. Organic Nomenclature: IUPAC rules form the basis for widely applied substitutive nomenclature.

C. Alkane Nomenclature: 10 rules
    1. The unbranched alkanes are named according to the number of carbons (i.e. hexane)
    2. For branched chains, determine and name the (longest continuous) principal chain.
    3. If there is a tie, choose the principal chain with the most branches.
    4. Number the carbons of the principal chain, starting with the side with the first branch.
    5. Name each branch and identify the carbon number of the chain.
        i. Branching groups are called substituents. Substituents of alkanes are alkyl groups. To name them, drop "ane" and add "yl."
        ii. Alkyl groups may themselves be branched. Common ones are as shown below:
    6. Write the carbon number from step four, a hyphen, the name from step 5, and the name of the principal chain (step 2). [Carbon #] – [Name][Principal Chain]
    7. Repeat as needed for other substituents. Use prefixes "di," "tri," etc for repeats.
    8. If substituents occur at more than one carbon, choose a numbering scheme that puts the smallest number at the first point of difference. When counting from both sides, ignore what the substituent is – consider only what number it's given.
    9. Cite substituents in alpha order (ignore di, tri, tert, and sec, but consider iso, neo, and cyclo).
    10. If all else fails for numbering, the first-cited group (probably butyl or ethyl) receives the lowest number.

D. Highly Condensed Structures
    1. Ex: $C(CH_3)_4$ is an alpha carbon with four methyl groups.
    2. WRITE THEM OUT. Success highly correlates with taking the time to write out intermediate steps.

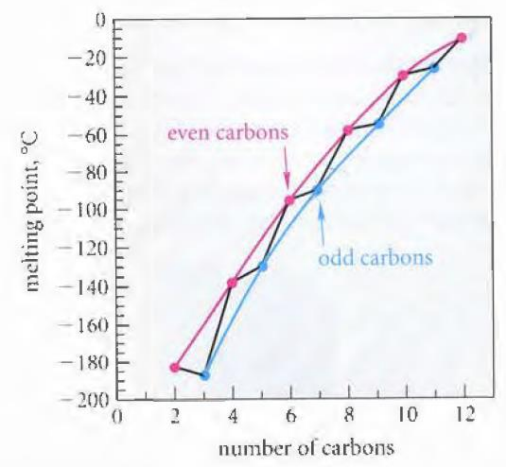
E. Classification of Carbon Substitution
    1. Primary, secondary, tertiary, quaternary carbons – bonded to 1, 2, 3, or 4 other carbons.
    2. Hydrogens bonded to a primary carbon are primary hydrogens, and so on.

2.5 Cycloalkanes and Skeletal Structures

A. Cycloalkanes are closed rings. The name given is cyclo+[X]+ane. NOT planar.
B. The general molecular formula is **C_nH_{2n}**, because the two hydrogens pop off.
C. Nomenclature follows the same rules as open-chain. The prefix (1-) is not necessary by itself. The principal chain cannot extend through a cyclic structure.
D. When a noncyclic carbon chain is longer than an attached ring, the ring is the substituent. <u>In this case, the attached carbon is automatically designated 1.</u>

2.6 Physical Properties of Alkanes

A. Boiling Points: vapor pressure equals atmospheric pressure
    a. Boiling point increases by 20-30°C per carbon atom in a series due to greater IMFs.
    b. Greater IMFs are created when temporary dipole moments cause induced dipoles and van der Waals attractions bring them together.
    c. Van der Waals attractions are proportional to the surface area of interacting electron clouds. This means compact or highly branched structures experience less attraction.



B. Melting points
    a. **Melting point assesses purity** - impurities lower and broaden the melting range.
    b. **Melting point reflects stabilizing IMFs** in the crystal and the molecular symmetry (number of indistinguishable ways in which the molecule fits into the crystal).
    A higher melting point means more stable crystal structure (relative to the liquid state)

c. The chart for melting point alternates in a sawtooth pattern because odd carbons don't fit together in crystals as well as even carbons.
d. **Branched structures have lower melting points** because (a) lower surface area = lower IMFs, and (b) branching interferes with regular packing.
e. **Symmetry increases melting point** because they fit together well = higher IMFs.

C. Other Physical Properties
a. Dipole moment: measures polarity. C and H have similar electronegativities = nonpolar.
b. Density: generally lower than water.

2.7 Combustion: Nothing new

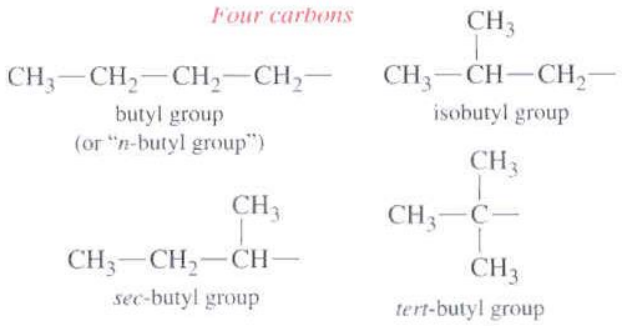
2.8 Occurrence and Use of Alkanes

A. Petroleum (crude) is separated into alkanes and aromatic hydrocarbons by fractional distillation. The mixture is slowly boiled to separate by boiling point.
B. Methane is in natural gas and anaerobic bacteria waste.
C. Catalytic cracking converts between molar masses (lower for motor fuels). Reforming creates branched chains (for ignition properties). The numbers 100 and 0 are assigned to 2,2,4-trimethylpentane and heptane. A weighted average gives the octane number.

2.9 Functional Groups, Compound Classes, and "R" Notation

A. Functional Groups and Compound Classes
a. Functional groups are characteristically bonded and have a recurring chemical reactivity.
b. Compound classes are compounds that contain the same functional group.
c. **Examples:** the C=C bond (FG) in alkenes (CC), or the –OH group (FG) in alcohols (CC).

B. R notation represents all alkyl groups – derived from alkanes
C. **Aryl groups** are derived from benzene and derivatives (Ar–). The simplest is the phenol group (Ph–), which is just a benzene substituent.
D. **Butyl group nomenclature**



Chapter 3 – Acids and Bases

3.1 Lewis Acid-Base Association Reactions

A. Electron-Deficient Compounds – short of octet by 1 or more e- pairs

B. Reactions of Electron-Deficient Compounds with Lewis Bases

   a. EDCs tend to undergo reactions that complete their octets ($BF_3 + F^- \rightarrow BF_4^-$)

   b. Lewis acids accept **e- pairs** (must be deficient!) to form bonds.
   Lewis bases donate **e- pairs** (must have free lone pair!) to form bonds.
   Donating or receiving e- from bonds does NOT make a Lewis acid/base.

   c. Lewis acid-base association reactions are when LAs and LBs form a single product. The reverse is a Lewis acid-base dissociation.

C. The Curved-Arrow Notation for Lewis Acid-Base Association and Dissociation Reactions

   a. Curved arrows are used to describe a flow of e- from source to acceptor.
   Remember that total charge is conserved.

3.2 Electron-Pair Displacement Reactions - Donation of electrons to atoms that aren't electron-deficient

A. When an e- pair is donated to an octet atom, another e- pair must leave the acceptor.
This is called an electron-pair displacement reaction.

3.3 Review of the Curved-Arrow Notation

A. Use of Curved-Arrow Notation to Represent Reactions
Two types of electron-pair reactions: association/dissociation, and displacement.

B. Use of the Curved-Arrow Notation to Derive Resonance Structures

3.4 Bronsted-Lowry Acids and Bases

A. Bronsted acid – donates protons; Bronsted base – accepts protons

   a. Bronsted Lowry acid-base reactions are just e- pair displacements on hydrogen.

   b. All Bronsted acid-base reactions have two conjugate acid-base pairs.

B. Nucleophiles, Electrophiles, and Leaving Groups

   a. **Nucleophile**: donates an electron pair to an atom. Synonymous with Lewis base, but usually refers to donating to atoms other than hydrogen.

   b. **Electrophile**: receives an e- pair from an atom. Synonymous with Lewis acid.

   c. **Leaving group**: accepts an electron pair from a breaking bond and runs with it.
   Downgraded double or triple bonded leaving groups don't actually leave.
   Note that a leaving group is a nucleophile in the reverse reaction.

C. Strength of Bronsted Acids

   a. The strength of a Bronsted acid is proportional to how well it transfers protons, measured by the dissociation constant $[A^-][H_3O^+] / [HA]$ (smaller is stronger).

   b. Direct determination is limited to acids with a pH between that of H_3O^+ (strongest acid in water) and H_2O. If you dissolve anything stronger, it ionizes to H_3O^+. Similarly, OH^- is the strongest base that can exist in water.

   c. The pK_a values of very strong or very weak acids are measured in other solvents and used to estimate aqueous pK_a. pK_a is very different in nonaqueous solutions, but relative values are roughly the same.

   d. pK_a of water (15.7) is different from K_w (14) because the former uses the concentration of water itself (55.5 M).

D. Strength of a Bronsted Base: inversely proportional to the strength of its conjugate acid

E. Equilibria in Acid-Base Reactions
   a. The equilibrium in acid-base reactions always favors the weaker acid/weaker base side
   b. For an amphoteric compound (H_2O), the acid strength is proportional to its pK_a, and the base strength is proportional to the pK_a of its conjugate acid (H_3O^+)
   c. $LH + R^- \leftrightarrows L^- + RH$

      $\log K_{eq} = pKa_{(RH)} - pKa_{(LH)}$ $\quad K_{eq} = 10\text{^}(pKa_{(RH)} - pKa_{(LH)})$

3.5 Free Energy and Chemical Equilibrium

A. Free energy of dissociation is $\Delta G^o = -RT \ln K_{eq} = -2.3RT \log K_{eq} = 2.3RT\ pK_{eq}$

   $K_{eq} = 10\text{^}(-\Delta G^o/2.3RT)$ Note: small changes in ΔG^o result in large changes in K_{eq}.

3.6 Relationship of Structure to Acidity

A. Three steps of dissociation
   a. Bond breaking: HA → H + A // Bond Dissociation Energy
   b. Loss of e- from hydrogen: H → H^+ + e- // Ionization Potential
   c. Electron transfer: e- + A →A- // Electron Affinity

B. Stabilizing the conjugate base decreases overall energy ($-\Delta G^o$) and increases acidity (K_a).

C. **The Element Effect** (LARGE)
   a. Bronsted acidity increases DOWN and ACROSS (RIGHT).
      i. Down a column, this is due to <u>weaker bonds</u>.
      ii. Across a period, this is due to <u>greater electron affinity</u>.

D. **The Charge Effect** (LARGE)
   a. Positively charged polyatomic ions have a much greater affinity for electrons, making them much more acidic.
   b. The opposite is true of negatively charged ions, which are generally much more basic.

E. **The Polar Effect** or Inductive Effect (small)
   a. Electronegative substituent groups increase acidity with number and proximity.
   b. Electron-withdrawing polar effect: electronegative elements stabilize negative charges in the conjugate base. The reverse is the e- donating polar effect.
   c. <u>Triple bonds and double bonds exhibit the polar effect as well.</u>

F. **Resonance Stabilization**
   a. Spreading around the electron density increases stability
   b. <u>Resonance stabilization is stronger than the polar effect!</u>

G. **Hybridization**
   a. Creating a negative charge on orbitals with greater s-character is more stable.

Chapter 4 – Alkene Structure and Reactivity

4.1 Structure and Bonding in Alkenes

A. Alkenes or olefins are unsaturated hydrocarbons with double-bonds.

B. Carbon Hybridization in Alkenes

   a. 2s orbital + three 2p orbitals →three sp^2 orbitals (120°) + $2p_z$ orbital (90°)
   Only two 2p orbitals are hybridized with the 2s.

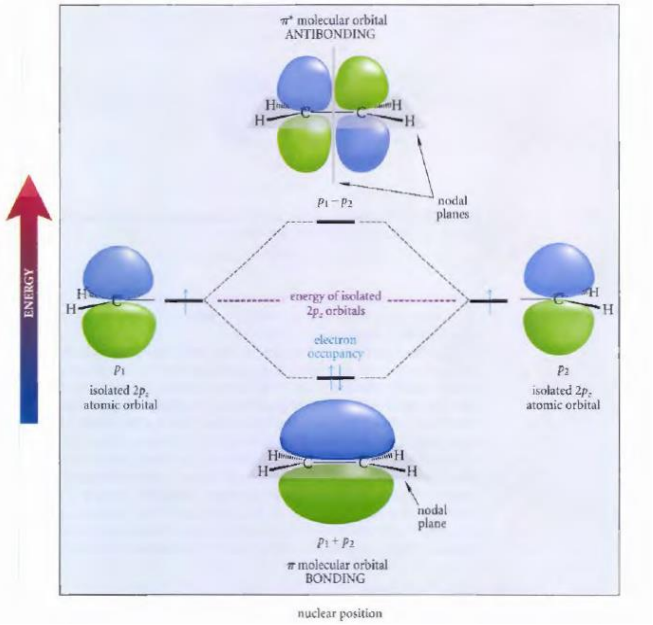
   b. Bond length is shorter because the greater electron density pulls them closer.
   Bond angle is larger (122°) due to repulsion from the electrons in the double-bond.

C. The pi bond: formed by the side-to-side overlap of p orbitals – one bond, two lobes.

   a. Pi bonds are not cylindrically symmetric – they can't twist b/c rotation breaks the bond.

   b. Pi electrons generally have higher energy than sigma and hybridized sp^x e- because p>s.

   c. Pi electrons are easier to remove:
   <u>side-to-side overlap is less effective</u>.



D. Double-Bond Stereoisomers (geometric isomers)

   a. Stereoisomers: same atomic connectivity, but different spatial arrangement.

   b. Double-bond stereoisomers (also: cis-trans or E,Z) are related by an internal rotation of 180°

   c. Cis– same side; Trans–opposite sides

   d. Stereocenter: an atom (usually DBC) where changing two groups gives a stereoisomer.

4.2 Nomenclature of Alkenes

A. IUPAC Substitutive Nomenclature

   a. Unbranched alkenes: specify the position of the double-bond, then replace –ane with –ene.
   EX: Hexane with a double-bond at one end becomes 1-hexene.

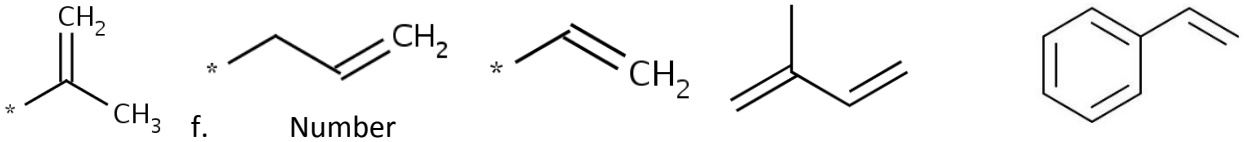
   b. Principal chain: most double-bonds. Overall length is the tiebreaker.
   Number from the end that gives the lowest numbers to double-bonded carbons.

   c. When the alkene contains an alkyl substituent, the position of the double-bond, NOT THE BRANCH, determines the numbering.

   d. For 2 double-bonds, –ene becomes –adiene. For 3 double-bonds, –ene becomes –atriene.

   e. Nonsystemic traditional names and substituent groups with double-bonds must be learned:

Isopropenyl **Allyl** **Vinyl** **Isoprene** **Styrene**



   f. Number other substituents from point of attachment. Drop –e for –yl (butane → butenyl)

B. Nomenclature of Double-Bond Stereoisomers: the Cahn-Ingold-Prelog E,Z System

   a. E,Z involves relative priorities according to a set of sequence rules.
   Z configuration: higher priority groups on the same side. E configuration: opposite sides.

b. Steps of the E,Z System
    1. For atoms directly attached to DBC, give priority to the higher atomic number (atomic mass is the tie-breaker for isotopes)
    2. If atoms directly attached to the DBC are the same, then consider the atoms attached. Arrange in descending priority order and do a pairwise comparison. Give priority based on rule 1 at the first point of difference.
    3. If the sets of attached atoms are identical, move away from the bond to the next atom following the path of highest priority and apply rule 2 to the new set of attached atoms.
    4. If C is double bonded with O, you pretend C has 2 single bonds with O, and O has 2 single bonds with C. With triple bonds, you pretend C has 3 single bonds, etc.

4.3 Unsaturation Number or Degree of Saturation (U)

A. The unsaturation number is equal to the number of rings and multiple bonds (double=1, triple=2).
B. The maximum H in a hydrocarbon is 2C+2. Because each ring and double bond takes away 2 hydrogens, the unsaturation number is half the difference between max H and actual H.
C. Nitrogen takes a spot, but adds 2 more (net 1), and halogens count as hydrogens.
D. End formula: $U = (2C + 2 + N – H) / 2$, where N is nitrogen, and H is hydrogens and halogens.

4.4 Physical Properties of Alkenes

A. Compared to alkanes: similar boiling point, density, and solubility; higher melting point and greater dipole moment. The last one is because sp^2 orbitals in alkenes tend to have higher s-character, with the electron density closer to the nucleus making it more electronegative than sp^3 in alkanes.

4.5 Relative Stabilities of Alkene Isomers

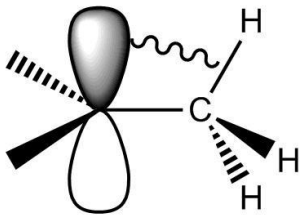
A. Heats of Formation: (ΔH_f^o is the heat change that occurs when a compound is formed from its elements at STP. Exothermic: heat is released. Endothermic: heat is absorbed.
B. We can burn ($4C + 4H_2$) and (2-butene) and measure difference in ΔH_f^o to get heat of formation.
C. Hess' law of constant heat summation: chemical reactions and associated energies can be added algebraically because the energy difference is not dependent on the path or reactions.
D. Relative Stabilities of Alkene Isomers
    a. Most Z (and cis) alkenes are less stable than E (and trans) alkenes because the sterics are unfavorable when larger groups occupy the same side.
    b. Alkenes are stabilized by alkyl substituents on the double-bond.
        i. Placing the alkyl group at the double-bond gives you an sp^2-sp^3 C-C bond, which is stronger than the sp^3-sp^3 C-C bond that would be formed if the alkyl group were elsewhere. More s-character → e- closer to nucleus → more electronegative → (-)sp^2–sp^3(+) dipole → electrostatic interaction.
        ii. Hyperconjugation: alkyl groups dump e- density into the pi orbitals.
    c. The number of alkyl groups matters more than their identities.

