Ch. 1 Intro and Review
1.1 Intro to Organic Chemistry
"Organic":

"Organic Chemistry":

- Focus on carbon, with H, N, O, and halogens all major contributors
- Biochemicals are all carbon-based
  - Food, hair, skin, muscles, etc.
  - Clothes, plastics, fuels, etc.

The abundance of carbon, by mass:

Universe	<<0.1%
Earth	<1%
Body	18% (60% of body mass is water)
Non-water body mass	45%

>90% of known molecules are organic!

Why is carbon so special?
1. Versatile bonding! 4 covalent bonds per carbon enables:

   a.

   b.

2. Modest Electronegativity enables:

   a. strong bonds to other C's, H's, and other nonmetals

Orbitals and Bonding: Review (Chapter 1:1-5,7)
1. Atomic orbitals for 2nd-row elements (C, N, O):
   - Note: for organic, we won't need to fuss with d or f orbitals

2. Valence electrons: electrons in an atom's outside shell
3. Octet Rule: atoms transfer or share electrons to obtain a filled shell (which is 8 for C, N, O, halogen)
   - Note: **never** draw C, N, or O with > 8 electrons!!!
4. Bond Types:

a. Covalent bonds	H_2
1. Between **nonmetals**	
2. Involve shared electrons	H_2O
b. **Ionic**:	
1. Negligible sharing of electrons	
2. Metals transfer electron(s) to nonmetal	LiF
• If formula has a **metal**, assume **ionic** bonding	
a. Special case of ionic bonding in absence of metals: ammonium salts	NH_4Cl

Normal Bonding (Chapter 1)

### Summary of **Normal, Ideal Bonding** (No Formal Charge)

	Valence Electrons	Valence Bonds	Lone Pairs
$-\overset{\displaystyle |}{\underset{\displaystyle |}{C}}-$	4	4	0
$-\overset{\displaystyle ..}{\underset{\displaystyle |}{N}}-$	5	3	1
$-\overset{\displaystyle ..}{\underset{\displaystyle |}{O}}:$	6	2	2
H—	1	1	0
:Cl— :Br— :I— :F—	7	1	3

Rules for Drawing Lewis structures for organic molecules:
1. Try to provide normal bonding for C, N, O atoms **if possible**. (Works > 95% of time)
2. Double or triple bonds will often be involved.
   - Double or triple bonds are often required to achieve normal bonding.
3. In any formula that has a charge, there will always be an atom with that formal charge.
4. In any formula that includes a metal, assume ionic bonding.
   - Assume positive charge for the metal,
   - Assume negative charge for the organic portion.
5. Do not draw bonds between nonmetals and metals, as if they were covalently bound.
6. Be sure to specify the formal charge on any atom that has formal charge.
7. Always be aware of how many lone pairs are on any atom
   - Note: We will often omit lone pairs. But you must know when they are there!

Lewis Structure Practice
1. Draw Lewis structures for the following formulas: (Include lone pairs or formal charges if necessary)

   a. CH_3CH_3

   b. CH_3CH_2OH

   c. CO_2

   d. HCN

   e. CH_3CHO

   f. $NaOCH_3$
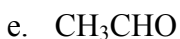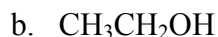
Formal Charge (Section 1.6): When an atom does not have its normal bonding
- Atoms with formal charge dominate reactivity. Therefore the ability to recognize and identify atoms with formal charge is really important!

- **Skills**:
    1. Identify the formal charge for any atom that does not have normal bonding
    2. Identify the number of bonds and lone pairs associated with any atom whose formal charge is specified

- Note: Designation of formal charge is required. If you don't write the charge sign next to an atom that should have formal charge, you will lose test points!

Formal Charge Equations:
1. FC = group # - (bonds + unshared e's)   (use to calculate FC)
2. Group # - FC = bonds + unshared electrons   (given formal charge, use to find lone pairs)


Practical: (memorize)
- C   4 bonds ⟷ neutral
         3 bonds and zero lone pairs ⟷ cation +1
         3 bonds and one lone pair ⟷ anion -1
- N   4 bonds ⟷ cation +1
         3 bonds and one lone pair ⟷ neutral
- O   3 bonds and one lone pair ⟷ cation +1
         2 bonds and 2 lone pairs ⟷ neutral
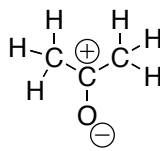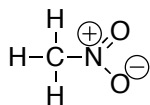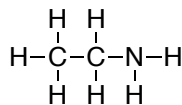   1 bond and three lone pairs ⟷ anion -1
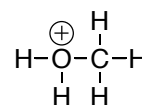

FORMAL CHARGE

# of Bonds	C	N	O	F
4	0	+1		
3	-1 or +1	0	+1	
2		-1	0	
1			-1	0

Formal Charge Practice (Section 1.6)

1. Assign any **formal charges** to atoms that need them:
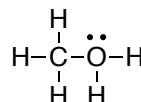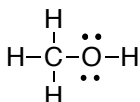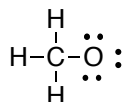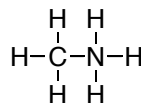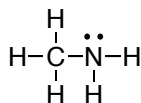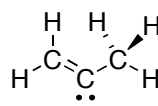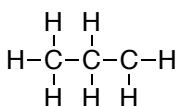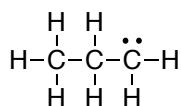
2. Fill in lone pairs on any atoms that need them (whether atoms with formal charge or neutral atoms):
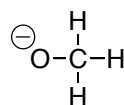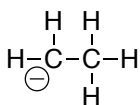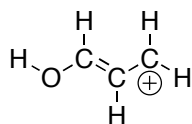
Notice: **With the exception of carbocations, all other C/N/O atoms end up with a combined total of four when you sum up their bonds and lone-pairs**. So apart from carbocations, if you know the number of bonds, you can fill in the correct number of lone pairs without even thinking much!

Electronegtivity and Bond Polarity (Section 1.5, 1.11)
Electronegativity: the ability to "hog" electrons in covalent bonds
-when two atoms are unequal, one will always attract bond electrons more strongly than the other
-the more electronegative atom has a δ- charge, the less electronegative atom a δ+ charge

H 2.2					
		C 2.5	N 3.0	O 3.4	F 4.0
					Cl 3.2
					Br 3.0
					I 2.7

Patterns:
1. Increases left to right

2. Increases bottom to top

3. C-H bond are pretty comparable, essentially nonpolar

4. C-other non-metal, C is always less electronegative, δ+ on C

5. C-metal, C is always more electronegative, δ- on C

**Ionic Structures: The Importance of Recognizing Ionize Structure (1.2)**
1. If you see a metal in a formula, treat it as ionic rather than covalent/molecular
    a. -always put a positive charge on the metal
    b. -never draw a "bond" between the metal and the non-metal
    c. -always figure there must be a negative charge on the non-metal portion of the formula, with a formal negative charge on something
2. The one time you see ions without metals is with ammonium ions

LiOH   NaH NH_4OCH_3

Resonance Structures (Section 1.8)
Sometimes a single Lewis structure does not provide an adequate picture.

Example: O_3 (ozone)

2 Resonance Forms

Actual Species Is a
Hybrid of the Resonance Forms
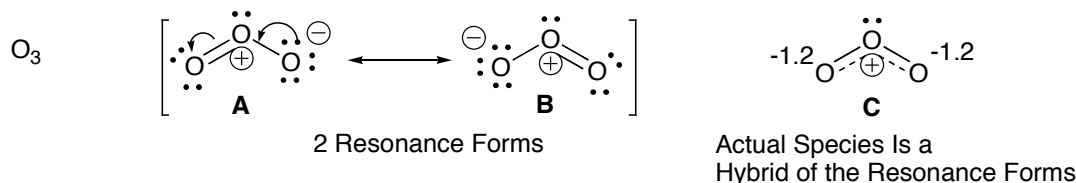
Notes/observations:
1. Neither form **A** nor **B** can avoid formal charges.
    *   The majority of resonance situations have some formal charge involvement
2. The <u>real molecule</u> is <u>hybrid</u>: see picture **C**
    *   The central oxygen has + charge
    *   Each of the outside oxygens is -1/2
    *   Both of the bonds to the outside oxygens are equal in length/strength
    *   The actual length/strength of the oxygen-oxygen bonds reflect 1.5 bonds (shorter and stronger than single bonds; longer and weaker than double bonds)
3. Why not just draw the hybrid?
    *   Hard to do, without first working through resonance structures first.
    *   Hard to keep track of the electrons, which help explain reactivity/mechanism
4. **Resonance Recognition**: When are Two Structures related as Resonance Structures?
    *   Atoms must be connected in exactly the same way.
        o   Resonance forms differ **only in the placement of electrons.**
    *   If two Lewis structures have the same atomic connectivity, but differ **only** in the placement of some electrons/formal charges, they are related as resonance structures.
    *   If the placement/connectivity of atoms differ, then the two structures are <u>not</u> <u>resonance structures</u> (they may perhaps be related as "isomers", see later.)
    *   KEY: FOR RESONANCE STRUCTURES, ELECTRONS MOVE BUT ATOMS DO NOT MOVE. IF ATOMS MOVE, YOU DON'T HAVE RESONANCE STRUCTURES
   *   Note: The real molecule is represented by the hybrid, and electrons are not actually jumping back and forth.
5. Resonance involves the **delocalization** of electrons and charge
    *   In ozone, neither outside oxygen gets stuck with a full negative charge. The charge is shared so that both outside oxygens have a more manageable -1/2 charge
    *   This delocalization of electrons/charge is stabilizing.
    *   **KEY: RESONANCE IS STABILIZING**
6. Resonance always involves electrons in double bonds and/or lone pairs (π electrons)
7. "Allylic resonance": The most frequent resonance situation is when a charged atom is attached to a double bonded atom
8. When resonance structures are equal in stability, the hybrid is the average of the forms
9. When resonance structures are unequal, the more stable structure dominates the hybrid
    *   **Ranking Stability:**
        1. **More bonds** → more stable (but don't exceed octet rule!). (**Priority rule**)
        2. Bonds being equal, consider **electronegativity** (tiebreaker rule):
            *   **negative charge** is better on **more electronegative atom**;
            *   **positive charge** is better on **less electronegative atom**
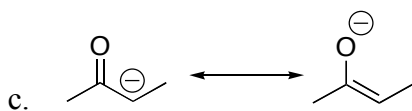
Resonance Problems
1. Which of the following are related as resonance structures?

1.   **2.**

3.   **4.**

5.
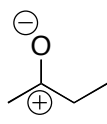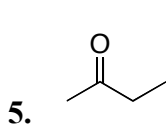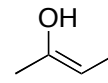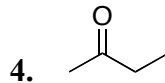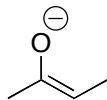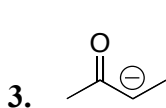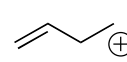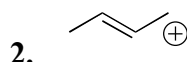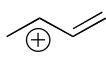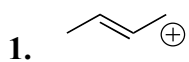
2. Draw a resonance structure for the following allylic resonance structures

a.

b.
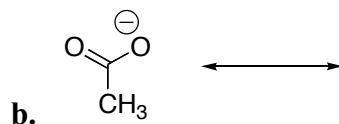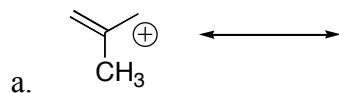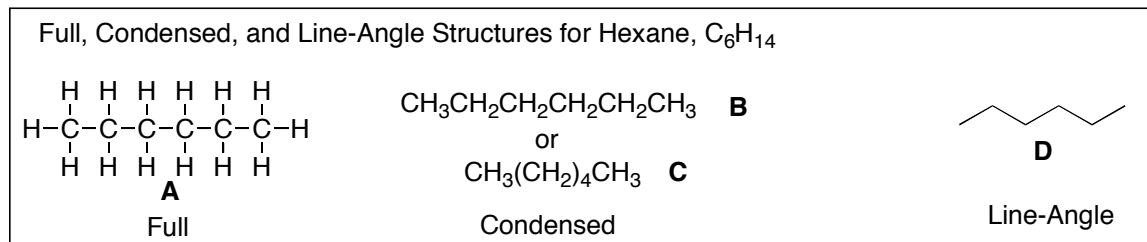
3. Which Resonance Structure is Better and would make a more than 50% contribution to the actual hybrid?   Why, bonds or electronegativity?

a.

b.

c.
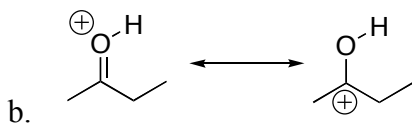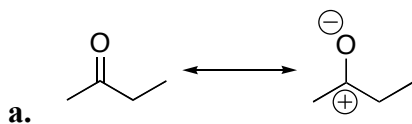
Structural Formulas (Section 1-9)
1. Full Structural Formulas
2. Condensed Formulas
3. Line-Angle (Skeletal) Formulas

Since organic structures are large and complex, full Lewis structures are often a hassle. You'll need to be proficient in both condensed and line-angle formulas.

Full, Condensed, and Line-Angle Structures for Hexane, C_6H_{14}

$CH_3CH_2CH_2CH_2CH_2CH_3$ **B**
or
$CH_3(CH_2)_4CH_3$ **C**

A   Condensed   **D**

Full   Line-Angle

Condensed Formulas: Central atoms are shown with attached atoms, essentially in sequence
- Challenges:
  1. Handling parentheses
  2. Handling double and triple bonds
  3. Handling branches
  4. Handling ketones/aldehydes/esters/amides/carboxylic acids
  5. In general, recognizing when an oxygen is double-bonded off a carbon, and when it is single bonded both to carbon and to something else.

Line-Angle (Skeletal) Formulas:
1. Each vertex represents a carbon
2. C-H bonds are often omitted: assume enough H's to give four bonds or the appropriate formal charge
3. Oxygen and Nitrogen atoms must be specified, and O-H and N-H bonds are **not** omitted
   - Line-angle formulas are routinely the fastest and cleanest to draw.
   - Line-angle is essential and optimal for showing 3-dimensional organic shape.

Formula Practice
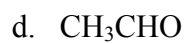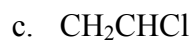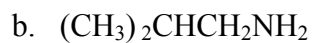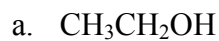Time race illustration: Draw as many copies of C_6H_{14} hexane as you can in 20 seconds:

Full:

Condensed:

Line-Angle:

Draw the full structure, given the condensed structure.   Point being illustrated

a. CH_3CH_2OH

b. $(CH_3)_2CHCH_2NH_2$

c. CH_2CHCl

d. CH_3CHO

e. CH_3CO_2H

Fill in the full structure, including attached hydrogens and attached lone pairs, for the following line-angle structures. If given a condensed structure, convert it to a line-angle.

a.   b.

c.   d.

e.   OH   f.

g.   h.

i.

j. $CH_3CH_2CH_2CH_2CH_3$

k. CH_3CO_2H
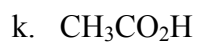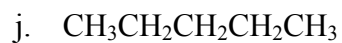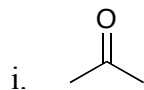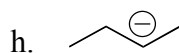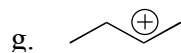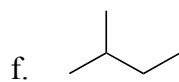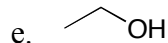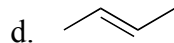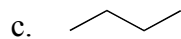
3-D Structure, Hybridization, and Orbitals

1.10 "VSEPR" and Molecular Shape: **V**alence **S**hell **E**lectron **P**air **R**epulsion

Concept: electron groups repel, determine structure

      4 electron groups: tetrahedral, 109° angle

      3 electron groups: trigonal planar, 120° angle

      2 electron groups: linear, 180° angle

2 Types of "Electron Groups"

1. "B" = bonds to other atoms.
   - Whether it's a single, double, or triple bond, it still counts as one "electron group" or one "bond group"
2. "L" = Lone pairs

B+L	Electron Geometry	Bond Angle	Hybridization	Remaining π -orbitals
4	Tetrahedral	$\approx 109°$	sp^3	0
3	Trigonal Planar	$\approx 120°$	sp^2	1
2	Linear	$\approx 180°$	sp	2

EXAMPLES
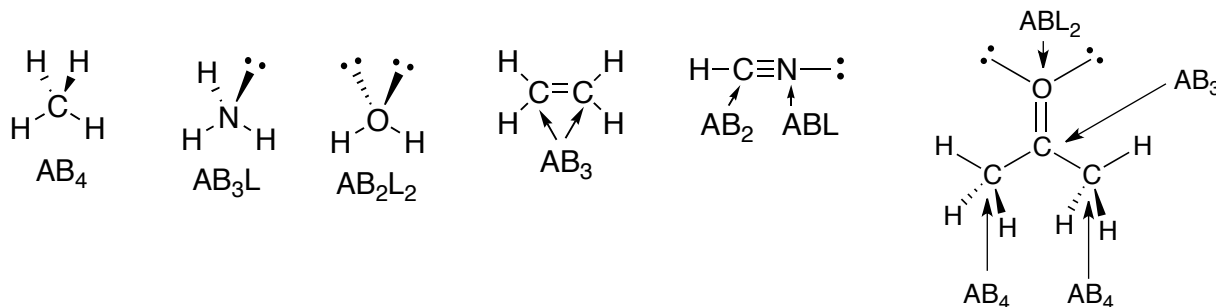
DRAWING 3-D, Given VSEPR Shapes and Line-Angle Structures

Guidelines for Drawing Models:

A. In-Plane/Out-of-Plane
   - Designate an atom **in front** of plane with a **wedge**
   - Designate an atom **behind** plane with a **hash**
   - Designate an atom **in the plane** plane with a **straight line**

B. 3-D Perspective
   1. Keep as many atoms as possible in a single plane (plane of the paper) by zig-zagging.   Connections within the paper are drawn with straight lines.
   2. Use wedges to indicate atoms that are in front of the plane.
   3. Use hashes to indicate atoms behind the plane.

C. For any tetrahedral atom, only 2 attachments can be in the plane, 1 must be in front, and 1 behind.
   a. -if the two in the plane are "down", the hash/wedge should be up
   b. -if the two in plane are "up", the hash/wedge should be down.
   c. -the hash/wedge should never point in same direction as the in-plane lines, or else the atom doesn't looks tetrahedral
   d. -for polyatomic molecules, it is strongly preferable to NOT have either of the in-plane atoms pointing straight up. Straight-up in-plane atoms do not lend themselves to extended 3-D structures.
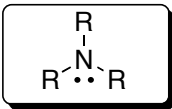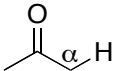
Good! Look tetrahedral   Bad! These don't look tetrahedral!
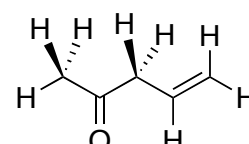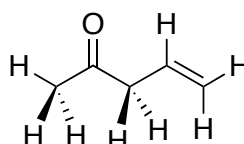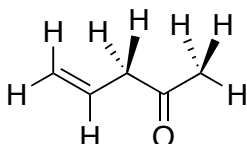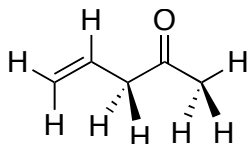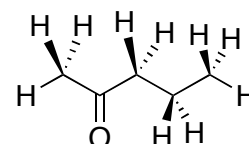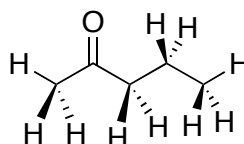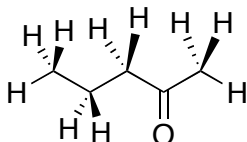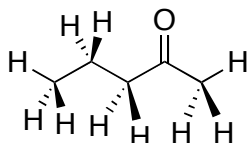
Draw:

C_2H_6 C_4H_{10}

CH_3COCH_3 $CH_3CH=CHCl$

Acid-Base Chemistry (Section 1.13-18)

Acidity/Basicity Table

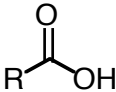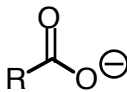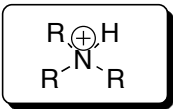| Entry	Class	Structure	K_a	Acid Strength	Base	Base Strength
1	Strong Acids	H-Cl, H_2SO_4	10^2		$Cl^{\ominus}$, $HO-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-O^{\ominus}$	
2	Hydronium	H_3O^+, ROH^+ cationic	10^0		H_2O, HOR neutral	
3	Carboxylic Acid	$\overset{O}{\underset{R}{\overset{\|}{C}}}{-}OH$	10^{-5}		$\overset{O}{\underset{R}{\overset{\|}{C}}}{-}O^{\ominus}$	
4	Ammonium Ion (Charged)	$R-\overset{\oplus}{N}(H)(R)-R$ Charged, but only weakly acidic!	10^{-12}		$R-\overset{R}{N}(:)-R$ Neutral, but basic!	
5	Water	HOH	10^{-16}		$HO^{\ominus}$	
6	Alcohol	ROH	10^{-17}		$RO^{\ominus}$	
7	Ketones and Aldehydes	$\overset{O}{\overset{\|}{C}}-\alpha H$	10^{-20}		$\overset{O}{\overset{\|}{C}}-\alpha^{\ominus}$	
8	Amine (N-H)	$(iPr)_2N$-H	10^{-33}		$(iPr)_2N^{\ominus}Li^{\oplus}$	
9	Alkane (C-H)	RCH_3	10^{-50}		$RCH_2^{\ominus}$	

Quick Checklist of Acid/Base Factors
1. Charge
2. **Electronegativity**
3. **Resonance/Conjugation**

> ▪ **When neutral acids are involved, it's best to draw the conjugate anionic bases, and then think from the anion stability side.**

- The above three factors will be needed this semester. The following three will also become important in Organic II.

4. Hybridization
5. Impact of Electron Donors/Withdrawers
6. Amines/Ammoniums

More Detailed Discussion of Acid/Base Patterns/Factors to remember

1. Charge Factor: central atom being equal, cations are more acidic than neutrals (H_3O^+ > H_2O, NH_4+ > NH_3), and anions more basic than neutrals (hydroxide > water).

2. Electronegativity Factor:
   - Acidity   H-C < H-N < H-O < H-X (halogen)

   - Anion Stability $\overset{\ominus}{C} < \overset{\ominus}{N} < \overset{\ominus}{O} < \overset{\ominus}{X}$

   - Basicity $\overset{\ominus}{C} > \overset{\ominus}{N} > \overset{\ominus}{O} > \overset{\ominus}{X}$

   - Electronegativity $\overset{\ominus}{C} < \overset{\ominus}{N} < \overset{\ominus}{O} < \overset{\ominus}{X}$

   - Why: All neutral acids produce an anion after losing an H
   - **The more stable the anion Z^- that forms, the more acidic the parent H-Z will be**. (The Product Stability/Reactivity principle).
   - **The anion stability correlates the love for electrons (electronegativity).**
   - Summary of Key Relationships:
     - ANION STABILITY and the ACIDITY of a neutral acid precursor.
     - ANION STABILITY and the BASICITY of the anion (inverse relationship)
     - ANION BASICITY and the ACIDITY OF THE CONJUGATE ACID are inversely related (the stronger the acidity of the parent acid, the weaker the basicity of the conjugate anion)
   - KEY: WHEN THINKING ABOUT ACIDITY AND BASICITY, FOCUS ON THE STABILITY OF THE ANION.

3. Resonance/Conjugation: Anion resonance is stabilizing, so **an acid that gives a resonance-stabilized anion is more acidic.** And an anion that forms with resonance will be more stable and less basic.

   - Oxygen Series Examples:
     Acidity: sulfuric acid > carboxylic acid > water or alcohol

     Anion Basicity: $HO-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-\overset{\ominus}{O}$ < $\overset{O}{\underset{O^{\ominus}}{\|\!\!\!\bigwedge}}$ < $\diagup\!\!\!\diagdown\overset{\ominus}{O}$

     Anion Stability: $HO-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-\overset{\ominus}{O}$ > $\overset{O}{\underset{O^{\ominus}}{\|\!\!\!\bigwedge}}$ > $\diagup\!\!\!\diagdown\overset{\ominus}{O}$

   - Note: Resonance is normally useful as a tiebreaker between oxygen anions, nitrogen anions, or carbon anions

Acid/Base Problems

Choose the More Acidic for Each of the Following Pairs: Single Variable Problems

1. NH_3 $\oplus NH_4$

2.   (ethyl-$\overset{\oplus}{O}H_2$)   (ethyl-OH)

3.   (propyl-OH)   (propyl-NH_2)   (propyl-CH_3)

4.   (CH$_3$C(=O)OH)   (ethyl-OH)

5.   (CH$_3$C(=O)NH_2)   (ethyl-NH_2)
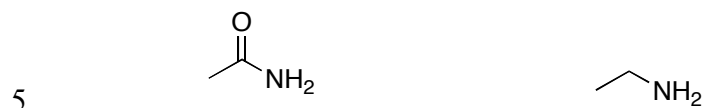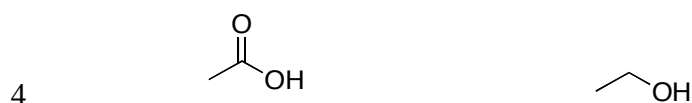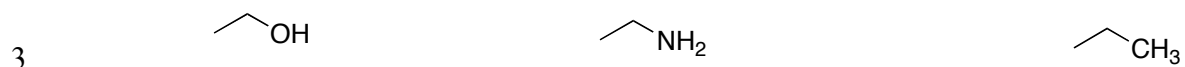
6.   Rank the Acidity from 1 → 5, 1 being most acidic. (Think Anion! And Draw
        Anion!)

HF H_2O CH_3NH_2 (H-C(=O)-OH) CH_4

7.   For the anions drawn in problem 6, rank them from 1 → 5 in terms of **basicity**.

Choose the More **Basic** for Each of the Following Pairs (Single Variable)

1. NH_3 $NaNH_2$

2.   NaOH H_2O

3.   Ph⁀O⁻   Ph–C(=O)–O⁻

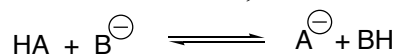4.   ⁀O⁻   ⁀NH⁻

Predicting Acid/Base Equilibria: Any acid base equilibrium favors the side that has the more stable, less reactive base

5. Draw arrow to show whether equilibrium favors products or reactants. (Why?)

a. H_2O + ⁻NH_2 ⁻OH + NH_3

b. H_2O + H–C(=O)–O⁻   ⁻OH + H–C(=O)–OH

Generic acid/base reaction, with anionic base and neutral acid:

HA + B⁻ ⇌ A⁻ + BH

Stronger acid → weaker conjugate base
Weaker acid → stronger conjugate base

- Acid-base reactions always favor formation of the weaker acid and weaker base
- The weaker acid and weaker base are always on the same side
- The more stable anion is the weaker base

THEREFORE:
- The equilibrium will always favor the WEAKER, MORE STABLE ANION
- **IF YOU CAN IDENTIFY WHICH ANION IS MORE STABLE, YOU CAN PREDICT THE DIRECTION THE REACTION WILL GO**.
- This logic can be used to predict whether an anion can successfully deprotonate a neutral species.

6. Can H_3C⁻ deprotonate H_2O?
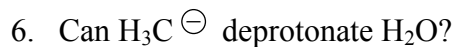
Some Arrow-Pushing Guidelines (Section 1.12, 18)

1. Arrows follow <u>electron movement</u>.

2. Some rules for the appearance of arrows
   - The arrow must begin from the electron source. There are two sources:
     a. An atom (which must have a lone pair to give)
     b. A bond pair (an old bond that breaks)
   - An arrow must always point directly to an <u>atom</u>, because when electrons move, they always go to some new atom.

3. Ignore any Spectator Atoms. Any metal atom is always a "spectator"
   - When you have a metal spectator atom, realize that the non-metal next to it must have negative charge

4. Draw all H's on any Atom Whose Bonding Changes

5. Draw all lone-pairs on any Atom whose bonding changes

6. **KEY ON BOND CHANGES**. Any two-electron bond that changes (either made or broken) must have an arrow to illustrate:
   - where it came from (new bond made) or
   - an arrow showing where it goes to (old bond broken)

7. **Watch for Formal Charges and Changes in Formal Charge**
   - If an atom's charge <u>gets more positive</u> ⇒ it's donating/losing an electron pair ⇒ <u>arrow must emanate from that atom or one of it's associated bonds.</u> There are two "more positive" transactions:
     - <u>When an anion becomes neutral</u>. In this case, an arrow will emanate from the atom. The atom has donated a lone pair which becomes a bond pair.
     - <u>When a neutral atom becomes cationic</u>. In this case, the atom will be losing a bond pair, so the arrow should emanate from the bond rather than from the atom.

   - If an atom's charge <u>gets more negative</u> ⇒ it's accepting an electron pair ⇒ <u>an arrow must point to that atom</u>. Ordinarily the arrow will have started from a bond and will point to the atom.

8. **When bonds change, but Formal Charge Doesn't Change, A "Substitution" is Involved**
   - Often an atom gives up an old bond and replaces it with a new bond. This is "substitution".
   - In this case, there will be an incoming arrow pointing directly at the atom (to illustrate formation of the new bond), and an outgoing arrow emanating from the old bond that breaks

Examples of "Arrow Pushing" and "Mechanism" (Section 1-12, 18)

Reaction: HO$^{\ominus}$ + CH$_3$Br $\longrightarrow$ HOCH$_3$ + Br$^{\ominus}$
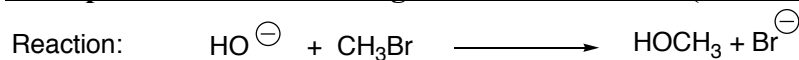
Mechanism, with arrows to show how electrons move,
how the new bond forms, and how an old bond breaks:
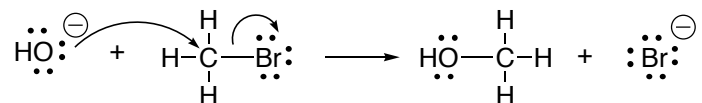
Notes:
1. Arrows are drawn to show how electron pairs are moving as new bonds form or old bonds break.
2. Mechanisms help us to understand and generalize when and why bonds make or break, so that we can understand when and why reactions will occur and what products will form.
3. Each arrow always goes from an electron source (either an atom with a lone pair or else a bond pair) to an acceptor atom
4. **Terms:**
   - "**Nucleophile**" = source of electon pair   ("Lewis base")
   - "**Electrophile**" = acceptor   ("Lewis acid")
5. An arrow always proceeds from a nucleophile and points toward an electrophile.
6. Arrow-pushing is very helpful in relating two resonance structures

1. Use arrows to show how the electrons "move" from the first to the second resonance structures:

a.

b.

c.
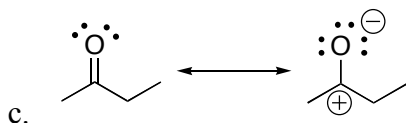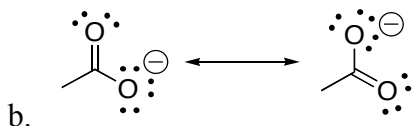
2. Use arrows to show the mechanism for the following acid-base reaction.
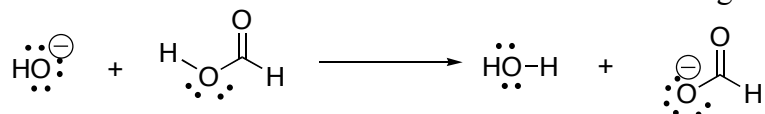
3. Use arrows to show the mechanism for the following two-step reaction. For the first step, identify the "nucleophile" and the "electrophile".
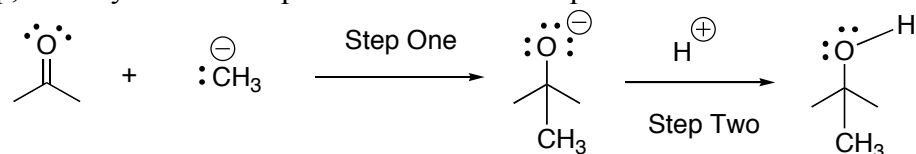
Hybrid Orbitals; σ bonding (Chapter 2.1-7, 2.20, 2.21)
1s + 3p → 4 sp^3 hybrids   109°
1s + 2p (+ 1 unhybridized p)→ 3 sp^2 hybrids (+ 1 unhybridized p)   120°
1s + 1p (+ 2 unhybridized p's)→ 2 sp hybrids (+ 2 unhybridized p's)   180°

Why does hybridization occur?
1. Hybrid orbitals are big and point in one direction. Their **directionality** leads to **better overlap** which leads to **strong bonds**.
2. Hybrid orbitals leads to nice VSEPR angles

If hybridization is so great, why aren't pure monatomic atoms hybridized?
1. For an isolated atom, having 1 s and 3 p atomic orbitals is better than 4 sp^3 hybrid orbitals
2. However, when covalent bonds can result, the small price of hybridizing is paid off a thousandfold by the payoff of making strong, good VSEPR bonds

If hybridization is so great, why aren't all carbons sp^3 hybridized? Why do some stay sp^2 or sp, and withhold some p orbitals from hybridization?
1. p orbitals are withheld from hybridization for the sole purpose of using them to make π bonds.
2. Only when double bonds or triple bonds are involved is the hybridization less than the full sp^3
3. Each π bond requires the attached atoms to use p orbitals

2 Kinds of Covalent Bonds
1. sigma (σ) bonds: electron density is along the axis between the nuclei
   • σ bonds always involve the overlap of s or s-containing hybrids (s, sp, sp2, sp3)
2. pi (π) bonds: electron density is either above/below or before/behind, but not along the internuclear axis
   • π bonds involve the overlap of parallel p orbitals

The first bond in any bond (whether single, double, or triple), is a σ bond. The "extra" bonds in a double or triple bond are π bonds.

Bond	σ	π
Single	1	0
Double	1	1
Triple	1	2

π bonds are weaker and more reactive than σ bonds. Most organic reactions involve π bonds

2.8-2.12, 1.9   Bond Rotations, Structural Isomers, and Stereoisomers
Rotation is allowed for single bonds
    • No bonds break, the sigma bond is fine
Rotation is forbidden for double bonds
    • The p-bond overlap breaks, between the two p orbitals that need to be parallel

isomers-different compounds with the same molecular formula.

**structural isomers (or constitutional isomers)**-isomers that have their atoms connected in a different order. (2.8-2.10)
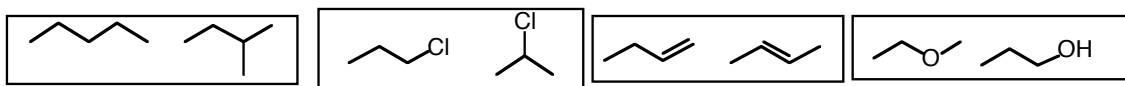
stereoisomers (or configurational isomers)-isomers in which atoms are joined in the same order but differ in the way their atoms are arranged in space. (3.11)
1. Stereoisomers have the same condensed formula (if not, they aren't stereoisomers)
2. Stereoisomers can not be interconverted by bond rotation or by being turned over
    • If two things can be interconverted by bond rotation or being turned over, then they aren't stereoisomers!
3. Stereoisomers are subdivided into two categories: **enantiomers** and **diastereomers**.
    o **Diastereomers**: have **cis/trans** relationship
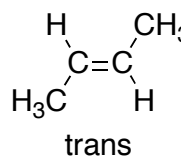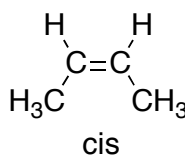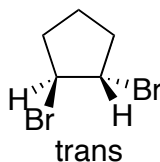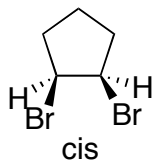
    o **Enantiomers**: have **mirror image** (left hand/right hand) relationship
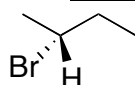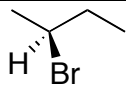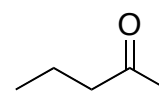

Problem: For the following pairs of structures, classify whether they are related as **same**, **structural isomers**, or **stereoisomers**.
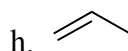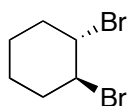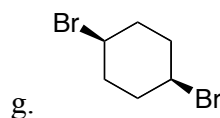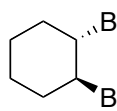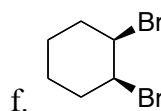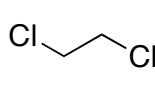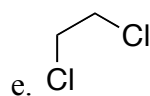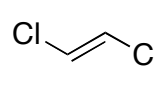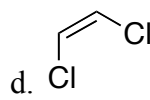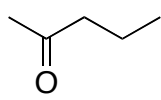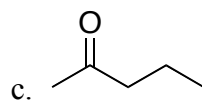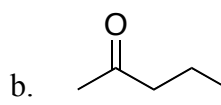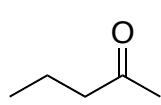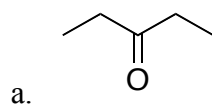
2.17, 2.22, 4.6 Intermolecular Forces and Boiling Points
1. Hydrogen bonding (O-H or N-H)
2. Dipole-Dipole
    • Much weaker than hydrogen bonds
3. London Forces
    • Increases with increasing molecular weight
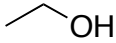
Intermolecular Forces impact:
a. Boiling points and melting points
b. Solubility

For Boiling Points:
1. If weight is about equal → H-bonder > polar > nonpolar
2. If H-bonding/polarity is comparable: high mw > lower mw

Problem: Rank the boiling points, 1 being highest

1.   ⌃⌃OH   ⌃O⌃   ⌃⌃

2.   ⌃⌃   ⌃⌄⌃   ⌃⌄⌃⌃

3. H_3C–OH H_3C–$\overset{H_2}{C}$–OH

Intermolecluar Forces and their Impact on Solubility (4.6)

2 Practical Rules:
   • The more N's or O's in a molecular, the greater it's water solubility
   • The more C's, the lower it's water solubility

Facts/Theory
1. "Like dissolves like"
       a. enthalpy and entropy factors

Good solubility	Bad solubility
a. Polar solvent-polar solute	a. Polar solvent-nonpolar solute
b. Nonpolar solvent-nonpolar solute	b. Nonpolar solvent-polar solute

2. Water is very polar

3. Any molecules with N or O can H-bond with water (even if it can't necessarily H-bond itself) (Rule 1)
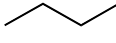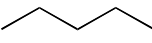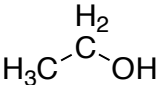
4. Adding C's adds C-C, C-H nonpolar bonds → reduces water solubility (Rule 2)

5. Hydrocarbons and halocarbons are insoluble in water
   • Many other organics have low solubility in water
   • Depends on the ratio of nonpolar/polar, N or O to C

Problems: Circle the more water soluble of the following pairs:

1.