4.6 Addition Reactions of Alkenes

A. Addition at the double-bond because pi bonds are higher energy: C=C + X–Y → CX–CY

4.7 Addition of Hydrogen Halides to Alkenes

A. (1) H–X breaks and H+ attaches (forming C+ at the other site); (2) X- attacks C+.
B. HBr and HI are used for addition instead of HCl because they're faster.
C. Regioselectivity of Hydrogen Halide Addition
    a. Unsymmetrically located double bonds → 2 possible constitutionally isomeric products.
    b. Markovnikov's Rule: Hydrogen prefers to bond to the DBC with fewer alkyl groups, because this forms the carbocation at the carbon with more alkyl groups (more stable). The halide then bonds to the carbocation (which used to be the DBC with more alkyl groups).
    tl;dr – them that has (H), gets (H).
    c. Regioselective reaction: when one possible isomer is formed a lot more.
D. Carbocation Intermediates in Hydrogen Halide Addition (2 successive steps)
    a. Step 1: the pi bond electrons are donated to the hydrogen. The double-bond is protonated on one side (C–H), and becomes electron deficient (+) on the other (C+ carbocation).
        i. This is an electron pair displacement reaction and a Bronsted acid-base reaction.
    b. Step 2: The electrophilic C+ reacts with the nucleophilic halide (Lewis acid-base association).
    c. Reactive (unstable) intermediates: react so rapidly that they never accumulate.
E. Structure and Stability of Carbocations
    a. Primary, secondary, and tertiary carbocations have 1, 2, and 3 alkyl groups, respectively. The energy difference from primary to tertiary is 202, 181, 165 kcal/mol.
    b. Alkyl substituents strongly stabilize C+ because it means more sp^2-sp^3 C-C bonds. Same mechanism of stabilization as in alkenes, but much more pronounced.
    c. Stability of C+: primary < secondary < tertiary. Greater stability = lower energy.
    d. Hyperconjugation: the overlap of bonding electrons from adjacent sigma bonds (usu sp^3-1s C–H) with the unoccupied 2p orbital of C+. This gives a <u>partial pi-bond character</u>, making the C-C single bonds shorter and stronger than usual. The resonance hybrid shows a sigma bond donating e- to form a double bond (minor contributor).

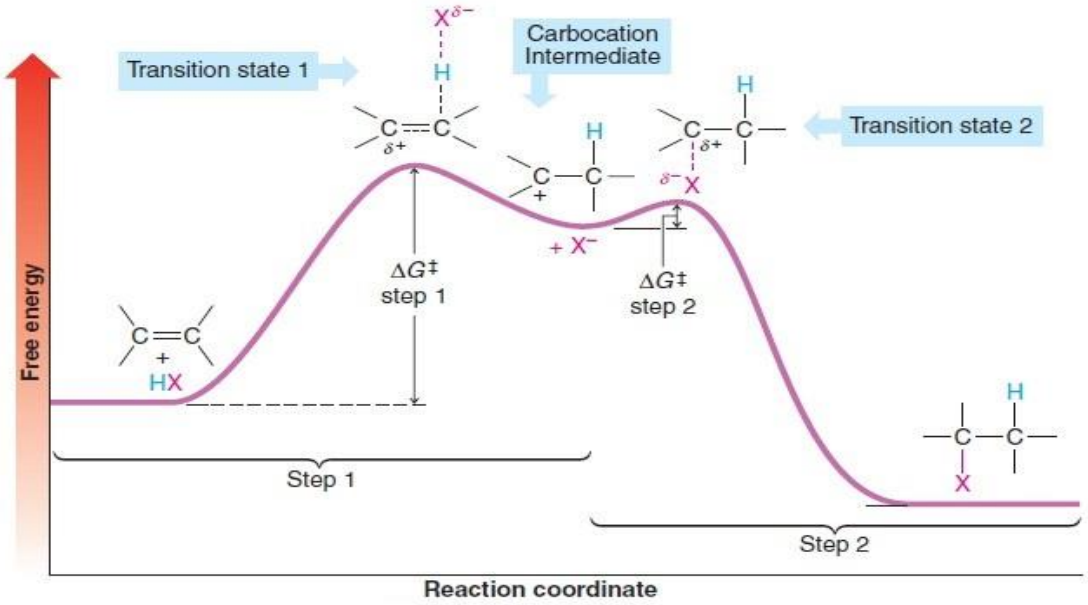


    e. Being bonded to more alkyl groups means more hyperconjugation, because every single sigma bond 1 bond away can interact with the 2p orbital. If a hydrogen is bonded to the carbocation, no conjugation comes from that side.
F. Carbocation Rearrangement in Hydrogen Halide Addition
    a. Rearrangement: an initial group moves to a different final position. It makes a new product possible, which is not necessarily the major product.
    b. Mechanism: the H bonds normally, by Markovnikov's rule. Then, a group adjacent to but not attached to the DBC hops over to C+, moving it further out. This happens because the sigma bond is dumping electron density via hyperconjugation. The transition state is this weird "handing-over" of the methyl group where the 2p orbital overlaps the 1s-sp^2 sigma bond.
    c. Rearrangement can stabilize the carbocation by moving it to where it has more alkyl substituents. C+ is a Lewis acid and the migrating group is a Lewis base.
    d. Alkyl shift: migration of an alkyl group with its bonding electrons.
        i. Common when a quaternary carbon is bonded to a secondary carbocation.
        ii. This can lead to ring expansion, which helps relieve some ring strain.
    e. Hydride shift: migration of hydrogen *with its bonding electrons*.
        i. Common when a tertiary carbon is bonded to a secondary carbocation.
        ii. Preferred over alkyl shifts because it leads to a C+ bonded to more alkyl groups.

4.8 Reaction Rates

A. The Transition State
   a. Rate: number of reactant molecules converted to product in a given time.
   b. Transition state (‡): unstable state of maximum free energy. Represents an energy barrier.
   c. Reaction coordinate: progress of reactants to products. Reactants define one end, and products define the other (basically the x-axis).
   d. Intermediate (IM): local energy minimum.
   e. Standard free energy of activation ($\Delta G^{\ddagger}$): difference in energy between the reactant/intermediate and the next transition state.
   f. Reaction rate depends on $\Delta G^{\ddagger}$ - higher $\Delta G^{\ddagger}$ → higher barrier → slower rate, and vice versa.
   g. Irreversible reaction: product ratio depends on relative rates – there is no equilibrium!

B. Multistep Reactions and the Rate-Limiting Step



Rate = $A * e^{-G/RT}$ $\log(\frac{Rate_A}{Rate_B}) = \frac{\Delta G_B - \Delta G_A}{2.3 * RT}$

   a. Multistep reactions: form reactive intermediates.
   b. Rate-limiting/determining step: slowest step in a multistep chemical reaction, equal to the overall rate. <u>This is almost always the step that goes through the highest transition state</u>, in this case, step 1.

C. Hammond's Postulate
   a. Hammond's Postulate: When an intermediate has a much higher energy than its reactants or products, it gives a good approximation of the structure and energy of the transition state.
   b. Endothermic (unfavorable) reactions: "late" (product/intermediate-like) transition states. Exothermic (favorable) reactions: "early" (reactant-like) transition states.
   c. Thus, we can find which product is preferred in regioselective reactions by comparing the stability and energies of the carbocation intermediates, instead of crying over transition states we know nothing about.

D. Other Stuff
   a. Maxwell-Boltzmann distribution: spread of energies of molecules
   b. ROUGHLY: reaction rate doubles per 10°C increase

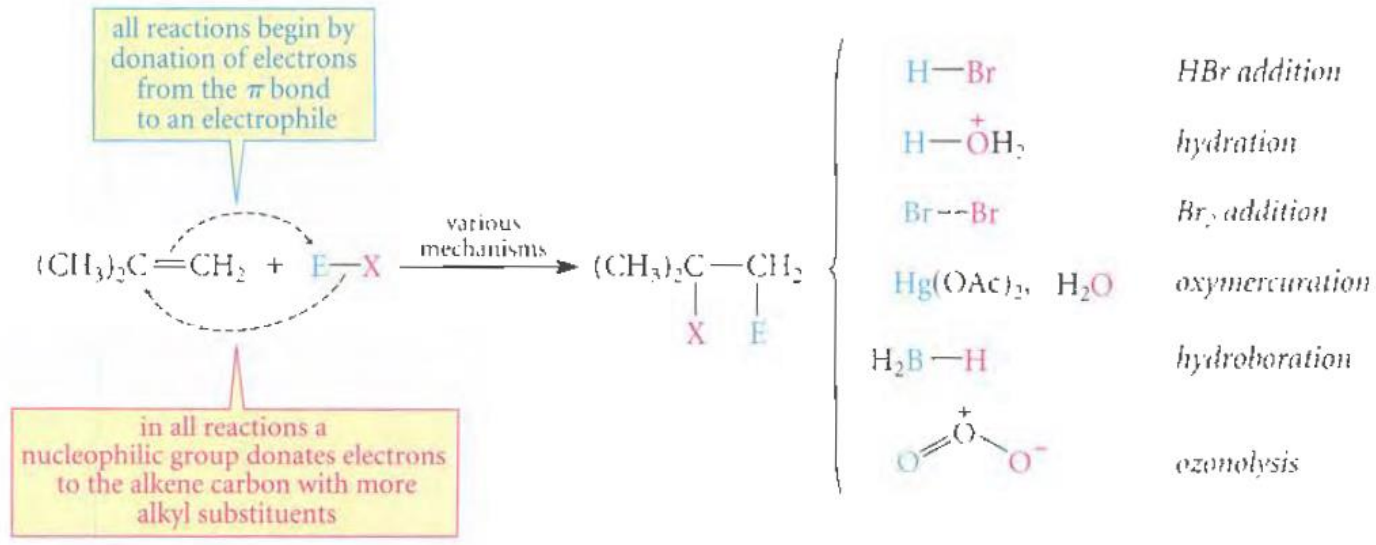
4.9 Catalysis

A. Catalysts increase the reaction rate for both forward and reverse reactions, do not get consumed, and do not affect the energies of reactants or products (doesn't affect ΔG or K_{eq})
B. Heterogeneous catalyst: exists in the separate phases. Homogeneous catalyst: soluble in reaction solution. Heterogeneous can be used in small amounts, and can be filtered off and reused,
C. Catalytic Hydrogenation of Alkenes:
    a. One of the best ways to convert alkenes → alkanes.
    b. Catalyst notation: Pl/C means platinum on carbon (precipitated on charcoal).
    c. Catalysts are often Pl, Pd, Ni, along with Al_2O_3, $BaSO_4$, or activated carbon.
    d. The catalyst forms reactive metal-C and metal-H bonds that then break to form products.
D. Benzene rings: relatively inert toward alkene reactions.
E. Alkene hydration: addition of water
    a. Double-bonds reacts with water to form single bonds when acid-catalyzed (homogeneous).
    b. This reaction is regioselective and follows Markovnikov's rule: hydrogen attaches to the DBC with fewer alkyl substituents, and the OH- group attaches to the DBC with more alkyl groups.
    c. Some alkenes give rearranged hydration products.
    d. Alcohol dehydration: the reverse of alkene hydration (acid-catalyzed removal of water to form double bonds). Industries once used Le Chatelier's principle (increase temperature and pressure) to create alcohols and neutralized the acid to isolate it.
    e. Principle of microscopic reversibility: for any reaction, the reverse reaction occurs by the exact reverse of the original mechanism (as long as it's under the original conditions).

Chapter 5 – Addition Reactions of Alkenes

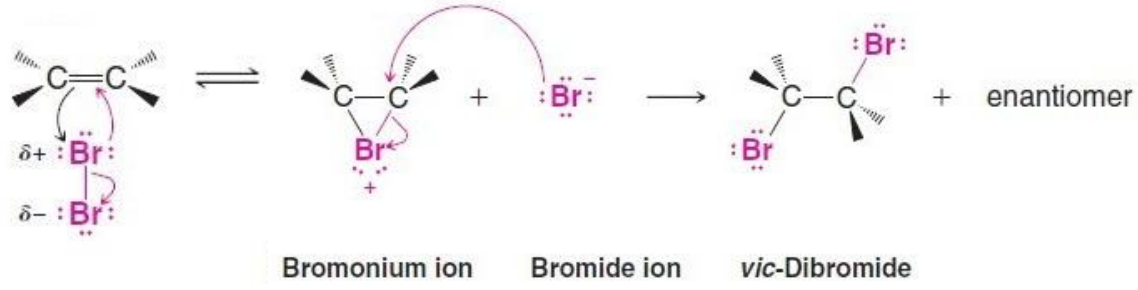
5.1 An Overview of Electrophilic Addition Reactions

A. Concerted mechanism: a reaction in a single step without intermediates; everything happens in concert (simultaneously).
B. General pattern:
    a. Step (1) the alkene pi bond (acting as a Lewis base) donates electrons to an electrophile, which attaches to the DBC with fewer alkyl groups.
    b. Step (2) the nucleophile donates electrons to carbocation, formed from the DBC with more alkyl groups.
C. The LESS electronegative species is usually the electrophile because it loses its electrons during dissociation and is therefore electron-deficient.



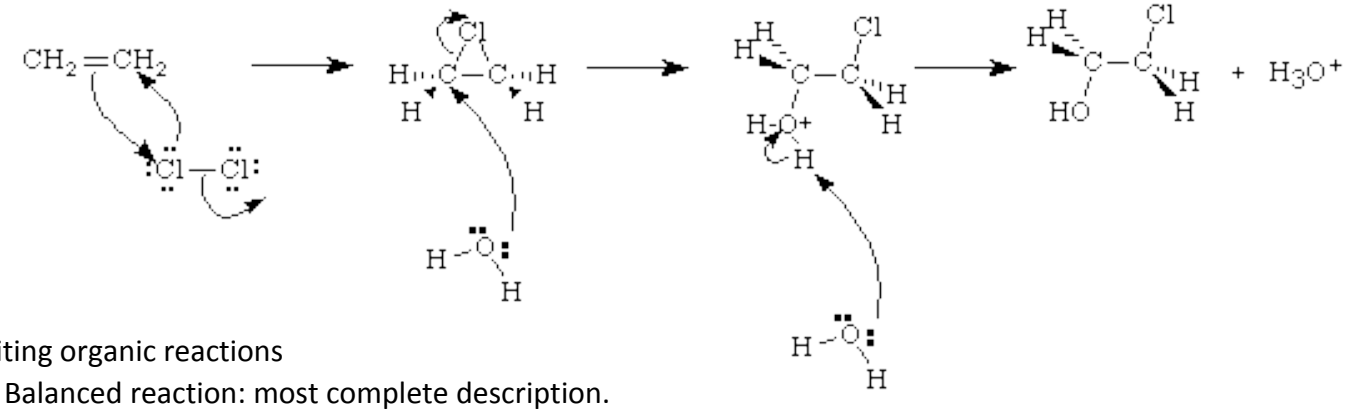
5.2 Reactions of Alkenes with Halogens (X_2)

A. Addition of Chlorine and Bromine
    a. Vicinal dihalides: compounds with halogens on adjacent carbons, formed by halogen-alkene addition (vicinal meaning “on adjacent sites”).
    b. Cl and Br are used. F is too violently reactive, and iodine forms unstable compounds that decompose easily. Br is liquid and easy to work with.
    c. Inert solvents like dichloromethane (CH_2Cl_2) and carbon tetrachloride (CCl_4) typically used for halogen addition because they dissolve both halogens and alkenes and won’t react with the reactants or intermediates.
    d. Bromonium ion: Br+ bonded to two carbon atoms. This happens in ONE STEP.



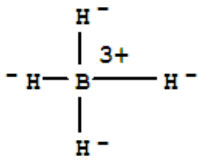
e. Br+ is more stable than a neutral Br with an incomplete octet. Other resonance contributors give both Br & C partial positive charges. The more substituted carbon is more positive.
f. Bromine addition is completed by the electron-pair displacement addition of the other Br^- to one of the DBCs. Br+ is very electronegative and happily accepts electrons from its bond to the more substituted carbon. This process also releases three-member ring strain.

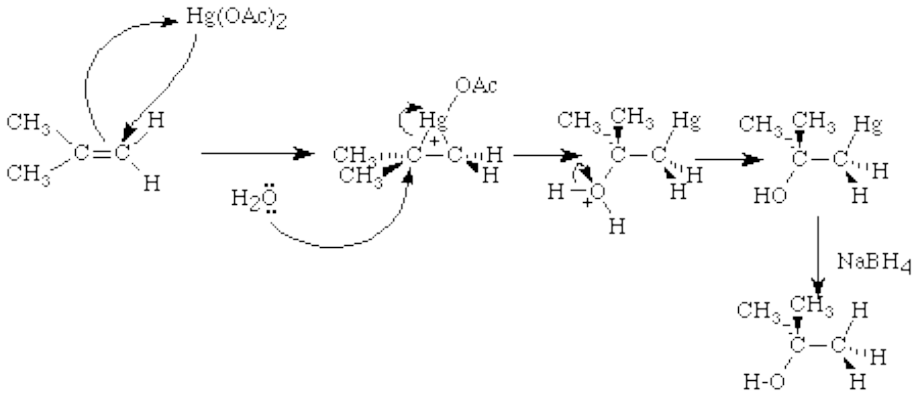
B. Halohydrins (OH—alkene—X)
a. Alkene + X_2 + H_2O → OH—alkene—X + HX
b. When the solvent is a Lewis base i.e. water, it can react with the bromonium ion as the nucleophile (Br^- is also okay, but not as plentiful or as strong a base).
c. Water loses its hydrogen to another water and forms a bromohydrin (with –OH and –Br).
d. –OH tends to bind to the more substituted DBC because it has a weaker bond with X.



5.3 Writing organic reactions
A. Balanced reaction: most complete description.
B. Shorthand writing: shows only the organic starting materials and major organic products. Reactants, catalysts, solvents, or other conditions are written over the arrow.

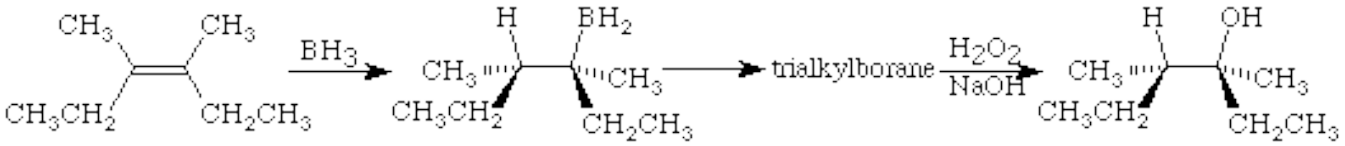
5.4 Conversion of Alkenes into Alcohols
A. Oxymercuration-Reduction of Alkenes
a. Mercuric acetate (AcO—Hg—OAc) reacts with alkenes in aqueous solution, adding —HgOAc (acetoxymercuric group) and –OH (hydroxyl group) to the double bond.
b. Tetrahydrofaran (THF) is a widely-used inert ether which is dissolves both water and many water-insoluble organic compounds. It's basically cyclopentane with O at a vertex.
The oxymercuration reaction is a lot like halohydrin formation (just a fancy X—X).
i. Step (1) formation of mercurinium ion (Needs AcO—Hg—OAc, H_2O, THC). The C—Hg bond to the more branched carbon is much weaker.
ii. Step (2) mercurinium ion reacts with the solvent water (Needs $NaBH_4$, NaOH, THF). Acetate ion *could* react as the nucleophile, but the reactants are in a sea of water.
iii. Step (3)—OAc anion acts as the base to take an H from —OH_2 → —OH. Water can also react, but it's a weaker base (we don't need to know the mechanism for step 3).
c. Oxymercuration is regioselective with a +1 alkyl advantange, but halohydrin formation needs at least a +2 alkyl advantage to be regioselective; otherwise, two major products.
d. $NaBH_4$ is a common "H^-" source (reducing agent). The electron density is polarized closer to hydrogens, which have partial negative charges.