2.

3.
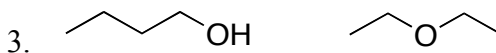
Problem: Box the higher boiling in each pair. Does water solubility and boiling point always correspond? Why or why not?

Classification of Organic Compounds. The Functional Groups (Sections 4.1)
Hydrocarbons: C + H only
0. Alkanes and Cycloalkanes
   a. Single bonds only
   b. Names end "ane" (methane, ethane, propane, etc.)
   c. "cycloalkanes": carbon rings
   d. alkanes are considered "nonfunctional"
      • no reactive π-bonds, lone pairs, heteroatoms, or highly polar bonds
   e. an "**alkyl group**" is <u>part</u> of a molecule that contains only C, H, and single bonds. (2.13)
      • Basically a part of the molecule that isn't going to be very reactive or "functional"
      • Symbol: R

1. Alkenes C=C
   a. contain C=C double bond
   b. names end "ene" (ethane, propene, butene, etc.)
   c. **double bonds can't rotate**
      • rotation is allowed for single bonds, but is forbidden for double bonds
      • Why:
      a. a single bond (σ) can rotate freely without compromising orbital overlap
      b. But a π-bond cannot rotate freely, because π-overlap breaks
      • The two π-bonded atoms have parallel and overlapping p orbitals. To rotate the bond completely breaks the π-bond half-way through the rotation.
      • The energy price is thus way too high.
   d. Restricted rotation results (sometimes) in cis/trans isomers

   e. A π-bond is much weaker than a s-bond, and thus is far more reactive. Thus, an alkene is viewed as a "functional group" because it reacts ("functions")
   f. Functional groups and "R" groups:

2. Alkynes: Triple bonds   Name end "yne"

3. Aromatics or Arenes: Resonance

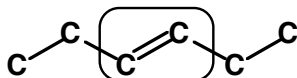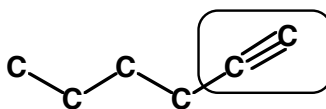# Twelve To Remember: The Functional Groups
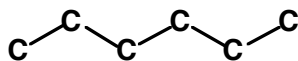
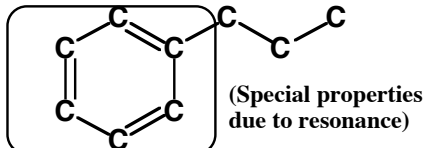**0. Alkane**
-all single bonds
-no heteroatoms

1. Alkene
-C=C double bond

2. Alkyne
-triple bond

Tip: A-E-I
so alkane, alkene, alkyne

3. Arene
-alternating double bonds
in a 6-carbon ring

(Special properties
due to resonance)

Br (Cl, I, F)
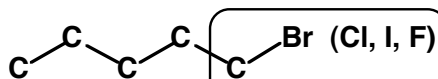
4. Haloalkane
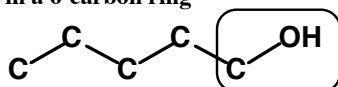
5. Alcohol
-oxygen
-OH
-single bonds
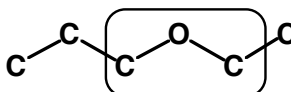
6. Ether
-oxygen
-no OH
-single bonds

Alcohols and Ethers Can be
Seen as H_2O Derivatives:
Oxygen Molecules With
Single Bonds Only
Tip: A before E
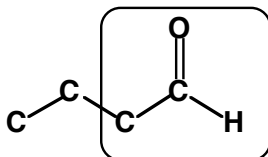
7. Aldehyde
-oxygen
-C=O double bond
-one H connected to C=O
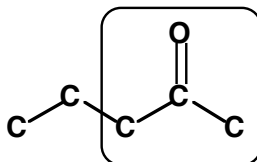
8. Ketone
-oxygen
-C=O double bond
-two C's connected to C=O

Aldehydes and Ketones
Have C=O (Carbonyl)
Double Bonds
Tip: A before kEy;
Aldehyde has less C's
attached to C=O
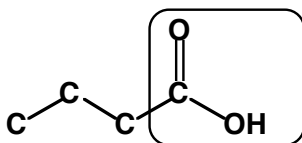
9. (Carboxylic) Acid
-2 oxygens
-C=O double bond, with
 O-H directly attached
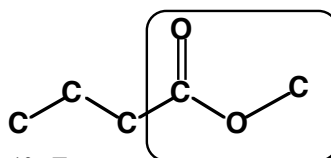
10. Ester
-2 oxygens
-C=O double bond, with
 O-C directly attached

A(cid) before E(ster)
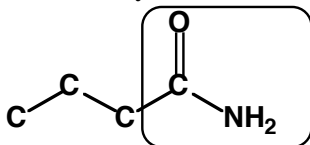
11. Amide
-one nitrogen, one C=O
-C=O double bond, with
N directly attached
-"D" for C=O double bond
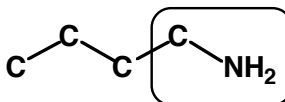
12. Amine
-one nitrogen, no C=O
-"N" for No C=O double bond

N compounds

4. Haloalkanes   R-X
  • bonds are polarized: R group is δ+, halogen is δ-
  • C-X bonds are often rather weak and breakable = "functional"

Oxygen Compounds
5. Alcohols   ROH

  a. contain OH group attached to an sp3 carbon
  b. names end "ol" (methanol, ethanol, etc.)
  c. Oxygen hybridization and shape:
      • sp3, tetrahedral electron geometry, approximately 109° bond angle
  d. Hydrogen-bonding: impacts boiling point and water solubility

6. Ethers   ROR

  a. Oxygen hybridization and shape:
      • sp3, tetrahedral electron geometry, approximately 109° bond angle
  e. Don't hydrogen-bond themselves, so lower boiling than ROH of equal weight.
  f. Oxygen lone pairs do hydrogen-bond to water hydrogens, so decent water solubility
  g. Relatively low reactivity

7,8. Aldehydes, Ketones   C=O
Aldehydes   Ketones

  a. C=O group = "carbonyl group"
  b. Carbonyl carbon: sp2, trigonal planar, 120° bond angles
 c. The carbonyl always has two other attachments, of which:
      • Formaldehyde has 2 H's attached to carbonyl
      • Aldehydes have one H attached to carbonyl
      • Ketones have no H's attached to carbonyl.
  d. Carbonyl bond is strongly polarized
      • Highly reactive
      • Highly electrophilic

9. Carboxylic Acids:

- **<u>Resonance stabilization of conjugate anions make these fairly acidic.</u>**
- Extremely important role in biological pH and biochemistry

10. Esters

- reactivity is similar to aldehydes and ketones, dominated by carbonyl
- Smell great!

Nitrogen Compounds
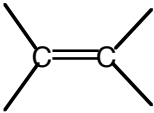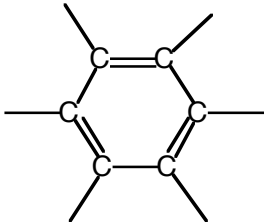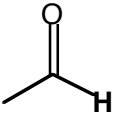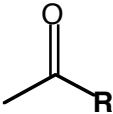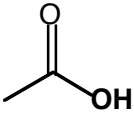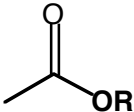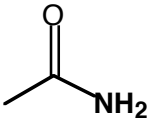
11. Amines

    a. polar
    b. usually hydrogen bonders
    c. Nitrogen lone pairs are basic (primary chemical and biological role)
    d. Many drugs are amines

12. Amides

    a. polar
    b. proteins and enzymes consist of multiple amides
    c. nitrogen is flat, sp^2, trigonal planar, thanks to resonance
    d. Nitrogen lone pair is not basic

The Functional Groups, R-Z

Functional Group Z	Name	Suffix (or Prefix) Used in Systematic Name	Nomenclature Review
-R	Alkane	-ane	methan- 1C
			ethan- 2C
	Alkene	-ene	propan- 3C
			butan- 4C
			pentan- 5C
			hexan- 6C
	Alkyne	-yne	heptan- 7C
			octan- 8C
			nonan- 9C
			decan- 10C
	Arene	not responsible	
-X (Cl, Br, I, or F)	Haloalkane	halo-	
-OH	Alcohol	-ol	
-OR	Ether	not responsible	
	Aldehyde	-al	
	Ketone	-one	
	Carboxylic Acid	-oic acid	
	Ester	-oate	
	Amide	-amide	
-NH$_2$	Amine	amino-	

ALKANE NAMES, Formulas, Properties (Memorize) (Sections 2.5-14)

# C's	Name	Formula	Bp (ºC)	Structure
1	**Methane**	CH_4	-162	$H\text{-}(CH_2)\text{-}H$
2	**Ethane**	C_2H_6	-89	$H\text{-}(CH_2)_2\text{-}H$
3	**Propane**	C_3H_8	-42	$H\text{-}(CH_2)_3\text{-}H$
4	**Butane**	C_4H_{10}	0	$H\text{-}(CH_2)_4\text{-}H$
5	Pentane	C_5H_{12}	36	$H\text{-}(CH_2)_5\text{-}H$
6	Hexane	C_6H_{14}	69	$H\text{-}(CH_2)_6\text{-}H$
7	Heptane	C_7H_{16}	98	$H\text{-}(CH_2)_7\text{-}H$
8	Octane	C_8H_{18}	126	$H\text{-}(CH_2)_8\text{-}H$
9	Nonane	C_9H_{20}	151	$H\text{-}(CH_2)_9\text{-}H$
10	Octane	$C_{10}H_{22}$	174	$H\text{-}(CH_2)_{10}\text{-}H$

Highlights: (Including some alkane properties)

1. Memorize names
2. Names all end in "ane"
3. From 5 up, come from Greek
4. Boiling points: more C's → high boiling point (London force)
5. Formula: for **acyclic alkanes → C_NH_{2N+2}**
6. Formula: for **cyclic alkanes → C_NH_{2N}**

Solubility: nonpolar
    1. → insoluble in water
    2. → soluble in nonpolar, hydrophobic solvents
    3. Density: < 1 (less than water)
    1. → float on top of water

Formula Notes:
-   Basically 2H per carbon
-   Thus for a **monocyclic alkane** there are exactly twice as many H's as C's = C_NH_{2N} (where N equals the **N**umber of carbons)
-   For an **acyclic alkane** there are two extra H's on the end carbons → C_NH_{2N+2}
-   Branching does not change the C_NH_{2N} = monocyclic and C_NH_{2N+2} = acyclic alkane rules.

Industrial Alkanes (2.16, For interest, not for test)

Name	# C's	Boiling Range	Use
Natural Gas	C_1-C_3 (70% methane)	Gas	Fuel
"Petroleum Gas"	C_2-C_4	<30º	Heating, Gas
Propane	C_3	-42º	Propane tanks, camping, etc.
Gasoline	C_4-C_9	30-180º	Car fuel
Kerosene	C_8-C_{16}	160-230º	Jet fuel
Diesel	C_{10}-C_{18}	200-320º	Truck fuel
Heavy Oils	C_{16}-C_{30}	300-450º	
Motor Oils		High temp	
Paraffin		Vacuum	
Asphalt		Never Distills	
Coke		Never Distills	

Nomenclature of Alkanes (Sections 2.11-14)

Systematic IUPAC Rules for Branched and Substituted Alkanes

1. Longest continuous C-chain → "core name"
2. Number core chain from an end nearest a substituent
3. Name substituents as "alk<u>yl</u>" groups:
4. Specify the location of substituents using numbers (hyphenate the #'s)
    1. If >2 substituents, list alphabetically
    2. Use di-, tri-, tetra- if the same substituent is repeated. (But ignore these in alphabetizing).

Punctuation Notes:
- Hyphenate numbers
- Do <u>not</u> put a space between substituents and the core name

Special Names for Some 3 or 4-carbon Substituents

Memorize	H_3C $\quad$CH— H_3C Isopropyl	CH_3 $H_3C-C—$ $\quad CH_3$ t-butyl or tert-butyl		
Others	H_3C C C $\quad H_2$ H_2 n-propyl (n for "normal")	H_3C C C C $\quad H_2$ H_2 n-butyl	CH_3 $\quad CH$ C H_3C H_2 isobutyl	H_3C C CH CH_3 $\quad H_2$ s-butyl

Another Classification System

Primary (1º): with one attached carbon
Secondary (2º): with two attached carbons
Tertiary (3º): with three attached carbons
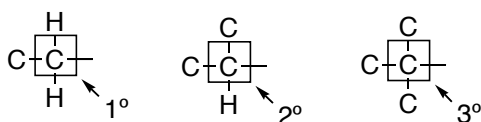
Very Complex Substituents (Not responsible)
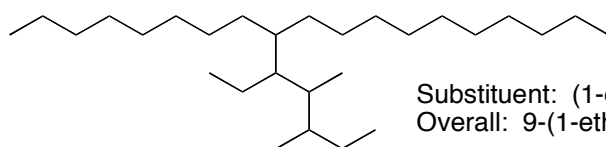
Substituent: (1-ethyl-2,3-dimethylpentyl)
Overall: 9-(1-ethyl-2,3-dimethylpentyl)nonadecane

Nomenclature Example Problems

1.

2.

3.

4.

5.

6.

7.

8.
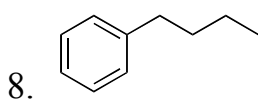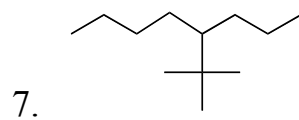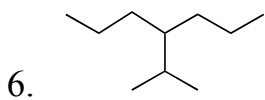
Structure, Conformations of Acyclic Alkanes (3.1)

A. "Conformations" = "Conformers" = "Rotamers" = different 3-D arrangements resulting from rotation around a single bond
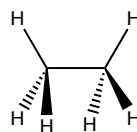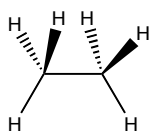
Normal zig-zag   "sawhorse"   "Newman Projection"
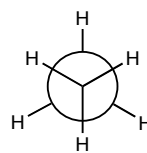
B. "Newman Projections": look straight down one C-C bond
   1. If both bonded carbons are tetrahedral, there will be three bonds extending from the front carbon, and three more bonds extending from the back carbon
   2. Terms:
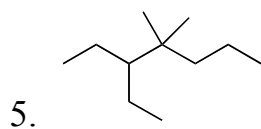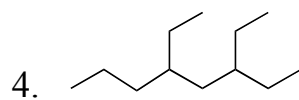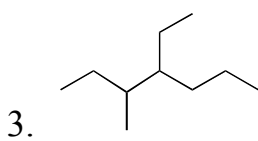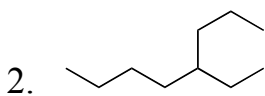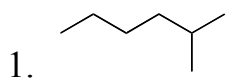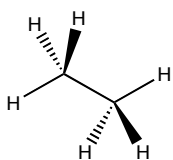   1. **Dihedral angle**: angle between a bond on the front atom relative to a bond on the back atom
      2. **Eclipsed**: when bonds are aligned. 0º, 120º, 240º, 360º dihedral angles
      3. **Staggered**: when bonds are as far apart as possible: 60º, 180º, 300º
      4. **Skew**: anything else in between the eclipsed and staggered extremes
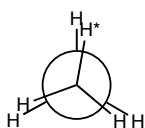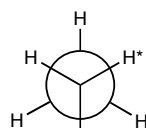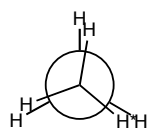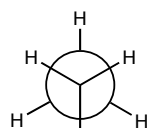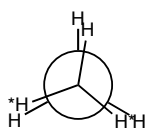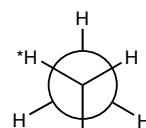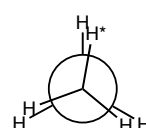
| 0º | 60º | 120º | 180º | 240º | 300º | 360º |
| eclipsed | staggered | eclipsed | staggered | eclipsed | staggered | eclipsed |

Energy: **Staggered best, eclipsed worst**
   1. Why: Torsional strain. **Repulsion between bonding electron pairs** is reduced in the staggered conformation, and is worst in the eclipsed conformation.

Rotation Barrier: energy gap between the best and worst conformation when you go through a full 360º rotation (as would take place in a full bond rotation)
   • Draw in Entergy diagram:
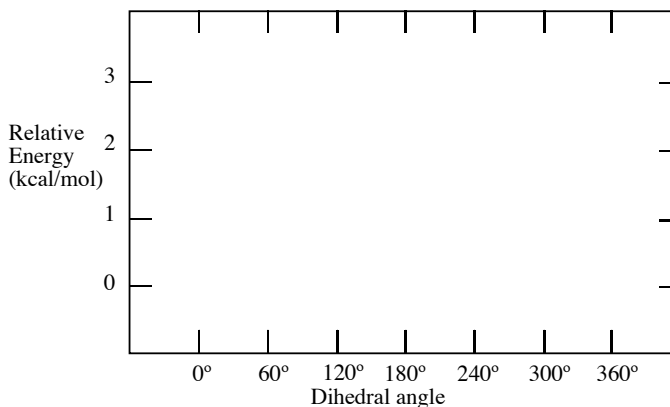
Conformations of Butane and Longer Alkanes (3.2,3)
$CH_3CH_2-CH_2CH_3$ is more complex. Focus down C2-C3 bond.

0°	60°	120°	180°	240°	300°	360°
eclipsed	staggered	eclipsed	staggered	eclipsed	staggered	eclipsed
Totally Eclipsed	**Gauche**	**Eclipsed**	**Anti**	**Eclipsed**	**Gauche**	**Totally Eclipsed**
6.0	0.9	3.6	0	3.6	0.9	6.0
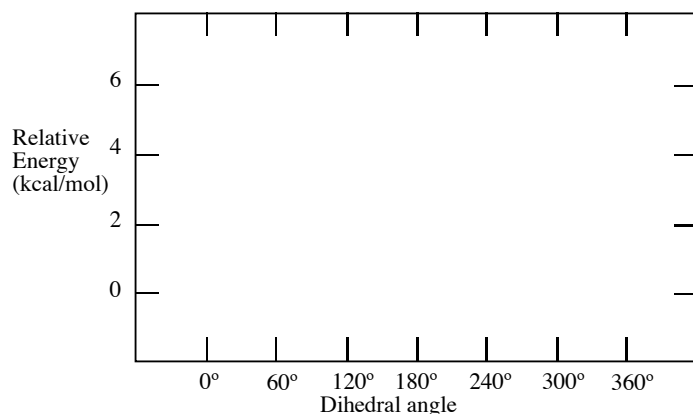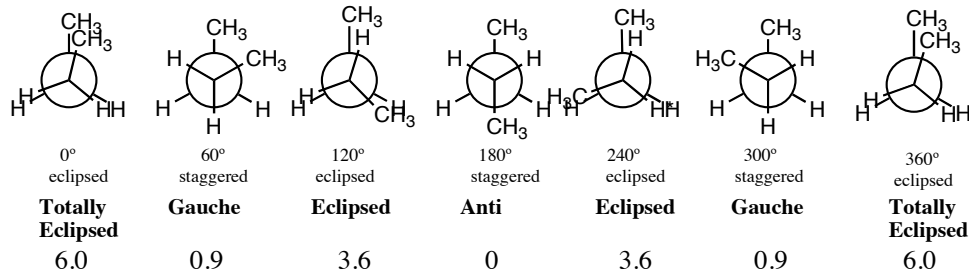
Questions
1. Draw the energy diagram

2. What would be the rotation barrier?

Strain Energy Factors:
1. **Torsional** strain (why all of the eclipsed type conformations are worse). Repulsion between bonded electrons
2. **Steric** strain: When atoms themselves get too close. Atom-atom repulsion.
3. **Angle** strain: When bond angles can't achieve ideal VSEPR angles. (No angle strain in ethane or butane)

Total Strain =	Torsional strain (are any bonds eclipsed?)
	+ Steric strain (are any atoms too close)
	+ Angle strain (are any bond angles forced to be other than ideal?)

Questions
1. In general, why are staggered better than eclipsed?

2. Why is eclipsed better than totally eclipsed?

3. Why is anti better than gauche?

4. Why is gauche better than eclipsed?

5. Why is anti better than totally eclipsed?

Summary
1. Anti < gauche < eclipsed < totally eclipsed
2. Steric and torsional reasons
3. The bulkier a substituent, the greater the steric strain in eclipsed and totally eclipsed
    conformations

Skills. Be Able to:
1. predict relative rotation barriers
2. write a conformational analysis (rotation/energy diagram)
3. draw Newman pictures for any bond in any structure
4. identify anti/gauche/eclipsed/totally eclipsed conformations

Steps to Drawing Newman Structure:
    1. Draw a circle (back carbon) with a dot in the middle
    2. Add three sticks extending from the periphery of the circle, with one of them straight up
    3. Add three sticks extending from the center dot (front carbon) to illustrate the bonds
        radiating from the front carbon
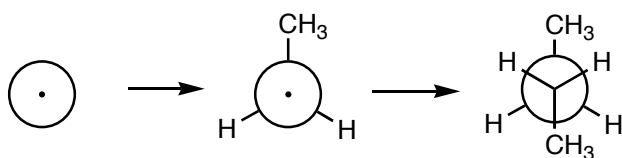
Problems
    1. Rank the rotation barriers for the following, relative to the indicated bonds
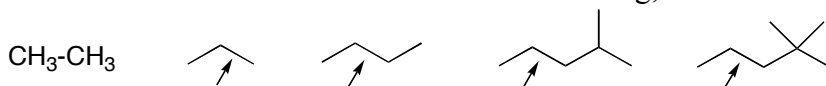
    2. Draw Newman projections for the best and worst conformations of the structure shown,

        relative to the indicated bond.   Use the 3rd carbon in the back.

Higher Alkanes
-for any alkane, anti conformations best = zig-zag layout

3.4-13 Cycloalkanes
Nomenclature (2.15): cyclopropane, cyclobutane, etc..

General formula: C_NH_{2N}
-this is also true for cycloalkanes with chain(s) attached

3.11 Substituted Cycloalkanes and cis/trans Isomers in Disubstituted Cycloalkanes
Nomenclature:
- Monosubstituted: alkylcycloalkane
- Disubstituted: cis- (or trans-)-x-alkyl-y-alkylcycloalkane
  - "Cis"-same side   "trans" – opposite sides
  - Number ring so as to minimize numbers

Ring Stability and Ring Strain (Section 3.4-3,7)

Ring Size	Total Ring Strain (kcal/mol)	Strain Per CH₂	Main Source Of Strain
3	28	9	Angle Strain
4	26	7	Angle Strain
5	7	1	Torsional Strain (eclipsing)
6	**0**	**0**	**-- STRAIN FREE**
7	6	1	Torsional Strain (eclipsing)
8	10	1	Torsional Strain (eclipsing)

Structural Isomer Problems
-   **Check formula first**. Is it an acyclic molecule (C_NH_{2N+2}), or not? (C_NH_{2N} could be a cyclic alkane, or perhaps an alkene …)
-   **Be systematic**.   Try the longest possible chain (or largest ring size) first, then systematically shorten it and find the branched isomers.
-   **Avoid duplicates**!
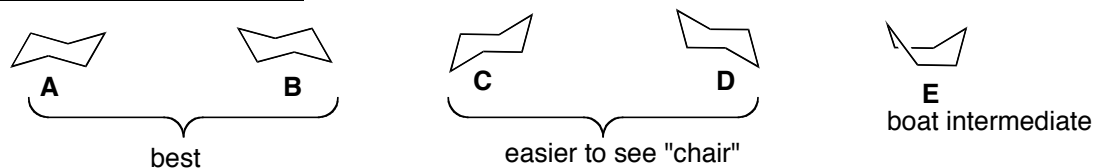o   Beware of things that look different but are really the same thing.

1. Draw all structural isomers of C_7H_{16}. (Be systematic; no duplicates!)

2. Draw all structural isomers of C_7H_{14}. (Be systematic; no duplicates!)

3.7-9 **Cyclohexane Chair Conformations**
 1. Cyclohexane has no angle strain or torsional strain
 2. Cyclohexane has perfect 109º angles with staggered, non-eclipsed C-C bonds
 3. Obviously it is not flat (natural angle for a flat cyclohexane would be 120º)

Chair Conformations:

A   **B**   **C**   **D**   **E**
                                                        boat intermediate
         best   easier to see "chair"

1. Chairs **A** and **B** are constantly interconverting via "boat" **E**
2. **A** and **B** are best to draw and work with.
3. But **C/D** make it easier to visualize why it's called a "chair": 4 carbons make the seat of the chair, one makes backrest, one a footrest.

Process for Drawing Both Chairs:

"Right-handed chair"

"Left-handed chair"
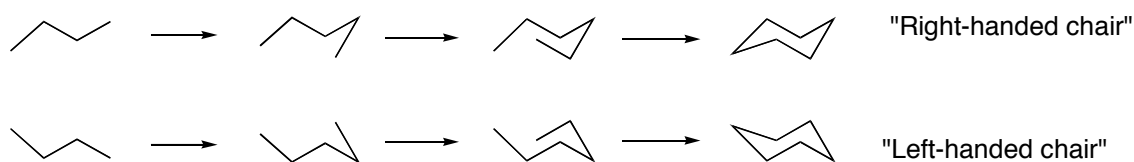
 1. Draw a 4-carbon zig-zag. It helps if your left-most carbon is a little lower than your 3rd carbon
 2. Add a 5th carbon and 6th carbon, but don't have them exactly underneath the 2nd and 3rd carbons.
 3. Connect the 6th carbon to the orginal 1st carbon
    • For a "left-handed chair", start up and zig-zag down.

"Axial" and "Equatorial" Positions for Substituents

axial: 3 vertical up   equatorial: 6 essentially   "uppers" and "downers"
        3 vertical down   horizontal
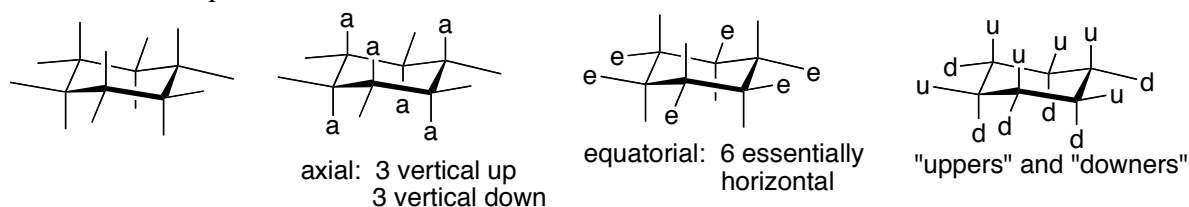
 1. Each carbon has one axial and one equatorial H's
 2. Always have six axial attachments
 3. 3 axials up (on alternating carbons)
 4. 3 axials down (on alternating carbons)

5. Always have six equatorial attachments
6. For processing cis/trans problems, it's helpful to recognize "upper" from "downer" positions
7. When a chair flips, what was equatorial becomes axial, and what was axial becomes equatorial

chair flip
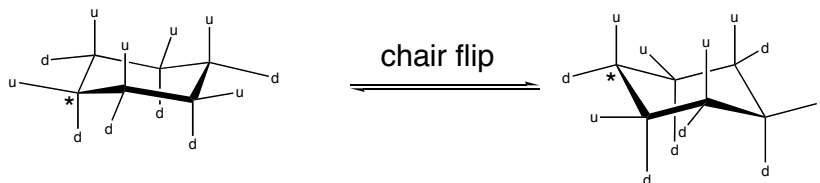
Drawing equatorial and axial bonds:
1. Make axial straight up or straight down (3 each)
2. Make equatorial bond lines almost exactly horizontal
3. Equatorials are easiest to draw on left and right-most carbons

Drawing Mono- and DiSubstituted Cyclohexanes (Sections 3-10,12)
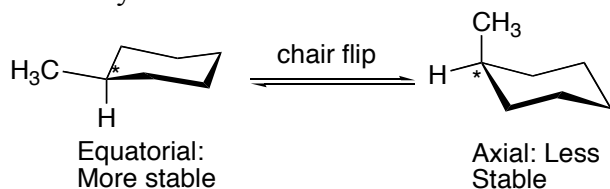- Always attach the first substituent onto the leftmost carbon (easiest to draw)

chair flip

Equatorial:
More stable

Axial: Less
Stable

- Draw in the H on any substituted carbon, but skip on H-only carbons
- **Equatorial is better than axial for steric reasons**. In the axial configuration, the substituent has destabilizing steric interactions
  - o   2 extra gauche interactions, and 1,3-diaxial interactions
- For disubstituted chairs, let the cis/trans relationship guide whether the second substituent should be in an "upper" or "lower" position relative to the original substituent.
- If one substituent is bigger than the other, the most stable chair will always have the larger substituent equatorial

Cis and Trans Disubstituted Cyclohexanes

Questions:
1. Draw both chair forms for cis-1-isopropyl-2-methylcyclohexane.
2. Which is the best chair for cis-1-isopropyl-2-methylcyclohexane?
3. Draw both chair forms and identify the best chair for trans-1-isopropyl-2-methylcyclohexane.
4. Which is more stable, cis- or trans-1-isopropyl-2-methylcyclohexane?
5. Then answer the same questions for the 1,3- and 1,4- isomers.

1,2-DiSubbed
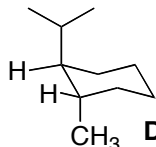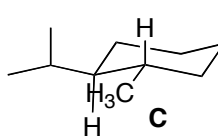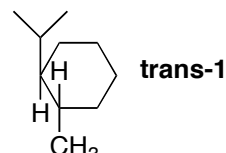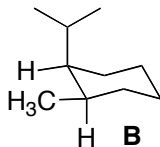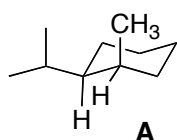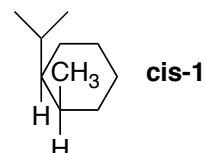
1,3-DiSubbed
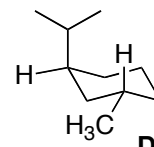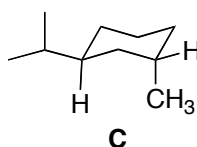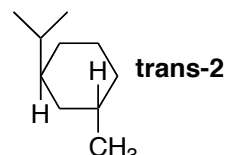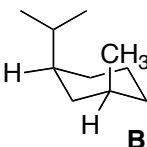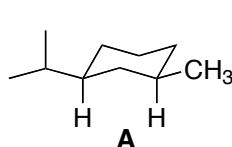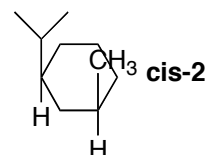
1,4-DiSubbed
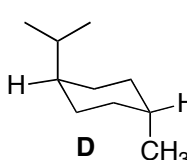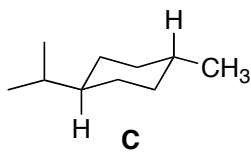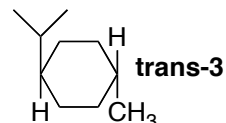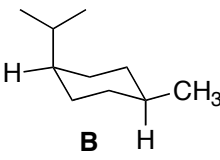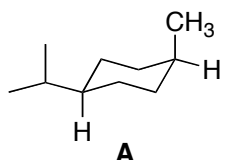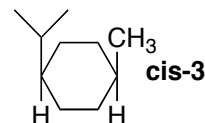
Ch. 4 Alkane Halogenation and The General Study of Chemical Reactions

Three Factors in Every Reaction:

1. Mechanism: what is the step-by-step pathway by which old bonds break and new bonds form?
2. Thermodynamics: what are the energy changes, both for the overall reaction and for individual steps in the reaction mechanism?
3. Kinetics: How fast does a reaction occur? How do changes in reactant structure, reaction solvent, or reaction temperature speed up or slow down a reaction?

4.15-18 The Chlorination of Methane: A Case Study

$CH_4 + Cl_2$ $\xrightarrow[\text{or } \Delta \text{ (heat)}]{\text{hv (photon)}}$ $\boxed{\begin{array}{c} CH_3Cl + HCl \\ \textbf{A} \end{array}}$ + $\underbrace{CH_2Cl_2 + CHCl_3 + CCl_4}_{\substack{\textbf{B} \qquad \textbf{C} \qquad \textbf{D}}}$

Polysubstituted Products
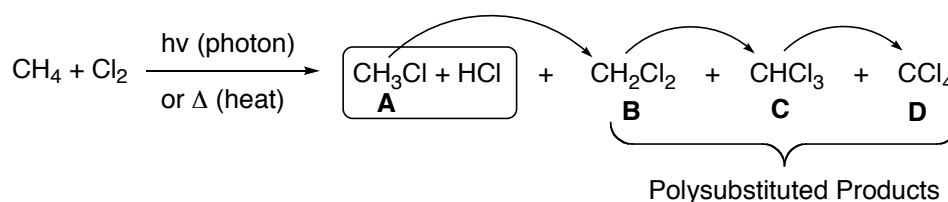
Observations
-usually a mixture of products forms, including not only mono-chlorinated product **A**, but also polychlorinated products **B-D**.

1. Light (or heat) is required to initiate the reaction (energy required)
2. Blue light, absorbed by Cl2, is most effective
3. High "quantum yield": one photon can result in conversion of thousands of methane reactant molecules into product molecules
   o Q: if light energy is needed, why isn't one photon needed for each reaction?

ANY MECHANISM MUST BE CONSISTENT WITH EXPERIMENTAL OBSERVATIONS

4.18 The Mechanism: Radical Chain Reaction

Balanced Reaction: $CH_4 + Cl_2 \xrightarrow{\text{hv}} CH_3Cl + HCl$
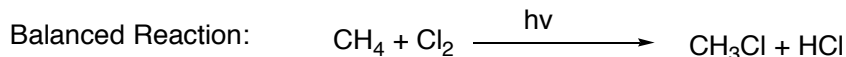
The mechanism must show all bonds broken and made:

| Bonds Broken | Bonds Made |
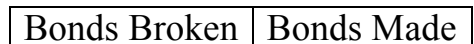
3 Phases in Mechanism
 1. Initiation (gets it started)
 2. Propagation (keeps on going and going and going)
 3. Termination (what happens when it sometimes stops)

Initiation

$Cl-Cl \xrightarrow{\text{hv}} :\overset{..}{\underset{..}{Cl}}\cdot + \cdot \overset{..}{\underset{..}{Cl}}:$ (2 Cl•)   "radical" something with an unpaired electron
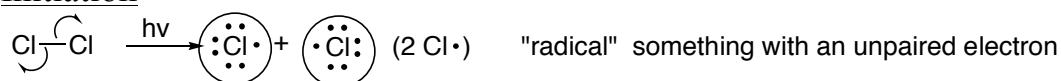
• In a radical initiation step, two reactive radicals form from a nonradical precursor

PROPAGATION

Propagation

Step 1 $Cl\cdot$ $H-CH_3$ ⟶ $\cdot CH_3$ + $H-Cl$

Step 2 $Cl-Cl$ $\cdot CH_3$ ⟶ $\cdot Cl$ + $Cl-CH_3$
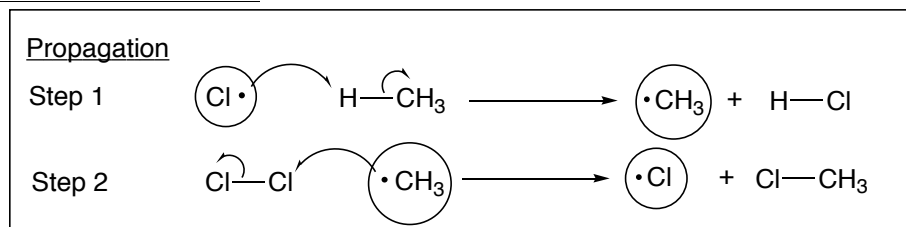
1. In each propagation step, one reactive radical reacts with a nonradical to produce a new
    reactive radical and a new nonradical.
2. Since a reactive radical is reproduced in each step, you always have another reactive
    radical ready to keep the chain going.
3. The chlorine radical produced in step two acts as reactant in step 1.
4. Thus you can sustain a repeating chain of step 1- step 2 -step 1- step 2 - step 1- step 2 -
    step 1- step 2 - step 1- step 2 - step 1- step 2 - etc.
    • As long as there is a radical around, the chain will keep going/propagating
5. The sum of the two propagation steps is the overall balanced reaction

Termination

$:\overset{..}{\underset{..}{Cl}}\cdot + \cdot\overset{..}{\underset{..}{Cl}}: \longrightarrow Cl-Cl$

or $:\overset{..}{\underset{..}{Cl}}\cdot + \cdot CH_3 \longrightarrow Cl-CH_3$

or $H_3C\cdot + \cdot CH_3 \longrightarrow H_3C-CH_3$
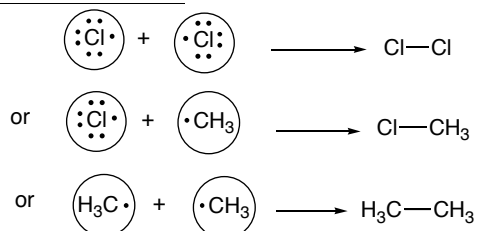
Mechanism Notes:
1. "**Radical**" = Something with an unpaired electron.
   • Radicals never satisfy octet rule→ highly unstable and highly reactive.

2. Initiation is needed to initially generate radicals. But once you've got some, radicals subsequently reproduce so that initiation isn't required any more.

3. **The main action is the propagation phase. Memorize how that works.**

4. The propagation phase involves a repeating chain of events (step 1 – step 2 – step 1 – step 2 etc.) that continuously regenerate radicals and continuously convert reactants to products. **"Chain reaction"**

5. The overall reaction is the sum of the two propagation steps. Notice that the methyl and chlorine radicals cancels themselves out, but the products and reactants don't.
   • The carbon radical produced in step one is consumed in step 2
   • The chlorine radical produced in step two is consumed in step 1
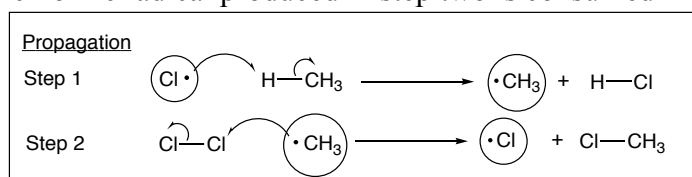
6. Like initiation, termination occurs only occasionally. This is in part because the concentration of radicals is really small, so it's improbable that they will collide.
   • If you have two radicals and a mole of methane and chlorine, is a radical more likely to collide with another radical or a neutral?