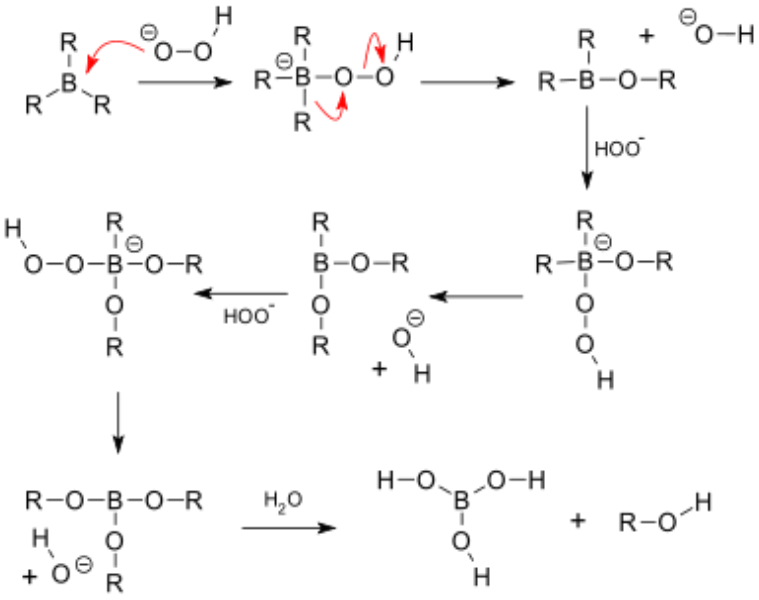


B. Conversion of Oxymercuration Adducts into Alcohols
   a. Oxymercuration products + $NaBH_4$ + NaOH → alcohols
   b. The sequential reactions are (collectively) oxymercuration-reduction of alkenes.
      i. When writing consecutive reactions in shorthand, number sequential reactions.
      ii. NET: addition of –H and –OH to an alkene double-bond.
   c. Highly regioselective: —OH always goes to the more branched DBC, like in acid-catalysis.
   d. Oxymercuration reductions are basically hydration reactions, but can be more convenient on a laboratory scale because they're free of rearrangements and other side reactions.

C. Hydroboration-Oxidation of Alkenes
   a. Conversion of Alkenes into Organoboranes
      i. USEFUL BECAUSE DIFFERENT OUTCOME → FORMAL ANTI-MARKOVNIKOV ADDITION
      ii. Borane (BH_3) adds regioselectively (boron → fewer alkyl DBC, H → more alkyl DBC). <u>Its incomplete octet makes it more electrophilic than H.</u>
      iii. Since borane has 3 B—H bonds, it can add to 3 alkenes → trialkylborane.
      iv. Boron's empty p-orbital reacts with the pi bond at the less substituted DBC. At the same time, H breaks from B and bonds with the pseudo-carbocation (the other DBC)



   b. Conversion of Organoboranes into Alcohols (steps): $R_3B + H_2O_2 + NaOH$ → alcohols.

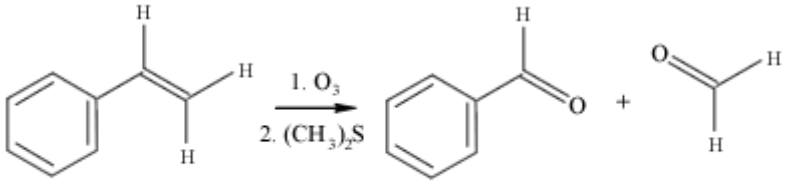


1. **Acid-base**: $H_2O_2 + OH^- \rightarrow HOO^- + H_2O$.
2. **R group transfer**: HOO^- adds to R_3B, and the weak O—O bond is broken. This regenerates the OH^-s used in step (1) and leaves an electron-deficient oxygen. The R group simultaneously shifts to the oxygen: $R_3B—O^+ \rightarrow R_2B—O—R \rightarrow B(OR)_3$.
3. **Exchange**: 3 OH^- attack B's p-orbital. $B(OR)_3 + 3\ OH^- \rightarrow 3\ RO^- + B(OH)_3$
4. **Acid-base**: $3\ RO^- + 3H_2O \rightarrow 3HOR + 3\ OH^-$

   c. No carbocation intermediate = no contamination by constitutional isomers.

5.5 Ozonolysis of Alkenes

A. Ozonolysis: ozone (O_3) adds to alkenes at low temperatures → unstable molozonides → ozonides (→ aldehyde, ketone, carboxylic acid) and the double-bond is completely broken.
B. Cycloaddition: addition reaction that forms a ring.
C. The net reaction from ozonolysis of an alkene followed by dimethyl sulfide (Me_2S) addition is the replacement of a C==C group with 2 C==O groups. Symmetrical = equivalent products.



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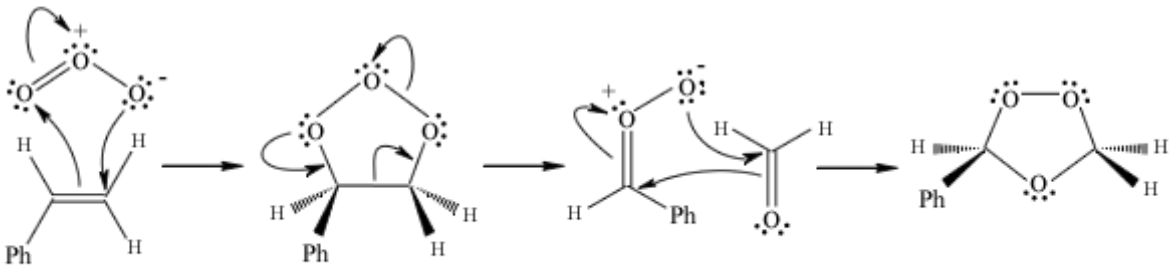

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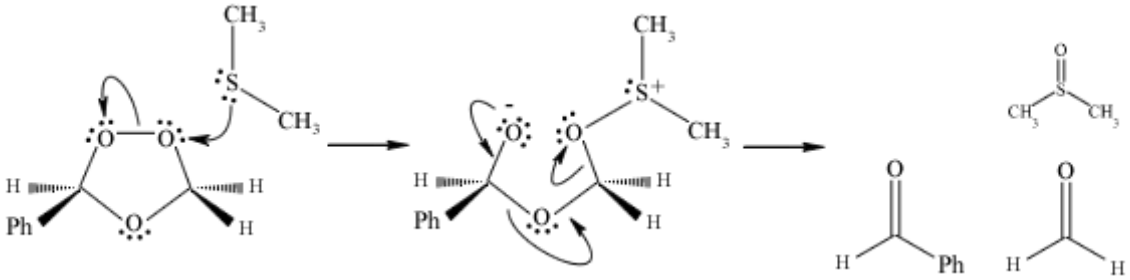
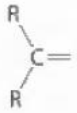
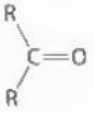
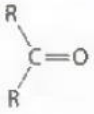
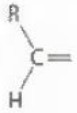
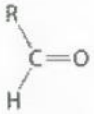
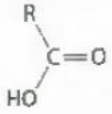
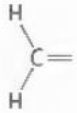
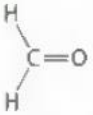
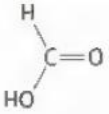


D. **<u>Adding H_2O_2/H_2O instead of Me_2S leads to hydration at any H group attached to a DBC.</u>**

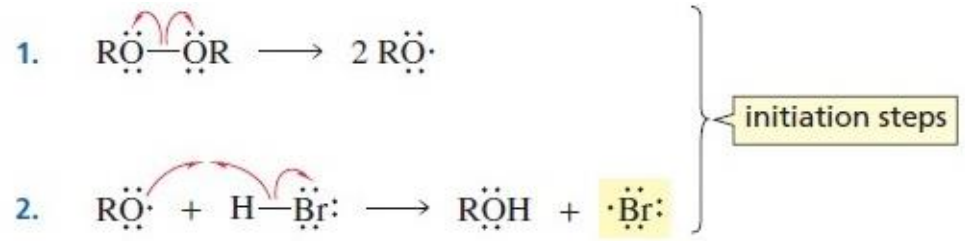
Alkene carbon	Conditions of ozonolysis: O_3, then $(CH_3)_2S$	Conditions of ozonolysis: O_3, then H_2O_2/H_2O
	 ketone	 ketone
	 aldehyde	 carboxylic acid
	 formaldehyde	 formic acid

5.5 Free-Radical Addition of Hydrogen Bromide to Alkenes (ONLY HBr)

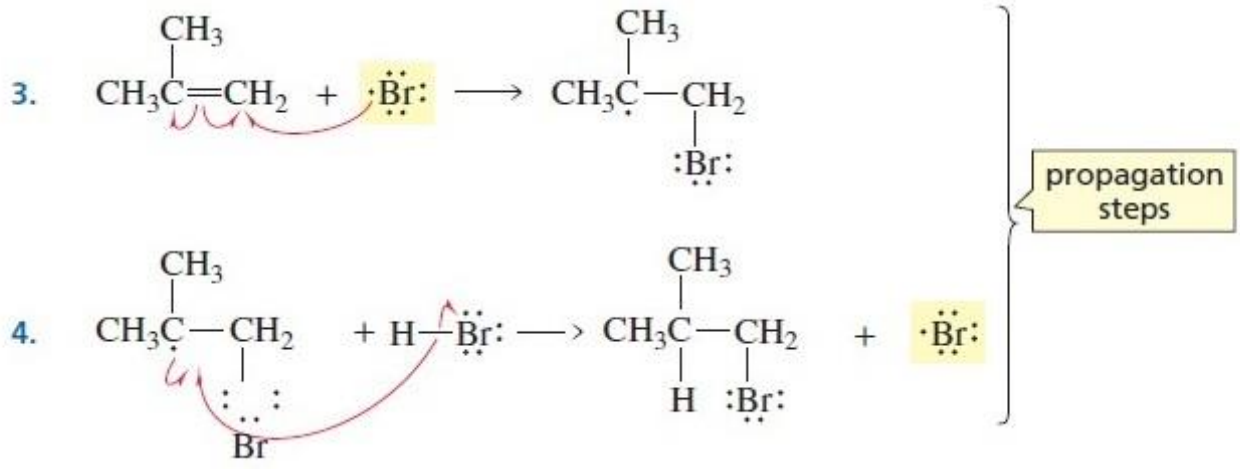
A. The Peroxide Effect
   a. Trace peroxides (ROOR) change the mechanism of HBr + alkene addition. The new mechanism is faster and reverses the regioselectivity (adding Br to the less branched DBC). ROOR is not a catalyst because it is destroyed during the reaction.

B. Free Radicals and the "Fishhook" Notation
   a. Heterolysis: bond-breaking where electrons move in pairs.
   b. Homolysis: bond-breaking where electrons move singly.
   c. Fishhook notation: single-barbed arrows designate electrons that move individually.
   d. Free radical: any species with an unpaired electron, often unstable, reactive intermediates.

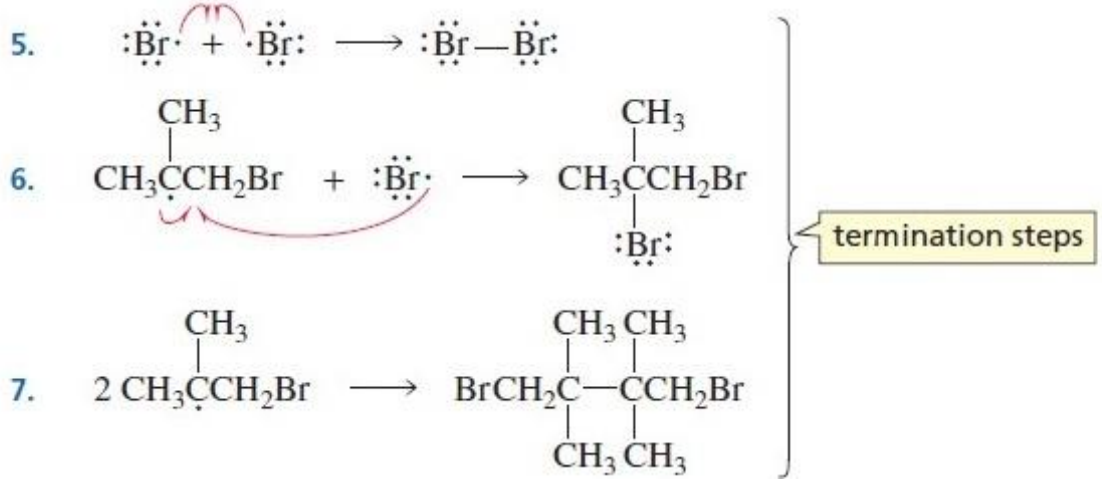
C. Free-Radical Chain Reactions
   a. Initiation: free-radical initiators (or source) tend to homolyse and form free-radicals.
      i. Step (1) – a peroxide bond dissociates to form 2 free radicals.
      ii. Step (2) – the free radical abstracts H from H—Br, forming the free radical Br·
      iii. Peroxides are good because they have weak O—O bonds (repulsion between 4 lone pairs on two adjacent oxygens), which is actually not found in H_2O_2.
      iv. AIBN (azoisobutyronitrile, –N=N–) is also unstable because it liberates stable N_2.
      v. Light energy helps initiate homolysis in reactants or a free-radical initiator.
      vi. Atom abstraction: when a free radical removes an atom from a molecule and a new free radical is formed.



   b. Propagation Steps: reactions occur sequentially with no net change in free radicals.
      i. Step (3) – Anti-Markovnikov reaction: free radical Br· adds to the C=C pi bond.
      ii. Step (4) – The new free radical abstracts H from HBr (C—H bonding is more favorable/stable than C—Br), and Br is a free radical again.
      iii. The free radicals catalyze the anti-Markovnikov reaction – only small concentrations (1-2%) are needed because collisions with reactants >>> collisions with other radicals.



c. Termination: free radicals are quenched (destroyed)
    i. Radical recombination reactions: when 2 free radicals covalently bond (opposite of a homolysis reaction). It's very favorable, but relative concentrations mean propagation happens much more often than termination (~10,000:1)
    ii. By-products are formed in small quantities.
    iii. Both propagation steps In HBr are exothermic, but the endothermic propagation step (1) for HI and step (2) for HCl mean termination dominates.



D. Explanation of Regioselectivity in the Peroxide Effect
    a. Primary, secondary, and tertiary free radicals bond to 1, 2, and 3 alkyl groups, respectively.
    b. Anti-Markovnikov because:
        i. Steric effects: the really big Br atom prefers to bond where there are fewer alkyl groups to get up in its van der Waals airspace, and
        ii. Free radical is more stable when more substituted: $1^o < 2^o < 3^o$
        Hyperconjugation occurs when sigma bonds from alkyl groups dump electron density into a partially filled p-orbital. Carbocation hyperconjugation is 5x stronger because:
            1. The positively charged cation attract more electrons
            2. An empty p-orbital allows more dumping than a partially filled one.

E. Bond Dissociation Energies (BDEs)
    a. Definition: the standard enthalpy ΔH^o of a gaseous HOMOLYTIC dissociation (X—Y →X· + Y·)
    Measures the intrinsic strength of a chemical bond.
    b. ΔH^o (rxn) = BDE (bonds broken) – BDE (bonds formed), independent of mechanism/rate.
    c. When using BDE to compare, it's ~101 > ~99 > ~96 kcal/mol for 1^o → 3^o.
    H_3C—H (zero alkyl groups) is like a 0^o carbon, at 105 kcal/mol.
    C—C sigma bond: 90 kcal/mol. C=C pi bond: 58 kcal/mol. —O—O— 38 kcal/mol (weak)
    H—F > H—Cl > H—Br 1^o C—F > 1^o C—Cl > 2^o C—Br
    d. Abstraction of H is preferred over abstraction of Br because the former is highly exothermic, and the latter is highly endothermic (C—H is more stable than C—Br).
    e. HCl never occurs because the dissociation of HCl is too endothermic, making the second step of propagation unfavorable. $ClCH_2{\cdot}CH_2CH_3$ accumulate, recombine, and terminate.

5.6 Polymers: Free-Radical Polymerization of Alkenes

A. Notation: subscript n designates an unknown, very large number of repeating units.
Ex: ethylene is a large number of $n H_2C{=}CH_2$ monomers → n—CH_2—CH_2—n

B. Free-radical polymerization: initiated when a radical R· aids in polymerization.

Chapter 6 – Principles of Stereochemistry

6.1 Enantiomers, Chirality, and Symmetry

A. Stereochemistry: study of stereoisomerism (same connectivity, different spatial arrangement) and its chemical effects. Molecular models are important here!

B. Enantiomers and Chirality

   e. Chirality: describes any molecule possessing a non-congruent and non-superimposable mirror image; handedness – think of right and left hands. Test: no internal symmetry.

   f. Achiral: possessing a superimposable mirror image.

   g. Enantiomer: two chiral stereoisomers that are mirror images of each other.

C. Asymmetric Carbon and Stereocenters

   a. Asymmetric carbon: bonded to four different groups. A molecule with only 1 asymmetric carbon is always chiral. Molecules with multiple asymmetric carbons can be achiral.

   b. Stereocenter: an atom at which the interchange of two groups gives a stereoisomer. Includes all asymmetric atoms and E,Z DBCs.

   c. Symmetry elements are points, lines, or planes that relate equivalent parts.

      i. Plane of symmetry (internal mirror plane): divides an object into identical halves.

      ii. Point of symmetry (center of symmetry): a point through which any line through the center contacts exactly equivalent parts at the same distance in both directions. It exists if you can reproduce a molecule by rotating its mirror image by 180°.

      iii. Having a plane/point of symmetry automatically makes a molecule achiral.

6.2 Nomenclature of Enantiomers: The Cahn-Ingold-Prelog R,S System

1. Assign priorities 1-4 (1 is highest, 4 is lowest) with the E,Z system.
2. Rotate the molecule to put the lowest priority group (4) at the back.
3. R configuration: CLOCKWISE count 1→3; decreasing priority, (to the **R**ight).
   S configuration: COUNTERCLOCKWISE count 1→3; decreasing priority.
4. Hand trick: use your thumb to point to the lowest group and see if the curl of your fingers matches 1, 2, 3. If it matches: Right hand = R, Left hand = S.

6.3 Physical Properties of Enantiomers: Optical Activity

A. Polarized Light

   a. Melting/boiling points, densities, heats of formation, solubilities, and other properties are identical for enantiomers in an achiral environment.

   b. R and S enantiomers interact differently with chiral molecules, and they also have different effects on polarized light.

A. Racemate or racemic mixture: contains equal amounts of two enantiomers.

B. Racemates have different physical properties. The melting point of optically pure lactic acid is 53°C and the melting point of racemic lactic acid is 18°C. This is due to different crystal structures – packing 10 right or left shoes in a box is easier than packing 5 left and 5 right.

C. The optical rotation of a racemate is always zero, because the equal halves cancel out.

D. Racemization: forming a racemate from a pure enantiomer.

6.4 Stereochemical Correlation

A. Absolute configuration/stereochemistry: the actual 3D arrangement of a molecule.
B. Anomalous dispersion: variation of X-ray crystallography that can be used to determine absolute configuration.
C. Stereochemical correlation: using chemical reactions to correlate them with other compounds of know absolute configurations.