7. Notice:
   • Initiation: one nonradical in → two radicals out
   • **Each Propagation Step: radical + nonradical → nonradical + radical**
   • Any Termination Step: radical + radical → one nonradical

Free Energy, Enthalpy, Entropy (Gen Chem Review…) (p 118, 6.10)
$$\Delta G = \Delta H - T\Delta S$$

   ΔG: Free Energy: favorable reactions have negative ΔG
   ΔH: Enthalpy: heat lost or gained
      • $\Delta H < 0$ exothermic $\Delta H > 0$ endothermic
   ΔS: Entropy: degree of randomness, disorder

   In organic, enthalpy almost always dominates
   **Exothermic → Favorable   Endothermic → Unfavorable**

   If you can figure out whether a reaction will be exothermic or not, you can tell whether it is energetically favorable or not.
      • But, being energetically favorable still doesn't prove it will happen very fast…
        That's the kinetics issue, see later…

4.17 Bond Energies, Bond Breaking, and Radical Stability

- **Exothermic reactions break weaker bonds and form stronger bonds**
- Exothermic steps (in a multistep reaction) also trade weaker for stronger
- Extensive tables of bond energies are available (Table 4.3) for when bonds break in half (to give two radicals)
- Often relative bond energies can be predicted by inspection

Bond Strength	Bond Energy (kcal/mol)	Molecule	Products	Radical Stability
		H—F →		
		H—Cl →		
		H—Br →		
		H—I →		
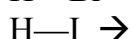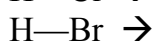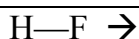
Skills:
1. Given bond energies, be able to rank bond strengths
2. Given bond energies, be able to rank radical stabilities
3. Given known radical stabilities, be able to predict relative bond strengths
4. **Memorize the stability pattern for the halogen radicals**
5. **Memorize the bond strength pattern for H-X bonds**
6. **Memorize: C-X bonds have the same pattern: iodide is the weakest**

H_3C—F	H_3C—Cl	H_3C—Br	H_3C—I
109	84	70	56

- Just as acidity reflects <u>anion</u> stability, bond energy values reflect <u>radical stability</u>

Why are H-F and C-F bonds stronger than H-I and C-I bonds?
1. **Electronegativity and radical stability: (Remember)**
   a. Radicals are short of octet rule → electron poor
   b. The more electronegative fluorine is least willing to be electron poor. As you go down the table, electronegativity decreases and it's less problematic to become radical

2. Atomic size and orbital overlap:
   - Fluorine is small, and it's orbitals match up well size-wise with H and C resulting in strong overlap and strong bonds.
   - Iodine is big, so it's orbitals don't match up well or overlap so well with H or C resulting in weak bonds.

Problems:

1. H_3C—SeH bonds are weaker than H_3C—OH bonds. Which is more stable, •SeH or •OH?

2. Which is stronger, CH3CH2—Cl or CH3CH2—Br?

3. Problem: Rank the probable stability of the following radicals, 1 being most stable and 4 being least stable? (Use electronegativity to guide you…)

$H_3C•$ $H_2N•$ HO•   F•

Two Types of Bond Breaking and Mechanistic Arrow Pushing (4.17):

Heterolysis: one atom keeps both electrons (usual case)
a. Ions are involved
b. Arrow-pushing involves double-barbed arrows (⤳)

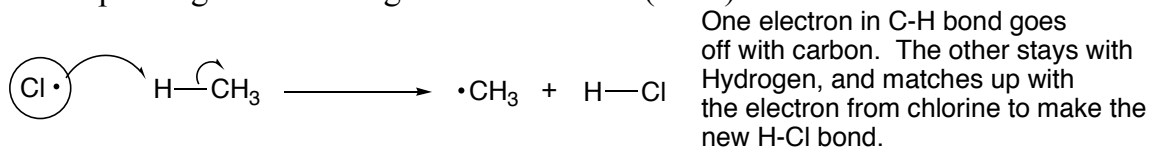$H_2O:$ H—$\ddot{C}l$: ⟶ $H_3O:^{\oplus}$ + :$\ddot{C}l$:$^{\ominus}$ Both electrons in the
                                                                                 H-Cl bond went with the chlorine
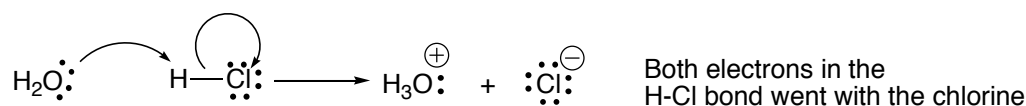
Homolysis: Bond breaks in half so that an electron goes with each atom (rare, but that's the type in this chapter)
   1. Radicals are involved
   2. Arrow-pushing involves single-barbed arrows (⌒)

Cl•   H—CH$_3$ ⟶ •CH$_3$ + H—Cl

One electron in C-H bond goes off with carbon. The other stays with Hydrogen, and matches up with the electron from chlorine to make the new H-Cl bond.

Using Bond Energies to Calculate Energy Changes (4.17)

ΔH = (bond energies of bonds broken) - (bond energies of bonds formed)

$$H{-}CH_3 \ + \ Cl{-}Cl \xrightarrow{\ h\nu\ } Cl{-}CH_3 \ + \ H{-}Cl$$

104	58		84	103

The weak bond whose replacement drives the reaction
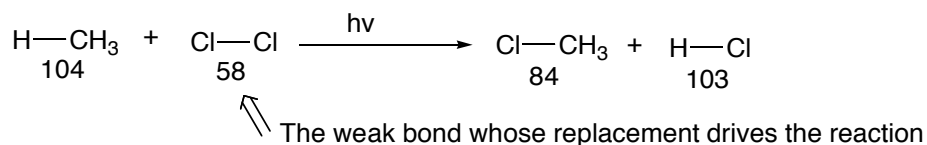
Q1: What is ΔH:

Q2: Is the overall reaction energetically favorable?
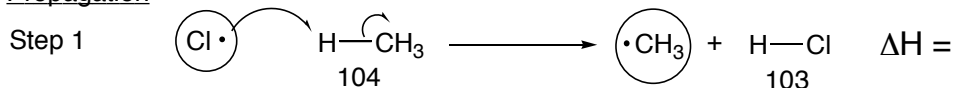
Notes:
1. Compare the energies of the bonds broken versus the bonds made
2. For an energetically **favorable** process, **weaker bonds are replaced by stronger bonds**
3. With known bond energies, you can quantitatively calculate ΔH
4. Even without bond energy numbers, a qualitative sense of bond strengths enables evaluation of whether or not a reaction makes sense energetically
5. This type of analysis can be applied both to overall reactions, but also for individual steps in a multi-step reaction.

Propagation

Step 1   Cl·   H—CH₃ ⟶ ·CH₃ + H—Cl   ΔH =
                   104   103

Step 2   Cl—Cl   ·CH₃ ⟶ ·Cl + Cl—CH₃   ΔH =
             58   84

Q1: Which step is better?

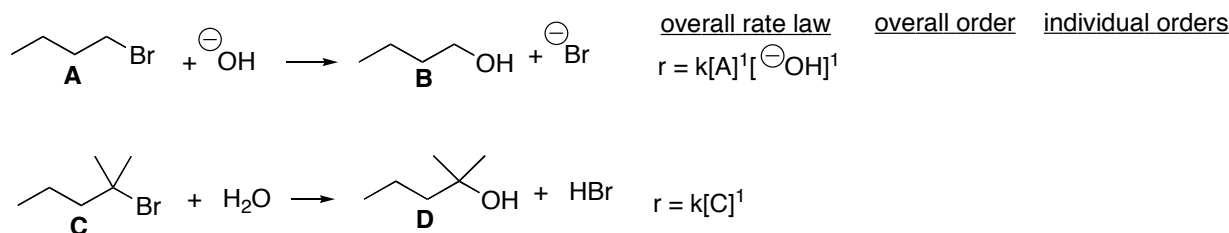Q2: Which step is likely to be the rate-limiting step?

Q3: Note: Can you see what initiation would cost, and why a good chunk of energy is required to make it happen?

Kinetics, Reaction Rates, and Rate Laws (Gen Chem Review, see section 4.9,13)
1. Lots of reactions with seemingly favorable ΔH energetics don't happen very fast or at all
2. We're often really interested in reaction speed ("kinetics"). Not so simple!
3. Rate Law: relationship between reactant concentrations and overall rate

General rate law: rate = k[A]^x[B]^y
1. k is rate constant: each reaction has it's own unique rate constant.
2. We will often be able to make qualitative predictions based on structural factors
3. "x" and "y" are the "orders" of reactants A and B
4. the "overall order" of a reaction = x + y
5. Shown below are key S$_N$2 and S$_N$1substitution reactions from chapter 8

	overall rate law	overall order	individual orders

A Br $+$ $^{\ominus}OH$ $\longrightarrow$ B OH $+$ $^{\ominus}Br$ $r = k[A]^1[^{\ominus}OH]^1$

C Br $+$ H_2O $\longrightarrow$ D OH $+$ HBr $r = k[C]^1$

Notes
  a. Different rate laws reflect different mechanisms
  b. Reactants that do not appear in a rate law do not appear in the mechanism until after the rate determining step
  c. The "k" values for the two reactions are **not** the same.
  d. Concentrations matter, for reactants that appear in the rate law
  e. Concentrations reflect not only how many moles of reactant are available, but also the amount of solvent.

Solvent impact: Rates are impacted not only by the amount of reactants but also by the amount of solvent. When you dilute a reactant, the reaction slows due to reduced collision frequency. The impact depends on the rate law and overall order.

Q1: If you use the same number of moles of reactants in reaction one above involving bromobutane **A** above, but you triple the volume of solvent, how much will the rate change?

Q2: If you triple the volume of solvent for reaction two involving 2-bromo-2-methylpentance **C**, again without changing the number of moles of reactants, how much will the rate change?

Activation Energies and Dependence of Rates on Temp (Gen Chem Review)
- So, if every reaction has it's own rate law and it's own k value, what influences the "k" value?
- Arrhenius Equation: $k = Ae^{-Ea/RT}$
  - o A is a constant
  - o **E_a or E_{act} is the "activation energy"**
  - o R is the ideal gas constant
  - o **T is the temperature**

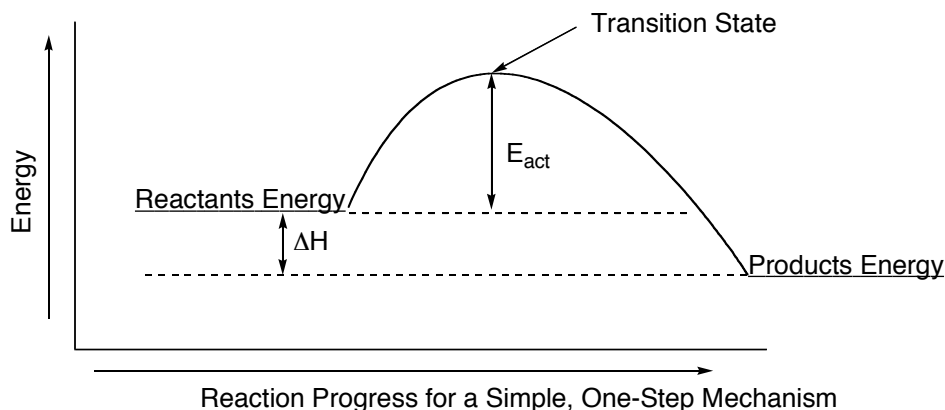Practical Stuff. k-values (and thus rates) are impacted by:

---

1. Temperature:
  - a. Higher temp → higher k → faster reaction
  - b. Lower temp → smaller k → slower reaction
  - c. Crude guide: for every 10° rise in temp, the k value and reaction rate will double for an ordinary reaction. (This is super, super, super crude, though…)

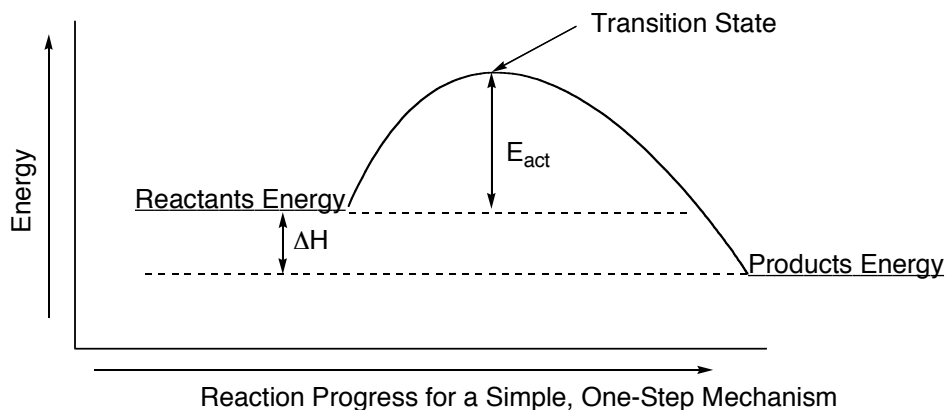2. Activation Energy or Energy of Activation or Activation Barrier, E_{act}
  - a. It's the minimum energy required to cross the energy barrier between reactants and products
  - b. **The height of the barrier influences reaction speed.**
  - c. Activation barriers explain why many exothermic, energy-favorable reactions don't actually occur at room temperature
  - d. Temperature reflects the average kinetic energy of the molecules; but some are always above average.
    - a. An increase in temperature can strongly increase the reaction rate because a small temperature increase can substantially increase the population of molecules with E_{act}


Reaction Progress for a Simple, One-Step Mechanism

Transition States

Reaction Progress for a Simple, One-Step Mechanism

*   The transition state is the **highest, worst energy spot** on the road from reactants to products

---

**Since rates are affected by E_{act}, and E_{act}'s are determined by Transition States, →
Transition states influence reactions rates.**
*   Lower transition state → faster reaction
*   Higher transition state → slower reaction

---

*   Why are T-states usually higher in energy than either products or reactants? And why do reaction with very favorable ΔH often have fairly high T-states?
    o   Because one full bond is better than two partial bonds. At the T-state, you are routinely at the transition between a breaking bond and a forming bond.
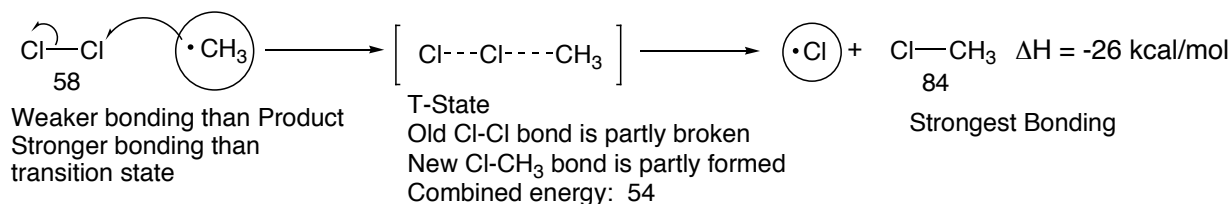
Three Stability/Reactivity Principles
1. **Transition-State Stability/Reactivity Principle**: The more stable the transition state, the faster the reaction will be.
2. **Reactant Stability/Reactivity Principle: The more stable the reactant, the slower it reacts**
    *   A more stable reactant has lower starting energy. Therefore it has a larger E_{act} to get over the transition state.
    *   A less stable reactant has a higher starting energy, is closer to the T-state, and thus has a smaller energy barrier to cross.
3. **Product Stability/Reactivity Principle: The more stable the product, the faster it forms.**
    *   A more stable product has lower energy. Often the T-state is stabilized/lowered by the same structural factors that stabilize the products.

Rates of Multistep Reactions (more Gen Chem Review)

Reaction Progress for a Simple, Two-Step Mechanism
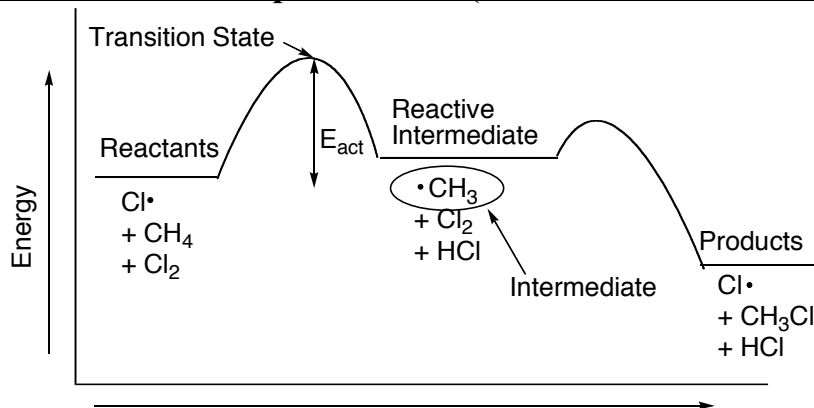
1. Most reactions involve 2 or more steps with one or more "intermediates" (•CH$_3$ for example)
   o An "**intermediate**" is something that forms temporarily, but then rapidly converts into something else. Normally the intermediate is highly reactive, has a short lifetime, and never builds up.
   o There is only one transition state for the overall process, no matter how many steps
   o The **transition state** for the overall reaction is still the **highest, worst energy spot** on the road from reactants to products
   o The step that goes through the transition state will be the **slowest step** and is referred to as **the rate-determining step** or the **slow step**.

Practical: To handle rates, identify and focus on the slowest step!!!

Practical Identification: The rate determining step is **always** the step leading to the least stable intermediate. (ex: •CH$_3$ is less stable than •Cl)
• Therefore the ability to recognize stability patterns for reactive intermediate radicals, cations, and anions is super useful

---

2. The Crucial Link Between "Slow Step" Identification and Application of Stability/Reactivity Principles
   • In a multistep reaction, **the reactants and products that matter kinetically are the reactants and products of the slow step**. Which are often reactive intermediates.
   • To apply the **Product Stability/Reactivity Principle**, (which says that <u>more stable the product</u>, the <u>faster the reaction</u>), you need to:
      o Know the mechanism. (What is the rate determining step? And what kind of reactive intermediate is produced in that rate-determining step?)
      o Know how structural factors impact the relative stabilities of reactive intermediates. (For example, is a 3° radical better or worse than a 1° radical?)
   • To apply the **Reactant Stability/Reactivity Principle**, (which says that <u>more stable the reactant</u>, the <u>slower the reaction</u>), you need to:
      o Know the mechanism. (What is the rate determining step?)
      o Know how structural factors impact the relative stabilities of a reactive intermediates. (For example, is Cl• more or less stable than Br•?)

Dependence of Halogenation Rates on Halogen (4.19)

General reaction: $CH_4 + X_2 \rightarrow CH_3X + HX$

Rate determining step: $CH_4 + \cdot X \rightarrow \cdot CH_3 + HX$

	Halogen	Rate Determining Step	E_{act} (kcal/mol)	•X Stability	•X Reactivity
Useless	F_2	$CH_4 + \cdot F \rightarrow \cdot CH_3 + HF$	1		
Useful	**Cl_2**	$CH_4 + \cdot Cl \rightarrow \cdot CH_3 + HCl$	4		
Most Useful	**Br_2**	$CH_4 + \cdot Br \rightarrow \cdot CH_3 + HBr$	18		
Useless	I_2	$CH_4 + \cdot I \rightarrow \cdot CH_3 + HI$	34		

- Iodine is not reactive enough; fluorine is actually too dangerous to use

Applying the Reactant Stability/Reactivity Principle: The <u>more stable the reactant</u>, the <u>slower</u> it will react.
- Since the halogen radicals are reactants in the rate determining step, and since fluorine radical is least stable and iodine radical is most stable => reactivity is F• > Cl• > Br• > I• , and => reactivity is $F_2 > Cl_2 > Br_2 > I_2$

4.19 Selective Halogenations of Higher Alkanes (Higher than Methane)
- **This is where most of the real problems will come from**

A. Chlorination of Propane
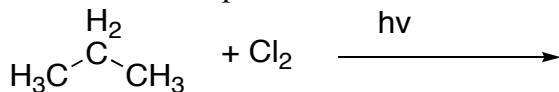
Notes

Why are 2º C-H's more reactive than 1º C-H's?
- Think rate determining step
- Which stability/reactivity principle should you apply, and how?
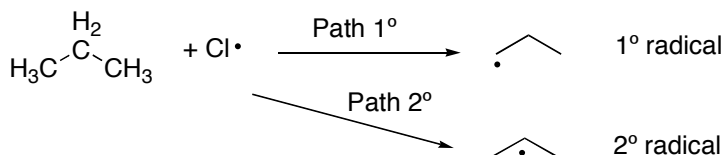
Path 2º is faster than path 1º because path 2º produces a more stable radical product. The path 2º transition-state is stabilized as a result. Product stability/reactivity principle.
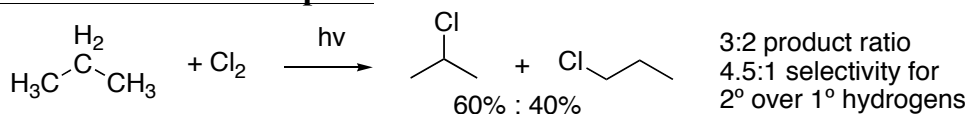
B. Free Radical Stability Pattern: 3° > 2° > 1° > methyl   Memorize!
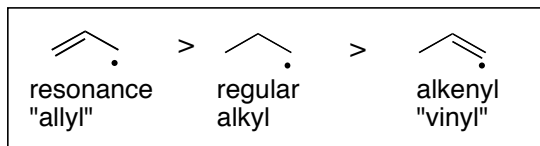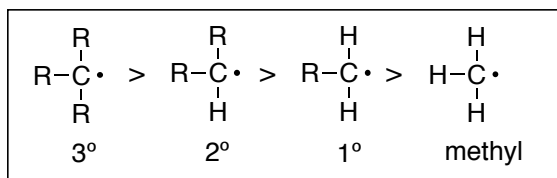
1. Resonance helps a lot ("**Allylic**")
2. Being on an alkene is bad ("**Vinylic**")

	CH_2 (H)	C (H)	H CH	CH_2 (H)	$H-CH_3$	CH (H)
Bond Energy	87	91	95	98	104	111
Class	Allylic	3°	2°	1°	Methyl	vinyl

C. Bromination of Propane
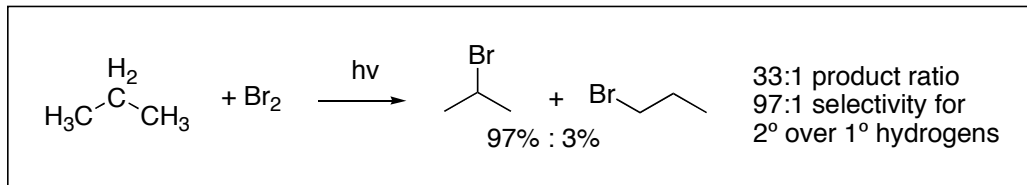
Notes
1. Bromine is **way** more selective than chlorine
2. Practical: to do a selective halogenation, use bromine rather than chlorine
3. Just as 2° > 1°, so allylic > 3° > 2° > 1° > methyl > vinyl

D. Why bromination is more selective than chlorination:

Reactant Stability/Reactivity/Selectivity Principle:

1. Review: When a reaction can give two products, the pathway leading to the more stable product will be preferred (product stability/reactivity principle).
2. New: the **selectivity** between formation of the more stable and less stable product **will vary depending on the stability of the reactant**.
   • In the propane example, propane is a reactant and the two competing products are the secondary and primary radicals, regardless of whether bromine or chlorine is used. But the differing stability/reactivity profiles of the bromine versus chlorine radicals is key

3. The <u>more stable the reactant</u>, the <u>less reactive</u> it will be and the <u>more selective it will be</u> <u>for the more stable product</u>.

4. A more stable reactant is less desperate to react, and is more choosy for the best path/product.
   o "Beggars can't be choosers": less stable reactant (the beggar) is less choosy/selective
   o More sophisticated: a more stable reactant has larger activation barriers to cross. It has trouble crossing even the lower activation barrier to the best product, and rarely has the energy to cross the higher barrier to the less stable product. A less stable reactant has more energy and can more easily cross the barriers to either product.

Application to the Propane Halogenation Situation:
• Br• is more stable than Cl•,
• Therefore Br• is more selective and choosy to make the better 2° radical (leading to 2-bromopropane) rather than the less stable 1° radical (leading to 1-bromopropane).
• Cl• is less stable, and really wants to react. So it doesn't wait around for a weak 2° hydrogen; it often settles for a stronger 1° hydrogen even though it gives an inferior 1° radical product (in the rate determining step)
• "Beggars can't be choosers": the less stable, more reactive Cl• is the "beggar" than can't be as choosy as the more stable, less reactive Br•

| • The energy gap between alternate T-states is almost as large as the energy gap between alternate products. • The strong energy difference between the two T-states results in high selectivity	• The energy gap between alternate T-states isn't nearly as large as the energy gap between alternate products. • The limited energy difference between the two T-states results in limited selectivity

**Alkane Brominations: (4.19). Where many of the problems will come**
Skills:
1. **Write the mechanism for chain propagation (with detailed arrows)**
2. Identify all possible monosubstituted products
3. **Identify the Major Product**
   - **Consider all possible radicals. The carbon that gives the most stable radical will be the carbon that gets brominated preferentially.**
   - This is true because the rate determining step is the step in which a hydrogen is abstracted and a carbon radical is formed.
   - Thus, according to the product stability/reactivity principle, the pathway leading via the best carbon radical is the preferred path.

1. Do all three things for:
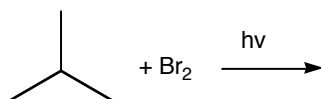
Mechanism

2. Identify the Major Product for each of the following:
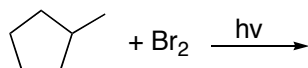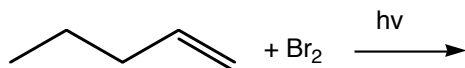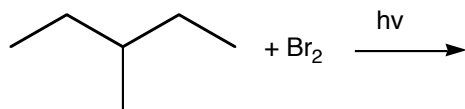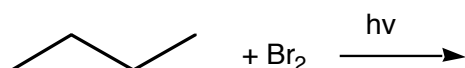
Reactive Intermediates: Stability Patterns (4.17, 4.10)

1. Shortlived, unstable, highly reactive intermediates
2. Normally lack normal bonding

These are tremendously important:
  1. They will be the **least stable intermediate** in any multistep mechanism
  2. When formed, they are **products of the rate-determining step**
  3. **Factors that stabilize them will speed up reaction rates**

Thus it is very important to know their stability patterns!

Class	Structure	Stability Pattern		
Carbocations	$-\overset{\mid}{\underset{\mid}{C}}\oplus$	Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbon Radicals	$-\overset{\mid}{\underset{\mid}{C}}{\cdot}$	Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbanions	$-\overset{\mid}{\underset{\mid}{C}}{:}\ominus$	Allylic > alkenyl (vinyl, aryl) > methyl > 1º > 2º > 3º	Electron Rich	Nucleophilic/ Basic

Notes
1. Both carbocations and radicals have the same pattern. So you don't need to memorize them twice!
2. Carbanions are almost exactly the reverse, except that being allylic is ideal for both.
3. All benefit from resonance (allylic).
4. Cations and radicals both fall short of octet rule. As a result, they are both electron deficient. Carbanions, by contrast, are electron rich.
5. Alkyl substituents are electron donors. As a result, they are good for electron deficient cations and radicals (3º > 2º > 1º > methyl) but bad for carbanions.
6. Alkenyl (vinyl or aryl) carbons are inherently a bit electron poor. This is excellent for carbanions, but terrible for cations or radicals.

Stability/Reactivity/Selectivity Principles

Reactant Stability/Reactivity: The <u>more stable the reactant</u>, the <u>less reactive</u> it will be.
- o   In terms of rates, this means that the <u>more stable the reactant,</u> the slower it will react.
- o   The concept here is that the more stable the reactant, the more content it is to stay as is, and the less motivated it is to react and change into something different
- o   **Key note:**   Often the "reactant" that's relevant in this context will not be the original reactant of the reaction, but will be the "reactant" involved in the rate determining step.
    - • So you need to both figure out what the mechanism is and know what structural factors will stabilize or destabilize the reactants.

1. **Basicity**

$$\text{CH}_2\text{Na} > \qquad \text{NHNa} > \qquad \text{ONa} \qquad > \qquad \text{C(=O)ONa}$$

A   B   C   D
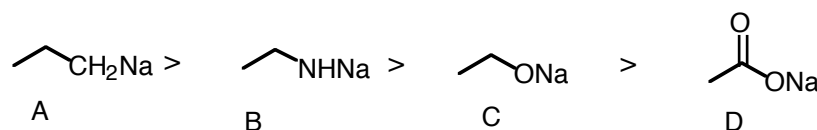
Why: As anion stability increases from A to D, the reactivity decreases

2. **Nucleophilicity**

$$\text{CH}_2\text{Na} > \qquad \text{NHNa} > \qquad \text{ONa} \qquad > \qquad \text{C(=O)ONa}$$

A   B   C   D
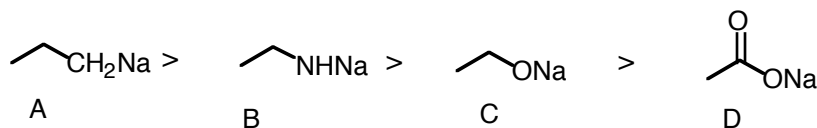
Why: As anion stability increases from A to D, the reactivity decreases

3. **Nucleophilicity**

$$\text{SeNa} > \qquad \text{SNa} > \qquad \text{ONa} \qquad > \qquad \text{C(=O)ONa}$$

A   B   C   D
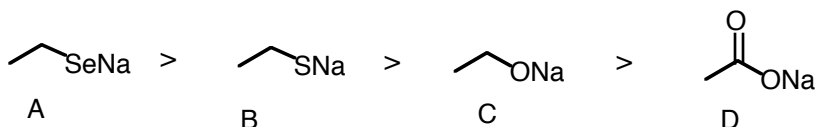
Why: As anion stability increases from A to D, the reactivity decreases

---

4. **Reactivity toward alkanes via radical halogenation**

$$F_2 \; > \; Cl_2 \; > \; Br_2 \; > \; I_2 \quad \text{because} \quad F\bullet \; > \; Cl\bullet \; > \; Br\bullet \; > \; I\bullet$$

Why: Chlorine is more reactive the bromine because chlorine radical is less stable then bromine radical.

---

5. **Electrophilicity (Reactivity in S_N2, S_N1, E2, E1 Reactions)**

$$\text{I} \qquad > \qquad \text{Br} \qquad > \qquad \text{Cl}$$
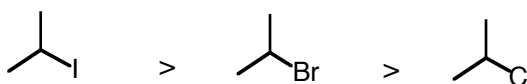
Why: As carbon-halogen bond stability increases, the reactivity decreases

Product Stability/Reactivity: The more stable the product, the faster it will form.

    a. In terms of rates, this means that the more stable the product, the faster the reaction.

    b. The concept here is that the more stable the product, the more favorable it will be to make that product.

    c. **Key note:** Often the "product" that's relevant in this context will not be the final product of the reaction, but will be the "product" of the rate determining step.

        1. So you need to both figure out what the mechanism is and know what structural factors will stabilize or destabilize the products.

1. Acidity

$$CH_3 \quad < \quad NH_2 \quad < \quad OH \quad < \quad \overset{O}{\underset{}{\|}}\!\!-OH$$
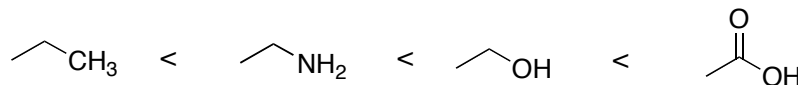
Why: Because as the stability of the anion products increases from A to D, the reaction gets faster = the reactivity of the parent acid increases

$$\underset{A}{CH_2Na} \quad < \quad \underset{B}{NHNa} \quad < \quad \underset{C}{ONa} \quad < \quad \underset{D}{\overset{O}{\underset{}{\|}}\!\!-ONa}$$

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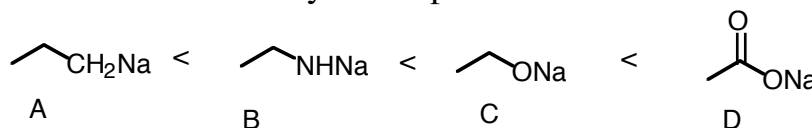
2. **Reactivity of alkanes toward radical halogenation**

$$H_3C-CH_3 \quad < \quad \quad < \quad \quad < \quad$$
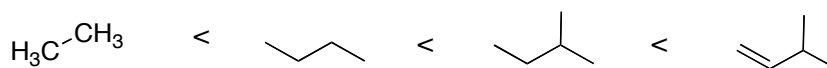
Why: Because as the stability of the radical produced during the rate-determining-step increases, the reaction gets faster

      1°   <   2°   <   3°   <   3° plus resonance

---
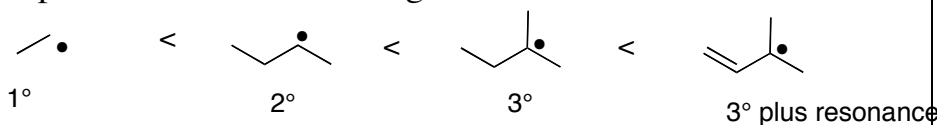
3. **S_N1, E1 Reactivity (see Ch. 8, test 2)**

$$Br \quad < \quad Br \quad < \quad Br \quad < \quad Br$$
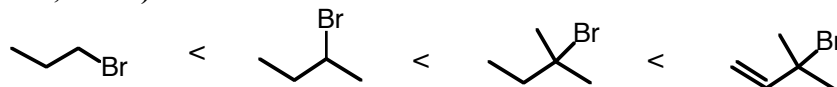
Why: Because as the stability of the cation produced in the rate-determining step increases, the reaction gets faster
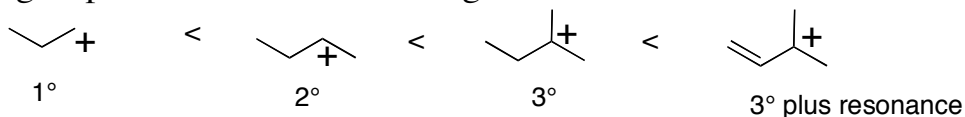
      1°   <   2°   <   3°   <   3° plus resonance

Transition-State Stability/Reactivity: The <u>more stable the transition state</u>, the <u>faster the reaction</u> will be. (The concept here is that the lower the transition state, the more easily it will be crossed.)

- **S$_N$2 Reactivity (ch. 8)**

3°   <   2°   <   1°   <   1° plus allylic
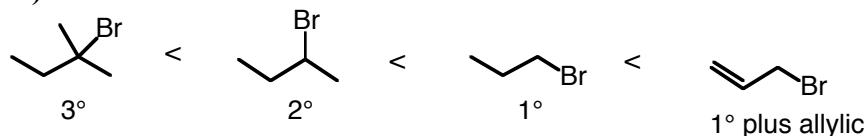
Why: The pattern reflects the relative stability of the transition states. In the case of 3˚ versus 2˚ versus 1˚, the issue is steric congestion in the transition state. The transition states for the more highly substituted halides are destabilized. In the case of allylic halides, the transition state is stabilized for orbital reasons, not steric reasons.

Reactant Stability/Reactivity/Selectivity: Often a reaction can proceed to give either of two products, of unequal stability. The pathway leading to the more stable product will be preferred.   However, the selectivity between formation of the more stable and less stable product will vary depending on the stability of the reactant. The <u>more stable the reactant</u>, the <u>less reactive</u> it will be and the <u>more selective it will be</u>. (The concept here is that a more stable reactant is less desperate to react, and is more choosy, better able to select the best possible pathway without using a less favorable pathway that would result in a less stable product. A more sophisticated picture is that a more stable reactant will have larger activation barriers to cross; it has a hard enough time crossing even the lowest transition state leading to the best possible product, and is much less likely to have the surplus energy required to cross the high transition state leading to the less stable product.)

> **Key note:** The "reactant" and "products" involved are those for the rate-determing step.

1. **Selectivity in the reaction of bromine versus chlorine with alkanes via radical halogenation**

Bromine is much more selective
Chlorine is much less selective

Why?
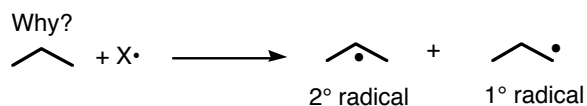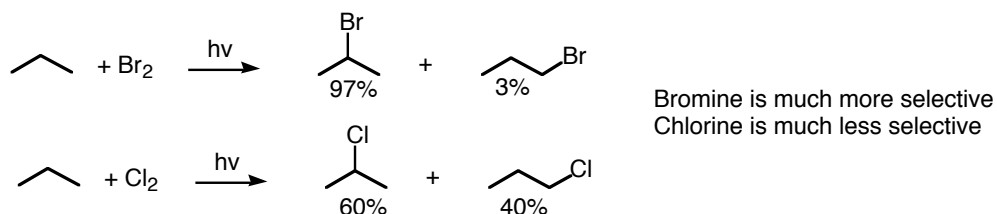
2° radical   1° radical

Formation of the secondary radical is more favorable then formation of the primary radical, in the rate determining step. Bromine radical, being less reactive, is more selective for the 2° radical. Cl•, being less stable and more reactive, is less choosy and less selective.

Ch. 7 Stereochemistry
- Stereoisomers have the same condensed formulas and basic bonding sequence, but have different 3-dimensional shape and cannot be interconverted

7.1,2,3 Chirality, Enantiomers, Planes of Symmetry, and Terminology
chiral-equivalent to "handed". A molecule is chiral if it is not superimposable on its mirror image.

achiral- A molecule is achiral if it is the same as its mirror image.

enantiomers-Two molecules that are mirror images of each other but are different and are not superimposable on each other.
- Note: "enantiomers" involves a relationship between two structures.
- "Chiral" is a term that applies to a single molecule.

Drawing Mirrors/Enantiomers: **Exchange of any two attachments** inverts the stereochemistry and produces a mirror image of the original:
1. front and back (hashes and wedges)
2. left and right (while keeping your hashed and wedged attachments unchanged)
3. exchanging a left or right with the hashed position in back
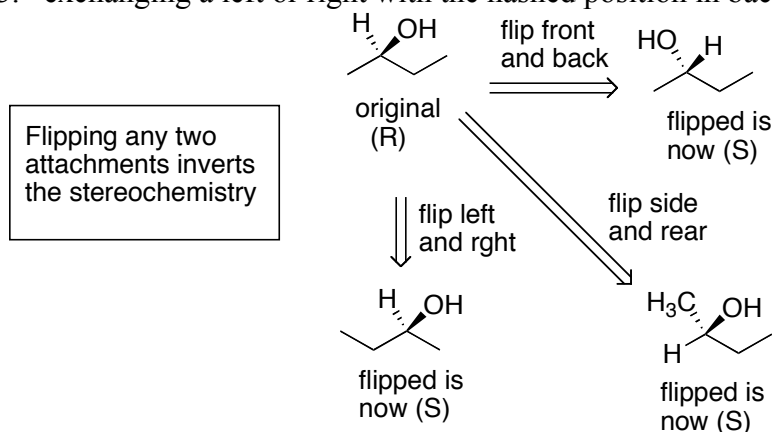
chiral carbon (or stereocenter or asymmetric carbon atom or chirality center)-an atom bearing groups such that interchange of 2 of the groups produces a stereoisomer.
> 1. Any tetrahedral atom that has four different attached groups is a chiral carbon.

Recognizing Chiral Molecules: Key is to look for chiral carbons/stereocenters
1. **zero** chiral carbons → molecule is **achiral**
2. **one** chiral carbon → molecule is **chiral**
3. If **two** (or more) chiral carbons → molecule may be **chiral or achiral**
   - no plane of symmetry under any conditions → chiral.
   - yes plane of symmetry (in one conformation or drawing perspective) → achiral
     a. if a molecule has ≥2 chiral carbons but has a plane of symmetry such that it is achiral, it is called a **meso** compound
     b. to recognize whether a molecule with ≥2 chiral carbons is achiral or chiral, try to draw it in a way such that the carbons are maximally symmetrical, so that it will be easiest to see whether or not a plane of symmetry exists. This may sometimes involve using a sawhorse rather than a zig-zag picture to maximize the ease of seeing potential symmetry.

1. Classify as Chiral or Achiral

a.

b.

c.

d.

e.

f.

g.

h.
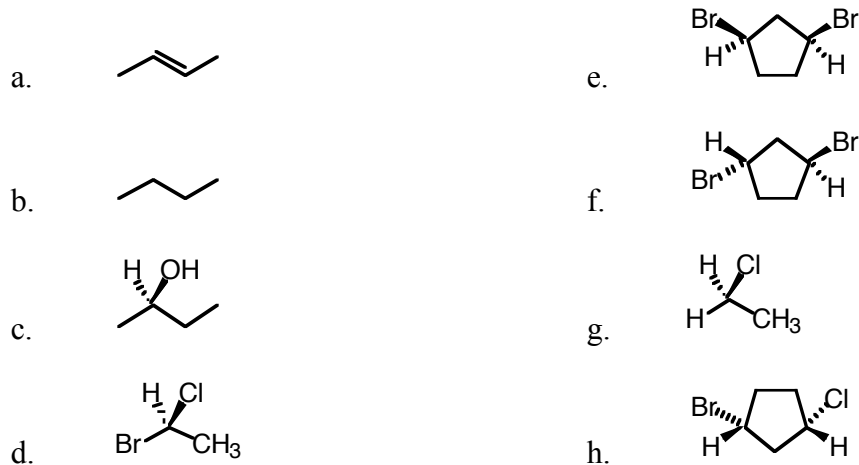
2. What is the Relationship Between the Following Pairs of Structures. Are they the same, or enantiomers?

a.

b.

c.

d.

e.

f.
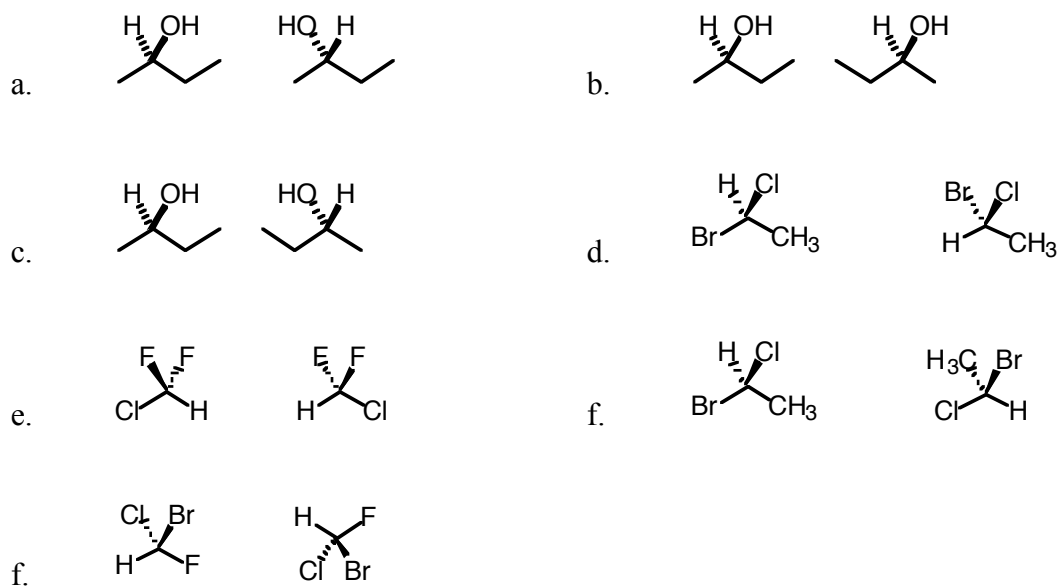
3. Identify each stereocenter with an asterisk, then classify the configuration of each stereocenter as (R) or (S). (Can do the same with the structures in problems 1 and 2)

a.

b.

c.

d.

7.5,6 R/S Classification for Chiral Carbons
1. **Assign Priority** of Atoms/Groups attached to a tetrahedral stereocenter (1 highest, 4 lowest)
   a. **Element**: An element with higher atomic number has higher priority
      • Halogen > Oxygen > Nitrogen > Carbon > Hydrogen
   b. **Carbon with attached heteroatom** > carbon without any attached heteroatom
   c. **CH > CH$_2$ > CH$_3$** for carbons with no heteroatoms

2. **In case of carbon versus carbon ties, differentiate at nearest point of difference.**
   • If you have to walk down the chain to find a difference, do it one carbon at a time

a. $CH_2OH > CH_2CH_3$ b. $CH_2OCH_3 > CH_2NH_2$ c. $C(=O)CH_3 > CH(OH)CH_3$

d. $CH(CH_3)_2 > CH_2CH_2CH_2CH_3$ e. $CH(CH3)2 > CH2C(=O)CH_3$ f. $CH_2NH_2 > CH(CH_3)CO_2H$

g. $CH=CH_2 > CH_2CH_2CH_2CH_3$ h. $CH=CH_2 > CH(CH3)_2$ i. $CH_2CH_2CH_2OH > CH_2CH_2CH_2CH_3$

3. Double or triple bonds are treated as if each of the bonds has extra C's attached. Rules 1b and 1c above still hold as usual.

4. If the low priority group 4 (normally H) is in the back (hashed), trace a path from 1→ 2 → 3.
   • If the path goes **clockwise**, the stereocenter is (R)
   • If the path goes **counterclockwise**, the stereocenter is (S)

5. If the low priority group 4 (normally H) is in front (wedged), then the situation is reversed.
   • If the path goes clockwise, the stereocenter is (S)
   • If the path goes counterclockwise, the stereocenter is (R)

6. If the low priority group 4 (normally H) is to the left or to the right, redraw by exchanging it with the group in the back (hashed), and trace the path on the resulting figure. The configuration in the original structure will be the opposite from in the redrawn structure.
   • If the path in the redrawn picture goes clockwise (R), the original stereocenter is (S)
   • If the path in the redrawn picture goes counterclockwise (S), the original was (R)

Drawing Structure, Given Name: Draw the easiest one, with H in back. If correct, great! If incorrect, simply redraw with the H in front.

Ex: Draw (R)-3-chloroheptane

7.4,8 Enantiomers and How They Differ
Enantiomers have indistinguishable properties in most ways:
1. Melting points
2. Boiling points
3. Solubility
4. Density
5. Chemical reactivity towards <u>achiral</u> reactants.

<u>Enantiomers Differ in only Two Ways</u>
1. Reactivity with <u>Chiral Chemicals</u> (Major chemistry difference)
    * Enzymes are like left-handed gloves, which routinely select left-handed over right-handed enantiomers
    * An achiral molecule is like a mitten that fits a left hand or right hand equally well.

> Chiral reactants discriminate between enantiomers and react with one faster than the other
>
> Achiral reactants do not discriminate between enantiomers and react equally with either one

2. Optical Activity: Enantiomers Rotate the Plane of Polarized Light in Opposite Directions (Section 7.4) (Major Diagnostic difference)
    * **"Optically Active"**: A **solution** is optically active if it rotates polarized light
    * Enantiomers rotate light in equal but opposite directions
    * **"Optically Inactive"**: A **solution** is optically inactive if it does not rotate light
    * Note: optical activity is a property of a bulk solution, not an individual molecule
    * A bulk solution is optically active if it has an excess of one enantiomer

> <u>Two Ways to Be Optically Inactive</u>
>   * If the solution has no chiral molecules present, or
>   * If the solution has a 50/50 mixture of chiral enantiomers (a "racemic mixture")
>
>   * **Note: "optically active" indicates the presence of chiral molecules, but "optically inactive" does <u>not</u> prove the absence of chiral molecules! It only means that there is no excess of one enantiomer over the other!**

Q: Classify each of the following as "optically active" or "optically inactive"

1. A solution of 1-bromopropane.

2. A solution with equal quantities of (R)-2-bromobutane and (S)-2-bromobutane

3. A solution of pure (R)-2-bromobutane

4. A solution with 80% (R)-2-bromobutane and 20% (S)-2-bromobutane

5. If pure (R)-2-bromobutane rotates light 100º to the right, what would happen to light applied to pure (S)-2-bromobutane?

6. If pure (R)-2-bromobutane rotates light 100º to the right, how much rotation would occur for a solution with 80% (R)-2-bromobutane and 20% (S)-2-bromobutane

Racemic Mixtures
1. **Racemic mixture**-a solution containing an equimolar, 50/50 mixture of enantiomers.
    a. A racemic mixture is optically inactive.
    b. It will not rotate light because the enantiomers cancel each other out.
    c. But a racemic mixture is still "chiral".
    d. Other aliases: racemic, racemic mix, racemate, a ($\pm$) pair, a (d,l) pair
2. **The vast majority of solutions containing chiral molecules are racemic.**

- Most reactions that produce chiral molecules provide a racemic, 50/50 mixture of enantiomers (7.10)
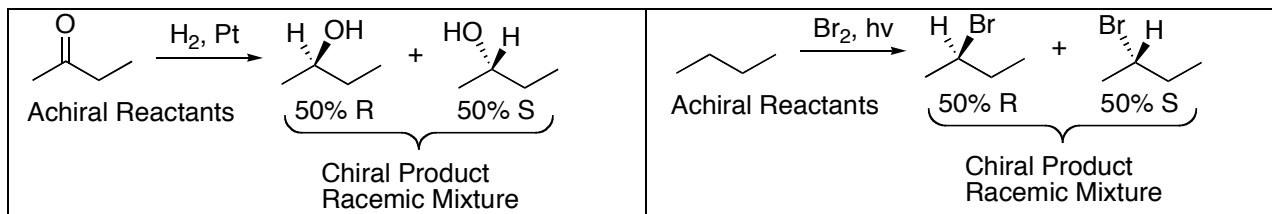
- For chiral molecules, assume a racemic mixture unless told otherwise
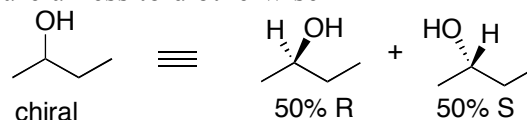
Enantiomeric Excess ("ee") and Optical Purity
a. **enantiomeric excess (ee)** = [(mole fraction major enantiomer)-(mole fraction minor enantiomer)] x 100

b. **optical purity** = [observed rotation/rotation of pure enantiomer] x 100

c. Note: Enantiomeric excess and optical purity values are exactly the same, but are used depending on the experimental method of measurement. Enantiomeric excess is used when you determine the mole/mole ratio of enantiomers by NMR or some other method; optical purity is used when you use optical rotation to characterize a solution containing a mixture of enantiomers.

Problem: A solution has 80% (R)-2-bromobutane and 20% (S)-2-bromobutane

a. What is the "enantiomeric excess" of (R)-2-bromobutane?

b. If pure (R)-2-bromobutane rotates light 100° to the right, how much rotation would occur for a solution with 80% (R)-2-bromobutane and 20% (S)-2-bromobutane

c. If a solution has a 50/50 mixture of (R)- and (S)-2-bromobutane, what would be the enantiomeric excess and the optical purity?

d. If a solution has a 50% ee, what would be the ratio of enantiomers?
    - 50% R, 50% S or
    - 75% R, 25% S

Chirality and Conformations
1. Avoid conformational pictures, which may deceptively give the appearance of chirality

---

If <u>any</u> conformation or drawing of a molecule has a symmetry plane, it is achiral

---
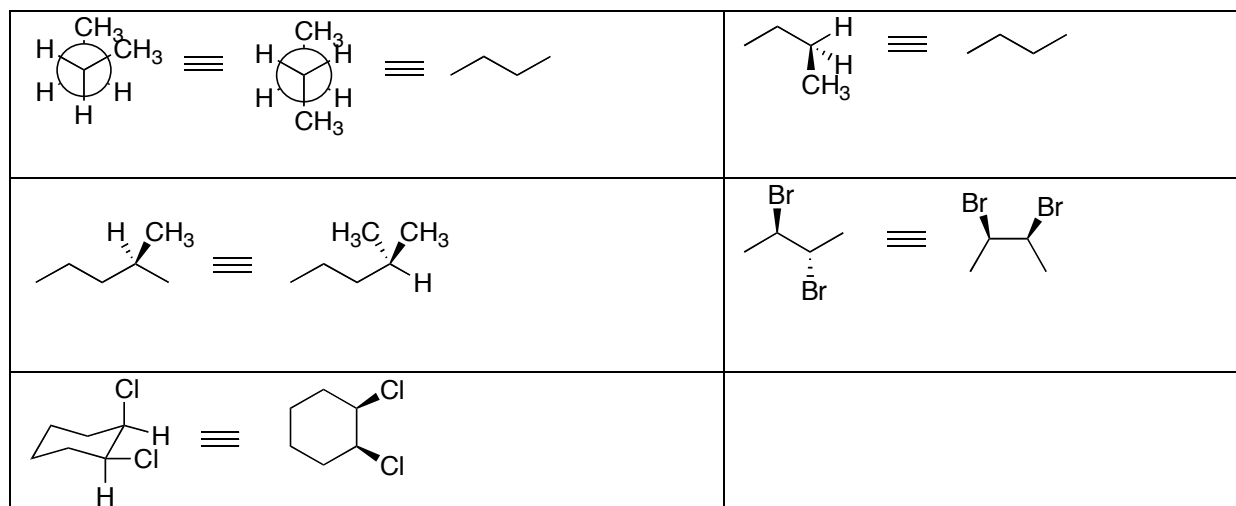
7.9 Freaks: Chiral Compounds without Chiral Carbons: Not Tested
1. There are some molecules that don't have a tetrahedral chiral carbon but are still chiral.
2. As with any chiral "handed"object, they must left/right and front/back differences and lack symmetry.
3. One case is allenes (shown)
4. Another is when two aromatics are connected to each other, sit perpendicular, and can't rotate for steric reasons.

Ex: Allenes
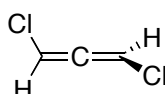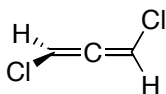
Mirror images are not superimposable

7.7 Fischer Projections: Not Tested Now. A Fischer Projection Handout is included on the website (http://www.mnstate.edu/jasperse/), for future reference.

7.11 Diastereomers: Cis/Trans Stereoisomers that are **Not** Enantiomers
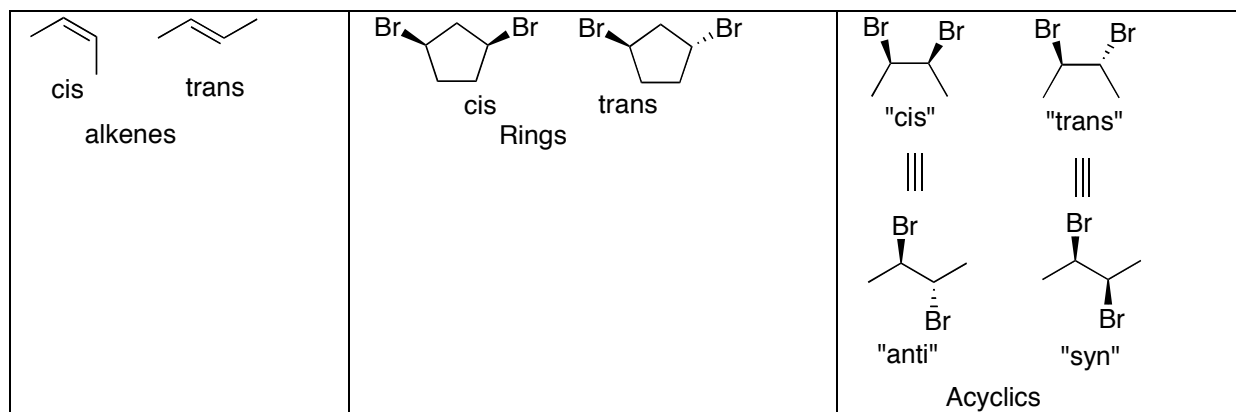
- Note: for acyclics you can rotate around and have different looks for the same molecule, depending on whether you're eclipsed or zig-zagged relative to the single bonds.
- Be consistent. If you zig-zag one, zig-zag the other. If you eclipse one, eclipse the other.
- Normally, for stereo questions, the zig-zag layout isn't conducive to recognizing symmetry.
- So for stereo questions, the more symmetric eclipsed layout is preferable
- Non-test note: Cis or trans is unambiguous for alkenes and rings, but not for acyclics. Often "syn" or "anti" is used instead, assuming the zig-zag layout.

Summary: Types of Isomers
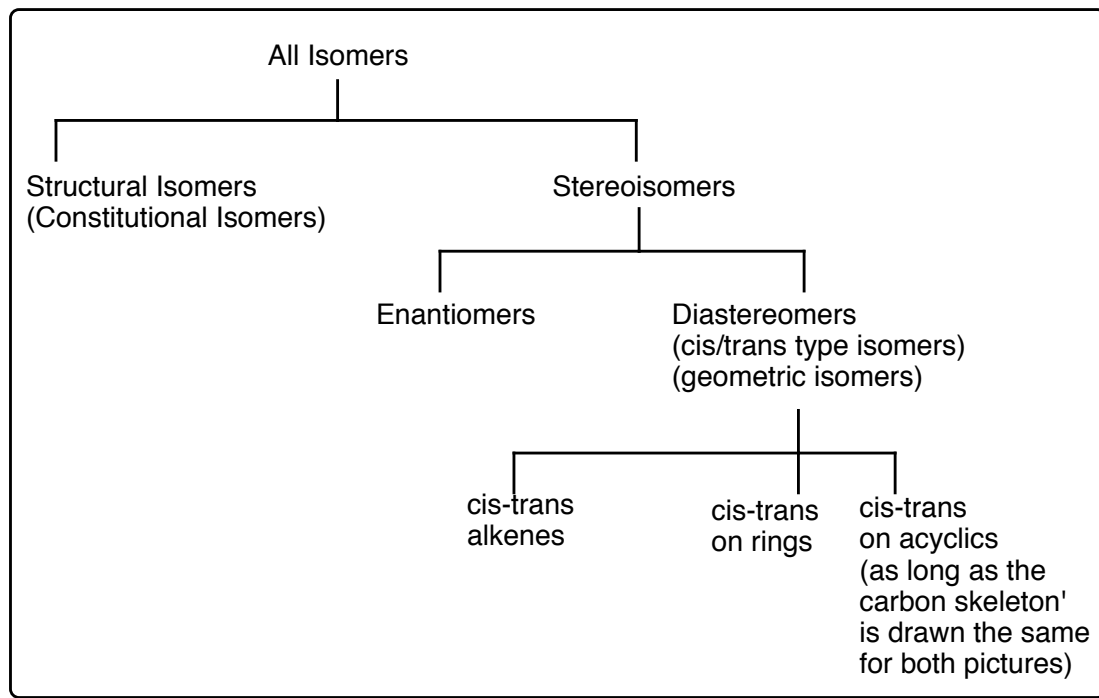
7.10 Molecules with ≥2 Chiral Carbons

1. **Rule: The maximum number of potential stereoisomers = 2^n (n = number of chiral carbons)**
2. Remember: If a molecule can be drawn with a plane of symmetry, then it is achiral and it's mirror image will be the same as the original.
3. If one possible isomer is achiral, then you won't get the maximum number of unique stereoisomers because two of them will be identical mirror images
4. **Suggestion: Try to draw molecules so as to maximize symmetry, regardless of actual conformational stability. This may often involve drawing an eclipsed picture rather than zig-zag**

Problem:
- Draw all unique stereoisomers of 2-bromo-3-chlorobutane.
- Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers.
- Identify each picture as chiral or achiral (meso)

7.12 Meso Compounds

o **meso compound**-an achiral, optically inactive molecule that contains tetrahedral stereocenters (usually two). Both of the Br-bearing carbons in cis-1,2-dibromocyclopentane are stereocenters, but the molecule itself has a plane of symmetry and is achiral.


meso, has stereocenters but is
achiral due to plane of symmetry

Br   Br
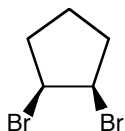
- Remember: If a molecule can be drawn with a plane of symmetry, then it is achiral and it's mirror image will be the same as the original.
- Meso compounds always involve 2 (or more) chiral carbons. Never just one.
- When a meso structure is involved, you won't get the maximum 2^nth number of stereocenters
- **Suggestion: Try to draw molecules so as to maximize symmetry, regardless of actual conformational stability. This may often involve drawing an eclipsed picture rather than zig-zag**
- **A meso compound will not have an enantiomer**
- To draw an enantiomer, invert **all** hash/wedges (but be sure you're chiral to begin with)
- To draw a diastereomer, invert one but not both hash/wedges

1. Problem:
    e. Draw all unique stereoisomers of 2,3-dibromobutane.
    f. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers.
    g. Identify each picture as chiral or achiral (meso)

2. Draw all unique stereoisomers of 2,3-dibromopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

3. Draw all unique stereoisomers of 2,4-dibromopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

4. Draw all unique stereoisomers of 2,4-dibromocyclopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

5. Identify each picture as chiral or meso

a.
Br

Br

b.
Br

Br

c.
Br

Br

d.
Br Br

e.
Br Cl

f.
HO   OH

g.
HO   OH

h.
HO   Cl
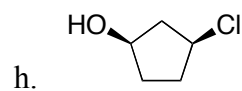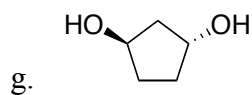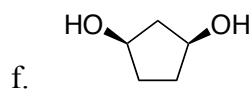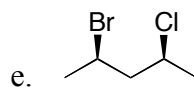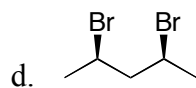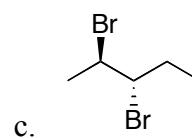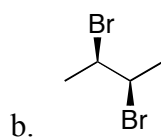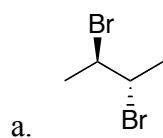
Diastereomers Differ in Physical Properties (Unlike Enantiomers)
- Diastereomers have different melting points, boiling points, solubilities, etc. (unlike enantiomers)

mp = 158   mp = 273
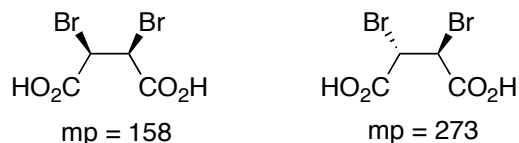
7.5 Absolute and Relative Configuration
Absolute: (R) or (S)
Relative: Comparison between 2 molecules or 2 chiral carbons (even if we don't know absolute)
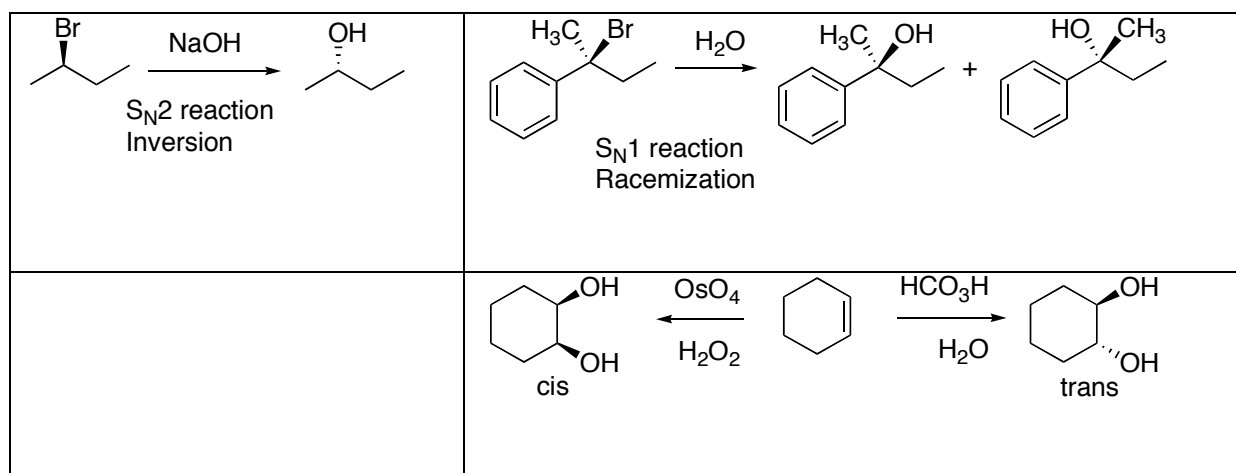
- Relative stereochemistry is often an important feature in mechanisms and product predictions

7.15 Separation of Enantiomers via Diastereomers
- Enantiomers can be separated by temporary attachment to an optically active thing → resulting in separable diastereomers → chop attachment following separation
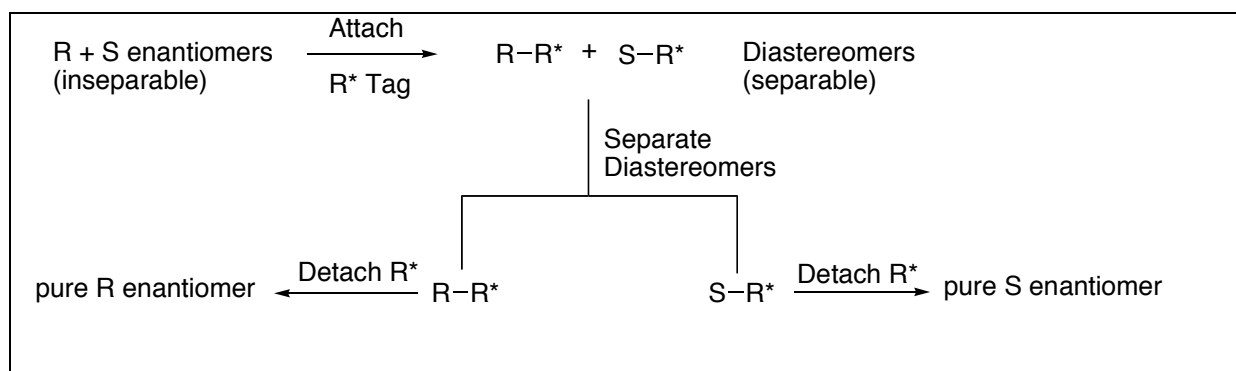
Chem 341 Chapter 7 Stereochemical Terminology Summary
Terms and Definitions

Classification of Isomers
isomers-different compounds with the same molecular formula.

structural isomers (or constitutional isomers)-isomers that have their atoms connected in a different order.
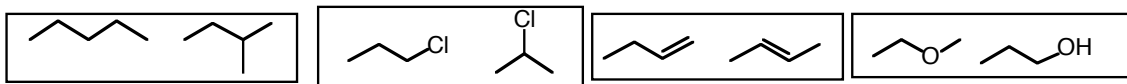
stereoisomers (or configurational isomers)-isomers in which atoms are joined in the same order but differ in the way their atoms are arranged in space. Stereoisomers are subdivided into two categories: **enantiomers** and **diastereomers**.

conformations-easily interconverted by σ-bond rotation or cyclohexane chair flips.   In butane, for example, the gauche, eclipsed, and staggered forms are considered to be different **conformations**; in cyclohexanes, the two chairs are conformations. Different conformations are not considered stereoisomers.
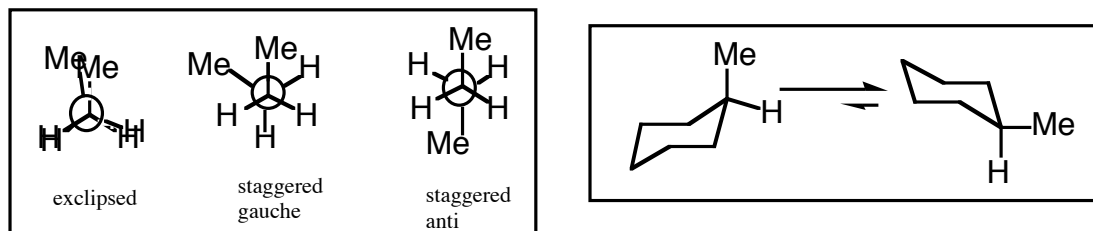
Summary: Types of Isomers
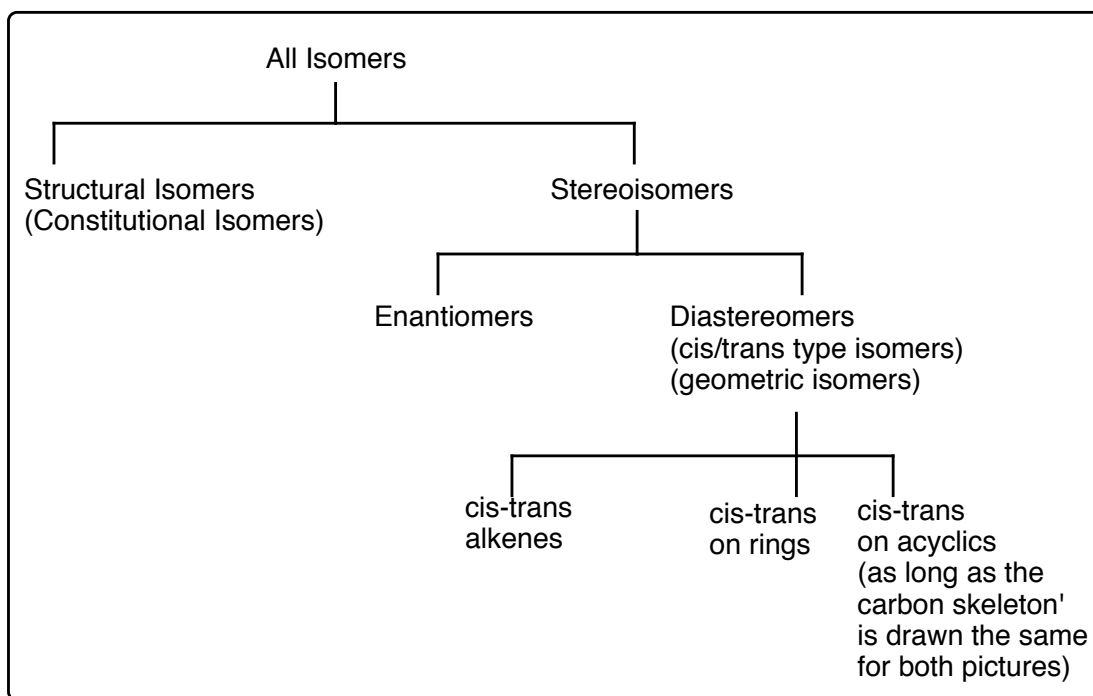
Classification of Stereoisomers

enantiomers-stereoisomers that are not superposable on their mirror reflections. Ex. (R)-2-bromobutane and (S)-2-bromobutane. Separate enantiomers rotate polarized light and are said to be <u>optically active</u>.

diastereomers-stereoisomers that are not enantiomers, that is, not mirror images of each other. Ex. cis- and trans-2-butene; cis- and trans-1,3-dimethylcyclopentane; (2R)-(3R)-2-bromo-3-chlorobutane and (2R)-(3S)-2-bromo-3-chlorobutane. Diastereomers are cis/trans-type isomers, although isomers such as those drawn below are sometimes called syn/anti instead. If the carbon skeletons are drawn analogously, two molecules whose hash/wedge attachments have a cis-trans type relationship will be diastereomers.
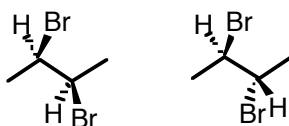
Miscellaneous Stereochemical Terms

chiral-equivalent to "handed". A molecule is chiral if it is not superimposable on its mirror image; an achiral molecule is superimposable on its mirror image.

chiral carbon (or stereocenter or asymmetric carbon atom)-an atom bearing groups such that interchange of 2 of the groups produces a stereoisomer. <u>Any tetrahedral atom that has four different attached groups is a chiral carbon.</u>

• Most molecules containing tetrahedral stereocenters are chiral (the exception being "meso compounds".) The configuration of a tetrahedral stereocenter can be designated as (R) or (S).

configuration-the particular arrangement of atoms in space that is characteristic of a given stereoisomer. The configuration of each stereocenter can be designated as (R) or (S).

racemic mixture-a 50/50 mixture of two enantiomers that will not rotate light.

meso compound-an achiral, optically inactive molecule that contains tetrahedral stereocenters (usually two). Both of the Br-bearing carbons in cis-1,2-dibromocyclopentane are stereocenters, but the molecule itself has a plane of symmetry and is achiral.
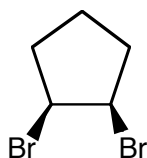
meso, has stereocenters but is achiral due to plane of symmetry

R/S Classification for Chiral Carbons

1. **Assign Priority** of Atoms/Groups attached to a tetrahedral stereocenter (1 highest, 4 lowest)
    a. **Element**: An element with higher atomic number has higher priority
        - Halogen > Oxygen > Nitrogen > Carbon > Hydrogen
    d. **Carbon with attached heteroatom** > carbon without any attached heteroatom
    e. **CH > CH$_2$ > CH$_3$** for carbons with no heteroatoms

2. **In case of carbon versus carbon ties, differentiate at nearest point of difference.**
    - If you have to walk down the chain to find a difference, do it one carbon at a time

3. Double or triple bonds are treated as if each of the bonds has extra C's attached. Rules 1b and 1c above still hold as usual.

4. If the low priority group 4 (normally H) is in the back (hashed), trace a path from 1→ 2 → 3.
    - If the path goes **clockwise**, the stereocenter is (R)
    - If the path goes **counterclockwise**, the stereocenter is (S)

5. If the low priority group 4 (normally H) is in front (wedged), then the situation is reversed.
    - If the path goes clockwise, the stereocenter is (S)
    - If the path goes counterclockwise, the stereocenter is (R)

6. If the low priority group 4 (normally H) is to the left or to the right, redraw by exchanging it with the group in the back (hashed), and trace the path on the resulting figure. The configuration in the original structure will be the opposite from in the redrawn structure.
    - If the path in the redrawn picture goes clockwise (R), the original stereocenter is (S)
    - If the path in the redrawn picture goes counterclockwise (S), the original was (R)

7. In Fisher projections, since H is always in front, clockwise is (S) and counterclockwise is (R)

Drawing Mirrors/Enantiomers: Exchange of any two attachments inverts the stereochemistry and produces a mirror image of the original:
1. front and back (hashes and wedges)
2. left and right (while keeping your hashed and wedged attachments unchanged)
3. flipping something on a side (could be the left side or the right side) with the hashed position in back
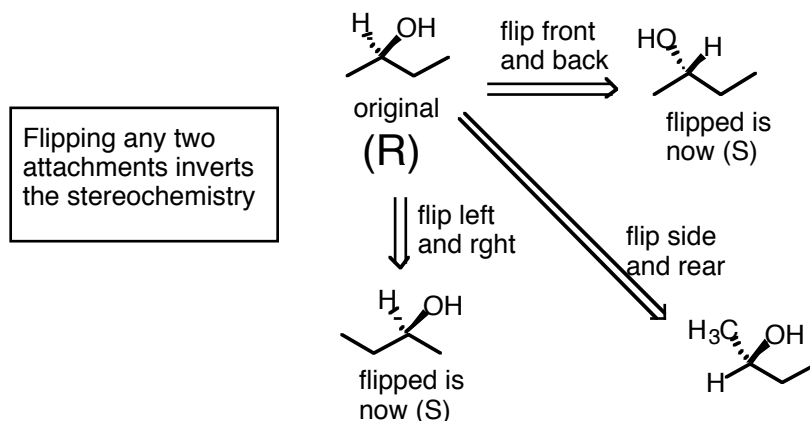
Recognizing Chiral Molecules: Key is to look for chiral carbons/stereocenters
1. If **zero** chiral carbons → molecule is **achiral**
2. If **one** chiral carbons → molecule is **chiral**
3. If **two** (or more) chiral carbons → molecule may be **chiral or achiral**
    o if it has no plane of symmetry under any conditions, it is chiral.
    o If it has a plane of symmetry (in one conformation or drawing perspective), then it is achiral
    o if a molecule has ≥2 chiral carbons but is achiral with a plane of symmetry, it is called a **meso** compound
    o to recognize whether a molecule with ≥2 chiral carbons is achiral or chiral, try to draw it in a way such that the carbons are maximally symmetrical, so that it will be easiest to see whether or not a plane of symmetry exists. This may sometimes involve using a sawhorse rather than a zig-zag picture to maximize the ease of seeing potential symmetry.