6.5 Diastereo(iso)mers

A. Diastereomers: stereoisomers that are NOT enantiomers. All stereoisomers are either enantiomers or diastereomers.
B. Test: if both stereocenters have opposite R,S configurations (RR-SS or RS-SR), they're enantiomers. If one stereocenter is the same and the other is opposite (RS-RR or SS-RS), they're diastereomers.
C. Epimers: stereoisomers that differ at a single stereocenter.
D. Diastereomers differ in all their physical properties, which allows conventional separation. They might be chiral and optically active, but their specific rotations are not related.

6.6 Meso compounds

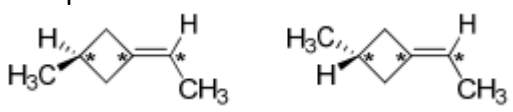
A. Meso compound: contains 2+ asymmetric atoms but still achiral. Two meso compounds are mirror images, like enantiomers, but are actually identical when rotated.
B. Without meso compounds, a molecule with *n* asymmetric carbons → 2^n stereoisomers, because each of them can be either R or S.
C. Test: if a molecule with two or more asymmetric atoms can be divided into halves with the same connectivity and opposite stereochemical configurations (R and S), the molecule is meso.
D. Test 2: if any conformation or rotation of a molecule with asymmetric carbons is achiral (has a point/plane of symmetry), the molecule is meso.

6.7 Enantiomeric Resolution

A. Enantiomeric resolution: isolation of pure enantiomers from a racemate.
B. Method: temporarily convert a racemate into a mixture of diastereomers by allowing the racemate to combine with a resolving agent (enantiomerically pure chiral compound). Conventional techniques separate the diastereomers, which are then converted back.
C. Diastereomeric salt formation: alkaline amines react with a carboxylic acid resolving agent to form salts. These salts have different properties when made from different enantiomers, and therefore can be separated and then extracted.
D. Selective crystallization: racemate solution is cooled to supersaturation and seeded to crystallization. The seed crystal adds molecules of the same enantiomer.

6.8 Chiral Molecules Without Asymmetric Atoms

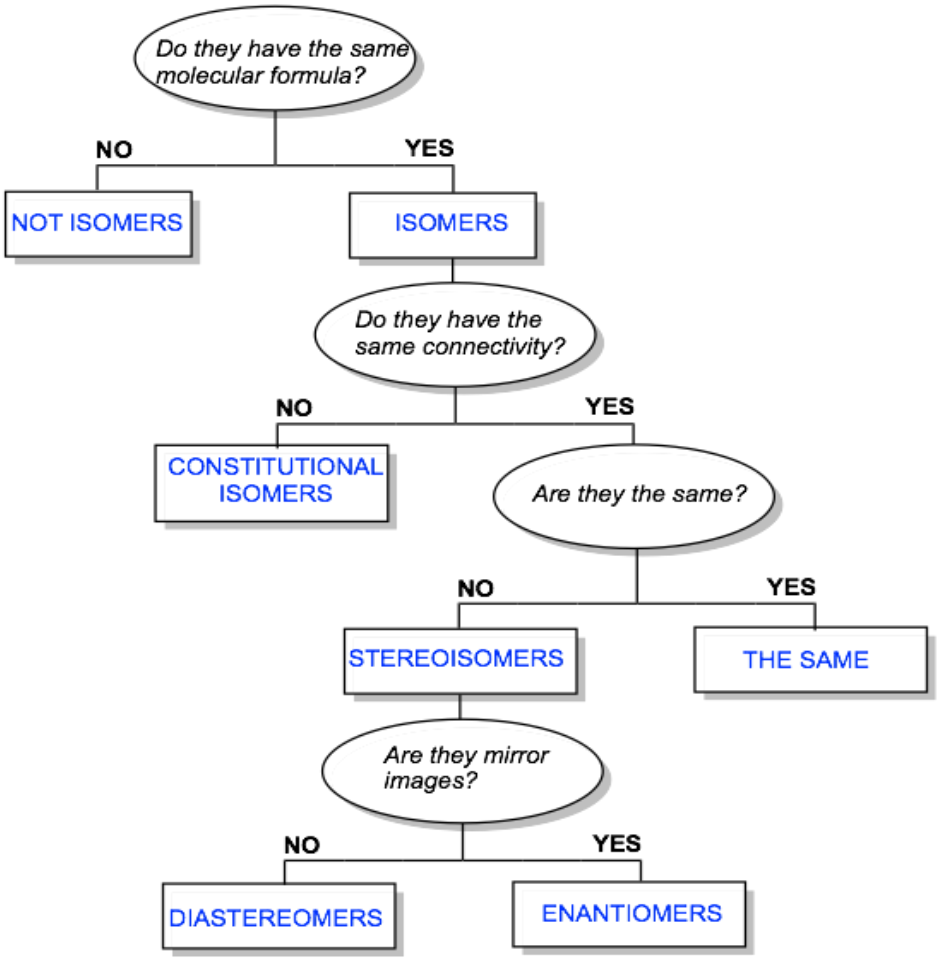
A. Asymmetric carbons are both insufficient and unnecessary for chirality.
B. Example: *stereocenters



6.9 Chiral Molecules Without Asymmetric Atoms

A. Stereoisomers Interconverted by Internal Rotations
   a. Conformational enantiomers: can be interconverted by conformational changes e.g. internal rotation in butane (anti is achiral, gauche is chiral)
   b. Adapted definition of achiral: consisting of rapidly equilibrating enantiomeric conformations that cannot be separated on any reasonable time scale.
   c. If there's even one achiral confirmation in rapid equilibrium, the molecule is achiral. This is because once it's achiral, formation of either enantiomer is equally likely.

B. Asymmetric Nitrogen: Amine Inversion
   a. Amine – :N bonded to 3 different groups and 1 lone pair; the lone pair counts as a separate group, and the amine can have non-superimposable mirror images.
   b. These are **<u>conformational isomers</u>**, NOT enantiomers. This is because the lone pair allows rapid interconversion between both forms. It doesn't take much energy to go from sp^3 → sp^2 hybridization, where the lone pair fills an unhybridized p-orbital (transition state) and then back to sp^3 the other way. Think of pushing the lone pair through the central N.
   c. This is another example of racemization.



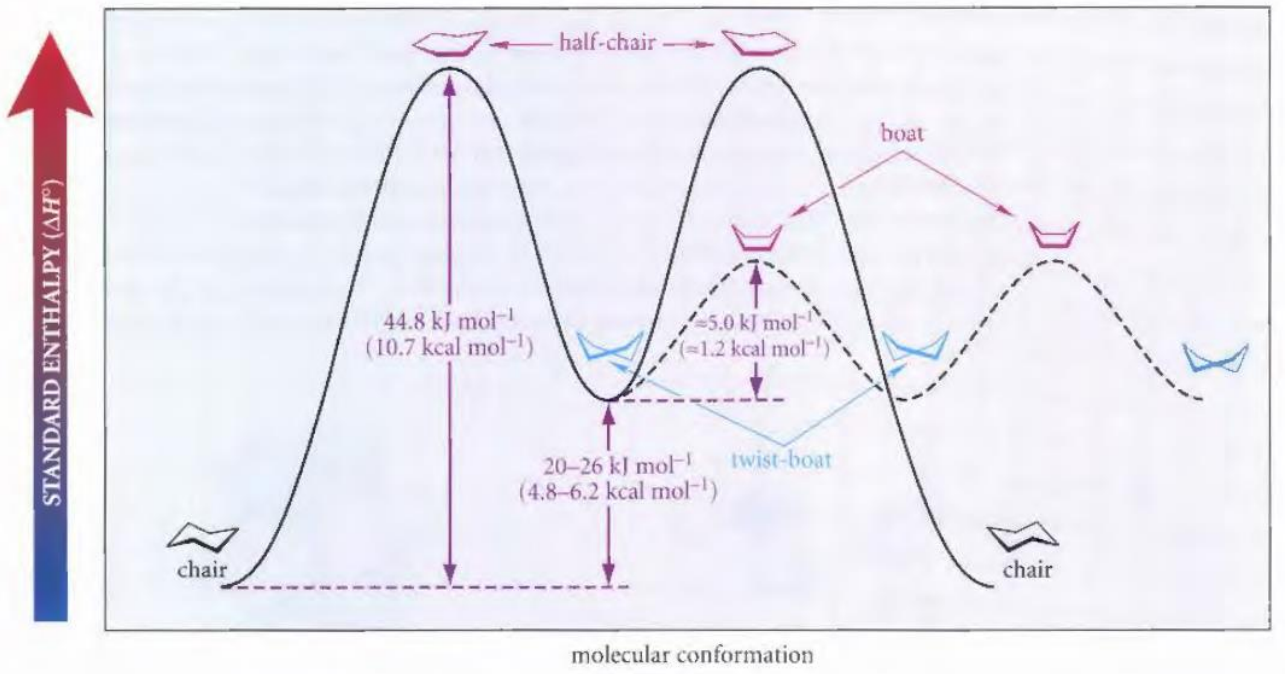
Chapter 7 – Cyclic Compounds and Stereochemistry of Reactions

7.1 Relative Stabilities of the Monocyclic Alkanes

A. Monocyclic compounds – contain a single ring.
B. Monocyclic alkanes have the same empirical formula CH_2 (Cyclic Alkanes: $C_nH_{2n} = n(CH_2)$
   We can compare ΔH_f^o per CH_2 to calculate the internal strain relative to that of linear alkanes.
C. Strain energy: three factors
   a. Bond (angle) strain: deviation from tetrahedral (109.5°)
   b. Torsion strain: eclipsed versus staggered conformation.
   c. Ring interactions: transannular non-bonded interactions.
D. Cyclohexane is the most stable cycloalkane: most negative heat of formation per CH_2. This number is –4.95 kcal/mol, exactly the same as an unbranched alkane.

7.2 Conformations of Cyclohexane

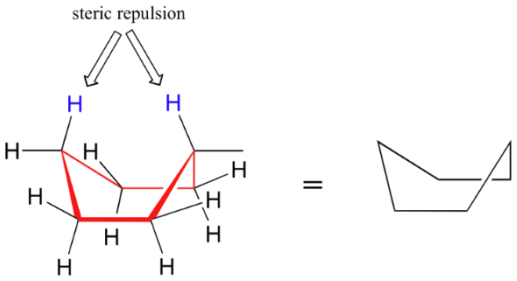
A. The Planar Conformation
   a. Bond angle strain: 120° > 109.5°
   b. Torsion strain: All twelve C—H bonds are eclipsed.
B. The Chair Conformation
   a. No angle strain: The bonds puckers to bring the angles to exactly 109.5°
   b. No torsion strain: Completely staggered system.
   c. Axial groups: the six perpendicular to the C—C bonds. There are 3 up-carbons and 3 down-carbons. The axial groups point up on up-carbons and down on down-carbons.
   d. Equatorial groups: the six parallel to the C—C bonds. The equatorial groups point down on up-carbons and up on down-carbons.
C. Interconversion of Chair Conformations
   a. Chair flip: axial groups interchange with equatorial groups. The activation energy is 10.7 kcal/mol, and the ΔG is 0. This means that interchange occurs rapidly at room temperature.



D. Boat and Twist-Boat Conformations

a. The boat formation is the chair with both "fins" up. There's no angle strain, but it's still 7 kcal/mol less stable than the chair due to the instability of: (1) the transannular interactions between the two "flagpoles", and (2) the eclipsed "sides" of the boat.

b. The boat can twist to decrease these, which makes it 5.5 kcal/mol more stable. Twisting can happen in two ways, so two twist-boats are related to any one boat.



7.3 Monosubstituted Cyclohexanes: Conformational Analysis

A. In interconversion, draw the mirror image chair and up-carbons ←→ down-carbons.

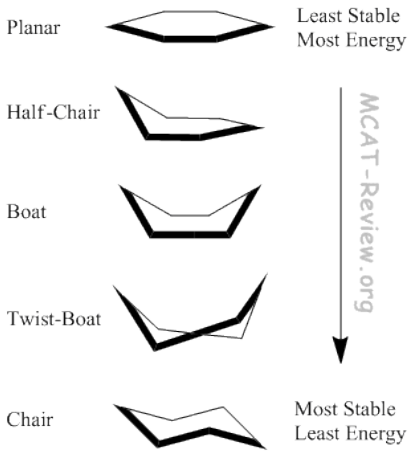
B. Equatorial is more stable than axial – monosubstituted chair flips are unfavorable.

C. 1,3-diaxial interactions: unfavorable van der Waals interactions between axial groups that destabilize axial substituents. *Gauche*-butane interactions are 1,3-diaxial CH_3—H interactions.

D. You can calculate the population proportions based on an energy difference.
$\Delta G = -RT\ln K_{eq} = 1.8$; $K_{eq} = e^{(-1.8/RT)} = 0.95$ = equatorial proportion of the population.

E. A value: the energy difference (ΔG) between equatorial and axial conformations for a substituent.

Substituent	*A value (kcal/mol)
Methyl	1.7
Ethyl	1.8
Isopropyl	2.2
**Tert-butyl	5.4



* When estimating A value, consider substituent bulk, hybridization, and possible orientations.

**Ethyl and isopropyl groups are about the same as methyl groups because they can just rotate away the larger group. This is not true of tert-butyl groups, which are forced to clash severely.

7.4 Disubstituted Cyclohexanes

A. Cis-Trans Isomerism in Disubstituted Cyclohexanes

a. Cis: two substituents are both up or both down.

b. Trans: one substituent is up and the other is down.

c. This nomenclature doesn't describe absolute configuration, and fails with > 2 substituents.

B. Conformational Analysis

a. When groups don't interact, their effects are additive. The positive and negative effects of different groups are directly added to give the overall stability.

b. For a symmetric system, chair flips have ΔG = 0. For an asymmetric system, the conformation that places the larger group in the equatorial position is more favorable.

c. Cis-1,3-dimethylcyclohexane – chair flips from diequatorial → diaxial are very unfavorable because they result in highly unfavorable steric interactions (>5 kcal/mol)

C. Use of Planar Structures for Cyclic Compounds
    a. It's just easier to use the dashed/wedge structure to represent some cyclic compounds.
    b. This doesn't convey conformational info. Chair interconversion gives the same structure.
    c. **Useful for identifying meso compounds because it makes planes of symmetry apparent.**

7.5 Cyclopentane, Cyclobutane, and Cyclopropane

A. Cyclopropane
    a. Cyclopropane is planar and puckering is impossible. The C—C bonds are curbed in a banana shape, which reduces angle strain, but also reduces effective overlap between orbitals.
    b. Bond angle strain: The internuclear C—C—C angle is 60° in cyclopropane. To help relieve strain, the C—C bonds have more p-character, and the C—H bonds have more s-character. The overlaps are not completely collinear – they're curved to make angles greater than 60°.
    c. Torsion strain: All six C—H bonds are completely eclipsed.

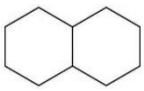
B. Cyclobutane
    a. C—C—C angles are much smaller than the ideal 109.5°, creating angle strain.
    b. Interchanging puckering helps avoid complete eclipsing. This is done by giving the C—C bonds more p-character and the C—H bonds more s-character. This also weakens the C—H bond and makes cyclopropane acidic.
    c. Bond angle strain: Same thing as cyclopropane, but 90°. Going from a 3-ring to a 4-ring does NOT significantly reduce ring strain.
    d. Torsion strain: All eight C—H bonds are eclipsed, but NOT COMPLETELY. "Puckering" lessens the ring strain by making the structure slightly staggered. Puckering trades off with bond-angle strain, so it only occurs to about 25°.

C. Cyclopentane
    a. Envelope conformation – puckered shape; undergoes very rapid conformational changes where each carbon alternates as the "point" of the envelope.
    b. Less stable than cyclohexane mostly due to forced eclipsing between hydrogen atoms.
    c. Substituted groups assume the equatorial position at the point of the envelope.

Cyclic Alkane	ΔH_f^o	ΔH_f^o per CH_2
3-ring	12.7	4.3
4-ring	6.8	1.7
5-ring	-18.4	-3.7
6-ring	-29.5	-4.9
7-ring	-28.7	-4.0

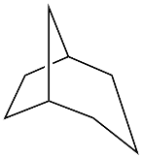
7.6 Bicyclic and Polycyclic Compounds

A. Classification and Nomenclature

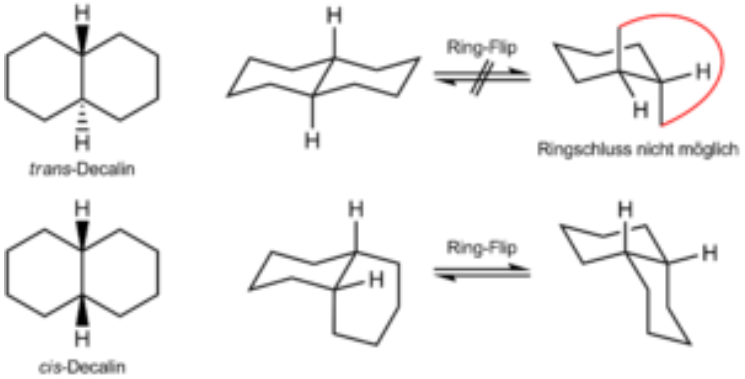


    a. Bicyclic compound: when two rings share a side. Decalin: 6 ring + 6 ring.
    b. Spirocylic compound: when two rings share a vertex.
    c. Bridgehead carbons: atoms at which two rings are joined in a bicyclic compound.
        i. Fused bicyclic compound: the two bridgehead carbons are bonded to each other.
        ii. Bridged bicyclic compound: the two bridgehead carbons are NOT adjacent.
        iii. X-carbon bridge: when there are X carbons between two bridgehead carbons.

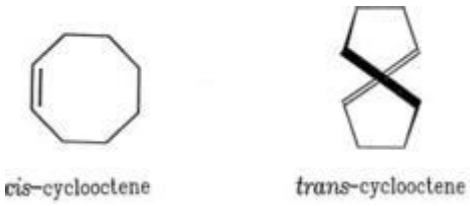
d. Nomenclature example: bicyclo[3.2.1]octane has 1, 2, and 3-carbon bridges.
e. Polycyclic Compound: contain many combined rings (basically any polyhedron e.g. cubane, dodecahedrane, etc.)



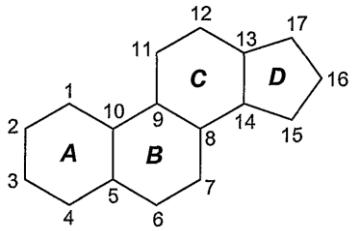
B. Cis and Trans Ring Fusion
   a. Two rings can be fused either trans or cis, depending on whether the hydrogens attached to the bridgehead carbons are up or down.
   b. Trans-decalin can't actually undergo chair flips because it would force the other ring apart.
   c. Small rings only undero cis fusion because bonds need to flex outward the same way.
   d. Large rings can undergo both trans and cis fusion, but trans is often more stable because everything is equatorial.