Terminology Related to Enantiomeric Purity
enantiomeric excess (ee) = [(mole fraction major enantiomer)-(mole fraction minor enantiomer)] x 100

optical purity = [observed rotation/rotation of pure enantiomer] x 100

Note: Enantiomeric excess and optical purity values are exactly the same, but are used depending on the experimental method of measurement. Enantiomeric excess is used when you determine the mole/mole ratio of enantiomers by NMR or some other method; optical purity is used when you use optical rotation to characterize a solution containing a mixture of enantiomers.

racemic mixture-an equimolar mixture of enantiomers. A racemic mixture will not rotate light.

Fischer Projections (7.7)
In Fischer projections, atoms attached to horizontal lines are viewed as being in front of the plane (wedged), and atoms attached to vertical lines are viewed as being behind the plane (wedged). In the following pictures, Et=ethyl, Me=methyl.
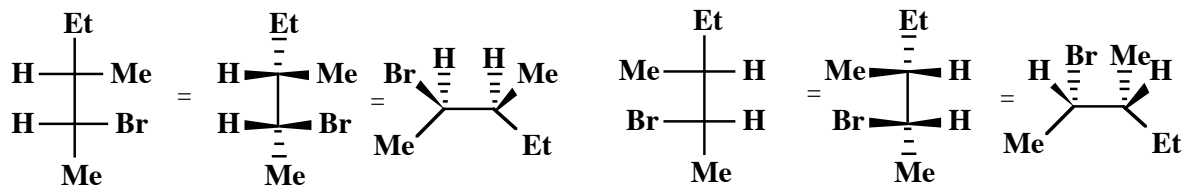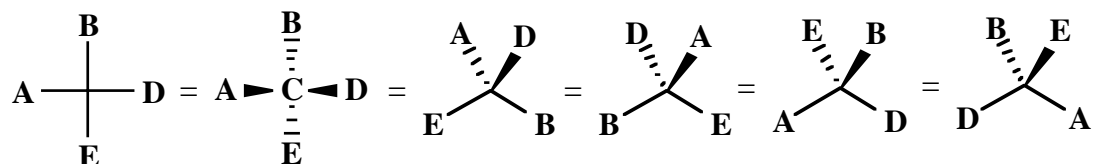
The two structures shown above are enantiomers
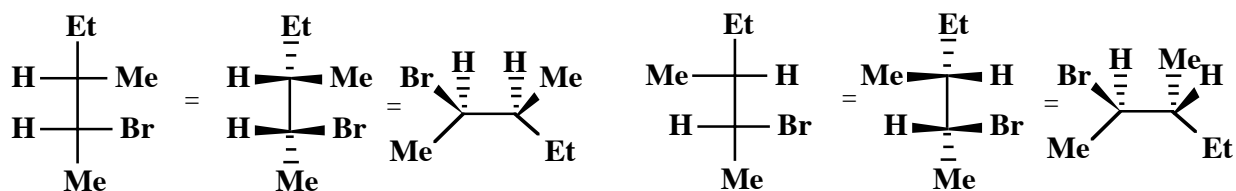
The two shown here are diastereomers.
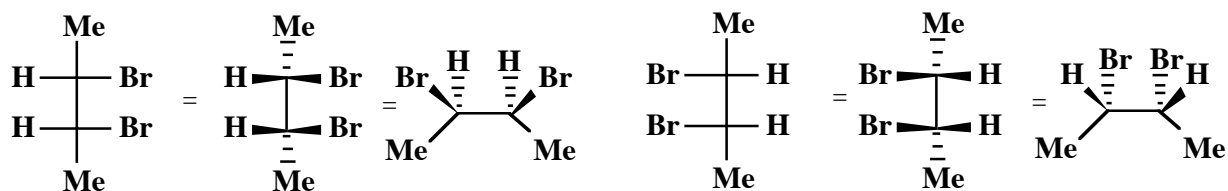
The two shown here are not stereoisomers; they are "meso compounds", because there is a plane of symmetry.

Chem 350 Jasperse Ch. 8   Summary of Reaction Types, Ch. 4-8, Test 2

1. Radical Halogenation (Ch. 4.19)

resonance stabilized>3°>2°>1°>alkenyl
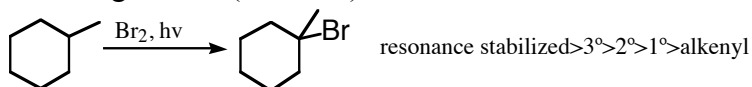
Recognition: X_2, hv

Predicting product: Identify which carbon could give the most stable radical, and substitute a Br for an H on that carbon.

Stereochemistry: Leads to racemic, due to achiral radical intermediate.

Mech: Radical. Be able to draw propagation steps.

slow step

+ H-Br

ready to repeat first step
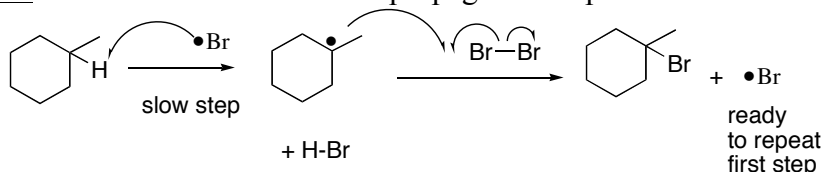
2. S_N2 Substitution (Ch 8)

S_N2: 1°>2°>3°> alkenyl
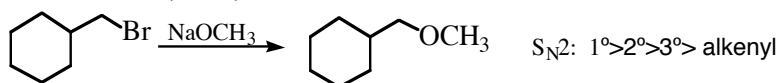
Any of a large variety of nuclophiles or electrophiles can work.

Recognition: A. Anionic Nucleophile, and
                             B. 1° or 2° alkyl halide

(3° alkyl halides fail, will give E2 upon treatment with Anionic Nucleophile/Base. For 2° alkyl halides, S_N2 is often accompanied by variable amounts of E2.)

Predicting product: Replace the halide with the anion nucleophile

Stereochemistry: Leads to Inversion of Configuration

Mech: Be able to draw completely. Only one concerted step!

S_N2: 1°>2°>3°> alkenyl

3. E2 Reactions. (Ch 5)

E2: 3°>2°>1°> alkenyl
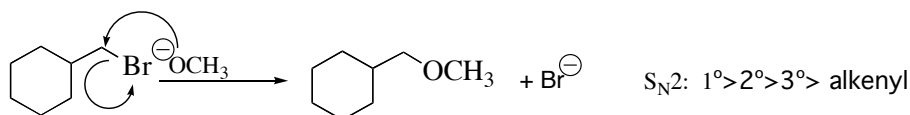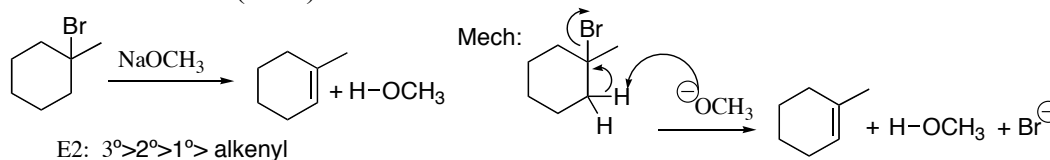
Recognition: A. Anionic Nucleophile/Base, and
                             B. 3° or 2° alkyl halide

(1° alkyl halides undergo S_N2 instead. For 2° alkyl halides, E2 is often accompanied by variable amounts of S_N2.)

Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7)

Predicting product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans, however.

Stereochemistry: Anti/trans elimination. The hydrogen on the neighbor carbon must be trans/anti.

Mech: Concerted. Uses anion. Be able to draw completely. Only one concerted step!

4. S$_N$1 Reactions. (Ch 8)
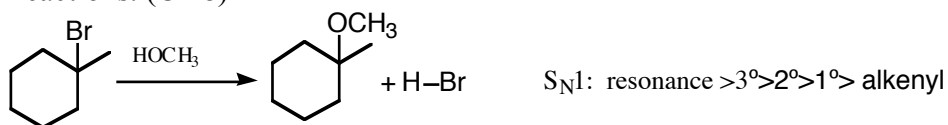
S$_N$1: resonance >3°>2°>1°> alkenyl

Recognition: A. Neutral, weak nucleophile. No anionic nucleophile/base, and
B. 3° or 2° alkyl halide. (Controlled by cation stability).
(1° alkyl halides undergo S$_N$2 instead. For 2° alkyl halides, S$_N$1 is often accompanied by variable amounts of E1.)
Predicting product: Remove halide and replace it with the nucleophile (minus an H atom!)
Stereochemistry: Racemization. The achiral cation intermediate forgets any stereochem.
Mech: Stepwise, 3 steps, via carbocation. Be able to draw completely.
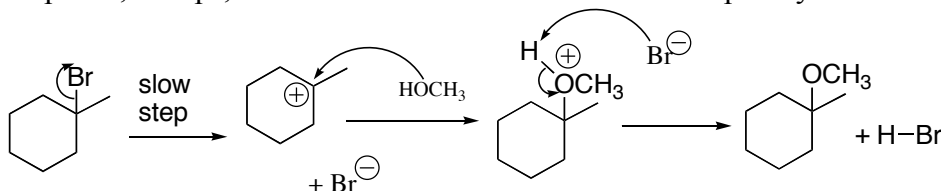
5. E1 Reactions. 3° > 2° > 1° (Ch 5, Controlled by cation stability)
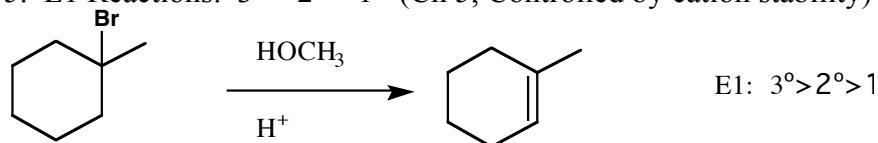
E1: 3°>2°>1

Recognition: A. Neutral, weak nucleophile. No anionic nucleophile/base, and
B. 3° or 2° alkyl halide. (Controlled by cation stability).
(For 2° alkyl halides, E1 is often accompanied by variable amounts of S$_N$1.)
Orientation: The most substituted alkene forms
Predicting the major product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.
Stereochemistry: Not an issue. The eliminating hydrogen can be cis or trans. .
Mech: Stepwise, 2 steps, via carbocation. Be able to draw completely.
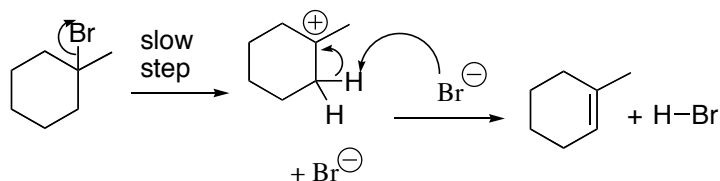
Sorting among S$_N$2, S$_N$1, E2, E1: How do I predict?
Step 1: **Check nucleophile/base**.
a. If **neutral**, then **S$_N$1/E1** → mixture of both
b. If **anionic**, then **S$_N$2/E2.**
Step 2: If **anionic**, and in the **S$_N$2/E2**, then **Check the substrate**.
    a. 1° → **S$_N$2**
    b. 2° → **S$_N$2/E2 mixture.**   Often more **S$_N$2**, but not reliable…
    c. 3° → **E2**

Ch. 8 Alkyl Halides: Nucleophilic Substitution and Elimination

4.4 Classification, Nomenclature
A. General Classification

"alkyl halide"		
"vinyl halide"		
"aryl halide"		
"allylic halide"		

B. 1°, 2°, 3° Classification

Br 3°   Br 2°   Br 1°
         H   H H
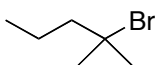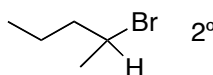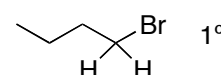
C. Systematic Naming: x-Haloalkane (test responsible) (Include number!)
D. Common Naming: "alkyl halide" (not tested)

Structure	Formal Name	Common Name
Cl		
Br		
		Isopropyl iodide

Systematic Nomenclature: x-Haloalkane (test responsible)
Common: "alkyl halide" (not tested)

Uses:
1. solvents
2. anesthetics
3. refrigerants
4. pesticides
5. **reactants**

4.5 Structure:

A. Polar		

B. Weak Bonds, Breakable

Stability	Bond	Bond Strength	Reactivity Toward Breakage
	C-Cl	81	
	C-Br	68	
	C-I	53	

4.6 Physical Properties
- boiling point: controlled by molecular weight (London force)
- water solubility: low, no hydrogen-bonding
- density: greater than water, so they sink (unlike hydrocarbons, which float)

4.19 Preparation of Alkyl Halides (Review)
1. Review: R-H + Br_2 → RBr + HBr   (under photolysis, Ch. 4)
2. We will learn other preparations later

Overview/Preview of Alkyl Halide Reactions: Substitution (S_N2 or S_N1, Ch. 8) or Elimination (E2 or E1, Ch. 5)
▪ Because R-X bonds are weak, halides are good leaving groups.

1. Substitution

$$R\text{-}X + NaZ \text{ or } HZ \rightarrow R\text{-}Z + NaX \text{ or } HX$$
$$\text{Anion or neutral}$$
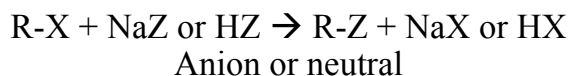
   2 Variants
   a. S_N2:
      o Anionic nucleophile
      o The R-X bond breaking is simultaneous with R-Z bond formation
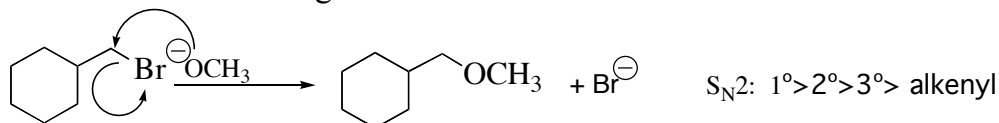
S_N2: 1°>2°>3°> alkenyl

   b. S_N1:
      o Neutral nucleophile
      o The R-X bond breaks first to give a carbocation in the rate determining step; formation of the R-Z bond comes later
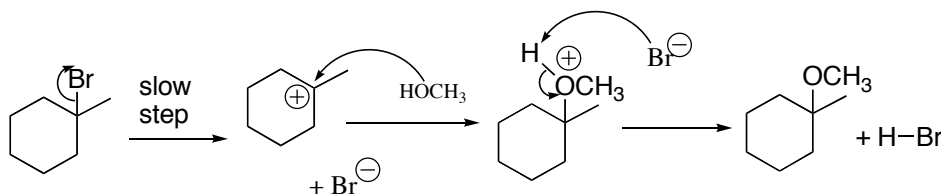
2. Elimination
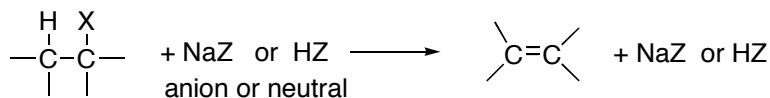
   2 Variants
   a. E2:
      o Anionic base
      o The R-X and C-H bond breaking is simultaneous with C=C bond formation
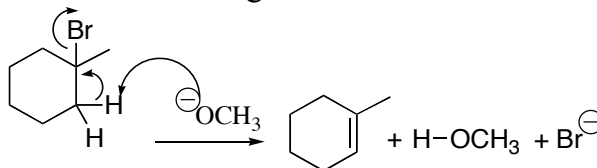
   b. E1:
      • Neutral base
      • The R-X bond breaks first to give a carbocation in the rate determining step. C-H bond cleavage and C=C bond formation comes later

8.1-5 The S_N2 Reaction

General:

"nucleophile"   "electrophile"   "leaving group"
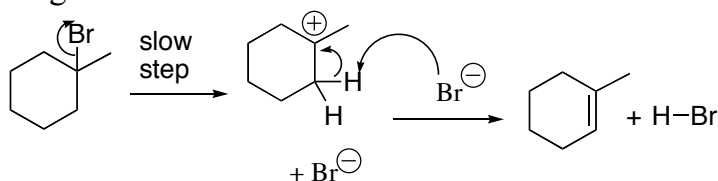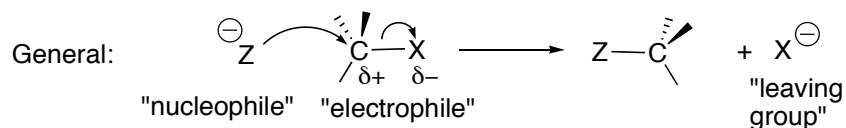
Example, with test-level mechanism:
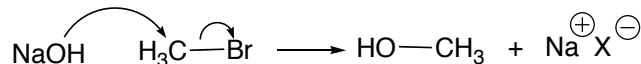
- double-barbed arrows (electron pairs move)
- Na^+ is a spectator

More Detailed Mechanism:

Transition-State
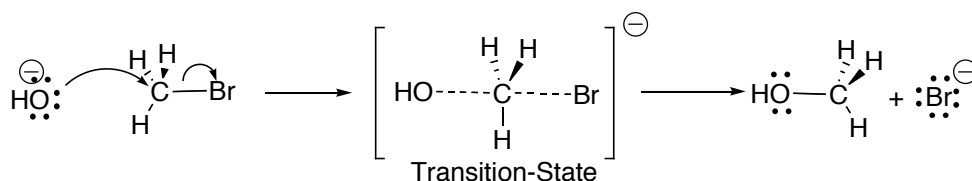
Notes:
1. Simple, concerted one-step mechanism. No intermediates.
2. The anion needs to be very reactive and thus not too stable. Normally **ANIONIC NUCLEOPHILE**.
3. Both nucleophile and electrophile are involved in the rate determining step.
   - Rate $= k[\text{anion}]^1[\text{R-X}]^1$
4. 2nd order rate law is why it's called S_N2: $\underline{S}$ubstitution$_{\text{Nucleophilic}}\underline{2}$nd order

5. The nucleophile attacks opposite side from the leaving group.
6. This "backside attack" (or opposite side attack) results in inversion of stereochemistry when a chiral, 2° R-X is involved

   Inversion of Stereochemistry at Chiral Center

7. The **transition state** involves a 5-bonded, trigonal bipyramidal carbon that **is more cluttered** than either the original tetrahedral reactant or the final tetrahedral product

8. Steric crowding in the transition-state makes the reaction very, very, very sensitive to steric factors
   a. For the electrophile R-X: CH_3-X > 1° R-X > 2° R-X > 3° R-X for steric reasons
   b. For the nucleophile it also helps to be smaller rather than larger

8.1 Generality of S$_N$2 Reactions
-many kinds of nucleophiles, give many products

1. R-X + NaOH → R-OH   Alcohols

2. R-X + NaOR → R-O-R   Ethers

3. R-X + NaO$\overset{O}{\overset{\|}{C}}$R → R$\overset{O}{\overset{\|}{O-C}}$R   Esters

4. R-X + KI → R-I   Iodides

5. R-X + NaCN → R-CN   Nitriles

6. R-X + $^{\ominus}$≡≡R → R——≡≡R   Alkynes
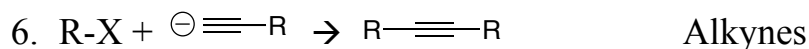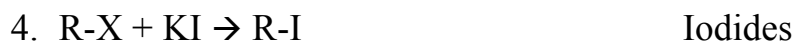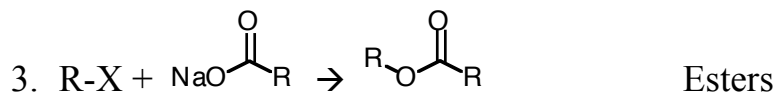
Etc.

Notes
   1. Most nucleophiles are **ANIONS**

   2. Various oxygen anions are good to make alcohols, ethers, or esters

   3. Halogen exchange useful route to iodides (more valuable and less
      accessible)

   4. There are a few neutral nucleophiles (not for test): nitrogen family

---

Predicting Products for S$_N$2 Reactions
1. Don't change the structure for the carbon skeleton
2. **Put the nucleophile in exactly the spot where the halide began…**
3. Unless the halide was attached to a **chiral** center; in that case invert the
   configuration for the product
   • If the halide was "wedged", the nucleophile should be "hashed"
   • If the halide was "hashed", the nucleophile should be "wedged"
4. Don't mess with any "spectator" portions: whatever was attached to the
   nucleophilic anion at the beginning should still be attached at the end

8.2-5 Structural Factors that Impact S$_N$2
A. Nucleophile (8.5)
   1. Anion versus Neutral: Should be **ANIONIC**

   2. Anion Stability: Less Stable should be More Reactive (Reactant Stability-
      Reactivity Principle)

     a. -anion nucleophilicity <u>decreases</u> across a **horizontal row**
       (electronegativity factor)

          CH$_2$Na >   NHNa >   ONa   >   NaF
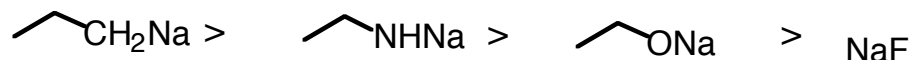
     b. -anion nucleophilicity <u>decreases</u> when an anion is stabilized by
       resonance

          ONa   >   ONa
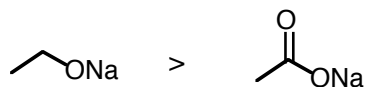
     c. -anion nucleophilicity <u>increases</u> down a **vertical column**

          NaSeH > NaSH > NaOH

   3. Size: all else equal, smaller is better than bigger

          ONa   >   ONa
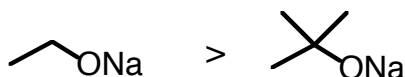
B. Electrophile (8.2, 8.4)
   1. Substrate: Allylic > 1º > 2º > >> 3º, alkenyl, aryl
     • **3º and alkenyl, aryl never do S$_N$2**
     • transition-state stability-reactivity principle
     • Steric clutter in the transition state explains the 1º > 2º > >> 3º pattern
     • Allylic benefits from a complex orbital resonance effect in the T-state
     • Alkenyl/aryl halides are bad for some molecular orbital reasons
       (backside attack doesn't work, particularly for aryl halides)

   2. Leaving Group: R-I > R-Br > R-Cl (8.2)
     • reactant stability-reactivity principle
     • weaker bonds break faster

8.3 Inversion of Stereochem in S$_N$2

In the mechanism, the nucleophile attacks from the "backside" or opposite side from the leaving group → inverts configuration

Transition-State
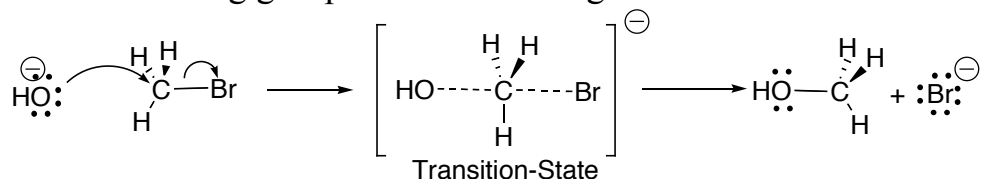
- Inversion occurs mechanistically in **every** S$_N$2 reaction
- But inversion is chemically relevant **only** when a chiral carbon is involved

Inversion matters, since product is chiral	Inversion doesn't matter, for achiral product

---
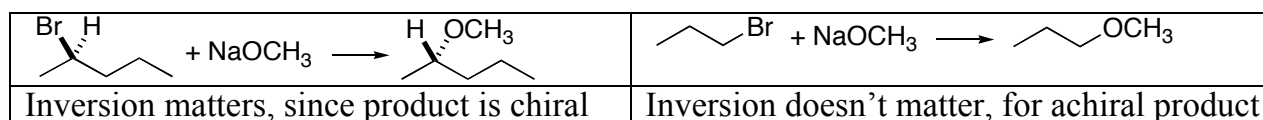
Predicting products when chiral carbons undergo inversion:
1. Keep the carbon skeleton fixed
2. If leaving group is "hashed", the nucleophile will end up "wedged" in the product
3. If leaving group is "wedged", the nucleophile will end up "hashed" in the product

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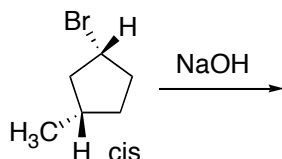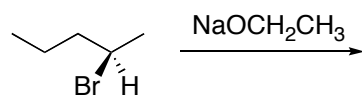
Two Standard Proofs for S$_N$2 mechanism:
- Inversion of configuration on a chiral carbon
- 2nd order rate law

Predicting Products for S$_N$2 Reactions
1. Don't change the structure for the carbon skeleton
2. **Put the nucleophile in exactly the spot where the halide began...**
3. Unless the halide was attached to a **chiral** center; in that case invert the configuration for the product
   a. If the halide was "wedged", the nucleophile should be "hashed"
   b. If the halide was "hashed", the nucleophile should be "wedged"
4. Don't mess with any "spectator" portions: whatever was attached to the nucleophilic anion at the beginning should still be attached at the end

S_N2 Problems: For each of the following
    a. Identify whether or not an S_N2 reaction would take place?
    b. If not, why not?
    c. For those that could undergo S_N2 substitution, draw in the product.

1. $\diagup\diagdown\diagup$I + H_2O $\longrightarrow$

2.   Br + NaOH $\longrightarrow$

3.   Br +NaO—C(=O)CH_3 $\longrightarrow$

4.   Br H + NaOCH_3 $\longrightarrow$

5.   Br H + KOCH_2CH_3 $\longrightarrow$

6.   Br + KCN $\longrightarrow$

7.   Br + CH_3OH $\longrightarrow$

8.   Br + NaSCH_3 $\longrightarrow$

9.   Br + NaOH $\longrightarrow$

10.   Br + NaOCH_3 $\longrightarrow$

11.   Br + NaOCH_3 $\longrightarrow$

12.   Br + NaOH $\longrightarrow$
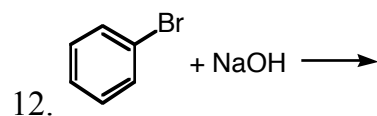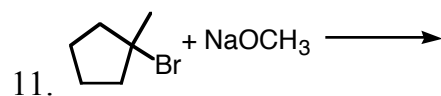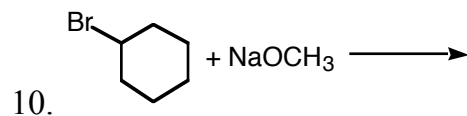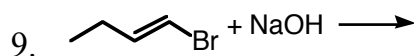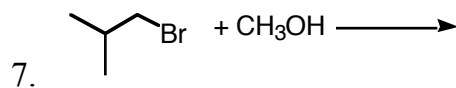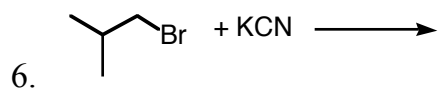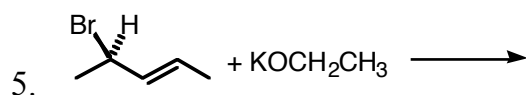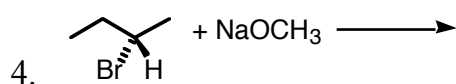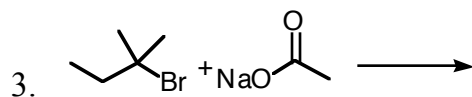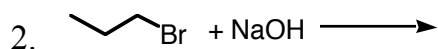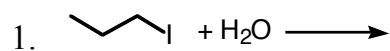
More S$_N$2 Problems
1. Rank the reactivity toward NaOCH$_3$ (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).
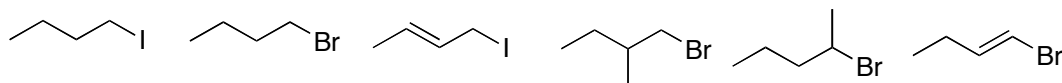
Issues:

2. Rank Reactivity toward (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

NaNH$_2$ NaOCH$_3$ CH$_3$OH
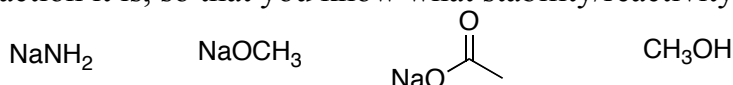
Issues:

3. What nucleophile should you use to accomplish the following transformations?
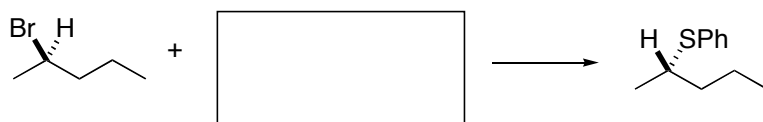
4. Draw the Products, Including Stereochemistry. (Stereochemistry will matter for S$_N$2 and S$_N$1 reactions anytime the haloalkane is 2°)
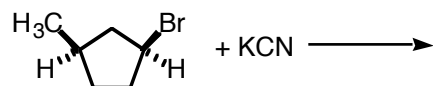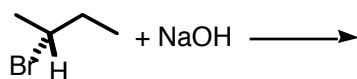
Issue:

5. Choose Reactants to make the following, from a haloalkane and some nucleophile.

Issues:

8.6-10 S$_N$1 = **S**ubstitution$_{Nucleophilic}$**1**st Order = "Solvolysis"
- Dramatic difference in mechanism, rates, structure dependence, and stereochemical outcome (compared to S$_N$2)

General: R-X + Z-H → R-X + HX
neutral
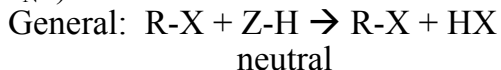
Neutral, **non-anionic** nucleophiles do the substitution
1. Often this is just the solvent (H$_2$O, ROH, RCO$_2$H are common)
    - For this reasons, these reactions are often called "solvolysis" reactions
2. Heat is often required
3. Acid is sometimes used to accelerate S$_N$1 reactions

Predicting Products for S$_N$1 Reactions
    1. Don't change the structure for the carbon skeleton
    2. Connect "R" and "Z", while taking the halide off of the electrophile and H off of the nucleophile
    3. Unless the halide was attached to a **chiral** center, a **racemic mixture** will result
    4. Maintain the integrity of the spectator attachments

Examples:

$+ H_2O \longrightarrow$

$+ CH_3OH \longrightarrow$
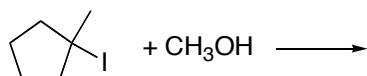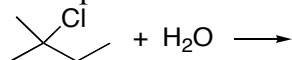
3-Step Mechanism
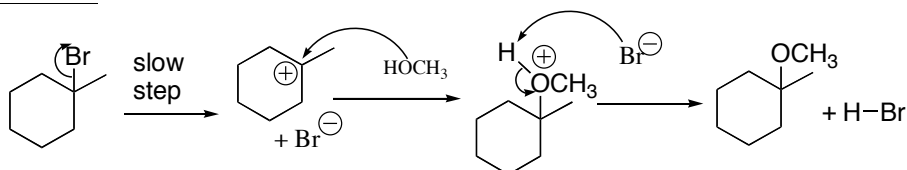
1. Step 1: Carbocation Formation. THIS IS THE SLOW STEP
    - **Therefore the rate is controlled by cation stability!**
2. Step 2: Carbocation capture by neutral molecule (usually a solvent molecule)
    - When cation and neutral combine, a cation is produced
3. Step 3: Deprotonation to get neutral

Notes:
1. Carbocation formation is key
2. Rate = k[R-X]   →   First order
3. See cations, not anions. Neutral, not anionic nucleophile.
4. Charge and atoms must balance in step 2. Thus, the oxygen retains the hydrogen.
5. Oxygen eventually loses the H, but only in step 3.
6. Rate can be enhanced by AgNO$_3$. The Ag+ cation helps strip the halide off in step 1.

Structural Factors that Impact S_N1 Rates

Nucleophile: Should be **NEUTRAL**, but otherwise non-factor

Electrophile
1. Substrate: Allylic > 3° > 2° >> 1° > alkenyl, aryl
    o   Resonance is huge
    o   alkenyl, aryl never do S_N2, 1° only with $AgNO_3$
    o   product stability-reactivity principle: in the rate-determining step, the more stable the product **cation**, the faster it will form
    o   In terms of 1°, 2°, 3°, S_N1 and S_N2 have exactly opposite patterns
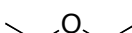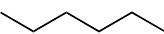
2. Leaving Group: R-I > R-Br > R-Cl
    o   reactant stability-reactivity principle: in the rate determining step, the weaker the C-X bond, the faster it will break
    o   This pattern is the same as for S_N2

3. $AgNO_3$ Helps
    •   Ag+ helps strip the halide off in step one

4. Polar Solvent Helps
    •   A polar solvent helps to stabilize the ions that form in the rate-determining step

Solvent Polarity:					
Solvent	H_2O	CH_3OH	![ketone]	![ether]	![pentane]
Relative Rate	8000	1000	1	0.001	0.0001

S_N1 Stereo: Racemization
Original stereochemistry is forgotten at the carbocation stage, get racemic R/S mixture
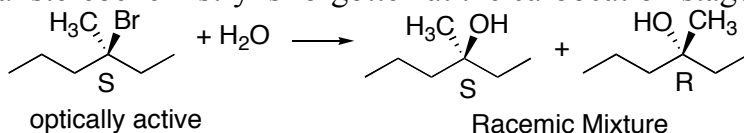
Why? Carbocation forgets original stereo:
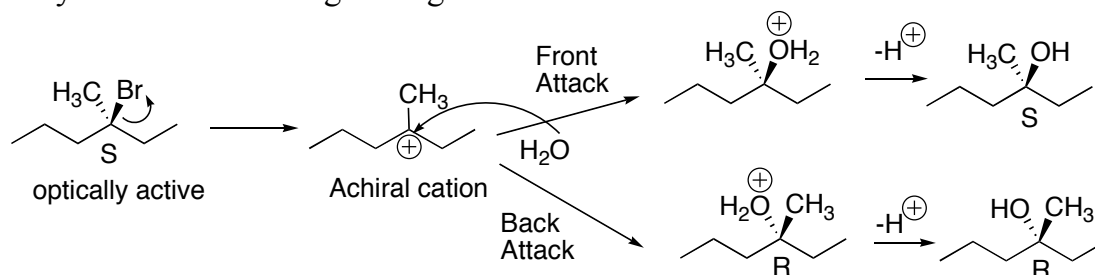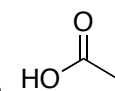
Ex.
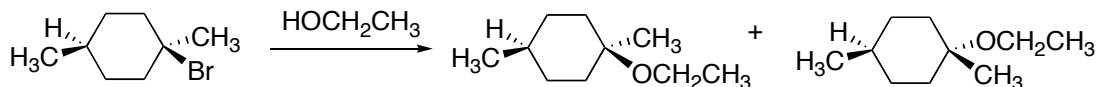
S_N1 Problems: For the following, which are and aren't S_N1 candidates? If not, why not? What would be the product if they are S_N1 candidates?

1.   ⟍⟋⟍I + H₂O ⟶

2.   ⟍⟋⟍ Br H + NaOCH₃ ⟶

3.   ⟍⟋⟍ Br H + HOCH₃ ⟶

4.   ⟍⟍Br + NaO + CH₃C(=O)O⁻ ⟶

5.   ⟍⟍Br + HO CH₃C(=O)OH ⟶

6.   Br H ⟍⟍⟍ + CH₃OH ⟶

7.   Br ⟍⟍⟍ + CH₃OH ⟶

8.   (cyclohexyl) Br + H₂O ⟶

9.   (phenyl) Br + H₂O ⟶
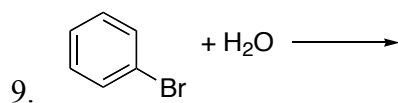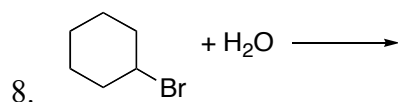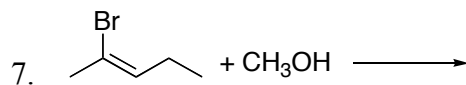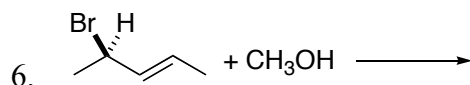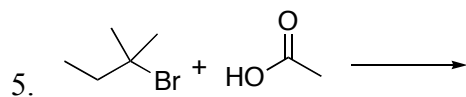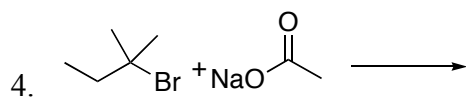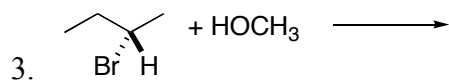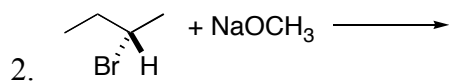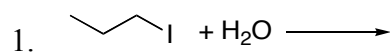
10. Rank Reactivity towards HO–C(=O)–CH₃ (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

   ⟍⟋I   ⟍⟋Br   ⟍⟋Cl   ⟍⟍⟨I   ⟍⟍⟨I   ⟍⟋⟍Cl
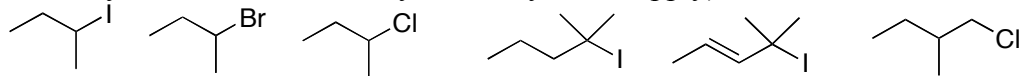
Issues:

Comparing S$_N$2 vs S$_N$1

		S$_N$1	S$_N$2
1	**Nucleophile**	**Neutral, weak**	**Anionic, strong**
2	**Substrate**	**3º R-X > 2º R-X**	**1º R-X > 2º R-X**
	Allylic effect…	Allylic Helps	Allylic helps
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	K[RX]	k[RX][Anion]
6	Stereochemistry (on chiral, normally 2º R-X)	Racemization	Inversion
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never

Identify as S$_N$1 or S$_N$2 or No Reaction. Draw the Product(s), if a reaction occurs.

1.   Br + NaOCH$_2$CH$_3$ ⟶

2.   Br + H$_2$O ⟶

3.   Br + H$_2$O ⟶

4.   H Br   + CH$_3$SNa ⟶

5.   H Br   + CH$_3$SH ⟶
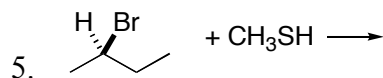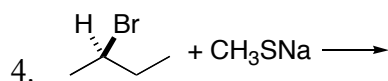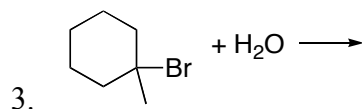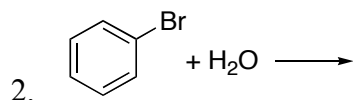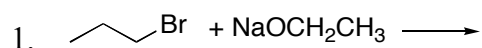
Which fit S$_N$1, which fit S$_N$2?
1. Faster in presence of silver nitrate?

2. Faster in water than in hexane?

3. When the moles of reactant is kept the same, but the volume of solvent is cut in half, the reaction rate increases by 2-fold?

4. By 4-fold?

5. 2-bromobutane reacts faster than 1-bromobutane?

6. 2-bromobutane reacts slower than 1-bromobutane?

E1 Elimination Reactions (5.18, 5.14-5.18)
Examples:
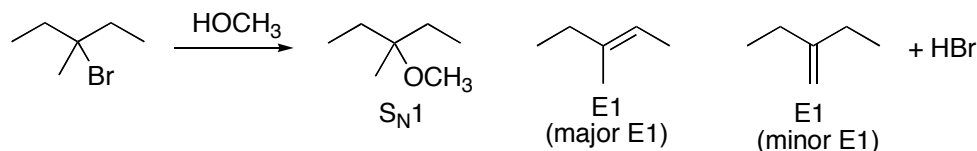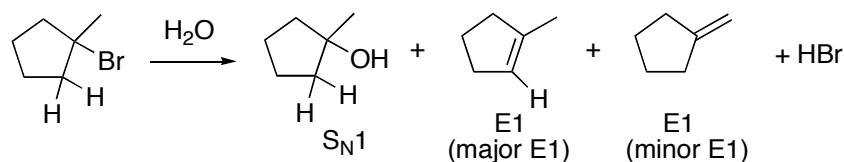
Notes
- Under S_N1 conditions, some elimination product(s) form as well
- E1 and S_N1 normally compete, resulting in mixtures
  - This is not good from a synthetic perspective.
- **Structurally Isomeric Alkenes can form**
  - **The double bond must involve the original halogenated carbon and any neighbor carbon (that had a hydrogen to begin with that can be eliminated)**
  - **Normally the alkene with fewer alkene H's is formed more extensively over alkenes with more alkene H's. (More C-substituted alkene is major).**
- Neutral/acidic (the formula starts neutral, but acid is produced)
- 1st order rate law $r = k[RX]^1$

E1 Mechanism: 2 Steps
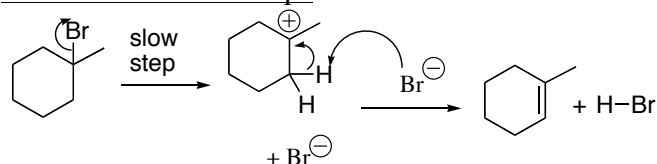
1. Step 1: Carbocation Formation. THIS IS THE SLOW STEP
   a. Therefore the rate is controlled by cation stability! Just like S_N1!
   b. Benefits from exactly the same factors that speed up S_N1 ($3° > 2°$, RI > RBr, polar solvent, etc..)
2. Step 2: Deprotonation from a carbon that neighbors the cation/original halogenated carbon
   a. Can draw bromide as base for simplicity
   b. But often it's actually water or alcohol solvent that picks up the proton

E1 Summary
   Recognition: A. Neutral, weak nucleophile. No anionic nucleophile/base, and
                       B. $3°$ or $2°$ alkyl halide. (Controlled by cation stability).
   (For $2°$ alkyl halides, E1 is often accompanied by variable amounts of S_N1.)
   Orientation: The most substituted alkene forms
   Predicting the major product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.
   Stereochemistry: Not an issue. The eliminating hydrogen can be cis or trans. .
   Mech: Stepwise, 2 steps, via carbocation. Be able to draw completely.

E2 Elimination Reaction (2nd Order, Under Anionic/Basic S_N2 type Conditions) **(5.15, 5.14-5.18)**

Examples

3° R-X → NaOCH₃ → E2 (major) + E2 (minor E2) + HOCH₃ + HBr

No Competing S_N2 for 3° R-X

3° R-X → NaOH → major + minor + H₂O + HBr

No Competing S_N2 for 3° R-X

2° R-X → NaOH → S_N2 (More of this than either E2 product) + major E2 (of the E2's) + minor E2 (of the E2's) + H₂O + HBr

S_N2 and E2 Compete for 2° R-X
Normally there is more S_N2 than E2

1° R-X → NaOH → S_N2 + NaBr

S_N2 only, no competing E2 Compete for 1° R-X
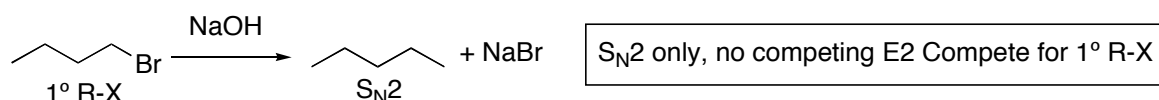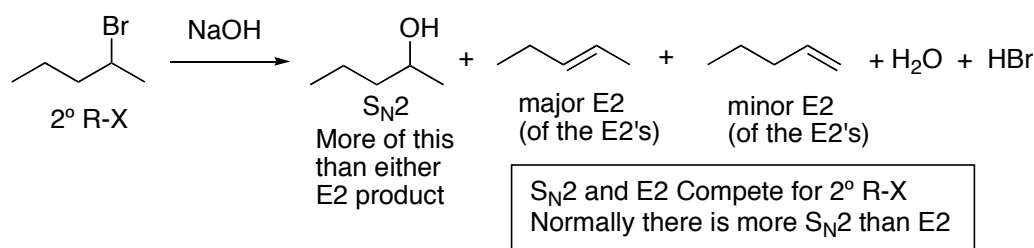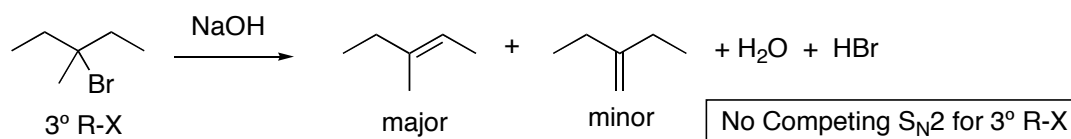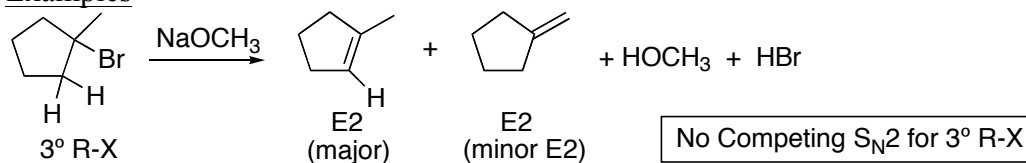
Notes
- E2 happens with **anionic nucleophiles/bases**, when S_N2 is hindered
- Structurally Isomeric Alkenes can form
  - The double bond must involve the original halogenated carbon and any neighbor carbon (that had a hydrogen to begin with that can be eliminated)
  - Normally the alkene with fewer alkene H's is formed more extensively over alkenes with more alkene H's. (More C-substituted alkene is major).

Mech

+ H−OCH₃ + Br⁻
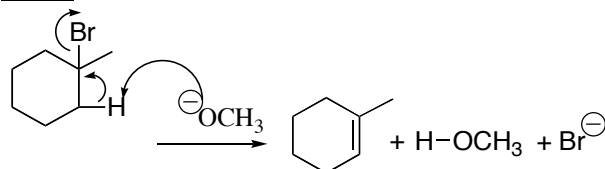
- anionic. Anion base gets things started.
- 2nd order rate law.   Rate = $k[\text{R-X}]^1[\text{anion base}]^1$
- It all happens in one concerted step, but there are three arrow to show all the bond making and breaking

Bonds Made	Bonds Broken
Base to hydrogen	C-X bond
C=C pi bond	C-H bond

E2 Summary
   Recognition: A. Anionic Nucleophile/Base, and
                            B. 3º or 2º alkyl halide
   (1º alkyl halides undergo S$_N$2 instead. For 2º alkyl halides, E2 is often accompanied
   by variable amounts of S$_N$2. For 3º halides, S$_N$2 doesn't compete. vinyl/aryl don't
   do E2)
   Orientation: The most substituted alkene forms (unless a bulky base is used, test
   3…)
   Predicting product: Remove halide and a hydrogen from the neighboring carbon
   that can give the most highly substituted alkene. The hydrogen on the neighboring
   carbon must be trans, however.
   Stereochemistry: Anti elimination. The hydrogen on the neighbor carbon must be
   trans/anti.
   Mech: Concerted. Uses anion. Be able to draw completely. Only one concerted
   step!

S$_N$1 vs E1
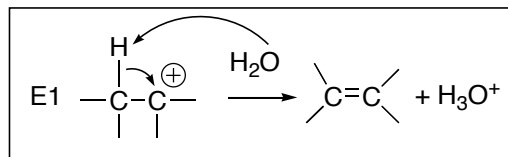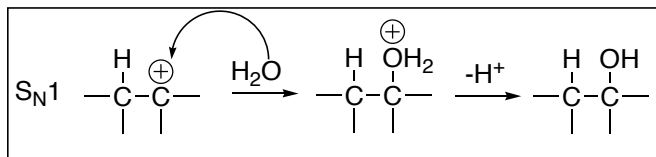
- Both satisfy the carbocation. They just meet it's bonding need with different
  electrons.

S$_N$2 vs E2
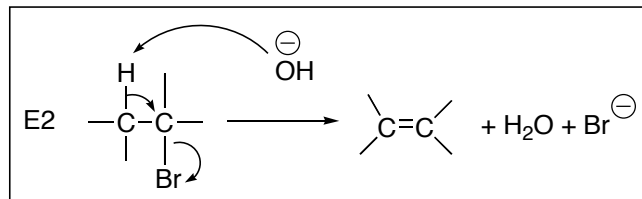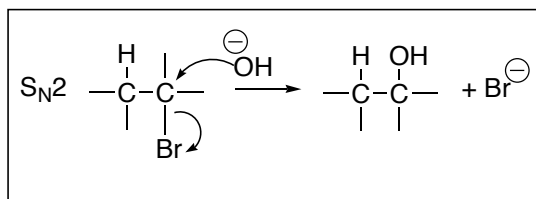
1. Both provide an electron pair to displace the C-Br bond pair. They just use different
   electrons.
2. Both involve the anion. It's called the nucleophile in the SN2, the base in the E2.
3. The SN2 involves a crowded transition state, and thus is strongly impacted by steric
   factors. The E2 does not have any steric problems (and in fact alleviates them).
4. The difference in steric profile explains why for SN2, 1º > 2º > 3º, but that for E2,
   the reactivity of 3º is just fine.

Zaitsev's Rule: When E1 or E2 elimination can give more than 1 structurally isomeric alkene, **the more highly Carbon-substituted alkene form will predominate over a less highly carbon-substituted alkene**. (5.10, 5.14)
a. **The fewer H's on the product alkene the better (product stability/reactivity rule).**
   - o   Every Alkene has four attachments. The fewer of these that are H's, the better.
   - o   When pictures are drawn in which the H's are not shown, the more highly substituted alkenes turn out to be the best.
b. Why? Product Stability-Reactivity Rule. Alkenes with more C's and fewer H's attached are more stable.
c. Alkene Stability is shown below: tetra- > tri- > di- > mono- > unsubstituted
   - o   Why?
     - ▪   Alkene carbons are somewhat electron poor due to the inferior overlap of pi bonds. (One carbon doesn't really "get" as much of the other carbon's electron as is the case in a nice sigma bond).
     - ▪   Since alkyl groups are electron donors, they stabilize electron-deficient alkene carbons.
     - ▪   Analogous to why electron-donating alkyls give the 3° > 2° > 1° stability pattern for cations and radicals
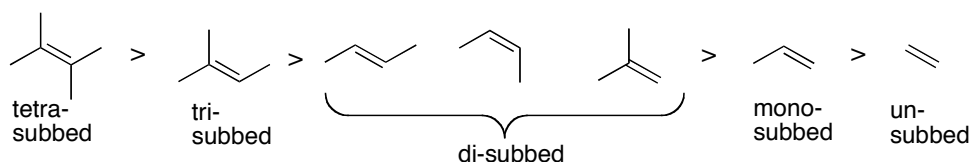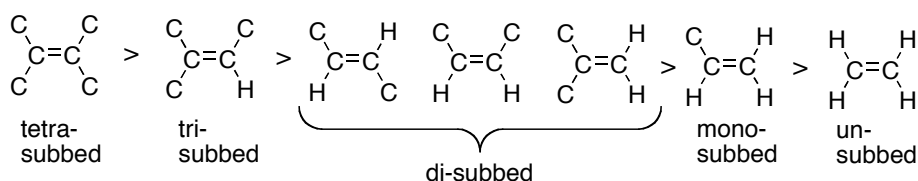
Examples
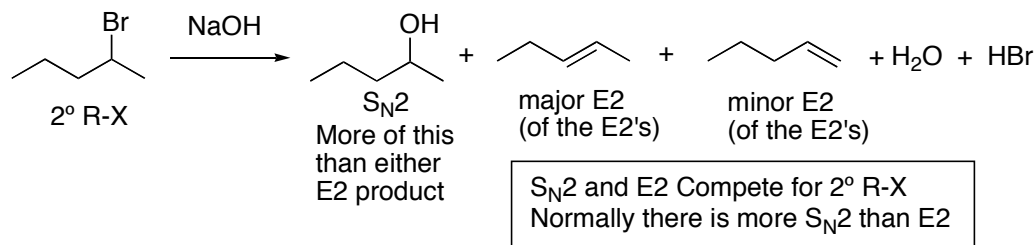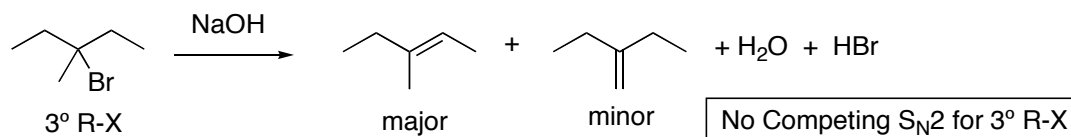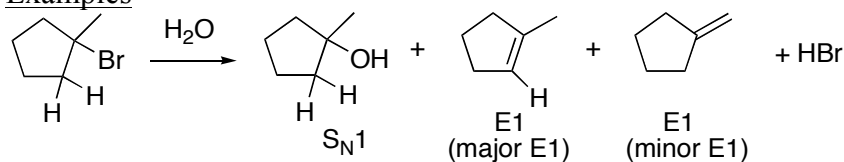
Stereochemistry of E2 Eliminations (5.16)
1. For E2 (not for E1) C-H and C-X bonds must be in the same plane (**coplanar**)
2. The halogen and the hydrogen being removed must be **trans** to each
3. Why?
    a. Due to orbital overlap requirements.
    b. In the concerted E2 mechanism, the electrons from the hydrogen must essentially come in backside to the leaving halide
    o   just as in backside-attack S_N2 mechanism

"D" is deuterium
isotopically labeled hydrogen

major   minor
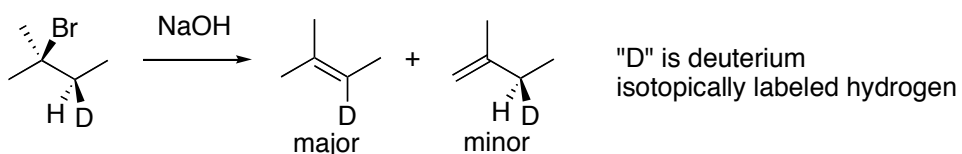
4. Sometimes, a molecule will need to single-bond spin into a "trans" conformation to enable a trans-elimination.

Can't react   Can React
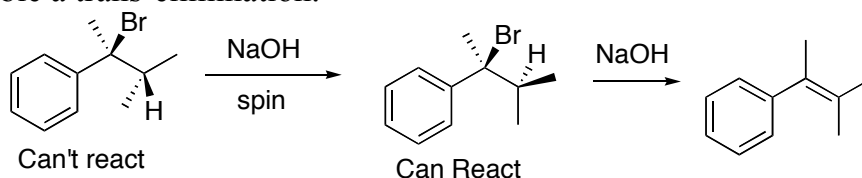
5. Eliminations in **Cyclic Compounds** are Often impacted by the Trans Requirement
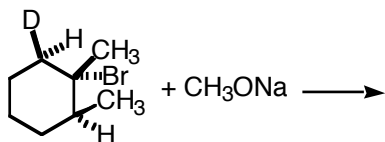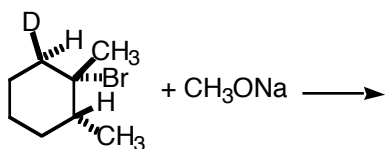
Comparing E2 vs E1

		E1	E2
1	Nucleophile/Base	Neutral, weak, acidic	Anionic, strong, basic
2	Substrate		3° RX not allowed
	Allylic effect…	Allylic Helps	Non-factor
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	k[RX]	k[RX][Anion]
6	Stereochemistry	Non-selective	Trans requirement
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never
9	Orientation	Zaitsev's Rule: Prefer more substituted alkene	Zaitsev's Rule: Prefer more Substituted alkene (assuming trans requirement permits)

Elimination Problems: Draw the major <u>Elimination</u> Product for the following Reactions. Classify as E1 or E2.   (There may be accompanying S_N2 or S_N1 material, but to whatever degree elimination occurs, draw the major product.)

1.   [structure with Br] + CH_3OH ⟶

2.   [cyclopentane with Br] + CH_3OH ⟶

3.   [structure with Br] + CH_3ONa ⟶

4.   [cyclopentane with Br] + CH_3ONa ⟶

5.   [structure with Br] + CH_3ONa ⟶

6.   [cyclohexane structure with D, H, CH₃, Br, CH₃, H] + CH_3OH ⟶

7.   [cyclohexane structure with D, H, CH₃, Br, CH₃, H] + CH_3ONa ⟶

8.   [cyclohexane structure with D, H, CH₃, Br, H, CH₃] + CH_3ONa ⟶

Comparing S_N2 vs S_N1 vs E2 vs E1:   How Do I Predict Which Happens When?

Step 1: **Check nucleophile/base**.
c. If **neutral**, then **S_N1/E1** → mixture of both
d. If **anionic**, then **S_N2/E2.**
Step 2: If **anionic**, and in the **S_N2/E2** pool, then **Check the substrate**.
   a. 1° → **S_N2**
   b. 2° → **S_N2/E2 mixture.**   Often more **S_N2**, but not reliable…
   c. 3° → **E2**

Notes:

1° R-X	S_N2 only	No E2 or S_N1/E1 (cation too lousy for S_N1/E1; S_N2 too fast for E2 to compete)
3° R-X	E2 (anionic) or S_N1/E1 (neutral/acidic)	No S_N2 (sterics too lousy)
2° R-X	mixtures common	

- Note: Aryl and Vinyl Halides will not undergo **any** of these types of reactions.
- If you see Br₂/hv type recipe, then you're back in the chapter 4 world of radical halogenation

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3° R-X	E2 (anionic) or S_N1/E1 (neutral/acidic)	No S_N2 (sterics too lousy)
2° R-X	mixtures common	

- Note: Aryl and Vinyl Halides will not undergo **any** of these types of reactions.
- If you see Br_2/hv type recipe, then you're back in the chapter 4 world of radical halogenation

For each mixture,
a. Classify the Type of Reaction (or "no reaction")
b. Draw the <u>major</u> product. (Or both a substitution and elim product..)

1. ![Br + NaO-C(=O)-CH3 →]

2. ![Br-C(CH3)2-CH2CH3 + NaOH →]

3. ![cyclopentyl-I + NaOCH3 →]

4. ![cyclopentyl-Br + propanol (OH) →]

5. ![cyclohexenyl-Br + H2O →]

6. ![CH2=CH-CH2-Br + KOH →]

7. ![cyclopentenyl-I + H2O →]

8. ![cyclohexyl with Br + PhSH →]

9. ![CH3CH2-CH2-Br + H2O →]

10. ![isobutyl/isopentyl structure + Br2 → hv]
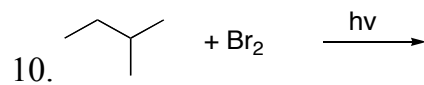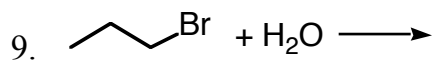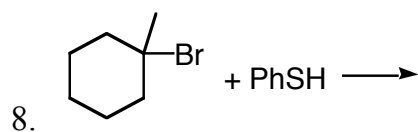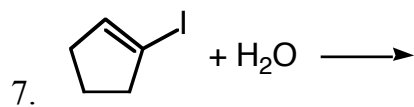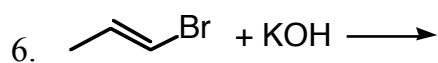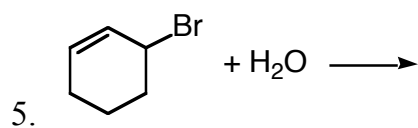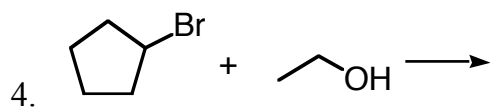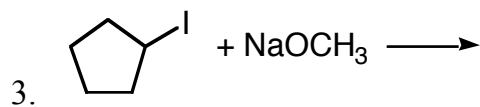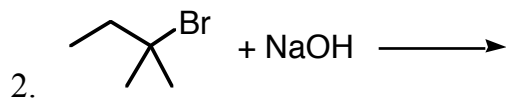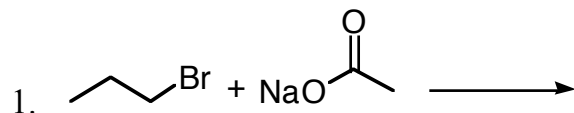
Design Synthetic Plans for converting the starting materials into the target molecules.

1. In each case, more than one chemical operation will be required.
2. Strategy: R-H → R-Br (via bromination) → Substitution product (via SN2) or alkene (via E2)

1.

2.   (no substitution side product)

3.

4.   (some alkene would accompany this product)
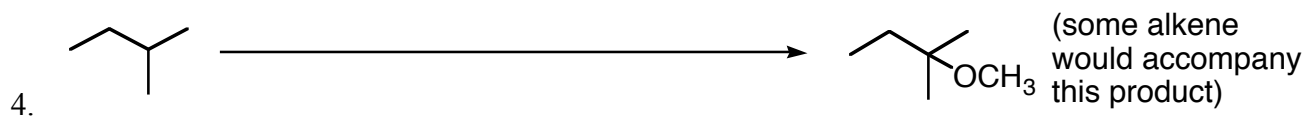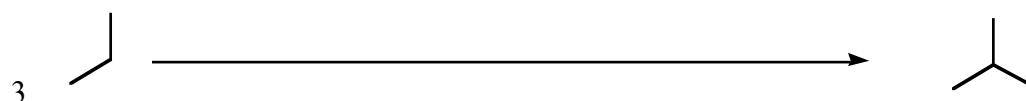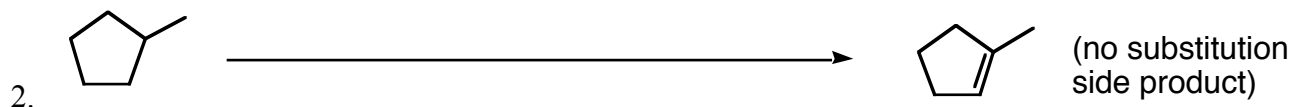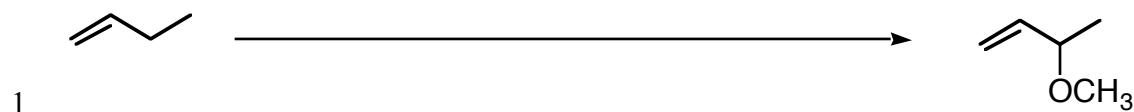
Keys:
1. These can't be done directly, in a single recipe. At least two laboratory operations are required.
2. Each sequence show above requires an increase in functional groups. An S_N2/S_N1 or E2/E1 changes functionality but does not create functionality. But radical bromination does create a functional group.

3. Thus the key reaction for creating the functionality: R-H →

4. Once you've converted the starting alkane to alkyl bromide, you can interconvert that bromide group into something else by S_N2/S_N1 or E2/E1

Practice: Mechanism Practice

Draw the **mechanism** for formation of the major product in each of the following reactions. In some cases where both elimination and substitution might compete, the problem specifies whether to draw the substitution or elimination mechanism.

A.

$+ H_2O$ (Subst.)

B.

$+ NaOCH_3$ elim.

C.

$+ Br_2$

D.

$+ NaO$ Subst.

E.

$+ H_2O$ elim
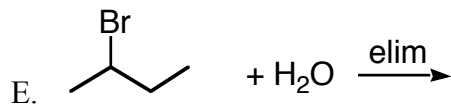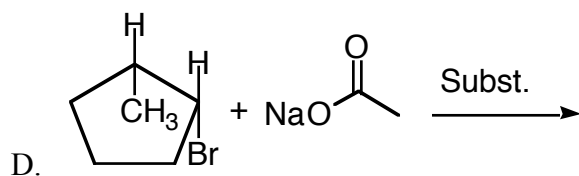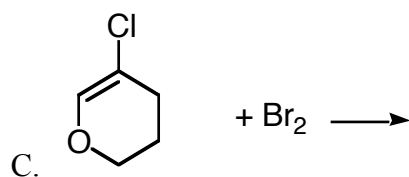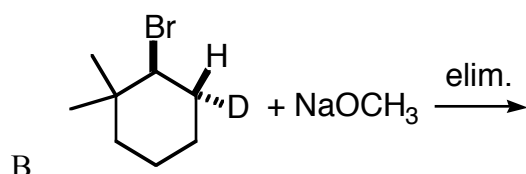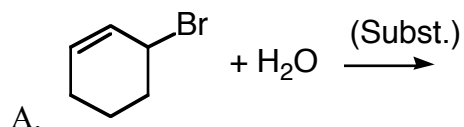
Practice: Ranking Practice
Rank the Reactivity of the chemicals shown toward the thing in the box. Keys:
  ▪ Identify the type of reaction that would be involved
  ▪ Think about the rate-determining step and how reactant or product or transition-state stability would influence the rate.

1.
2. Br₂, hv

3.

4.

5. (Sₙ1)

6. NaOH

H₃C–CH₃

Cl•   Br•   I•

CH₃OH

CH₃OH   ONa   ONa
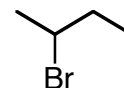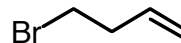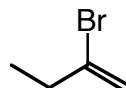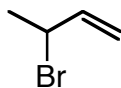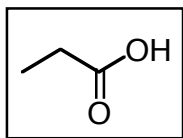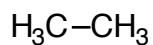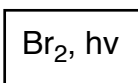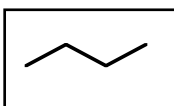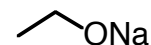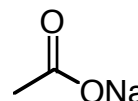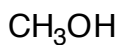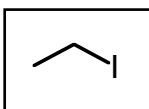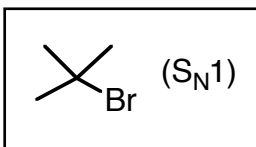
Solvent: Pentane   H₂O
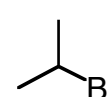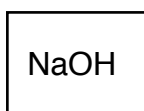
Practice: Predict-the-Product Practice
Give the Major Product(s) for each of the following. If it's likely to give a mixture of both substitution and elimination, just draw the substitution product. Designate stereochemical outcomes when stereochemistry is relevant ($2°$ substrates).
Key: Try to recognize what type of reaction will happen first.

1. Br + $NaOCH_3$ ⟶

2. + Br_2 $\xrightarrow{hv}$

3. + CH_3SNa $\xrightarrow{\text{show sub only}}$

4. + CH_3OH ⟶

5. + $NaOCH_3$ ⟶

6. + $NaOH$ $\xrightarrow{\text{show sub only}}$

7. + H_2O $\xrightarrow{\text{show sub only}}$

8. + $NaOCH_3$ $\xrightarrow{\text{show elim only}}$
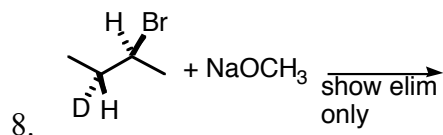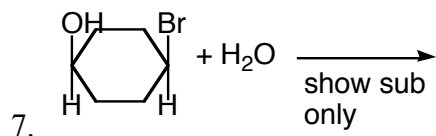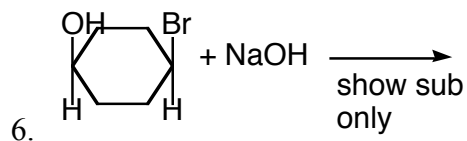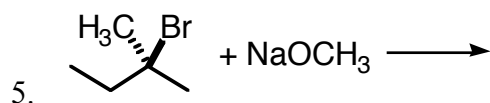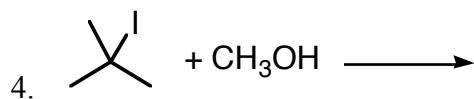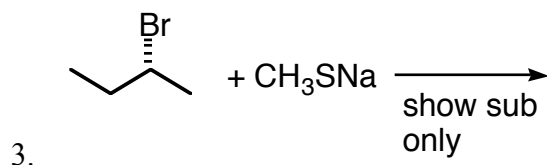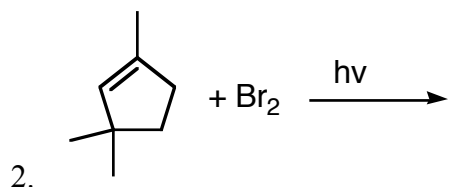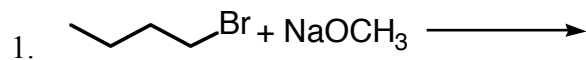
Provide Reactants for the Following (One of the Starting Chemicals must be an R-Br)

1.

2.

(trans only)

3.

(no substitution side product formed)

4.

(no elimination side product formed)

5.

Draw the Major <u>Alkene</u> Isomer, Following <u>Elimination</u>

6.

+ NaOCH₃   show elim only

7.

OH + H₂O   show elim only
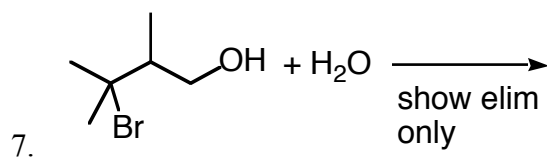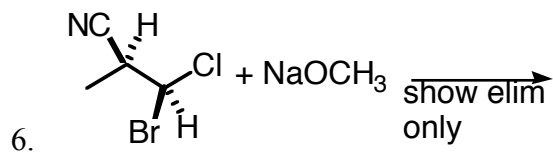
Carbocation Rearrangements (and their impact in S_N1 and E1 reactions) (5.13, 8.19)
1. Carbocations are very unstable, and sometimes rearrange to other more stable carbocations.
2. A rearrangement requires that a superior cation will result. Four cases:
    a. 2° → 3°
    b. non-allylic → allylic
    c. strained ring → unstrained or less strained ring
    d. 1° cation → 2° or 3° cation (rare, since 1° cations are hard to make and pretty rare)

Hydride Shifts		Alkyl Shifts
 2° 3°		 2° 3°
 2° 2° allylic		
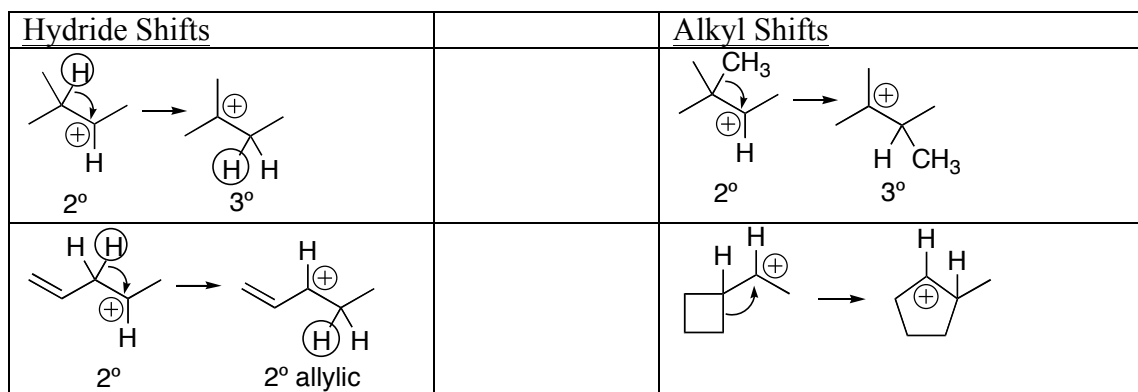
3. Two processes for cation rearrangement:
    a. Hydride shift (an H jumps over)
    b. Alkyl shift (a carbon jumps over)
        ▪ The resulting cation must always be on a carbon adjacent to the original
        ▪ rearrangement does not occur if you start with a good cation.
4. Most cation mechanisms that start with 2° or 3° cations don't undergo rearrangement because rearrangement does not lead to improved cation stability

Why Bother? No Stability Gain, No Motive, **Won't Happen**	 3° 2°		 2° 2°
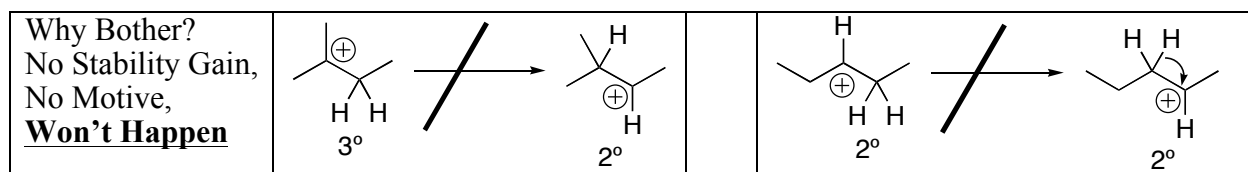
5. Examples in SN1
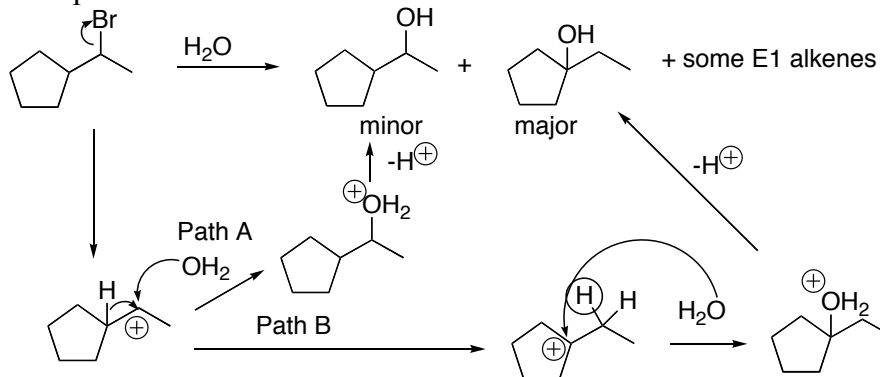
   • Product mixture results from competition between Path A and Path B.
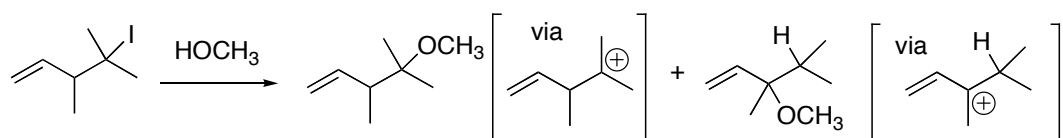
Ch. 5 Structure and Synthesis of Alkenes

7. 2 Review

Bond Strength	
C-C σ Bond	83 kcal/mol
C=C π Bond	63 kcal/mol

a. π Bonds are much weaker
b. π Bonds are thus more breakable and more reactive

  Double Bonds can't rotate

7.3 Elements of Unsaturation ("EU")/Index of Hydrogen Deficiency) (13.25)
- **"Saturated Alkane"**: C_NH_{2N+2}
- **Unsaturated** Formula: Has less than the maximum 2N+2 number of hydrogens
1. "**Element of Unsaturation**": Something that reduces the hydrogen count by two
   a. Double bond
   b. Ring

2. Each element of unsaturation reduces the hydrogen count by two
3. A molecule may well have several elements of unsaturation, each one progressively reducing it's hydrogen count by two.