C. Trans-Cycloalkenes and Bredt's Rule
   a. Cyclohexene and smaller cycloalkenes have cis or Z stereochemistry about the double bond. Trans-cycloalkenes strains either the bond angles or the double bond, which decreases orbital overlap.
   b. Bredt's rule: in a bicyclic compound, a bridgehead atom contained within small rings cannot form double bonds. Being part of small rings forces a significant angle deviation, which forces the pi bond to twist.



D. Steroids
   a. Steroids are usually trans and cannot undergo chair flips. This makes it conformationally rigid and stable, and relatively flat.
   b. Angular methyls: usually attached at carbons 10 and 13.



(I)

7.7 Relative Reactivities of Stereoisomers

A. Relative Reactivities of Enantiomers (not important for exam)
   a. Achiral reagent
      i. Same reaction mechanism: your chiral shoes will interact with an achiral shoe box the same way. If it squishes the big toe on one shoe, it'll do the same on the other.
      ii. Same reactivity/rate of reaction: they have identical free energies.
      iii. If you form chiral product, it will be racemic.
   b. Pure chiral reagent
      i. Different mechanism: two enantiomer feet interact differently with right-shoes.
      ii. Different reactivity/rate of reaction: the transition states of the two reactions are diastereomers, which have different free energies.
      iii. All enzymes are enantiomerically pure chiral catalysts, and only work on one enantiomer of a pair.

B. Relative Reactivities of Diastereomers
   a. All diastereomers react at different rates, with different activation energies.

7.8 Reactions That Form Stereoisomers

A. Shorthand for racemic compounds: write (±) by a single enantiomer.
B. Reactions of Achiral Compounds that Give Enantiomeric Products
    a. When achiral starting materials produce chiral products, both enantiomers of the product are formed at identical rates, because they have the same free energies. This will always form a racemate. Optical activity never arises from achiral compounds reacting.
    b. A chiral presence (reagent/solvent/catalyst) changes things, because it can make a diastereomeric transition state, with different free energies.
C. Diastereomeric products are always formed at different rates, in different amounts, because they go through diastereomeric transition states.

7.9 Stereochemistry of Chemical Reactions

A. Stereochemistry of Addition Reactions
    a. Syn-addition: two groups add to a double bond form the same face.
    b. Anti-addition: two groups add to a double bond from opposite faces.
    c. Syn- and anti- addition only make sense when both DBCs become stereocenters.
B. Stereochemistry of Substitution Reactions
    a. Retention of configuration: the two groups keep the same relative R,S configurations. This basically means that cis/trans stays that way.
    b. Inversion of configuration: when the two groups have different relative R,S configurations. This means that cis ←→ trans.
    c. Stereoselective reaction: when particular stereoisomers are formed in significant excess.
C. HBr addition
    a. 1-butene + HBr → butane + Br^-.
    b. The carbocation intermediate means that Br can attach at either the top or the bottom, giving either the R or S enantiomers, respectively, in equal proportion, giving a racemate.
D. Br_2 Addition – Terminal alkene
    a. Step 1: Terminal alkene + Br_2 → bromonium ion. This can attach at either the top of the bottom, making a racemic intermediate.
    b. Step 2: Br^- attaches with the opposite configuration of the Br^+ (anti). This causes an inversion in configuration. The original Br^+ is free to rotate, because it's not bonded to an asymmetric carbon.
E. Br_2 Addition – Symmetric Z-alkene
    a. Step 1: Symmetrical Z-alkene + Br_2 → bromonium ion. This attaches at the top or the bottom. These are actually identical, so this makes a MESO intermediate.
    b. Step 2: If Br attacks at the A site (R-configuration carbon), then the R flips to S, and you get S-S. If Br attacks at the B site (S- configuration carbon), then S flips to an R, and you get R-R.
F. Br_2 Addition – Symmetric E-alkene
    a. Step 1: Symmetrical E-alkene + Br_2 → bromonium ion. This attaches at the top and the bottom, which yields two different products.
    b. Step 2: The two compounds created by attacking the A/B sites are **achiral and meso** – there's a point of symmetry in the center, and a rotation of 180° superimposes them.
G. Both E/Z alkenes + B_2 give racemic products, unless E gets X-X addition, which makes it meso.
H. Br_2 Addition in water: hydrobromation forms racemic product, just like in regular Br_2 addition, except that OH adds instead of the second Br.

I. Summary: (1) formal anti-addition (add with opposite configuration), (2) E and Z alkenes give different stereoisomers.
J. Formal anti-addition happens in many reactions: Cl_2, Br_2, and either one in H_2O or ROH solvent.
K. Stereochemistry of Hydroboration-Oxidation
    a. Hydroboration is a stereospecific syn-addition. The B—H bond reacts simultaneously with the double bond, and therefore must react from the same side. It's racemic, because it has two asymmetric carbons, and the B—H bond could've reacted from the top or the bottom.
    b. Substitution of BR_2 for OH occurs with <u>retention</u> of stereochemical configuration (still cis).
L. Stereochemistry of Other Reactions
    a. Catalytic Hydrogenation: stereospecific syn-addition, because they can only attach from one side – the face of the Pt/C particulate. Meso.
    b. Oxymercuration: stereospecific anti-addition. It occurs with the cyclic-ion mechanism, which forces the nucleophile to approach from the other side. BUT, the reaction of the Hg-product + $NaBH_4$ brings loss of stereoselectivity. Racemic.
M. Different alkene stereoisomers give diastereomer products.
N. Non-selective addition: HX (mineral acid), H_2O + H_2SO_4 (catalyst), oxymercuration.
    These all give a mixture of syn/anti products.

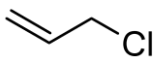
Chapter 8 – Alkyl Halides, Alcohols, Ethers, Thiols, and Sulfides

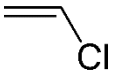
8.0 Key Terms

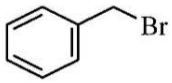
A. Alkyl Halides: halogen bonded to the carbon of an alkyl group.
B. Alcohols: a hydroxyl group (—OH) is bonded to the carbon of an alkyl group.
C. Primary, secondary, and tertiary refer to the number of alkyl substituents bonded to an alkyl halide or alcohol's associated carbon.
D. Glycerols: contain two or more —OH groups on adjacent carbons.
E. Thiols (Mercaptans): a sulfhydryl/mercapto group (—SH) bonded to an alkyl group.
F. Ether: oxygen is bonded to two alkyl groups.
G. Thioether (sulfide): sulfur is bonded to two alkyl groups.

8.1 Nomenclature

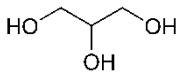
A. Meta-nomenclature
    a. Substitutive nomenclature: used for alkanes and alkenes.
    b. Radicofunctional nomenclature (also common nomenclature) is used for simple and common compounds. Historical usage dictates common and substitutive names.
B. Nomenclature of Alkyl Halides
    a. Common Nomenclature: alkyl group name + halide name (ethyl chloride).
        i. Allyl chloride Vinyl chloride Benzyl bromide:

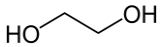


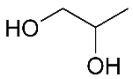




        ii. Haloforms: methyl trihalides ($HCBr_3$)
    b. Substitutive Nomenclature: Halogen substituents are fluoro, chloro, bromo, or iodo (add an "o" after the first syllable)
C. Nomenclature of Alcohols and Thiols
    a. Common Nomenclature: alkyl group name + "alcohol" or "mercaptan".
    Glycols have traditional names:
        i. Glycerol Ethylene glycol Propylene glycol

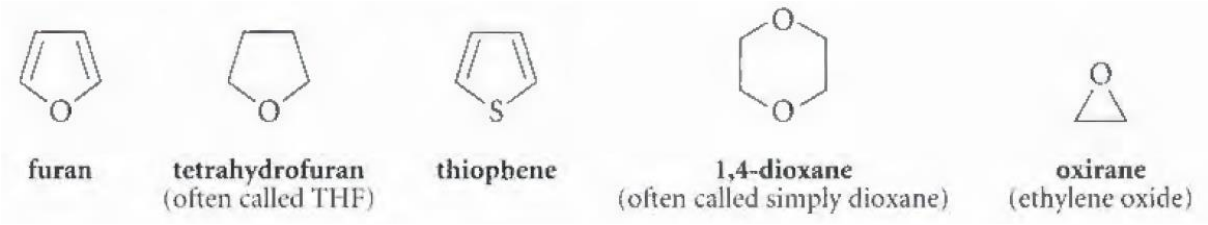




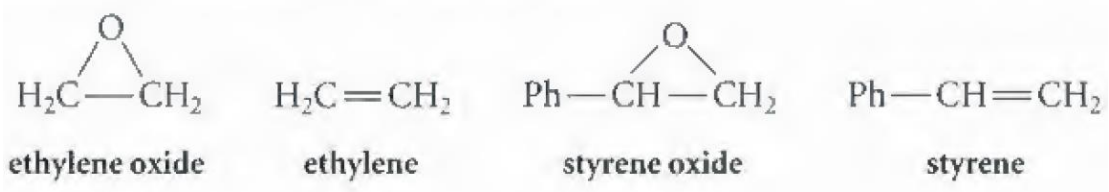


    b. Substitutive Nomenclature
        i. Principal group: basis of the name; always cited as a suffix in the name.
        ii. Alcohols: —OH is the principal group; ethane + ol = ethanol.
        iii. Thiols: —SH is the principal group; ethane + thiol = ethanethiol
        iv. RULES:
            1. Identify the principal group (—OH > —SH > alkane)
            2. Identify the principal carbon chain with the higher:
            (a) principal groups, (b) double/triple bonds, (c) length, (d) substituents.
            3. Number the carbons of the principal chain, giving the lowest numbers to:
            (a) principal groups, (b) double bonds, (c) triple bonds, (d) other substituents, (e) alphabetically first substituents.
            4. The numbering for the principal group comes before the suffix if a double bond takes the spot before the alkyl group. (5-hexen-2-ol).
            5. The prefix can be modified by "di", "tri", etc. (5-hexen-2,3-diol).

D. Nomenclature of Ethers and Sulfides
   a. Common Nomenclature: cite the two attached groups in alphabetical order, then "ether" or "sulfide". Ex: diethyl ether, ethyl methyl sulfide
   b. Substitutive Nomenclature
      i. Ethers and sulfides are never cited as principal groups. Instead, alkoxy groups (RO—) and alkylthio groups (RS—) are cited as substituents.
      ii. Alkoxy substituents are named by dropping "yl" and adding "oxy".
      Alkylthio substituents are named just adding "thio".
      iii. Use parenthesis to clarify associations, e.g. 2-(methylthio)hexane
   c. Heterocyclic Nomenclature
      i. Heterocyclic compounds: rings that contain at least one non-carbon atom.



      ii. Epoxides: three-member rings containing oxygen. Some are named as oxides of derived alkenes.



      iii. Most are named substitutively as derivatives of ethylene oxide, or oxirane.
      1 always goes to oxygen, and 2 goes to the carbon with higher:
      (a) principal groups, (b) double/triple bonds, (c) length, (d) substituents.

8.2 Structures
A. Bond angles: neutral oxygens in ethers and sulfurs in thiols are made tetrahedral by 2 electron pairs, and 2 bonded groups.
B. Sulfur will form longer bonds because S atom is larger than the O atom.
C. Sulfur will form a smaller angle because its unshared electron pairs are in the 3rd energy level, which take up more space.

8.3 Effect of Molecular Polarity and Hydrogen Bonding on Physical Properties
A. Boiling Points of Ethers and Alkyl Halides
   a. When shape and mass are equal, polarity raises boiling point.
   b. When mass is held approximately equal, the van der Waals forces of a long carbon chain are stronger than the dipole-dipole interactions of a polar compound in alkyl bromides/iodides. They're about the same in alkyl chlorides.
B. Hydrogen Bonding:
   a. H-bond donor: H - - - atom (N, O, or F)
   H-bond acceptor: H - - - atom (full/partial negative charge)
   These can be the same atom, as in water and alcohols. Ethers can only be acceptors because there's no H to donate. $^{+}NH_4$ is a good donor, but has no electron pairs to accept with.

b. Two forces in H-bonding: electrostatic attraction AND a partial covalent interaction.
    i. The electrostatic interaction is weighted far more in H-bonds than in dipole-dipole interactions because the two charges are much closer together.
    ii. The covalent interaction comes from electron density overlap; there can be partial dumping into the partially deficient H atom.
    iii. These add up to about 5 kcal/mol H-bonds.
c. H-bonding is analogous to the reaction between an acid (A^-—H^+) and a base (B^-). A is the H-bond donor, and B is the H-bond acceptor.
d. What makes a good A: acidic, highly polarized. What makes a good B: high negative charge (electrostatics), small orbitals (greater overlap with 1s H orbital)

8.4 Solvents in Organic Chemistry

A. Classification of Solvents
    a. Polar solvents have high dielectric constants, usually at least 15 (e.g., water, methanol, NOT alkanes, THF).
        i. Polar solvents muffle electrostatic interactions between ions in solution by forming ion dipoles (see donor interaction).
        ii. Polar molecules tend to form polar solvent, but it needs be at least as strong as a C—[N,O,F] bond.
        iii. There are other exceptions e.g., ethyl acetate, acetic acid because they dimerize and cancel each other out.
    b. Protic solvents are H-bond donors (e.g., alcohols, NOT CH_3Cl, THF, DMF, acetone, DMSO)
    c. Donor solvents are H-bonds acceptors, and donate unshared e- pairs.
B. Desired Characteristics of Solvents for Solute Reactions
    a. Good solvents must dissolve the starting materials (duh).
    b. Good solvents must not react with any step of the reaction.
    c. Good solvents give the desired reaction rate, which can affect product creation.
C. Solubility of Covalent Compounds
    a. Soluble: solids dissolving in liquid. Miscible: liquids “dissolving” in liquid
    b. Like dissolves like. The ability to donate/accept H-bonds and the presence of sizable hydrocarbon regions are important for polar and nonpolar solvents, respectively.
D. Solubility of Ionic Compounds
    a. Ion pairs: when each ion is closely associated with an ion of opposite charge.
    b. Dissociated ions: move more or less independently and are surrounded by a solvent shell or solvent cage, which solvates the ion. The shells are dynamic – molecules are rapidly exchanging with the bulk solvent.
    c. Dielectric constant: measures the ability of a solvent to separate ions. A higher dielectric constant makes it easier to separate and dissolve ions.
    d. Solvation shells are stabilized by effects similar to those in H-bonding (Na^+ - - - OH_2)
        i. Charge-dipole interaction: favorable electrostatic interactions of a polar solvent with cations and anions.
        ii. Covalent interactions:
            1. Donor interaction: donor solvents donate unshared electron pairs to a <u>cation</u>. Ellman calls these ion-dipole interactions.
            2. H-bonding interaction: <u>anions</u> accept H-bonds from protic donor solvent.

e. Polar aprotic solvents like acetone and DMSO have donor interactions with cations, but no H-bonding interactions with anions. Thus, their salts are less soluble in these than water, and you see more ion pairs.

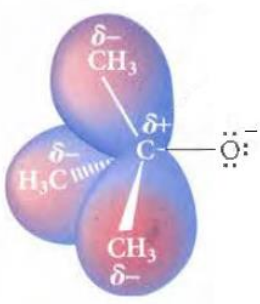
8.5 Applications of Solubility and Solvation Principles: skipped

8.6 Acidity of Alcohols and Thiols

Compound	**pKa (most acidic to less acidic)**	**Reason**
Phenol	10	Resonance
CF_3CH_2OH	12.4	Inductive effect
CH_3OH	15.1	Steric
CH_3CH_2OH	15.7	Steric
$(CH_3)_2CH_2OH$	17.1	Steric
$(CH_3)_3CH_2OH$	19.2	Steric

A. Three factors in stabilizing the conjugate base
   a. Resonance: helps delocalize negative charge.
   b. Polar/Inductive effect: pulls electron density to help delocalize negative charge. Cumulative.
   c. Sterics: stabilizing H-bonding between the solvent and the negative charge is impeded by steric effects with the other parts of the molecule. Only affects solvated molecules.

B. Role of the Solvent in Alcohol Acidity
   a. The acidities of alcohols in aqueous solution: methyl > primary > secondary > tertiary.
   b. In the gas phase, (a) acidity is vastly increased, and (b) the order of acidity is reversed.
   c. Branched alcohols are made much more acidic in the gas phase because alkyl substituents stabilize alkoxide ions better than hydrogens.
   d. Hydrogen bonding is very important in stabilizing conjugate-base anions while solvating them. Somehow, tertiary alkoxides adversely affect solvation, not via steric effects.



8.7 Basicity of Alcohols and Ethers

A. Alcohols, ethers, and their sulfur analogs are amphoteric. They form charged conjugate acids, which are very strong by the charge effect. This means that they are weak bases.

8.8 Grignard and Organolithium Reagents

A. Key Terms
   a. Organometallic compounds: contain carbon-metal bonds.
   b. Organolithium reagents: compounds of the form R—Li
   c. Grignard reagent: compounds of the form R—MgX, where X is a halogen.

B. Preparation of Alkyl Halides
   a. Overall Reaction: X_2 + R—H (xs) →(heat or uv light) → X—H + X—R
   b. Initiation: dihalogens have weak bonds and can homolyse without an initiator.
   c. Propagation: (1) X· + H—R → **X—H** + ·R (2) X—X + ·R → X· + **X—R**
   d. Termination: (1) R· + ·R → R—R (2) X· + ·X → X—X (3) X· + ·R → X—R

C. Preparation of organometallic compounds (R—X → R—M)
    a. These are very good nucleophiles/strong bases.
    b. Organolithium reagents – group I metals (don't have to learn mechanism)
        i. R—X + 2 Li → R—Li + Li^+X^- (salt)
        ii. Lithium dumps its electron into the antibonding orbital of the R—X molecular orbital, which breaks it apart.
    c. Grignard (rhymes with vineyard) reagents – group II metals.
        i. R—X + Mg → R—MgX (it literally just slots itself in).
        ii. The carbon-metal bond is so highly polarized (ionic character, with the negative charge on carbon) that Grignard and organolithium reagents react like carboanions.
    d. Reactions of organometallic compounds with anionic character
        i. R—MgX + H—OCH_3 → R + H_3CO—MgX
        ii. R—Li + D_2O → R—D + Li OD

Chapter 9 – Chemistry of Alkyl Halides

9.1 An Overview of Nucleophilic Substitution and β-Elimination reactions

A. Nucleophilic Substitution Reactions
   a. Nucleophilic substitution/displacement reaction: a nucleophilic Lewis base attacks an electrophilic carbon in an alkyl halide, expelling the halide ion.
   b. Substitution Nucleophilic 2nd order (S_N2) – $Nu:^- + R_3X$ (substrate) → $NuR_3 + X^-$

B. β-Elimination Reactions
   a. α-carbon: the carbon bonded to the halogen.
   b. β-carbons: adjacent carbons bonded to the α-carbon.
   c. Elimination reaction: two groups are lost within the same molecule. β-elimination is when two groups are lost by adjacent carbons.

C. Competition between Nucleophilic Substitution and β-Elimination Reactions
   a. All alkyl halides reacting with strong Lewis acids are in competition, but this is especially apparent with secondary alkyl halides, where both occur at comparable rates.
   b. Strong Lewis acids trigger S_N2 for primary alkyl halides, and β-elimination for tertiary alkyl halides (steric effects block S_N2 and shift the competition).