---

4. Knowing how many elements of unsaturation are present helps to classify, and helps in isomer problems.

---

5. Calculating EU
General Concept

$$EU = \frac{\text{Theory \# H's - Actual \# H's}}{2}$$

For Formulas With Nothing Other than C, H, or O

$$EU = \frac{(2C + 2) - H}{2}$$

C = # C's
H = # H's
N = # N's
X - # halogens

For Formulas That May Include Nitrogen or Halogens

$$EU = \frac{(2C + 2 + N) - (H + X)}{2}$$

6. Heteroatom Effect:
   - Oxygens: No effect
   - Nitrogen: each nitrogen increases the theory # H's by 1
   - Halogen: each halogen takes the place of a hydrogen and reduces the theory # H's by 1.
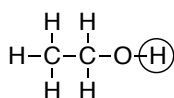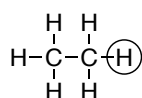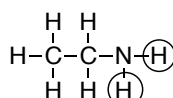
Oxygen: no impact   Nitrogen: adds one   Halogen: replaces one
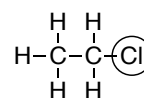
Calculate how many elements of unsaturation are in the following formulas:

1. C_5H_{12}

2. C_4H_8

3. C_3H_4O

4. C_5H_9Cl

5. $C_4H_{11}N$

Distinguishing Rings from Double Bonds by H₂/Pt Hydrogenation
    a. H_2/Pt will "saturate" **all** C=C double bonds by adding H_2 across each one.
    b. However, rings will not add hydrogen upon treatment with H_2/Pt
    c. Thus you can count how many of your EU's are rings versus double bonds
    d. Note: 2H's add per 1 double bond
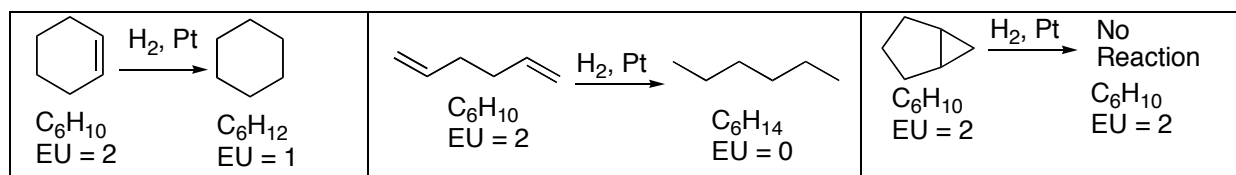
6. For C_4H_8 , draw all possible structures for isomer A and isomer B, given the following:

   a. C_4H_8 (A) $\xrightarrow{\text{H}_2,\ \text{Pt}}$ C_4H_{10}

   b. C_4H_8 (B) $\xrightarrow{\text{H}_2,\ \text{Pt}}$ No reaction
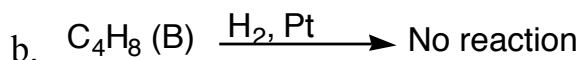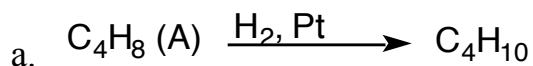
7. Which of the following is possible for structure C?

C_5H_8 (C) $\xrightarrow{\text{H}_2,\ \text{Pt}}$ C_5H_{10}
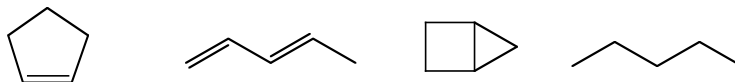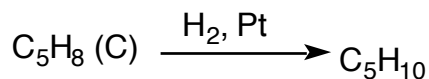
5.1,4 Alkene Nomenclature
A. When the Alkene is in the Core Name (the priority functional group)
1. Number the longest continuous alkene-containing C-chain from the end nearest the alkene
    → core name = "alk-x-ene"
2. Designate the position of the alkene by using the lower-numbered of the two alkene
    carbons
3. Attach and number substituents
4. When alkene stereoisomer issues apply:
    • Designate stereochemistry as (E) or (Z)

Give formal names for the following alkenes
Simple Acyclics

1.

Br   2.

Rings

3.   .CI
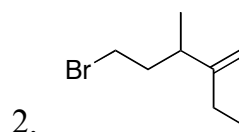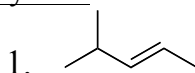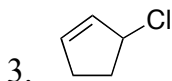
B. Alkenes as Substitutents
• Many functional groups have higher priority than alkenes, so that alkenes may
   need to be named as substituents rather than in the core name

Four to Memorize:

$^{\sim}C=C\overset{H}{\diagdown}$ $\overset{H}{}\quad\overset{H}{}$ Vinyl	$\overset{H_2}{\sim C}$ $\overset{}{}C=C\overset{H}{\diagdown}$ $\overset{H}{}\quad\overset{H}{}$ Allyl	$=CH_2$ Methylene	Phenyl = "Ph"

Name the following:

1.   2.   3.   4.
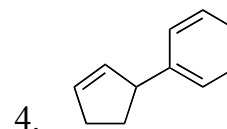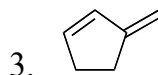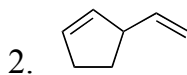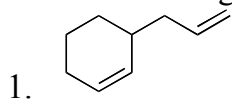
(E)-(Z) for Alkene Stereochemistry (5.4)
• Each carbon of an alkene has two attachments.

1. Check whether (E)/(Z) stereochemistry is relevant. If so:
2. Identify which of the two attachments on the left alkene carbon has higher priority.
   • Use the same priority rules as were used in R/S chirality context
3. Then identify which attachment on the right alkene carbon has higher priority.
4. Assign (E) or (Z) based on whether the two priority attachments are on same or opposite side
   • (Z) ("zusammen" = "together"): the priority attachments are cis
   • (E) ("entgegan = "opposite"): the priority attachments are trans
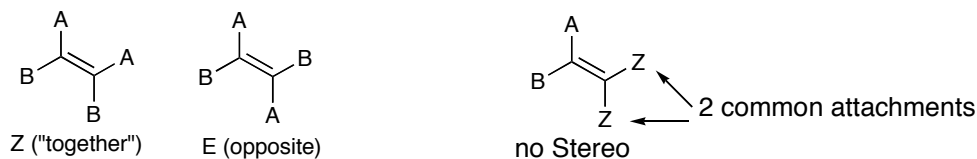
When does (E)/(Z) apply?
   • If either alkene carbon has two common attachments, then stereo doesn't apply

Assign as (Z) or (E)
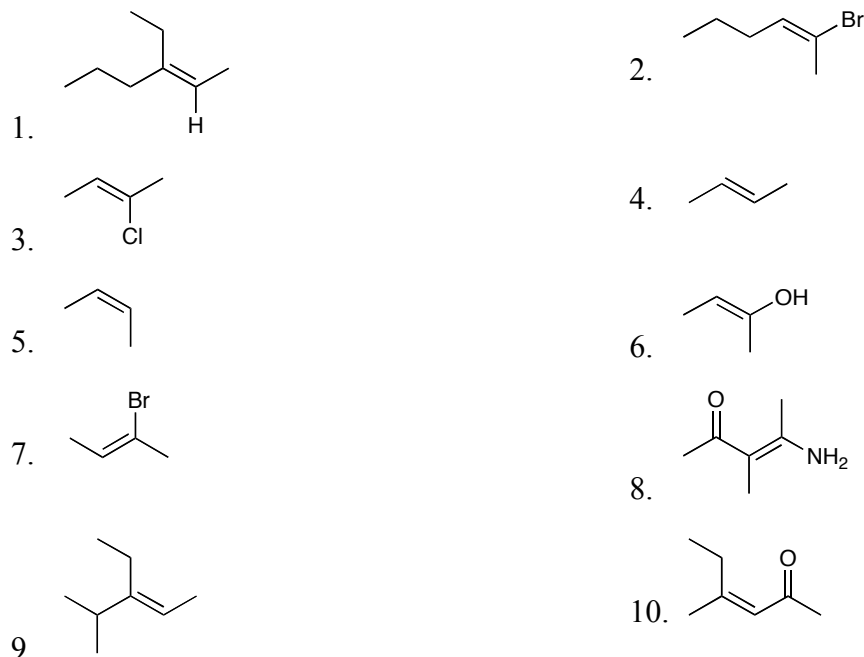
5.6 Alkene Stability Pattern
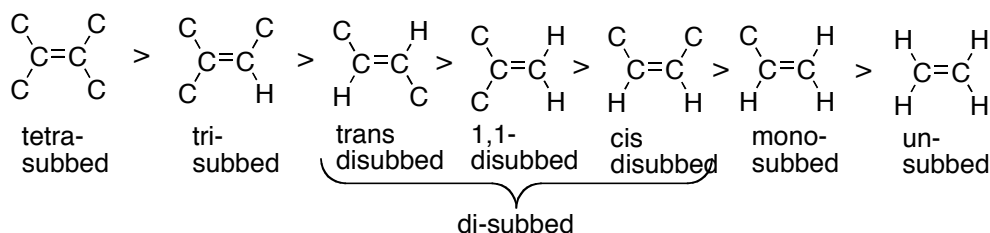
1. Increasing Substitution (# of non-hydrogens directly attached to alkene carbons) →
    Increased Stability
    •   Why? Electronic Reasons.
    a. Alkene carbons are somewhat electron poor due to the inferior overlap of pi bonds.
        (One carbon doesn't really "get" as much of the other carbon's electron as is the case
        in a nice sigma bond).
    b. Since alkyl groups are electron donors, they stabilize electron-deficient alkene
        carbons.
    c. Analogous to why electron-donating alkyls give the 3° > 2° > 1° stability pattern for
        cations and radicals

2. Trans is more stable than cis for 1,2-disubstituted alkenes
    •   Why?   Steric Reasons

3. Measuring Relative Stability of Isomers by Heats of Hydrogenation or Heats of
    Combustion (6.2)

ΔH = -30.3 kcal/mol
More exo, more energy released

ΔH = -26.9 kcal/mol
Less exo, less energy released
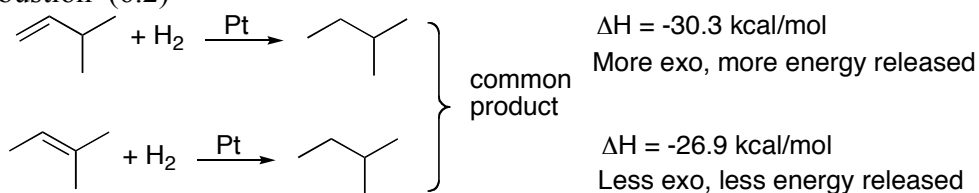
common product

    •   When 2 isomers can be converted to a common product, the relative magnitude of ΔH
        tells which isomer is more stable
    •   The more heat released, the less stable the isomer. The less heat released, the more
        stable.
    •   Heat of combustion works the same way (converts products to common CO_2 and H_2O)
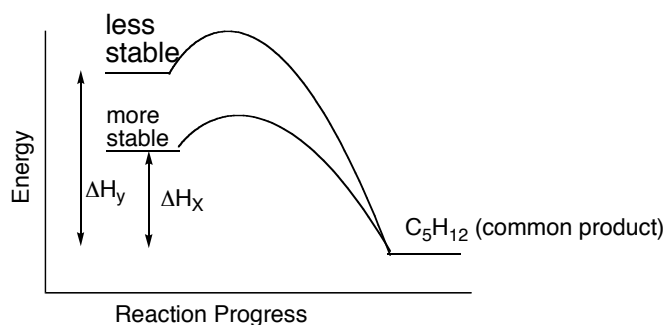
1. List the number of non-hydrogen substitutents on each alkene; rank the relative stability;
    rank by heat of hydrogenation, from 1 (most) to 4 (least)
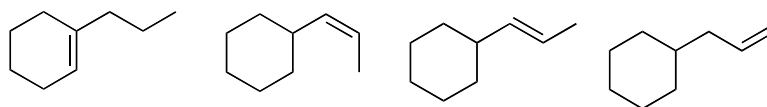
Stability:

Heat:

2. List the number of non-hydrogen substitutents on each alkene; rank the relative stability;
    When the following are burned, rank from the largest heat of combustion (1) to the
    smallest.
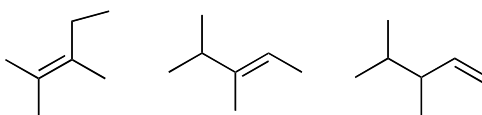
Stability:

Heat:

3. Which isomer is more stable, given the indicated heats of hydrogenation?

80 kcal/mol   74 kcal/mol
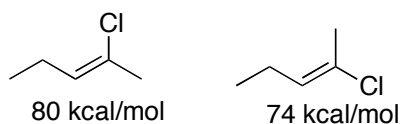
5.5 Physical Properties of Alkenes
• Nonpolar
• No hydrogen bonding
    • low boiling
    • Hydrophilic

5.14 Synthesis of Alkenes by E2 Elimination of Alkyl Halides (7.9A)
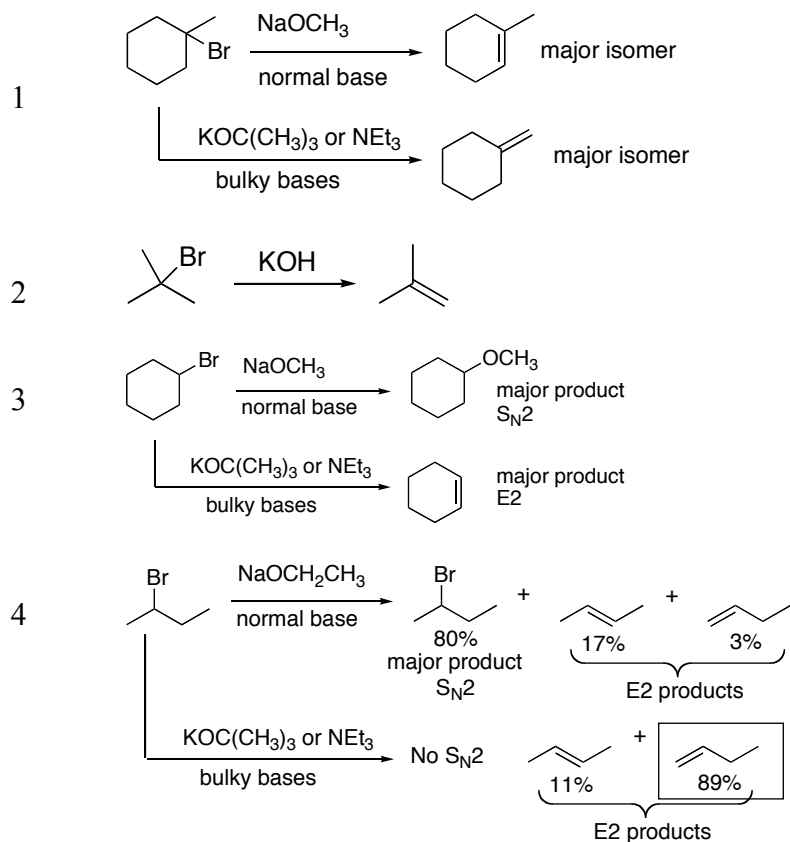
Factors to Consider
1. **3º R-X or 2º R-X**
    a. 3º R-X gives E2 with any base
    b. 2º R-X gives largely SN2 with normal anions.
    c. 2º R-X gives largely E2 with a **bulky base**. E2 prevails over S_N2
    •   Because SN2 backside attack is so sterically sensitive, bulky bases have problems
        doing SN2. Get E2 instead.
2. **Base Size: Bulky Base versus Normal Base**
    a. **Normal anions:**
    •   3º R-X give E2 only, no S_N2
    •   2º R-X give predominantly S_N2 rather than E2
    •   E2 elimiantions proceed with Zaytsev orientation: more-subbed alkene
        predominates
    b. **Bulky base.**
    •   3º R-X gives E2 only, no SN2 .
    •   2º R-X gives E2 only, no SN2 .
3. **E2's proceed via Hofmann orientation: less-subbed alkene predominates**
    •   For steric reasons: base goes after less sterically hindered neighbor hydrogen
4. **2 Bulky Bases to Memorize:**
    •   NEt3 (Triethylamine)
    •   KOC(CH3)3   potassium t-butoxide
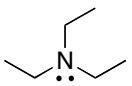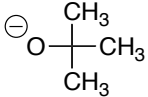
Bulky Bases: 2 to remember	Normal Bases
NEt₃ = "triethylamine" Neutral but amines are basic anyway KOC(CH₃)₃ = KOCMe₃ = ⊖O—C(CH₃)₃ "potassium t-butoxide"	NaOH, KOH, LiOH NaOCH₃, NaOCH₂CH₃, NaOCH₂CH₂CH₃ KOCH₃, KOCH₂CH₃, KOCH₂CH₂CH₃ etc.
Bulky bases are: 1. Good S_N2 nucleophiles only for 1° R-X 2. Do clean E2 with both 3° R-X and 2° R-X 3. Give Hofmann elimination (less substitued alkene major)	Normal bases are: 1. Anionic 2. Not especially bulky 3. Good S_N2 nucleophiles for 1° or 2° R-X 4. Only do clean E2 with 3° R-X 5. Give Zaitsev elimination (more substitued alkene preferred)

5. **Alkene Orientation: Zaytsev versus Hofmann Elimination**
   a. Zaytsev: most subbed alkene
      - The major E2 product involves removal of a hydrogen from the most substituted neighbor carbon
      - This results in a maximally substituted, maximally stable alkene (product stability)
      - Normal-sized bases give predominantly Zaytsev elimination
   b. Hofmann: least subbed alkene
      - The major E2 product involves removal of a hydrogen from the least substituted neighbor carbon
      - This results in a less substituted, less stable alkene
      - Bulky bases give predominantly Hofmann elimination
   c. Why: Steric reasons. A bulky base ends up having an easier time reaching a hydrogen on a less substituted carbon than on a more substituted carbon (transition-state stability-reactivity principle)

6. **Stereochemistry: A trans-hydrogen is required.**

7. **Mechanism: Concerted.**
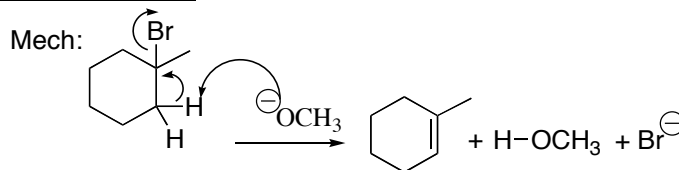
Predicting E2 Eliminations:
   1. Is the base normal or bulky?
   2. Is the R-X 3°, 2°, or 1°?
   3. Will E2 or S_N2 occur predominantly?
   4. Will you get Zaitsev or Hoffman elimination?
   5. Is there a trans hydrogen available?

Draw the major Product for each of the following Reactions.

1.

Br   NaOH →

NEt₃, heat →

2.

Br   NaOCH₃ →

KOC(Me)₃ →

3.

H Br
D   H   NaOH →
H⁗   CH₃

NEt₃, heat →

4.

H Br
D   CH₃   NaOH →
H⁗   H

NEt₃, heat →

5.

Br →

6.

Br →
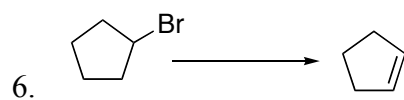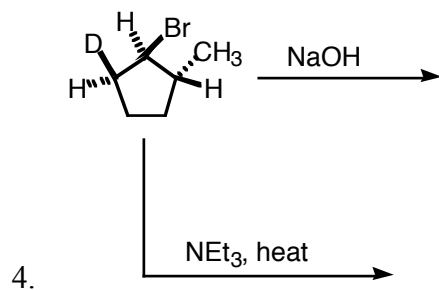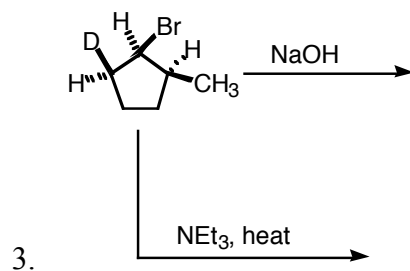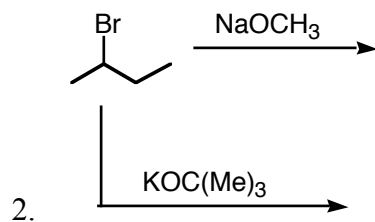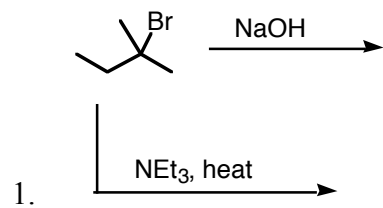
Indirect Route to Alkenes from Alkanes

Via 2 Reactions:
1. **Bromination (reaction 1) followed by**
2. **Elimination (reaction 2)**

H H   1. Br₂, hv   H Br   2. Base
—C–C—   ——————————→   —C–C—   ——————————→   C=C
                     Halogenation   E2 Elimination

Provide Recipe:

1.

2.
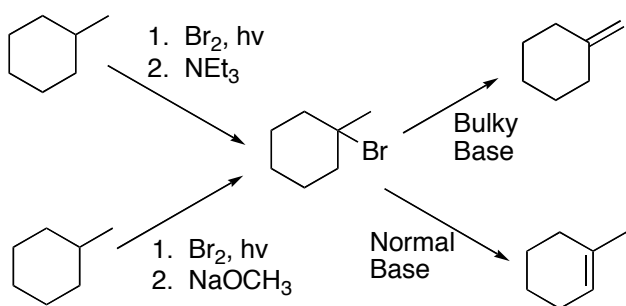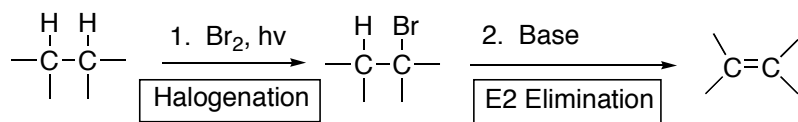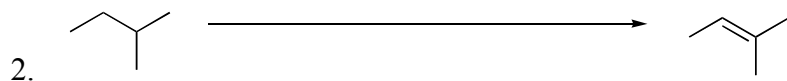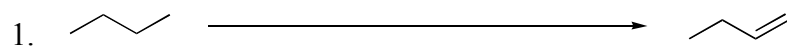
Synthesis of Alkenes from Alcohol (5.9-12)

General:

$$\underset{\text{H}\quad\text{OH}}{-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-} \quad \xrightarrow[]{\overset{H_2SO_4,\ \Delta}{\text{or } H_3PO_4}} \quad \overset{}{C}=\overset{}{C} \quad + H_2O$$

1   (+ isomers)

major

2

3
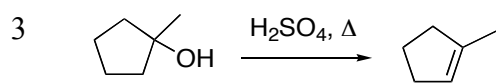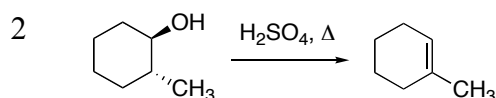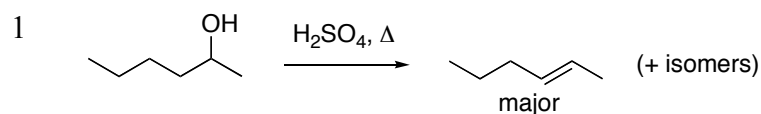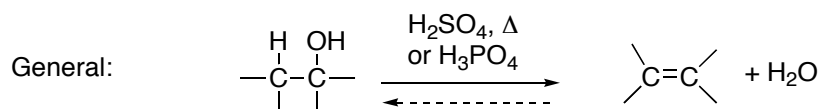
Observations:
1. Zaitsev, not Hoffman elimination.
2. No requirement for a trans hydrogen.
3. Acidic conditions, need an acidic mechanism.

Mechanism (Memorize)
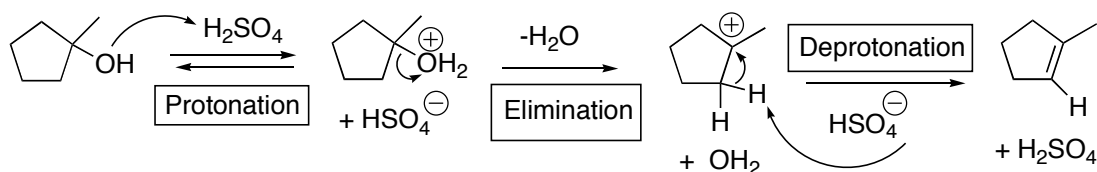
3 steps: Protonation – Elimination – Deprotonation

1. Protonation converts OH, a bad leaving group, into a very good leaving group (neutral water)
2. Carbocation formation is slow step (like E1 mechanism)
   • Cation stability dictates reactivity
   • Reactivity: allylic > 3° R-OH > 2° R-OH >>> 1° R-OH > vinyl, aryl
   • Allylic, 3°, and 2° work; 1°, vinyl, and aryl do not.
3. C-H cleavage comes last.

4. Mechanism typical for acid-catalyzed processes: protonate-react-deprotonate.
   • Protonation and deprotonation sandwich the key step.
5. Strong acidic conditions → intermediates should be positive, not negative
6. Because the cation is flat, and forgets original stereochemistry, there is no trans-H requirement.
7. The reaction is actually reversible, an equilibrium
8. Get complete E1, not S_N1, because the water that falls off in step 2 is converted to hydronium H_3O^+
9. Often the equilibrium is driven by distilling the alkene off as it forms (if it's low boiling due to loss of weight and being non-polar) or phase separating out from the acid layer.

Draw Products

a.   OH   H$_2$SO$_4$, heat
→

b.   OH   H$_2$SO$_4$, heat
→

c.   OH   H$_2$SO$_4$, heat
→

d.

H Z
D   CH$_3$ Z = OH
H   H   H$_2$SO$_4$, heat
→

Z = Br
→
NaOCH$_3$
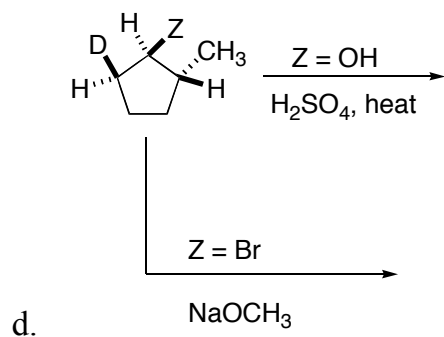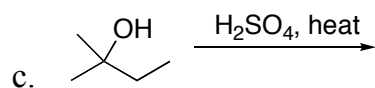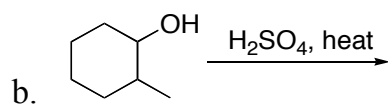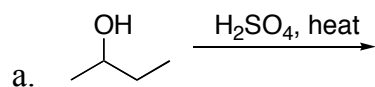
e. Rank the reactivity of the following toward H$_2$SO$_4$-catalyzed elimination (1 most). Why?

OH   OH   OH   OH
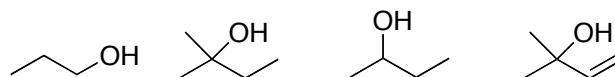
Key Issue:

Reactivity:

Reaction Mechanisms (Summary and Practice)

A. Recognizing/Classifying as Radical, Cationic, or Anionic

1. Radical
   • initiation requires both energy (either hv or Δ) and a weak, breakable heteroatom-heteroatom bond
      o Cl-Cl, Br-Br, O-O (peroxide), N-Br, etc..

   > 2 Guides for That are Usually Reliable:
   > hv → radical mechanism
   > peroxides → radical mechanism

2. Anionic
   a. **a strong anion/base appears in the recipe**
   b. no strong acids should appear in the recipe
   c. mechanisms should involve anionic intermediates and reactants, not strongly cationic ones
      o (except for do-nothing spectators like metal cations)
   d. The first step in the mechanism will involve the strong anion/base that appears in the recipe

3. Cationic
   a. **a strong acid/electrophile appears in the recipe**
   b. no strong anion/base should appear in the recipe
   c. mechanisms should involve cationic intermediates and reactants, not strongly anionic ones
      o (except for do-nothing spectators like halide or hydrogen sulfate anions)
   d. The first step in the mechanism will involve the acid that appears in the recipe. The last step will often involve a deprotonation step. Often the main step occurs in between the proton-on and proton-off steps

B. Miscellaneous Mechanism Tips

   1. Keep track of hydrogens on reacting carbons
   2. **Each step in a mechanism must balance**
   3. The types of intermediates involved (cation, anion, or radical) should be consistent with the reaction classification above
      a. **If the reaction is cationic, don't show anionic intermediates**
      b. **If the reaction is anionic, don't show cationic intermediates**
   4. Usually conditions are ionic.
   5. **Use a reactive species, whether strong anion or an acid, to start the first step**
      a. **If acidic, first step will involve protonation of the organic**
      b. **If anionic, the first step will involve the anion attacking the organic.**
   6. While it isn't always easy to figure out what is a good mechanism, you should often be able to eliminate an unreasonable mechanism.

1. Classify each mechanism as radical, cationic, or anionic.

a.

b.

c.

d.

----
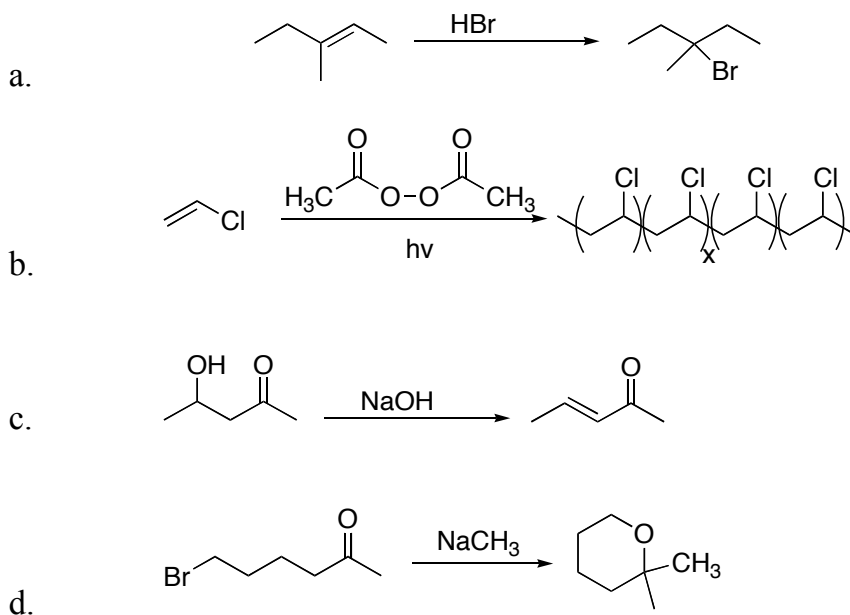
2. Which of the following mechanisms is reasonable or unreasonable for the transformation shown. Identify recognition keys for things wrong with those that aren't right.

Problems

1.

2.

3.

Q: Which of the following mechanisms is reasonable or unreasonable for the transformation shown:

$$\text{(alkene)} \xrightarrow{\text{H}_2\text{O, H}^+} \text{(isopropanol with OH)}$$

Identify recognition keys for things wrong with those that aren't right.

Problems

1.

2.

3.

4.

5.
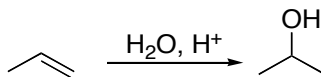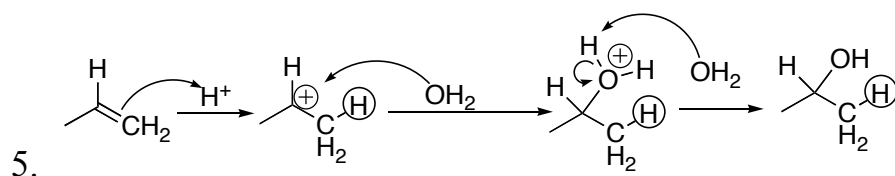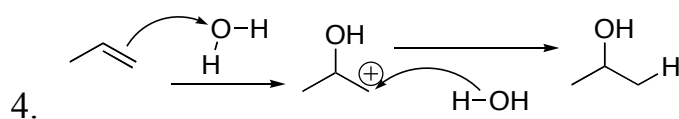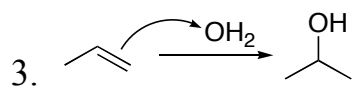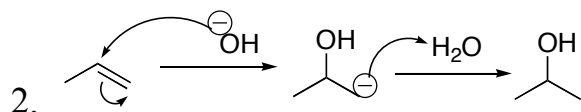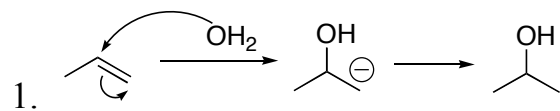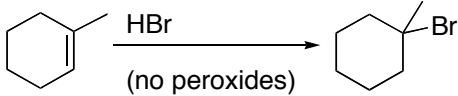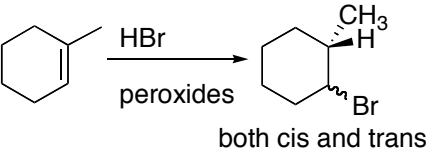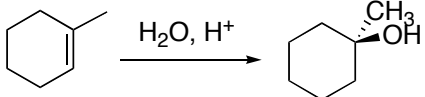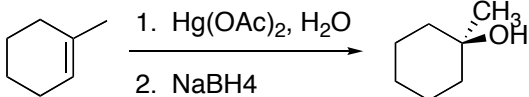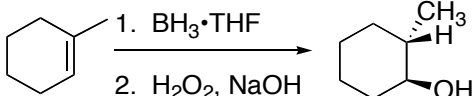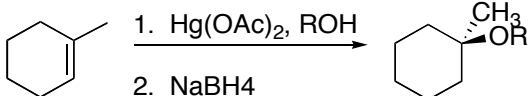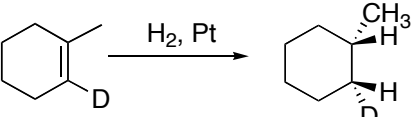
Summary of Alkene Reactions, Ch. 6.
Memorize Reaction, Orientation where Appropriate, Stereochemistry where Appropriate, and Mechanism where Appropriate.

-all are drawn using 1-methylcyclohexene as a prototype alkene, because both orientation and stereochemistry effects are readily apparent.

		Orientation	Stereo	Mechanism
1	HBr (no peroxides)	Markovnikov	None	**Be able to draw completely**
2	HBr peroxides — both cis and trans	Anti-Markovnikov	**Nonselective. Both cis and trans**	Not responsible
3	H₂O, H⁺	Markovnikov	None	**Be able to draw completely**
4	1. Hg(OAc)₂, H₂O 2. NaBH4	Markovnikov	None	Not responsible
5	1. BH₃•THF 2. H₂O₂, NaOH	Anti-Markovnikov	**Cis**	Not responsible
6	1. Hg(OAc)₂, ROH 2. NaBH4	Markovnikov	None	Not responsible
7	H₂, Pt	None	**Cis**	Not responsible

			Orientation	Stereo	Mechanism
8		CH₃ Br H Br	None	**Trans**	**Be able to draw completely**
9	Br₂, H₂O (or Cl₂)	CH₃ OH H Br	Markovnikov	**Trans**	**Be able to draw completely**
10	PhCO₃H	CH₃ O H	None	**Cis**	Not responsible
11	CH₃CO₃H H₂O	CH₃ OH H OH	None	**Trans**	**Be able to draw acid-catalyzed epoxide hydrolysis**
12	OsO₄, H₂O₂	CH₃ OH OH H	None	**Cis**	Not responsible

- t-butyl hydroperoxide often used instead of hydrogen peroxide

| 13 | 1. O₃ 2. Me₂S | | None | None | Not responsible |

Note: H-bearing alkene carbon ends up as aldehyde.

- Zn common option to (CH₃)₂S in step 2

| 14 | KMnO4 | | None | None | Not responsible |

H-bearing alkene carbon ends as carboxylic acid

Summary of Mechanisms, Ch. 7 + 8.
Alkene Synthesis and Reactions.
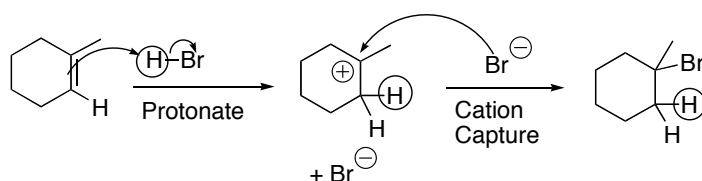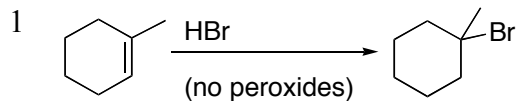
1

Note: For unsymmetrical alkenes, protonation occurs at the **less** substituted alkene carbon so that the **more** stable cation forms (3° > 2° > 1°), in keeping with the product stability-reactivity principle

Test Responsible
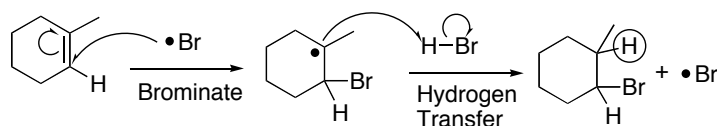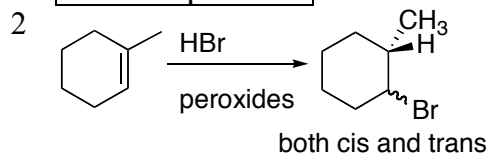
2

both cis and trans
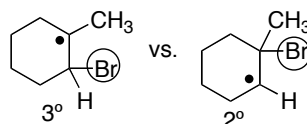
Note 2: Hydrogenation of the radical comes from either face, thus cis/trans mixture results

Note 1: For unsymmetrical alkenes, bromination occurs at the **less** substituted alkene carbon so that the **more** stable radical forms (3° > 2° > 1°), in keeping with the product stability-reactivity principle

Not test responsible

3
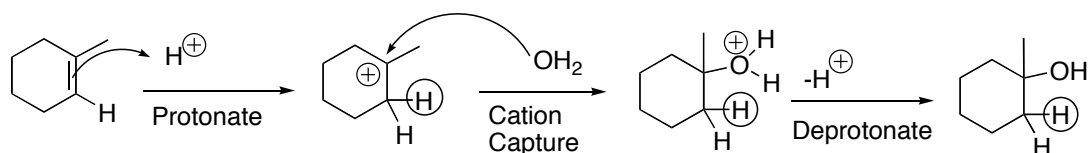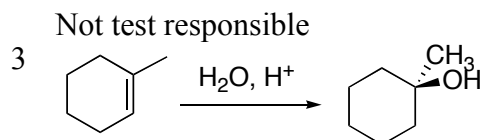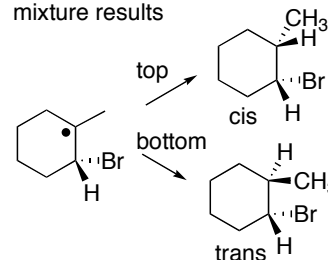
Note: For unsymmetrical alkenes, protonation again occurs at the **less** substituted end alkene, in order to produce the **more** stable radical intermediate (3° > 2° > 1°)

Test Responsible

4

1. Hg(OAc)₂, H₂O

2. NaBH4

Cation
Capture

-H⁺

Deprotonate

NaBH₄

Not test responsible

5

1. BH₃•THF

2. H₂O₂, NaOH
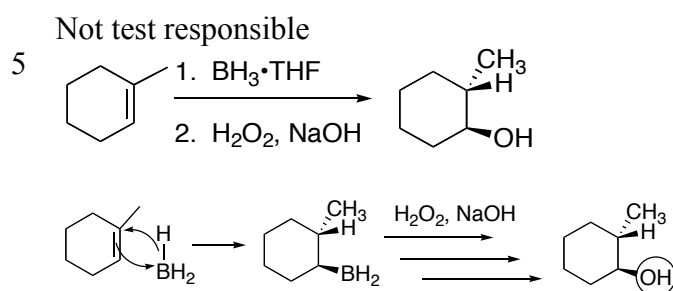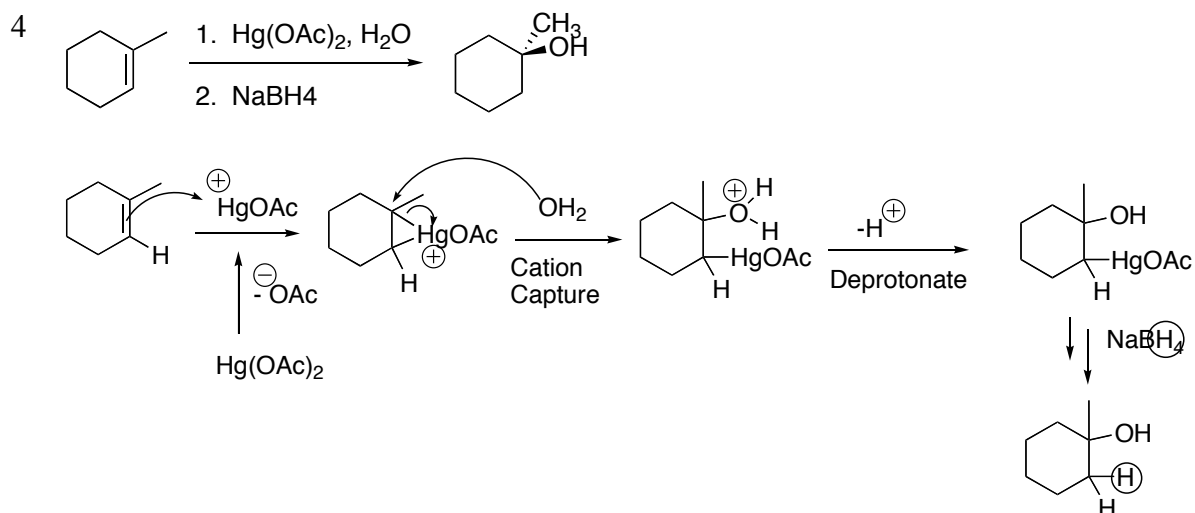
H₂O₂, NaOH

Notes
a. concerted addition of B-H across C=C
-explains the cis stereochemistry
b. the B-H addition is Markovnikov; the B is δ+, the H is δ-
c. The H₂O₂, NaOH process is complex, but replaces the B with OH with complete retention of stereochem
-the explains why the cis stereochemistry established in step one is preserved in step 2.