9.2 Equilibria in Nucleophilic Substitution Reactions

A. Nucleophilic substitution reactions are similar to Bronsted acid-base reactions – just replace the alkyl group with a hydrogen.
B. The equilibrium will always favor the side with the weak base.

9.3 Reaction Rates

A. Kinetics: reaction rate depends on both Nu^- and substrate concentration, because both are involved in the transition state. Rate r = k[Nu][substrate].
B. Frontside displacement: the nucleophile attacks at the same side as the leaving group.
   Backside displacement: the nucleophile attacks at the opposite side of the leaving group.
C. Stereochemistry differentiates possibilities: acetate + R-group leads only to inversion to S product, which occurs via backside displacement. Frontside displacement would have given the R product.
D. Orbital picture of mechanism:
   a. $F^- + CH_3Cl$ → $FCH_3 + Cl^-$
      F^- comes from the back and C partially dehybridizes from 4 sp^3 (tetrahedral) to 3 sp^2 (planar) + p (one lobe bonded to Cl^-, and one lobe sticking out the back).
      F^- attacks at the back lobe, ejecting Cl^-.
   b. Backside displacement minimizes negative charge proximity (F^- doesn't want to be near Cl^-).

E. Formation of Cyclic Compounds (connecting the nucleophile and substrate)

a. H_2N:—$(CH_2)_n$—Br.

N: bonds with the carbon attached to Br, forming an N^+ ring element and ejecting Br^-.

Ring Size	Relative Rate of S_N2 cyclization
3 (n=2)	0.1
4 (n=3)	0.002
5 (n=4)	**100**
6 (n=5)	1.7
7 (n=6)	0.03
10 (n=9)	10^{-8}
13 (n=12)	$3*10^{-4}$

b. $\Delta G = \Delta H - T\Delta S$.

i. ΔH is influenced by ring strain. Smaller rings have more strain → higher $+\Delta H$.

ii. ΔS measures the probability of the nucleophile colliding with the reaction center. It's always negative in ring formation because rings force specific conformations, while chains can freely rotate. A long chain gives up many more degrees of freedom than a small chain (larger S_0, bigger $-\Delta S$).

c. For a 3 membered ring, ΔH raised by ring strain, but ΔS is low because it's perfectly positioned to react (initial S is low).

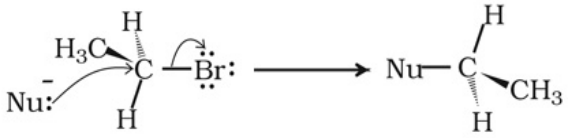
d. Relative rates go up then down because (a) the relative importance of ΔS increases exponentially, and (b) ring stain goes from being more and more favorable (up to 6), to less and less favorable (past 6).

F. Intermolecular and Intramolecular Cyclization

a. Intramolecular cyclization: more efficient than intermolecular reactions for rings 3, 5, and 6; rate = k[substrate].

b. Chains longer than 7 have very low reaction rates, and you'll get much more intermolecular reactions → polymer formation. For polymerization, rate = k[substrate].

c. You can minimize polymer formation by diluting the reaction so much that intermolecular reactions are again less likely.



9.4 The S_N2 Reaction

A. Structure of substrate

a. α-branching: creates certain steric effects that decrease the relative rate. When reacting with acetate anion, methyl halides are about 30 times faster than primary alkyl halides, which are 50 times faster than secondary alkyl halides. Tertiary alkyl halides will never undergo S_N2 reaction with competing reactions present.

b. β-branching: also slows the reaction via steric effects. When reacting with N_3^-, the relative rates are: methyl (1), primary (0.4), secondary (0.03), tertiary (0.0001).
Steric effects can be partially avoided in pentyl and isobutyl groups by rotation, but this is a trade-off because it changes the conformation from anti to gauche.

B. Nature of Leaving Group
   a. More acidic HX = faster S_N2 reaction. This is because acid/base and S_N2 reactions both require bond-breaking of X—H/R, and placing e- density on X.

Base	I^- (weakest)	Br^-	Cl^-	F^- (strongest)
pKa	-9.5	-8	-6	3.2
Relative rate	3	1	0.01	0

   b. Good leaving groups have pKa < 0 (e.g., I^-, Br^-, Cl^-, NOT F^-, N_3^-, $C_2H_3O_2^-$).

C. Nature of Nucleophile (more basic → faster reaction)
   a. Same atom: S_N2 rate: $HO^- > AcO^- > H_2O$
   b. Same row: S_N2 rate: $H_3C:^- > H_2:N:^- > H:O::^- > ::F::^-$

D. Solvent effects (same column):

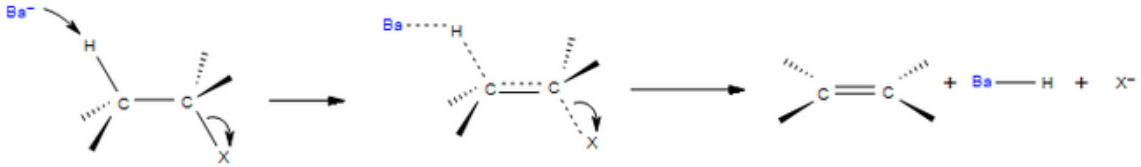
Nucleophile	**Rate in DMF (aprotic) $M^{-1}s^{-1}$**	**Rate in CH_3OH (protic) $M^{-1}s^{-1}$**
F^-	>3 (largest)	5 E-8 (smallest)
Cl^-	2.5	3 E-6
Br^-	1.3	8 E-5
I^-	0.4 (smallest)	3 E-1 (largest)

   a. Polar aprotic solvents
      i. Reaction rate increases with the basicity of the nucleophile ($F^- > Cl^- > Br^- > I^-$).
      ii. Solvent effects are minimal. The ion-dipole interactions with the ionic reactants are weak, and the solvation shell is easily stripped away to access the reaction center.
   b. Polar protic solvents
      i. Decreases reaction rate overall, and reverses the trend ($I^- >> Br^- > Cl^- >> F^-$). The decrease is especially great for highly electronegative 2nd row elements (N, O, F).
      ii. More basic elements are better hydrogen bond acceptors, and these bonds make it very hard to strip away the solvation shell.

E. When the starting materials or nucleophile structure results in a slow S_N2
   a. Bad leaving group (pKa > 0) → no reaction
   b. Good leaving group but hindered substrate or poor Nu: → other reactions compete.
      i. Elimination 2nd order (E2): basic Nu^-
      ii. Substitution Nucleophilic 1st order (S_N1): non-basic Nu^-
      iii. Elimination 1st order (E1): non-basic Nu^-

9.5 The E2 Reaction

A. Rate Law and Mechanism of the E2 Reaction
   a. Base-promoted β-elimination reactions follow a 2nd order rate = k*[substrate][base].



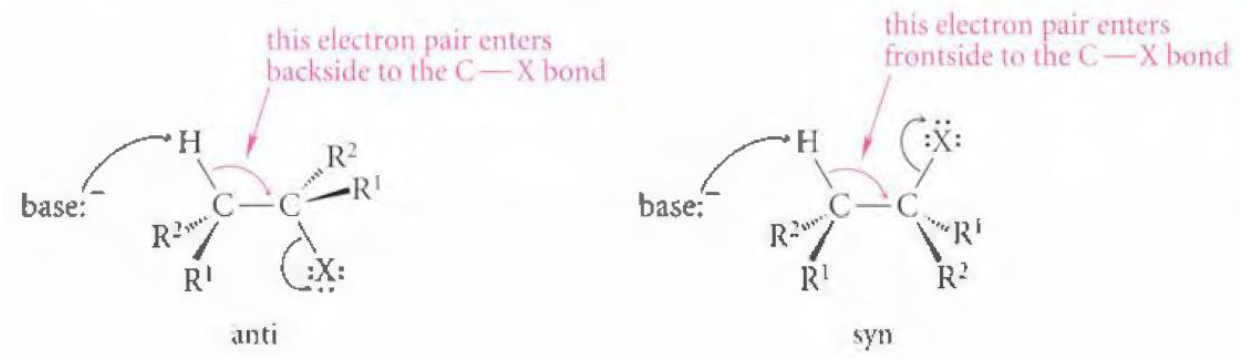
   b. The reaction mechanism involves 3 concerted curved arrows to avoid the formation of a carbon-anion intermediate. This intermediate *can* form if the β-proton is unusually acidic and the carbon-anion is stabilized.

c. The sp^3 orbitals adopt more sp^2 character, which gives the C—H bond and C—X bond more p-character. These ~p orbitals have some overlap – pi bond character.
    i. Anti-periplanar: H, X, and both C's are coplanar; H and X are on opposite sides.
    ii. Syn-periplanar: H, X, and both C's are coplanar; H and X are on the same side.
    iii. These two conformations give different stereoisomers (E/Z alkenes).

B. Leaving-Group Effects on the E2 Reaction: since the role of the leaving halide is the same as in S_N2, the same trends apply. More acidic HX → stronger electron acceptor → higher relative rates.

C. Deuterium Isotope Effects in the E2 Reaction
    a. Primary deuterium isotope effect: the stronger C—D bond makes it harder for the nucleophile to pull away deuterium as opposed to hydrogen, decreasing the rate by 2.5x-8x.
    b. The C—D bond is stronger because the heavier mass leads to a lower vibrational frequency, which is a lower energy and therefore more stable bond.

D. Stereochemistry of the E2 Reaction
    a. Only syn- and anti- eliminations are possible (dihedral angle = 0 or 180) because only these form the planar geometry of the alkene product.
    b. Syn-elimination: H and X leave from the same side.
    c. Anti-elimination: H and X leave from opposite sides. This is preferred because:
        i. Anti-elimination occurs through a staggered transition state, while syn-elimination occurs through an eclipsed transition state.
        ii. In anti-elimination, the base and the leaving group are out of each other's way. In syn-elimination, these two may experience unfavorable electrostatic interactions (both have a partial negative charge in the transition state).
        iii. Anti-elimination involves all-backside electron displacements from the C—H bond to the new double-bond, which is favored over frontside electron displacement.



E. Regioselectivity of the E2 Reaction
    a. With β-branching, the base can attack at different β-hydrogen sites → multiple products.
    b. When simple alkoxide bases are used, the most stable alkene isomer predominates (i.e. stabilized by the most alkyl substituents at the double-bond).
    c. Highly branched bases are sterically hindered (tert-butoxide), and thus attack at the outermost β-hydrogens, which forms less substituted alkenes.

F. Competition between the E2 and S_N2 Reactions
    a. Increased alkyl substituents on the substrate favors E2 reactions because (1) steric effects block the S_N2 reaction center but much less so with the peripheral β-hydrogens, and (2) alkyl substituents stabilize the double-bond of the alkene product in E2 reactions.

Branching Pattern	S_N2 yield	E2 yield
≤ Secondary α	100	0
Secondary α + secondary β	11	89
Tertiary α	0	100

b. Highly branched bases favor E2 due to steric effects blocking the S_N2 reaction center but much less so with the peripheral β-hydrogens.
Ex: the primary ethanol favors S_N2, while the tertiary tert-butyl alcohol favors E2.

c. More nucleophilic Lewis bases favor S_N2 reactions, while stronger Bronsted bases favor E2 reaction. These are usually the same. But when the Lewis base because really big and reduces orbital overlap, as in higher periods (I^-), you get an excellent nucleophile and weak Bronsted base, which favors S_N2.
Ex: with AcO^-, S_N2 outcompetes E2. With the more basic $C_2H_5O^-$, S_N2 is faster, but E2 outcompetes because it's much more dependent on basicity.

9.6 The S_N1 and E1 Reactions (NO strong Lewis base)

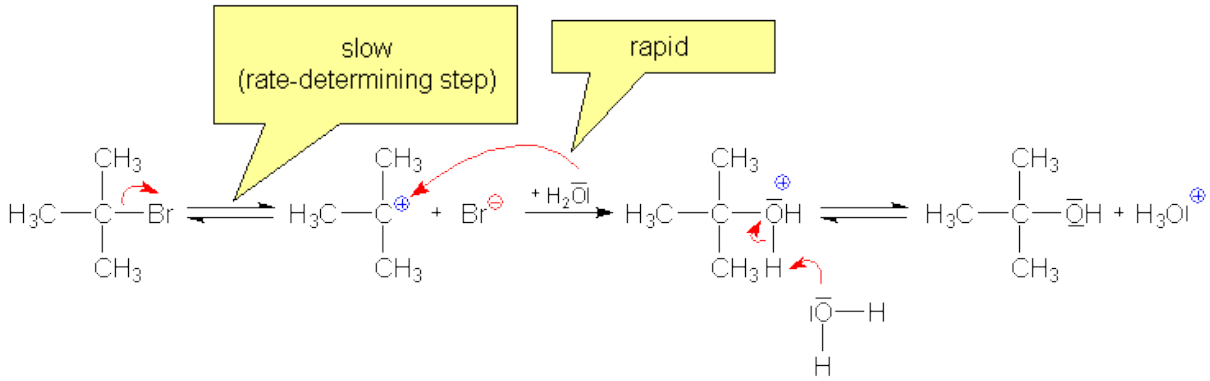
A. Solvolysis: bond breaking by solvent.

a. It follows a first-order rate law: rate = $k[(CH_3)_3CBr]$, because the nucleophile is NOT involved in the rate-determining first step.
Solvents are not present in the rate law because the concentration can't be changed.

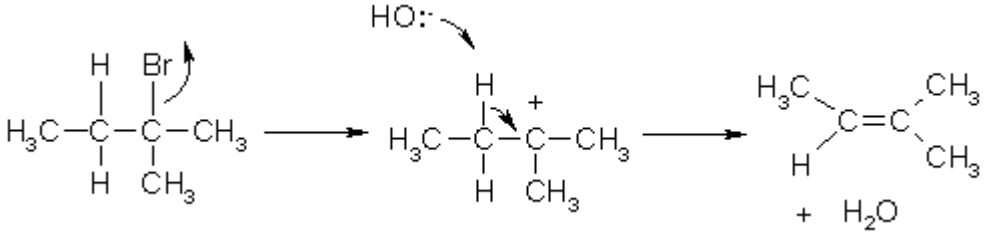
b. Solvolysis is fastest in polar, protic, donor solvents (best at solvating ions). The rate-limiting step is basically ionic dissolution, which is favored when ions can be solvated.

B. Both substitution and elimination reactions occur, so these must be in competition.
Step 1 in *both* reactions is ionization of the C—X bond into C+ and X^-. This is the rate-limiting step, which happens spontaneously but slowly in protic solvent.

a. S_N1: the nucleophile's lone pair attacks at C+, and the H is removed by the anion.
^Note: At step 3, Ellman wrote that Br^- deprotonates the OH_2, not the solvent.



b. E1: the nucleophile's lone pair attacks H, which donates its bond to a double-bond at C+.



C. Important Factors for S_N1
   a. Leaving group (X^-): pKa HX < 0 (rate: F^- << Cl^- < Br^- < I^-). This is because both processes involve breaking a bond to a halide, which takes on an electron pair.
   b. Substrate structure: 3° RX >> 2° RX >> ~~1° RX~~; carbocation stability limits reaction rate.
   c. Solvent Effects: <u>much</u> faster in protic solvent (opposite of S_N2), because hydrogen bonds stabilize the halide anion. The cation is stabilized by donor interactions, but these are present in all polar solvents and not specific to protic solvents.

D. Rate-Limiting and Product-Determining Steps
   a. S_N1 and E1 reactions have a common rate-determining step, so relative amounts are determined by subsequent product-determining steps, which do not affect reaction rate.
   b. Reactivity of alkyl halides in S_N1 and E1 reactions: tertiary >> secondary >> ~~primary~~ (~0)

E. Reactivity and Product Distributions in S_N1 and E1 Reactions
   a. S_N1 is favored over E1 when (a) there is no beta branching, or (b) when you use a strong mineral acid (HCl, HBr, HI…)
   b. Rearrangements occur due to the carbocation intermediate.

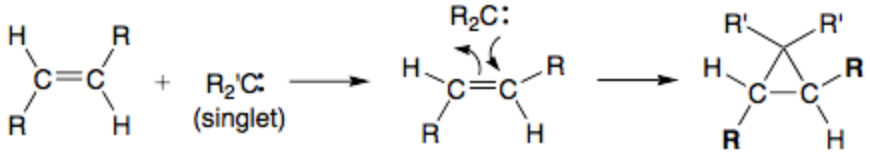
F. Stereochemistry of the S_N1 Reaction
   a. Carbocations are achiral because they only have 3 groups attached. This means that their products must be racemic.
   b. When the carbocation is closely associated with its counterion, it acts as a chiral ion pair. The counterion blocks solvent access from the front side, which forces backside substitution.
   c. Ellman calls it a "contact ion pair."
   d. It takes just 10^{-8} seconds for a counterion to diffuse away, but C+ reacts even faster.
   e. The effect is small: ~40-60%.

G. Questions to Answer for Alkyl Halide Reactions
   a. Is the alkyl halide primary, secondary, or tertiary? If primary or secondary, is there significant alkyl substitution at the beta-carbon?
   b. Is a Lewis acid present? Is it a good nucleophile, strong Bronsted base, or both?
   c. What's the solvent? Is it protic or aprotic?

9.7 Carbenes

A. Carbenes (R_2C:) are sp^2-p hybridized, with 1 electron pair (Lewis base) and 1 empty p orbital (Lewis acid). Carbene are neutral but highly reactive due to an unfilled octet.

B. Carbene Reagents/Reactions
   a. Dichloromethylene (Cl_2C:)
      i. Generation: RO^- deprotonates $HCCl_3$ → $^-CCl_3$, which loses a Cl^- to form Cl_2C:
      ii. Reaction (cyclopropane formation): The empty p orbital accepts the double-bond, and the lone pair donates at the carbocation.



iii. This is a concerted reaction, so stereochemistry is retained.
Cl_2C: can attack from the bottom or the top, so it forms a racemic product.
To make any cyclopentane with groups 1 and 2 attached, you add a strong base and G_1G_2CHBr, and H/Br are eliminated to leave G_1G_2C:

b. Simmons Smith reaction ("H_2C:")
   i. Carbenoid: a compound that acts like a carbene.
   ii. CH_2I_2 + Zn-Cu couple → I—CH_2---ZnI
   iii. This behaves like :CH_2 because the polarized C---Zn bond easily breaks and kicks off I^-.
   iv. This is a concerted reaction, so stereochemistry is retained.

Entry no.	Alkyl halide structure	Good nucleophile?	Strong Brønsted base?	Type of solvent?*	Major reaction(s) expected
1	Methyl	Yes	Yes or No	PP or PA	S_N2
2	Primary, unbranched	Yes	No	PP or PA	S_N2
3		Yes	Yes, unbranched	PP or PA	S_N2
4	Primary with β-substitution	Yes	Yes, unbranched	PP or PA	E2 + S_N2
5	Any primary	Yes	Yes, branched	PP or PA	E2 + S_N2
6		No	No	PP or PA	No reaction
7	Secondary	Yes	Yes	PP or PA	E2; some S_N2 with isopropyl halides; only E2 with a branched base
8		Yes	No	PA	S_N2
9		No	No	PP	S_N1–E1
10		No	No	PA	No reaction
11	Tertiary	Yes	Yes	PP or PA	E2
12		Yes	No	PP	S_N1–E1
13		Yes	No	PA	no reaction, or very slow S_N2
14		No	No	PP	S_N1–E1
15		No	No	PA	No reaction

Other Notes:
Bad leaving group (not Cl, Br, or I): NO reaction
Primary: NO unimolecular reactions.
Tertiary: NO S_N2. Strong base will ALWAYS give E2.
Aprotic solvents give much slower reactions.

Chapter 10 – Chemistry of Alcohols and Thiols

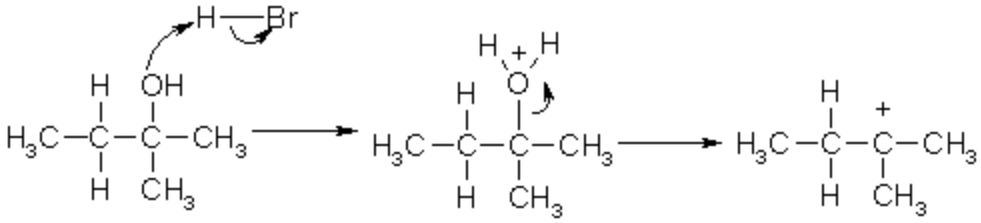
10.1 Dehydration of Alcohols

A. Dehydration: when H and OH are lost from starting material. This is generally a β-elimination reaction that forms a double-bond.

B. Alcohol dehydration and E2 in alkyl halides are both β-elimination, but strong bases don't promote dehydration like they promote E2 because (a) OH is a very poor leaving group, and (b) a strong base will tend to remove the O—H proton.

C. Reverse reaction of the acid-catalyzed hydration of alkenes. Shift the equilibrium to choose product.

D. Acid catalysis:
   a. Acid protonates —OH (poor leaving group) into $+OH_2$ (good leaving group),
   b. $+OH_2$ dissociates, leaving C+
   c. Water (or some other base) abstracts H from a β-hydrogen, forming a double bond.
   d. $H_2PO_4^-$ and HSO_4^- are generally used as poor nucleophiles, so S_N1 does not occur.

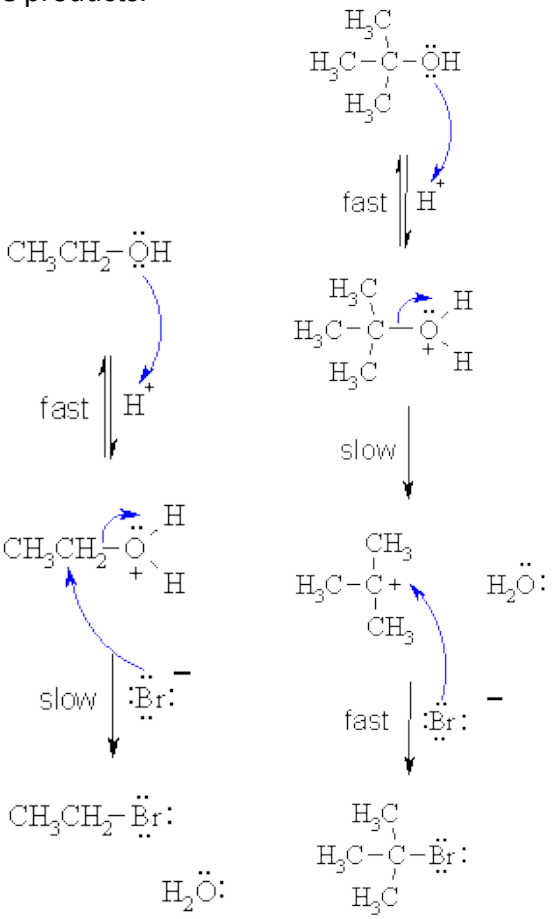


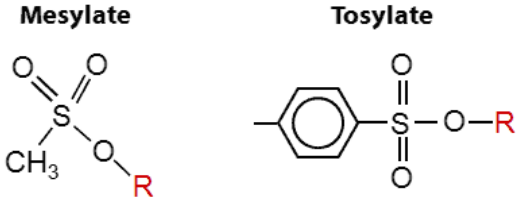
E. Carbocations allow rearrangement, and determine rate of dehydration. Tertiary > secondary because a more substituted C+ makes a more stable transition state. Primary doesn't happen.

F. More than one type of β-hydrogen means a mixture of alkene products.

10.2 Reactions of Alcohols to form Alkyl Halides

A. Reactions of 1°, 2°, and 3° alcohols with HX gives RX.
   a. Original reaction: ROH + HX → RX + H_2O.
      Shift right by adding acid and removing water.
   b. For 1° ROH, the reaction proceeds by S_N2.
      The O on alcohol accepts the H from H—Br. Br^- attacks the carbon bonded to —OH and ejects H_2O as the leaving group, forming RX.
   c. For 2° and 3°, the reaction proceeds by S_N1.
      H_2O leaves and Br^- attacks to form RX.
   d. Rearrangements are possible. Racemization because RX is achiral.



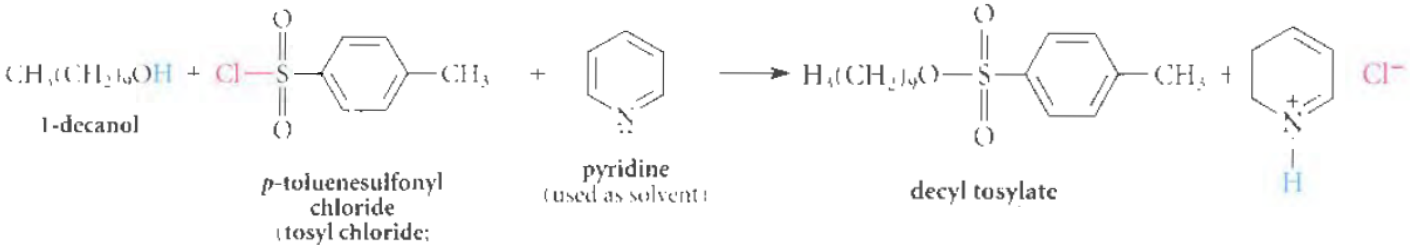


B. Sulfonate Ester Derivatives of Alcohols

a. Sulfonate esters (R-OSO_2-R')

i. Tosylates and mesylates may also be abbreviated as —OTs and —OMs.

ii. Preparation of sulfonate esters (not by S_N2)



iii. Sulfonates are good leaving groups. pKa < 0 (the O^-'s stabilize S^{2+}). Thus, reactivity parallels RX. (S_N1/S_N2 and E1/E2 reactions)

iv. Comparison of methods: evaluating retention and inversion for S_N1 and S_N2 reactions. NaN_3 is inversion, pyridine and PBr_3 (S_N2) are inversion, TsCl is retention. There was a table here, but I didn't get it ☹

C. Alkylating Agents

a. Alkylating agents: react with nucleophiles in S_N1/S_N2. Nucleophiles that substitute for a halide on an alkyl group is said to be alkylated.

b. Alkyl esters (R—O—S) of strong inorganic acids are great alkylating agents because their leaving groups are weak bases.

D. Reactions of Alcohols with Thionyl Chloride ($SOCl_2$) and Phosphorus Tribromide (PBr_3)

a. Milder conditions for preparing 1° and 2° RX by S_N2.

b. Use $SOCl_2$ to prepare 1° and 2° R-Cl

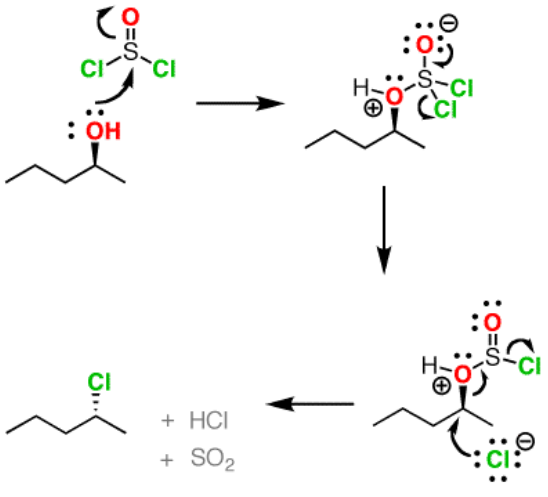
i. ROH + $SOCl_2$ + pyridine (solvent) → R-Cl + SO_2 + pyridine$^+$ + Cl^-

ii. Mechanism: the O on alcohol attacks S^+, which kicks off Cl. H is abstracted by pyridine. Cl^- substitutes for the O, which snaps off the other Cl^-

iii. Rearrangements possible with 2° ROH

How it works: *Formation of alkyl chlorides*

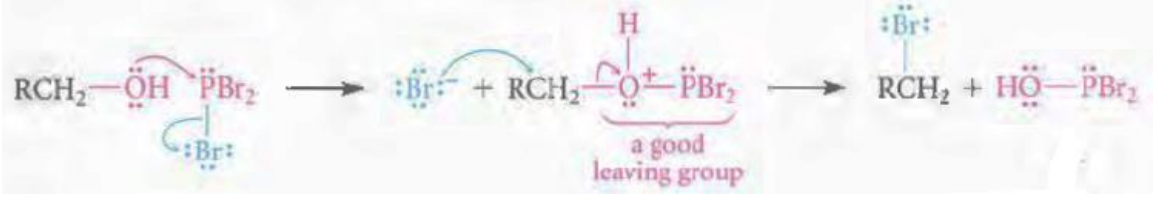
Since the reaction proceeds through a backside attack (S_N2) there is inversion of configuration at the carbon



c. Use PBr_3 to prepare 1° and 2° R-Br

i. (3 equiv) ROH + PBr_3 → (3 equiv) RX + $:P(OH)_3$

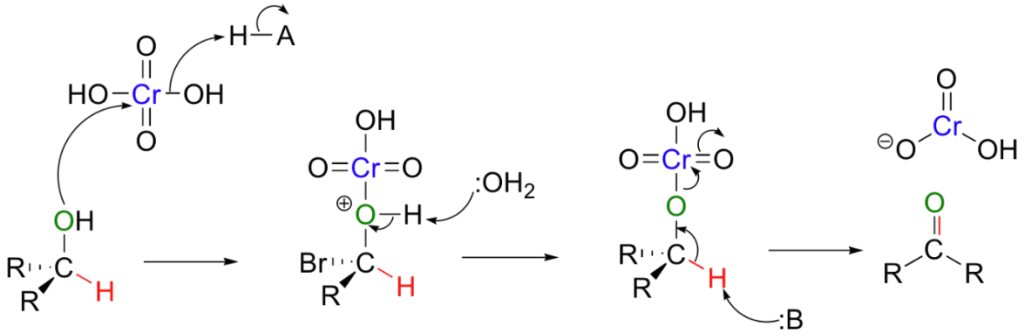
ii. Mechanism: O on alcohol attacks the lone pair on $:PBr_3$, ejecting a Br^-, which later substitutes for O. This occurs 3 times before the PBr_3 is converted to $:P(OH)_3$.



E. Methods for preparation of alkyl halides:
   a. 3 reactions: (1) HX, (2) Sulfonate esters + halide S_N2 reaction, (3) $SOCl_2$, PBr_3
   b. 2 methods of converting to a good leaving group:
      (1) protonation, (2) conversion to sulfonate/inorganic ester.
   c. Primary alcohols: concentrated HBr or PBr_3.
      PBr_3 avoids strongly acidic conditions. Sulfonate esters work too; 2 reactions (formation of sulfonate ester, then reaction of the ester with halide – S_N2).
   d. Tertiary alcohols: HCl/HBr under mild conditions. No sulfonate ester because no S_N2.
   e. Secondary alcohols: no beta-alkyl substitution: $SOCl_2$ → RCl, PBr_3 → RBr.
      Sulfonate esters + halide ions in polar aprotic solvent can help avoid rearrangements.
      HBr leads to rearrangements.

10.6 Oxidation of Alcohols

A. Carbon is oxidized ([o]) when H and C substituents are replaced with more electronegative elements (e.g., O, N, X)
B. Oxidation to Aldehydes and Ketones
   a. Cr(VI) → Cr(III): great oxidizing agent – used in H_2O.
      a. Forms: chromate (CrO_4^{2-}), dichromate ($Cr_2O_7^{2-}$), and chromium trioxide (CrO_3)
      b. The first two are used in strongly acidic conditions, the last in basic pyridine.
      c. Reaction products:
         i. Secondary alcohols → Cr(VI) → ketones
         ii. Primary alcohols + Cr(VI) → chromate ester → aldehydes (anhydrous)
         Aldehydes + water → carboxylic acids (hydrated)
         iii. Last step below is essentially E2 elimination.



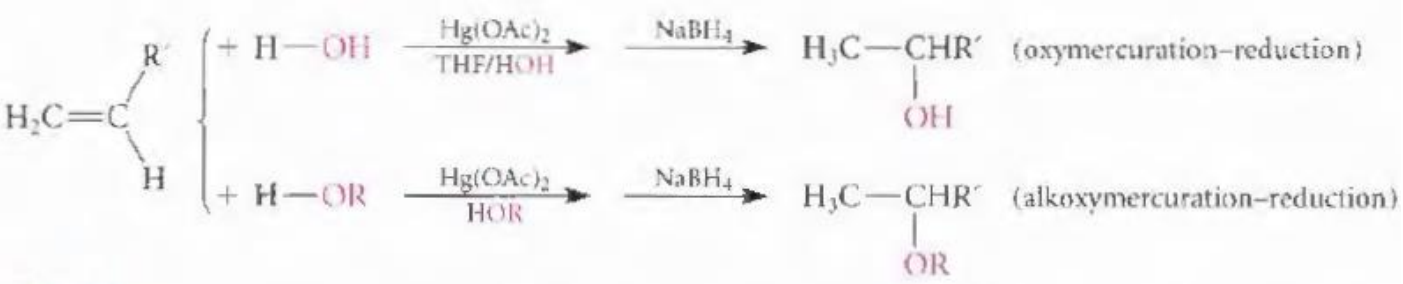
      d. Pyridinium chlorochromate (PCC) – used in organic solvents ($C_2H_2Cl_2$)
C. Oxidation Results
   a. Primary alcohols oxidized by Cr(VI) to aldehydes (in the absence of water), or carboxylic acids (in aqueous solutions)
   b. Primary alcohols + $KmnO_4$ (basic) + acidification → carboxylic acids
      i. Cannot be used with double bonds, or with secondary alcohols to make ketones because it reacts with alkene C=C's.
   c. Secondary alcohols oxidized to ketones
   d. Tertiary alcohols NOT oxidized. There's no H to be abstracted, so you can't have E2, and the ether is basically a dead end.
   e. Primary alcohols oxidized to carboxylic acids with alkaline $KmnO_4$, followed by acid.

Chapter 11 – Chemistry of Ethers, Epoxides, Glycols, and Sulfides

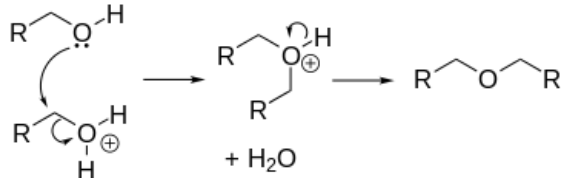
11.1 Synthesis of Ethers and Sulfides

A. Williamson Ether Synthesis (Preparation of ethers R—O—R')
   a. S_N2: $RO^- + R'X \rightarrow R—O—R' + X^-$, where X is any good leaving group.
   b. Limited to 1° RX and MeX, because more alkyl groups allows for E2 elimination.
   c. Limited to unhindered alkoxides, because hindered ones lead to E2 elimination.

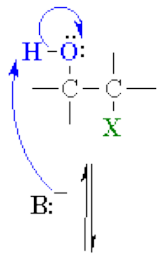
B. Alkoxymercuration-Reduction of Alkenes: RO—H instead of HO—H solvent makes an ether.



C. Ether Synthesis under Acidic Conditions + Heat
   a. Preparation of symmetrical ethers from 1° ROH
      i. 2 ROH → (H_2SO_4) → R—O—R + H_2O
      ii. Mechanism: ROH (1) is protonated, ROH (2) adds via S_N2 and is then deprotonated.

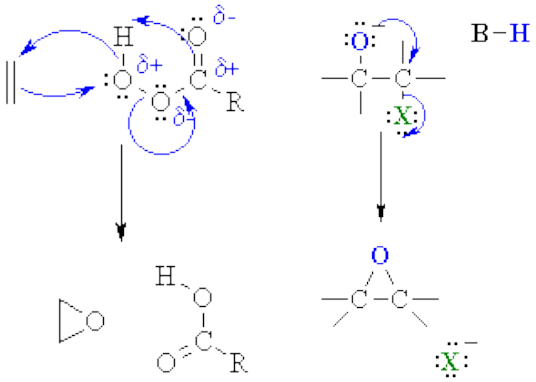


      iii. 2° and 3° ROH fail because E1 competes.
      iv. Heat required because alcohols are poor nucleophiles.
   b. Preparation of unsymmetrical ethers from 1° and 3° ROH
      i. tBOH + ethyl alcohol (solvent) + H_2SO_4 (catalytic) → tB ethyl ether.
      ii. S_N1 mechanism: acid protonates tB alcohol, which exudes H_2O and forms a tertiary C+ that ethyl alcohol adds to.
      iii. MUST be unhindered 1° ROH, and 3° ROH with stabilized C+, in order to be fast enough to compete.



11.2 Synthesis of Epoxides

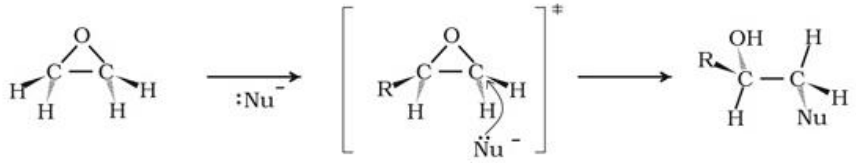
A. Oxidation of alkenes with peracids (RCO_3H)
   a. The weak O—O breaks and the C=O---H hydrogen-bond forms O—H.
   b. Syn-addition: both bonds from O add at the same side.



B. S_N2 cyclization of halohydrin under basic conditions
   a. ~Intramolecular Williamson ether synthesis.
   b. S_N2 mechanism: ^-OH or NaH deprotonates the —OH group to ^-O, which ejects the halide.
   c. Backside displacement: must be anti-periplanar.

C. Addition to epoxide in basic conditions: opens through S_N2 with inversion.

c. The release of ring strain allows epoxide opening. The transition state breaks one of the epoxide bond and lengthens the other → lower energy state. This enables reaction despite the bad leaving group (RO^-).



d. Generally, Nu is ^-OH from a strong base.

e. The base attacks at the least branched site and breaks the nearest bond to the ether. The new ^-O abstracts H from water to form —OH.

f. No elimination because ring strain.

11.3 Cleavage of Ethers

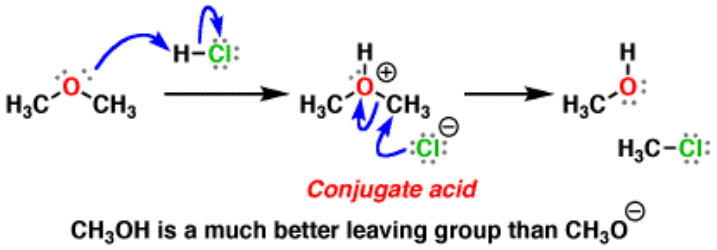
A. Ether linkage: relatively unreactive; good solvents.

B. Bases and nucleophiles: No E2 or S_N2 because ^-OR is a bad leaving group (pKa ~15)

C. Strong acids: cleave ethers via S_N2.

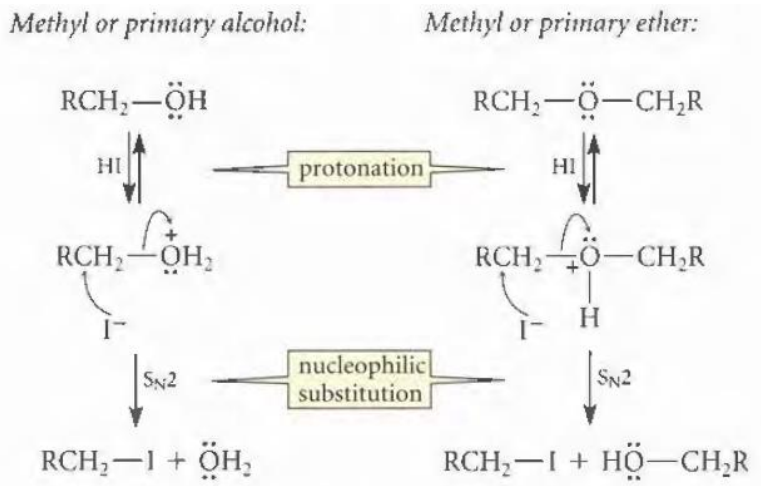
a. Symmetric: Dimethyl ether + 2 HCl →(heat)→ 2 MeCl + H_2O

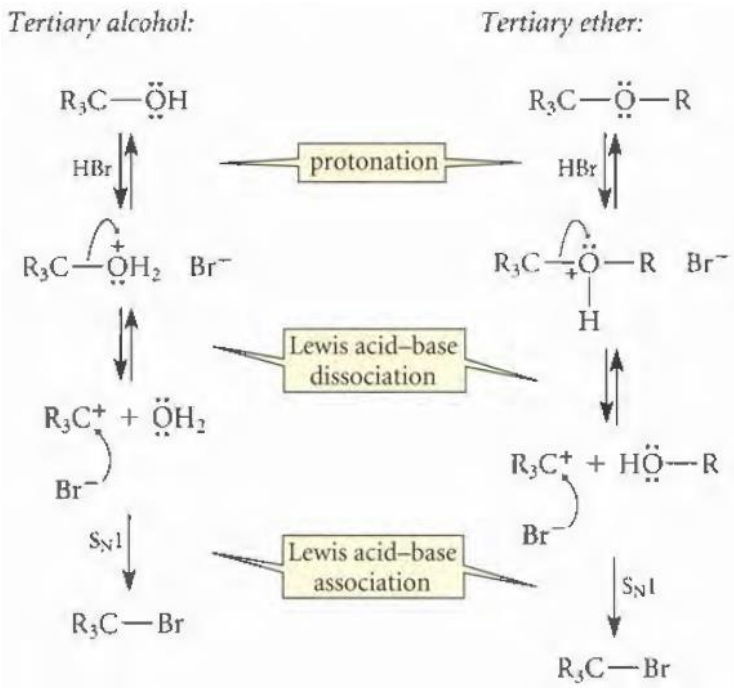
b. Step (1) S_N2 mechanism:



Step (2) S_N2 mechanism: MeOH + HCl → heat → MeCl + H_2O

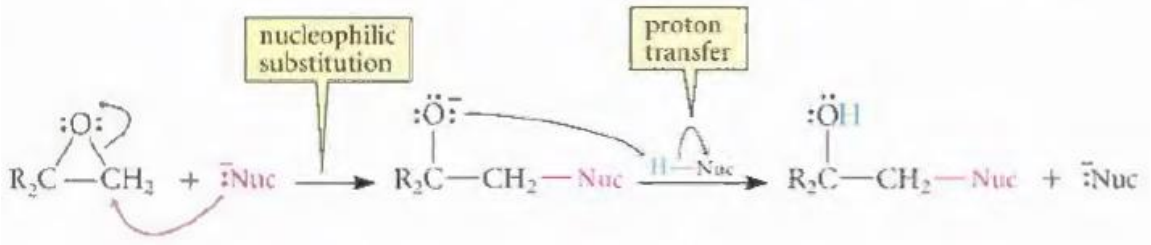
c. Tertiary ether: stabilized C+ S_N1.
tB ethyl ether + HBr →(heat)→ tB bromide and ethyl bromide.



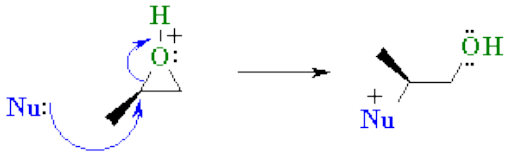


11.4 Sn1 and Sn2 in Epoxides

A. Ring-Opening Reactions under Basic Conditions
   a. Sn2 mechanism: The base deprotonates ROH solvent → RO^- alkoxide, which attacks at the BACKSIDE of the LESS SUBSTITUTED carbon to break the ring (branching retards Sn2 attack).
   b. The epoxide O is the "leaving group," even though it stays. O^- is protonated into —OH.

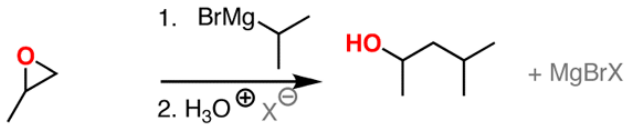


B. Ring-Opening Reactions under Acidic Conditions (mild, catalytic quantities)
   a. Dimethyl epoxide + Ethyl OH → H_2SO_4 → opened epoxide at the C—C bond, with inversion.
   b. Step (1) H protonates the O in epoxide, which forms a leaving group.
      Step (2) nucleophile attack at the TERTIARY carbon to break the epoxide bond.
      The more substituted group is the major product in primary and secondary,
      but there's a mix because branching creates van der Waals repulsions.
   c. The resonance structure has a weaker bond at the more substituted site because the alkyl groups can stabilize a partial carbocation (0.7 for tertiary) – the reaction resembles Sn1.



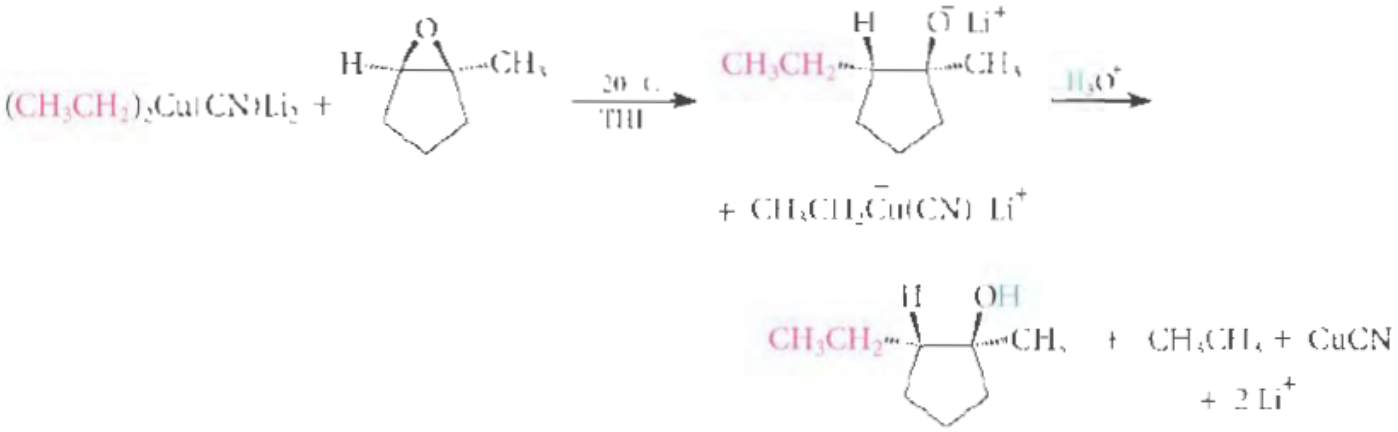
   d. This allows the not-very-nucleophilic solvent to react. This is the solvent, NOT its alkoxide conjugate base, which can't exist in acidic solution.
   e. Inversion of configuration due to backside displacement.
   f. When water is the nucleophile, the product is a trans glycol (1,2-diol) – inversion.

C. Reaction of Epoxides with Organometallic Reagents (R—M)
   a. In Grignard reagents (R—MgBr), the highly basic carbanion attacks at the LESS SUBSTITUTED epoxide carbon. At the same time, Mg coordinates to the epoxide oxygen, making it a better leaving group.
   b. CAUTION: (1) Only use ethylene oxide because Grignard reagents are so strong, they make E2 competitive. (2) This must be done in aprotic solvent (THF), or you'll just protonate it.
   c. S_N2-like mechanism:



D. Organocuprates
   d. These give higher yield than RMgBr because they are less electropositive, which makes a more balanced and more covalent bond with carbon.
   e. 2 R-Li + CuCl → $[R_2Cu]^- Li^+$ + LiCl
   f. 2 R-Li + CuCN → $R_2Cu(CN)Li_2$ (higher order organocuprate)

g. Epoxide + $Et_2Cu(CN)Li_2$ → attack at less substituted site, opening, and inversion.



h. Sn2 mechanism: a carbanion nucleophile is delivered from the copper to the epoxide carbon; epoxide opening is assisted by lithium ion.

11.5 Preparation and Oxidative Cleavage of Glycols

A. Glycols: compounds containing hydroxyl groups on adjacent carbons

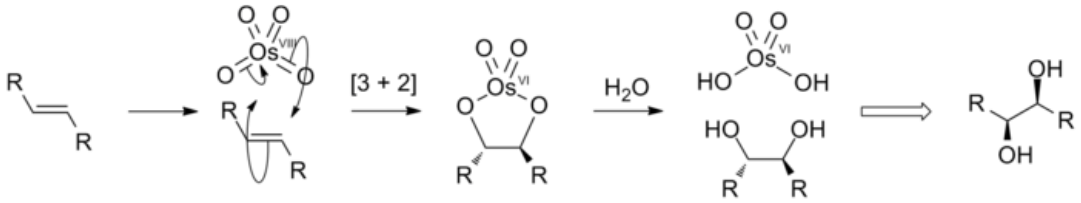
B. Preparation of Glycols (2 methods, opposite stereoisomer outcomes)

a. Epoxidation followed by H_2O opening (harsh acidic or basic conditions – NaOH, H_2SO_4).

i. Racemic, **<u>anti-addition</u>** because OH/H_2O comes in at either side (racemic), and the frontside attack displaces the epoxide O(H) to the back and vice versa (anti-addition).

b. Alkene dihydroxylation – oxidation of alkenes with OsO_4 → glycols

i. (E) 2,3-methyl-2-butene → OsO_4 (cat), NMMO ($H_3N^+—O^-$), H_2O → :NH_3 + diol.



ii. Step (1) concerted **<u>syn-addition</u>**, step (2) NMMO regenerates OsO_4.

iii. The syn-addition is because OsO_4 attacks from one side. This means that alkene dihydroxylation gives the opposite stereoisomer outcomes (from the products of E and Z alkenes) as epoxidation/H_2O opening.

c. KMnO is also okay, but it oxidizes the glycol product further, which decreases yield.

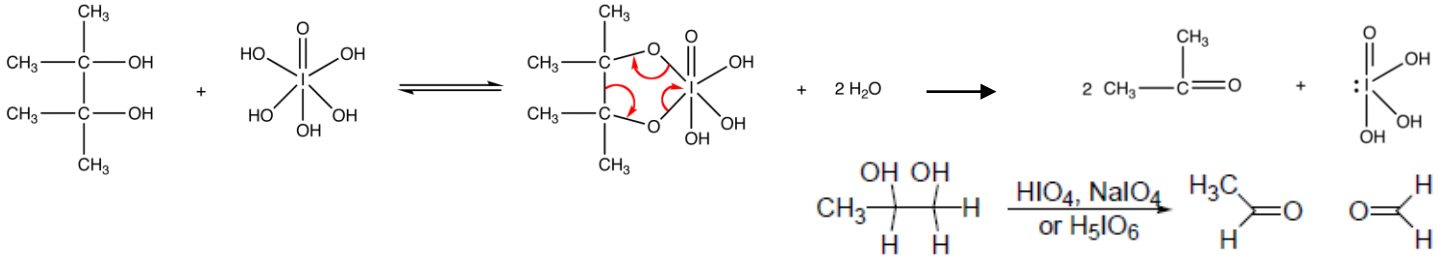
C. Oxidative Cleavage of Glycols

a. Periodic acid (HIO_4) cleaves the C—C bond between the two vicinal diols.

b. You can also use the dihydrate ($HIO_4 \cdot 2H_2O$, **H_5IO_6**, para-periodic acid)

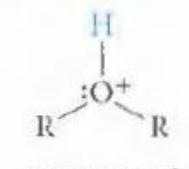
c. The solvent is acetic acid: polar protic.

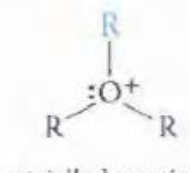
d. Alkene → epoxide → glycol → cleaved products = same products as from ozonolysis.

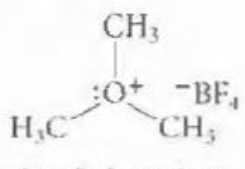


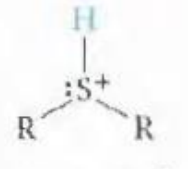
11.6 Oxonium and Sulfonium Salts

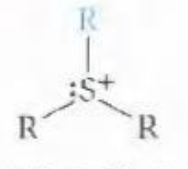
A. Definitions
   a. Oxonium salt: acidic hydrogen of a protonated ether is replaced with an alkyl group
   b. Sulfonium salt: the sulfur analog of an oxonium salt.
   c. The counterion must be a poor nucleophile, like $^{-}BF_4$.

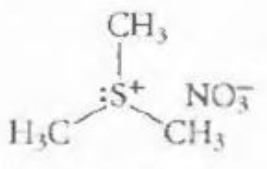

a protonated ether


a trialkyloxonium ion

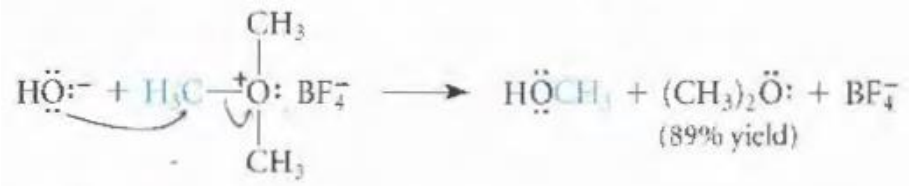

trimethyloxonium tetrafluoroborate (an oxonium salt)


a protonated sulfide


a trialkylsulfonium ion

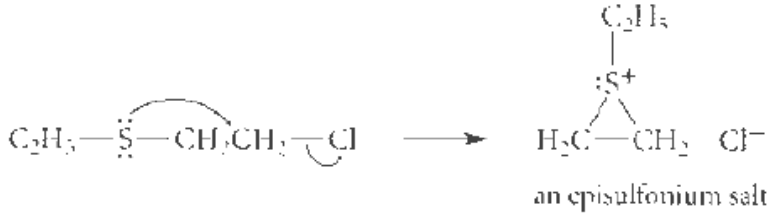

trimethylsulfonium nitrate (a sulfonium salt)

B. Reactions of Oxonium and Sulfonium Salts
   a. Oxonium salts strong alkylating agents and react rapidly with nucleophiles.
   b. Sulfonium salts are considerably less reactive, sometimes requires heat.



11.7 Intramolecular Reactions and the Proximity Effect

A. Neighboring-Group Participation
   a. NGP or anchimeric assistance: covalent involvement of neighboring groups in reactions.
   b. The Sn2 reaction $CH_3(CH_2)_5Cl + H_2O \rightarrow CH_3(CH_2)_5OH + HCl$ is 3,200 times slower than the analogous Sn2 reaction $CH_3CH_2{:}S{:}CH_2CH_2Cl + H_2O \rightarrow CH_3CH_2{:}S{:}CH_2CH_2OH$.
   c. $CH_3CH_2{:}S{:}CH_2CH_2Cl$ forms a reactive episulfonium ion (analogous to protonated epoxide)


an episulfonium salt

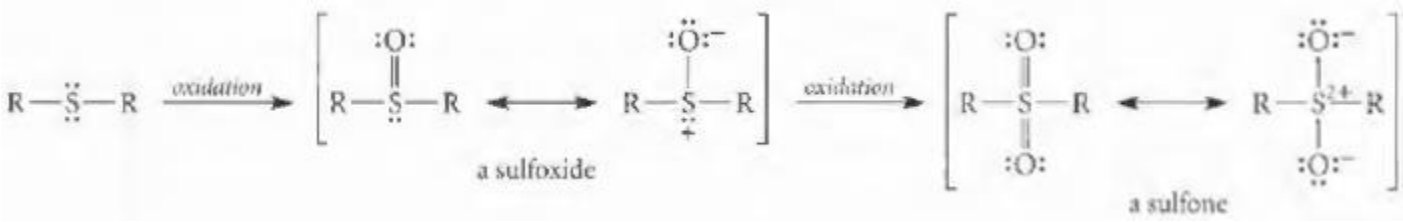
   d. Water rapidly breaks the three-membered ring and thereby forms $CH_3CH_2{:}S{:}CH_2CH_2OH$.
   e. The neighboring-group mechanism outcompetes ordinary intermolecular Sn2.
   f. Intramolecular interactions are much faster because they're more likely ($-\Delta S$, $+\Delta G$)

B. Proximity Effect and Effective Molarity
   a. Proximity effect: rate acceleration of intramolecular (1) > intermolecular (2). Expressed quantitatively as: proximity effect = k_1/k_2.
   b. Since k_1 is first-order and k_2 is second-order, the proximity effect has units of molarity (M). Thus, the proximity effect is also called the effective molarity.
   c. Intramolecular is especially common in 3, 5, and 6-membered rings because the energy tradeoff of ring strain v. reaction probability is maximized.

C. Stereochemistry of Neighboring-Group Participation
    a. Two substitution-with-inversion reactions: (1) Intramolecular Sn2 by sulfur nucleophile to give episulfonium ring, and (2) ring-opening by water. The net result is retention.

11.8 Oxidation of Ethers and Sulfides

A. Ethers are normally inert, but can be autoxidized in air to form peroxides.
B. Disulfides (unlike peroxides) are stable. Sulfides can be oxidized to sulfoxides and sulfones.



11.9 Three Fundamental Operations of Organic Synthesis

A. Functional Group Transformation: most common synthetic operation.
B. Control of Stereochemistry: involves syn/anti, and inversion/retention.
C. Formation of C—C bonds: cyclopropane formation from carbenes/carbenoids + alkenes, and Grignard/organocuprate reagents + epoxides.

Chapter 12 – Hydrogen and Carbon NMR

To be copied from powerpoints later.