Not test responsible

6

1. Hg(OAc)₂, ROH

2. NaBH4

Cation
Capture

-H⁺

Deprotonate

NaBH₄
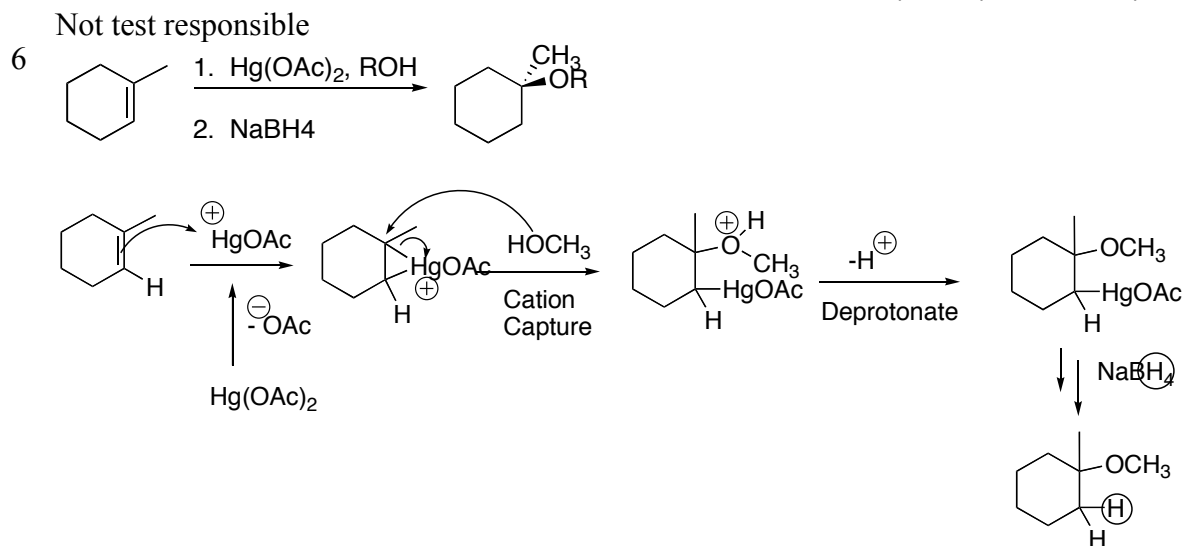
Not test responsible

8
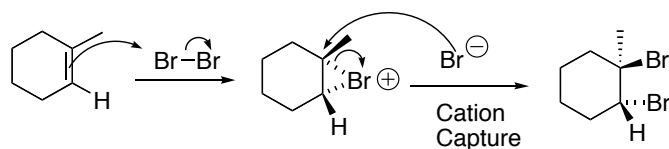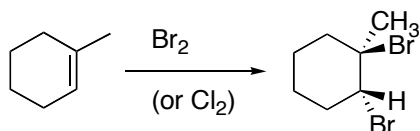
3 Notes
1. Cation intermediate is cyclic bromonium (or chloronium) ion
2. The nucleophile captures the bromonium ion via backside attack
-this leads to the trans stereochemistry
3. The nucleophile attacks the bromonium ion at the *more* substituted carbon

Test Responsible

9
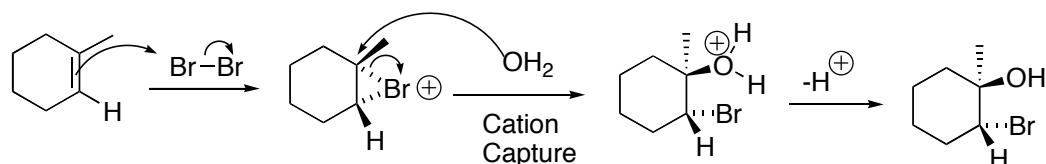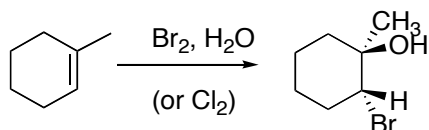
4 Notes
1. Cation intermediate is cyclic bromonium (or chloronium) ion

2. The nucleophile captures the bromonium ion via backside attack (ala SN2)
-this leads to the trans stereochemistry

3. The nucleophile attacks the bromonium ion at the *more* substituted carbon
-this explains the orientation (Markovnikov)
   • There is more + charge at the more substituted carbon
   • The Br-C bond to the more substituted carbon is a lot weaker
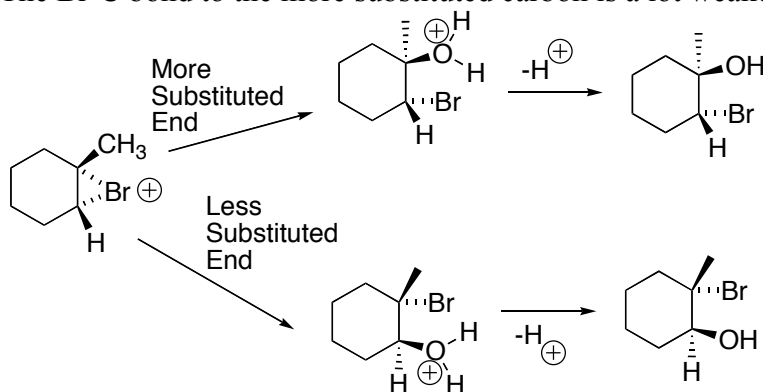
4. Alcohols can function in the same way that water does, resulting in an ether OR rather than alcohol OH.

Test Responsible

10

PhCO$_3$H
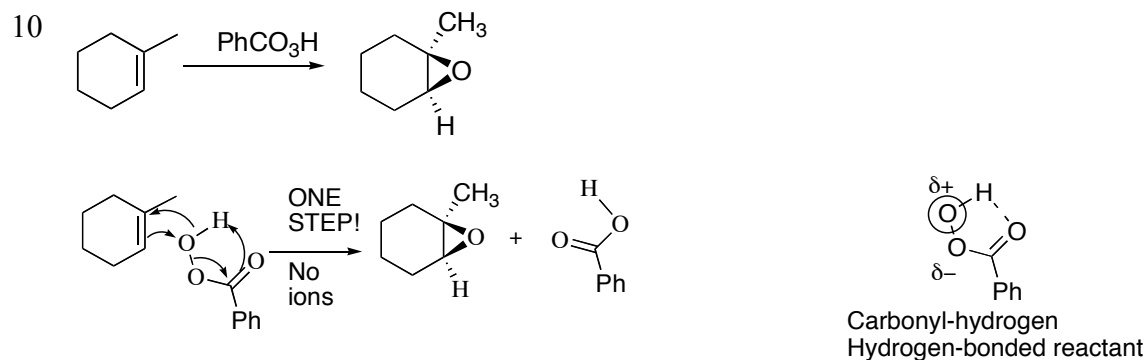
Notes
1. Complex arrow pushing
2. No ions required
3. The carbonyl oxygen picks up the hydrogen, leading directly to a neutral carboxylic acid
-The peracid is already pre-organized for this' via internal H-bonding between carbonyl and H
Not Test Responsible
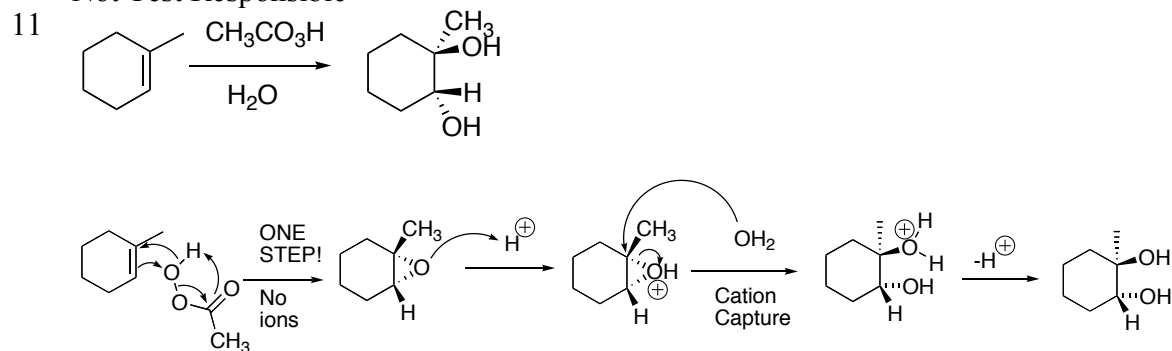
11

CH$_3$CO$_3$H

H$_2$O

Notes:
a. The nucleophile (water) attacks from the more substituted end of the protonated epoxide
   • More δ+ charge there
   • The C-O bond to the more substituted end is much weaker
b. The nucleophile adds via S$_N$2-like backside attack. Inversion at the top stereocenter, but not the bottom, explains the trans stereochemistry.

Test Responsible for Epoxide Opening

12

OsO$_4$, H$_2$O$_2$
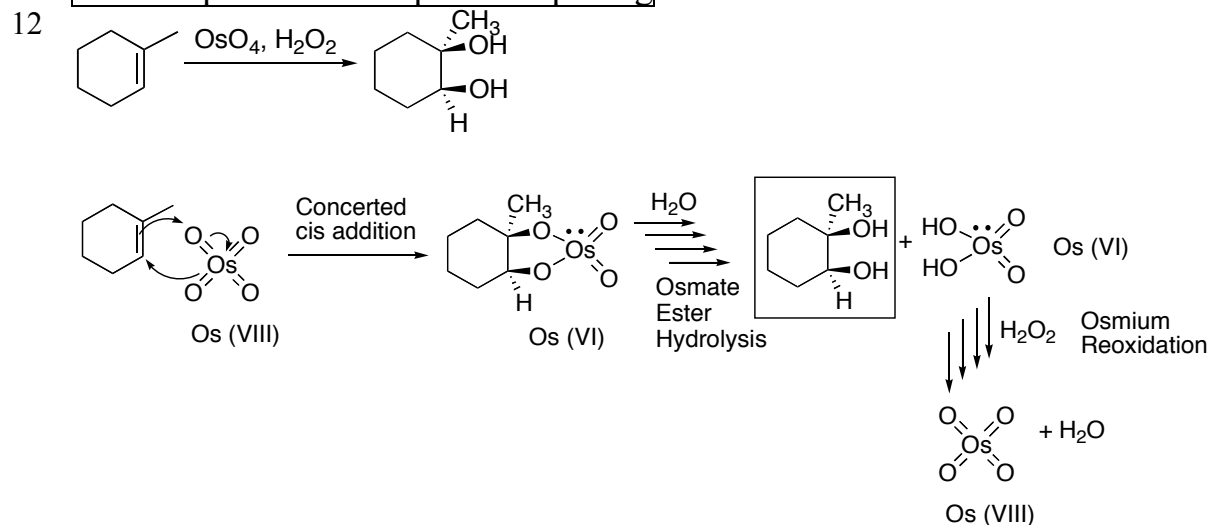
Not Test Responsible

Chapter 7 Reactions and Mechanisms, Review

E2
On
R-X,
Normal
Base
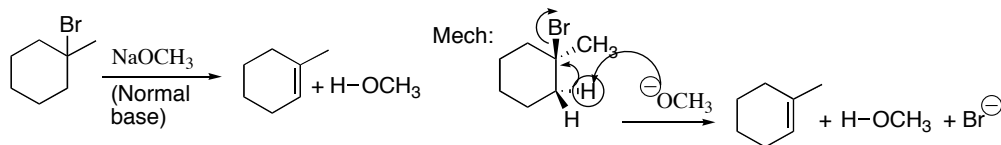
Notes
1. Trans hydrogen required for E2
2. Zaytsev elimination with normal bases
3. For 3º R-X, E2 only. But with 2º R-X, S_N2 competes (and usually prevails)
4. Lots of "normal base" anions.

Test Responsible

E2,
On
R-X, Bulky
Base
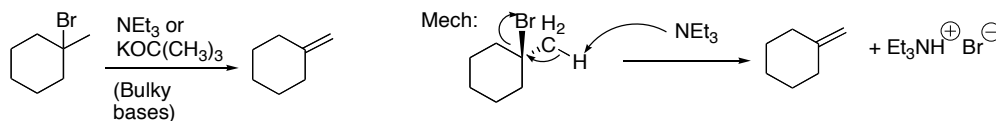
Notes:
1. Hoffman elimination with Bulky Bases
2. E2 dominates over S_N2 for not only 3º R-X but also 2º R-X
3. Memorize NEt_3 and $KOC(CH_3)_3$ as bulky bases.

Test Responsible

Acid-
Catalyzed
E1-
Elimination
Of
Alcohols
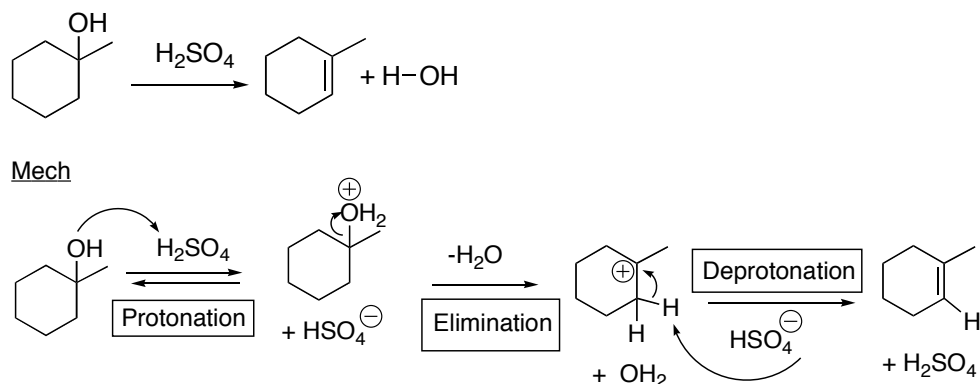
Notes:
1. Zaytsev elimination
2. Cationic intermediate means 3º > 2º > 1º
3. 3-Step mechanism

Test Responsible

Ch. 6 Reactions of Alkenes

Introduction

Addition Reaction
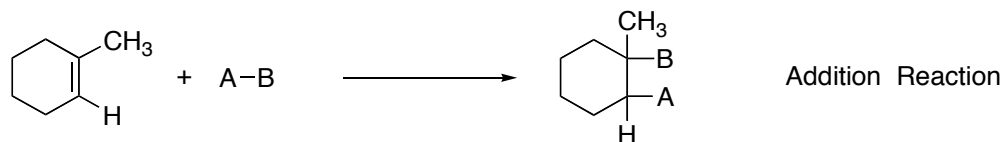
1. Thermodynamics: Usually exothermic
    *   1 π + 1 σ → 2 σ bonds
2. Kinetics: p bond is exposed and accessible

Generic Electrophilic Addition Mechanism
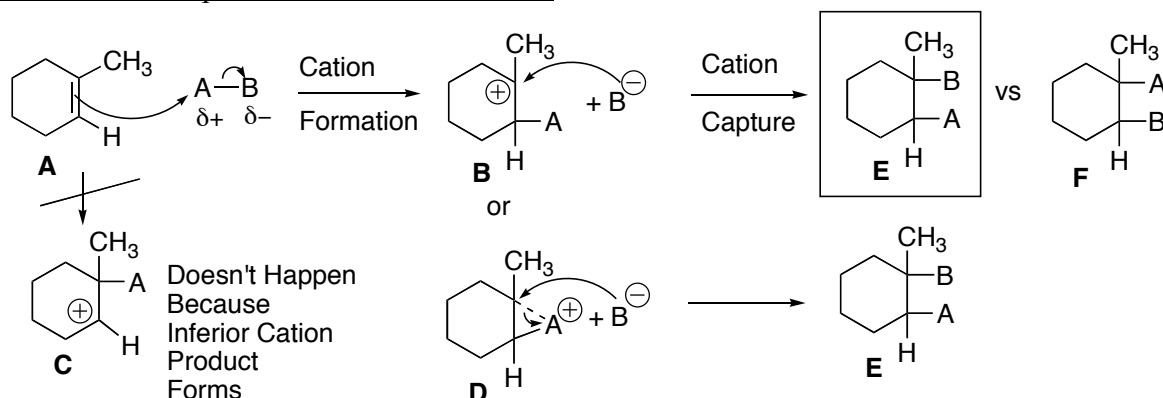
2 Steps: Cation formation and cation capture
*   Cation formation is the slow step
    o   Cation stability will routinely determine the orientation in the first step
        ▪   Which is preferred, **A → B** or **A → C?**
*   Often the cation is a normal cation **B**. Sometimes 3-membered ring cations **D** will be involved.
*   In some cases, the cation will be captured by a neutral species (like water), in which case an extra deprotonation step will be involved

4 Aspects to Watch For in Addition Reactions
1. Orientation
    *   Matters only if both of two things are true:
        o   The alkene is unsymmetrical, and
        o   The electrophile is unsymmetrical

2. Relative Stereochemistry
    *   Matters only if both the first and the second alkene carbons are transformed into chiral centers

3. Mechanism

4. Relative Reactivity of Different Alkenes
    *   Stability of cation formed is key

6.4-6 H-X   Hydrogen Halide Addition: Ionic/Cationic Addition in the Absence of Peroxides

(Reaction 1)

General: $\overset{\diagdown}{\diagup}C=C\overset{\diagup}{\diagdown}$ $\xrightarrow{\text{H}-\text{X}}$ $-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$ (H X on top)

		Orientation	Stereo	Mechanism
1		Markovnikov	None	**Be able to draw completely**

HBr (no peroxides) → product with Br
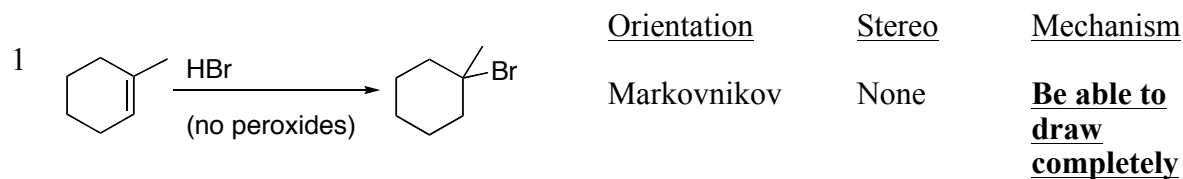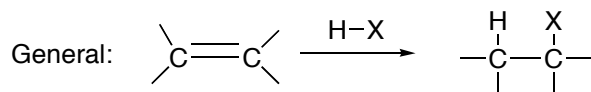
Markovnikov's Rule (For Predicting Products):   When H-X (or any unsymmetrical species $A\delta^+B\delta^-$) adds to an unsymmetrical alkene: (6.5)
- the H^+ (or $A^{\delta+}$) adds to the less substituted carbon (the one with more H's)
- the X^- (or $B^{\delta-}$) adds to the more substituted carbon (the one with more non-H's).
- Note: Markovnikov's rule does not apply if either the alkene or the atoms that are adding are symmetrical

---

Examples, Predict the Products.

Does Markovnikov's Rule matter?

1   (pent-2-ene) $\xrightarrow{\text{HBr}}$

2   (2-methylbut-1-ene) $\xrightarrow{\text{HCl}}$

3    $\xrightarrow{\text{HI}}$

4   (cyclohexene) $\xrightarrow{\text{HBr}}$

5   (1-methylcyclopentene) $\xrightarrow{\text{HBr}}$

6   (pent-1-ene) $\xrightarrow{\text{I}-\text{Cl}}$
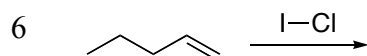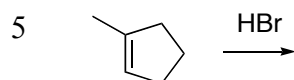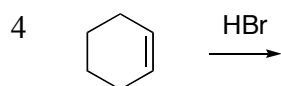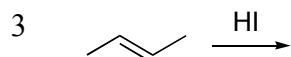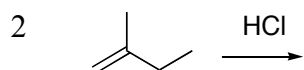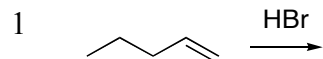
Mechanism (6.6)
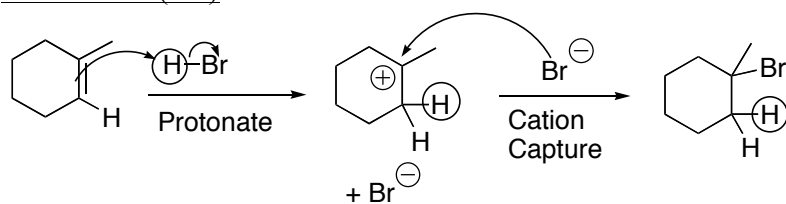
- Protonate first
- Capture cation second
- Cation formaton (step 1) is the slow step

Rank the Reactivity of the following toward HBr addition.
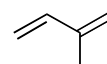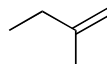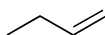
Issue:

Why Does Markovnikov's Rule Apply? Product/Stability Reactivity Rule.
  o   Formation of the most stable carbocation results in Markovnikov orientation
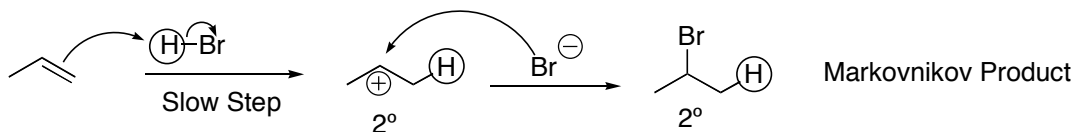

For unsymmetrical alkenes, protonation occurs at the less substituted alkene carbon so that the more stable cation forms (3° > 2° > 1°), in keeping with the product stability-reactivity principle
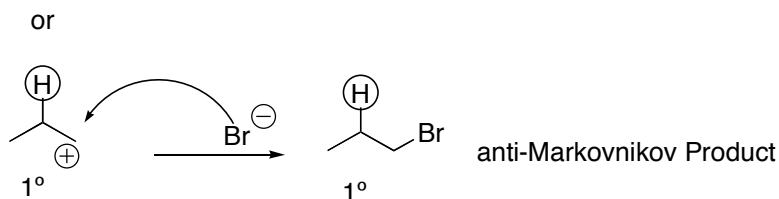
  o   This same logic applies anytime something adds to an alkene.
  o   You want to make the best possible intermediate in the rate-determining step.

Draw the mechanism for the following reaction:
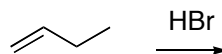
6.18   Free Radical Addition of HBr with Peroxide Initiator: Anti-Markovnikov Addition (Rxn 2)

2

Anti-Markovnikov

Nonselective.   Not   test
Both cis   responsible.
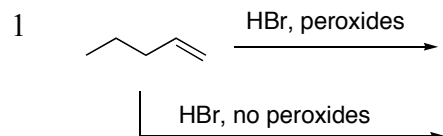**and trans**

both cis and trans
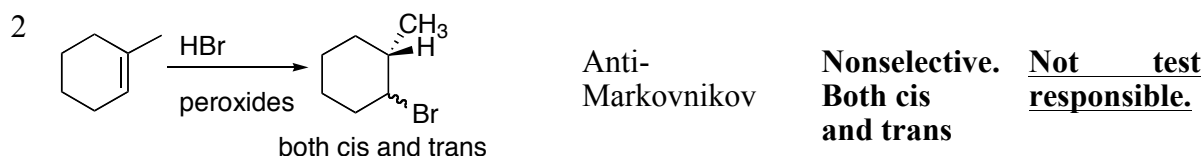
1. Peroxides are radical initiators, and cause the mechanism to shift to a radical mechanism
2. With peroxides, the orientation is reversed to anti-Markovnikov: now the Br adds to the less substituted end and the H adds to the more substituted end of an unsymmetrical alkene
   a. No peroxides: Br goes to more substituted end
   b. With peroxides: Br goes to less substituted end
3. The anti-Markovnikov radical process works only with HBr, not HCl or HI
4. The radical process is faster, and wins when peroxides make it possible. In the absence of peroxides, the slower cationic process happens.

Mechanism, and Reason for AntiMarkovnikov Orientation

For unsymmetrical alkenes, **bromination** occurs at the less substituted alkene carbon so that the more stable **radical** forms ($3° > 2° > 1°$), in keeping with the product stability-reactivity principle

Examples, Predict the Products.

Does Markovnikov's Rule matter?

1

HBr, peroxides

HBr, no peroxides

2

HBr, peroxides

HBr, no peroxides

3

HBr, peroxides

HBr, no peroxides
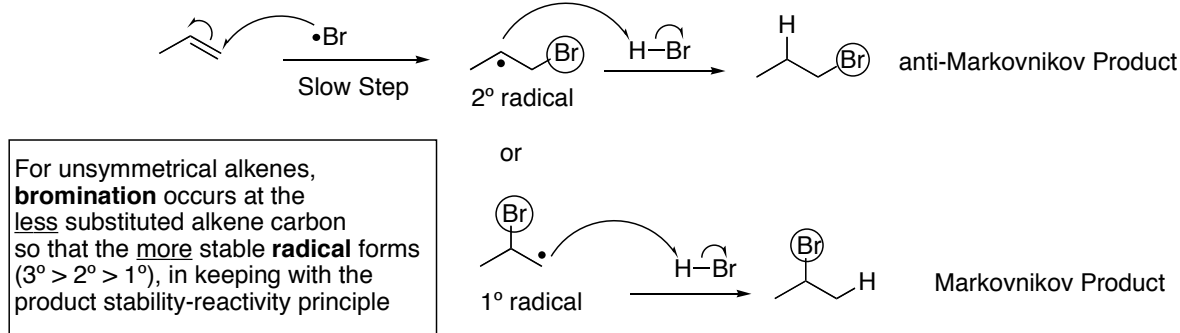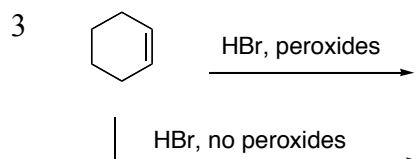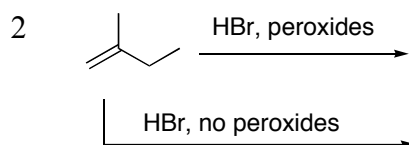
6.9 Addition of H-OH. Direct acid-catalyzed addition. (Reaction 3)

General:

3
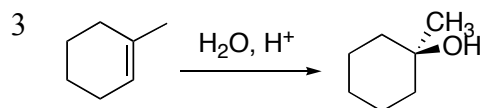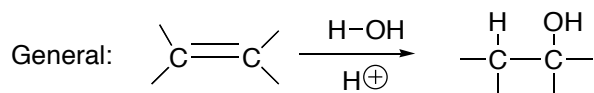
Markovnikov   None   **Be able to draw completely**

Markovnikov: Hδ⁺OHδ⁻ → H adds to the less substituted end of the alkene, OH adds to the more substituted end
   • **OH ends up on more substituted end of the alkene**

Mechanism: 3 Steps.
   1. **Protonation**
   2. **Cation Capture**
   3. **Deprotonation**

For unsymmetrical alkenes, protonation occurs at the less substituted alkene carbon so that the more stable cation forms (3° > 2° > 1°), in keeping with the product stability-reactivity principle
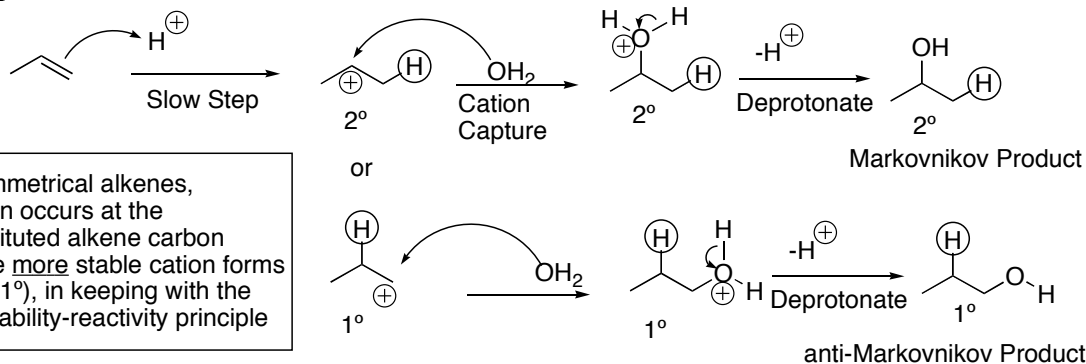
Notes
1. The sequence in which key step (cation capture in this case) is sandwiched by proton on-proton off protonation-deprotonation is super common for acid-catalyzed reactions.
   • **Whenever you see an acid-catalyzed process, expect to use H⁺ in first step and to deprotonate in the last step**

2. Cation stability dictates reactivity

3. Cation stability explains why the Markovnikov orientation occurs. This involves the more substituted, more stable carbocation product in the rate-determining step.

4. The actual reaction is an equilibrium.
   • The reverse of alcohol dehydration to make alkenes!
   • A key drive is to have excess water. That pushes the equilibrium to the alcohol side.
   • Under alcohol → alkene conditions, the equilibrium is often driven to the alkene side by having no water, or by distilling off the lower-boiling alkene as it forms.

Examples, Predict the Products.

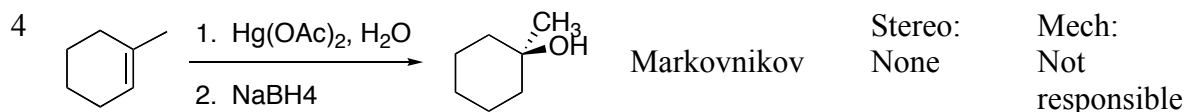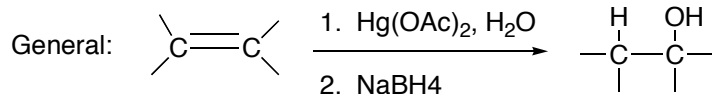Does Markovnikov's
Rule matter?

1   H$_2$O, H$^+$

2   H$_2$O, H$^+$

3   H$_2$O, H$^+$

4   H$_2$O, H$^+$

5   H$_2$O, H$^+$
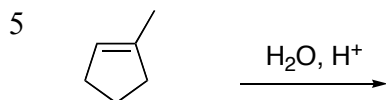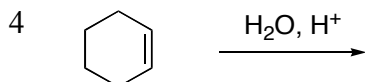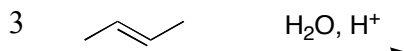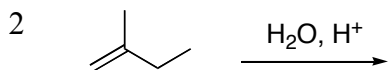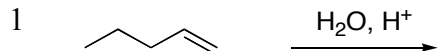
Problems with Acid-Catalyzed Addition of Water to Alkenes
1. Alkenes with poor water solubility often don't add very well.
    •   Can't drive the equilibrium strongly to the alcohol side in that case
    •   Solvent mixtures can often help, but not always good enough
2. Alcohol/Alkene equilibrium sometimes poor
3. Carbocation rearrangements can be a problem
4. The degree of Markovnikov selectivity isn't always satisfactory
    •   99:1 isomer selectivity is a lot nicer than 90:10…
    •   Especially if you have to purify!
5. Obviously you can't get the reverse, anti-Markovnikov alcohol products.

Each of these limitations, when they are a problem, can be solved by alternative recipes that indirectly add H-OH.

Draw the mechanism for the following reaction: H$_2$O, H$^+$

(p275) Indirect Markovnikov Addition of H-OH via Oxymercuration/Demercuration.
Reaction 4.

General:

$$C=C \xrightarrow[\text{2. NaBH4}]{\text{1. Hg(OAc)}_2, \text{H}_2\text{O}} \quad \begin{array}{cc} \text{H} & \text{OH} \\ -\text{C}-\text{C}- \end{array}$$

4

1. Hg(OAc)$_2$, H$_2$O

2. NaBH4

CH$_3$
OH

Markovnikov

Stereo:	Mech:
None	Not responsible

Notes:
1. Often higher yields, cleaner, faster, and easier
2. No restrictions
3. No cation rearrangements
4. **Very strong**, often superior **Markovnikov selectivity**
    o OH adds to the more substituted end, H to the less substituted end

Does Markovnikov's
Rule matter?

1

H$_2$O, H$^+$

1. Hg(OAc)$_2$, H$_2$O

2. NaBH4

2

H$_2$O, H$^+$

1. Hg(OAc)$_2$, H$_2$O

2. NaBH4
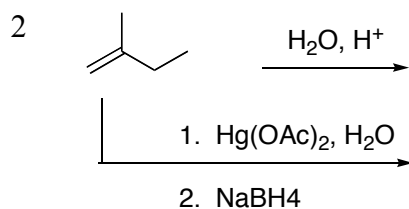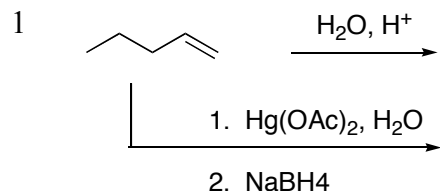
H$_2$O/H$^+$ vs Oxymercuration/Demercuration: Which should I use?
1. Both normally give same product
2. For predict-the-product problems, be able to handle either recipe
3. **For provide-the-right-recipe problems, I will accept either answer.**
    • H$_2$O/H$^+$ is easier to write!
4. In the real lab, the choice is decided on a case-by-case basis.
    • Default to H$_2$O/H$^+$
    • Go to oxymercuration/demercuration when direct acid-catalyzed hydration doesn't
      work as well as you'd like

Mechanism (For interest sake. Not for memorization, not for test.)

Overall pathway:

"Oxymercuration"   "Demercuration"
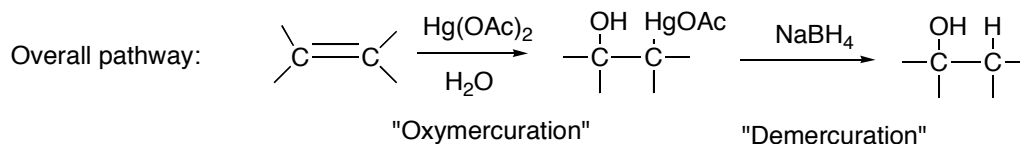
More Details for the Oxymercuration Phase

"Mercurinium Ion"

OAc = "acetate" =
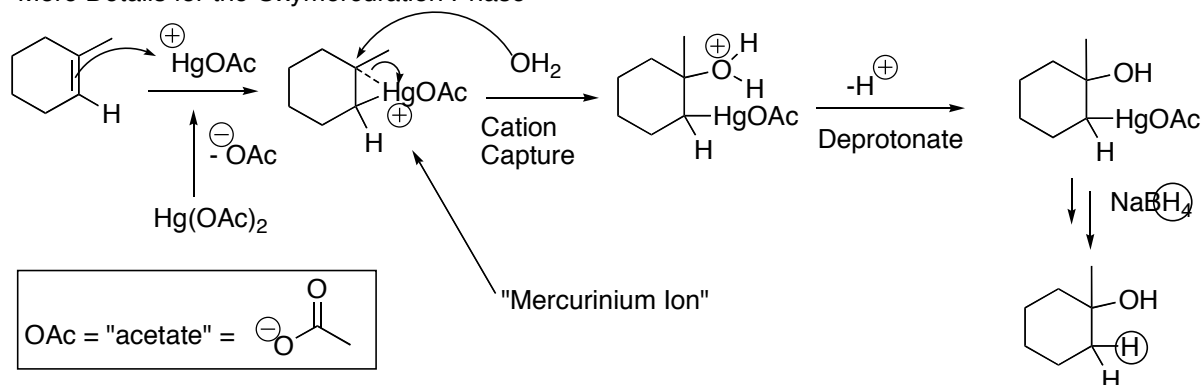
Notes:
1. "demercuration" with NaBH4 replaces the mercury with a hydrogen
2. The initial "oxymercuration" essentially adds (HgOAc)$_\delta{}^+$(OH)$_\delta{}^-$, and follows Markov.'s rule
3. The interesting new thing here is the "mercuronium" ion
4. This is normally drawn as a 3-ring, but can also be viewed as a resonance structure of a hybrid

Mercuronium Ion

A
Mercuronium
Ring

B
3° Cation

C
2° Cation
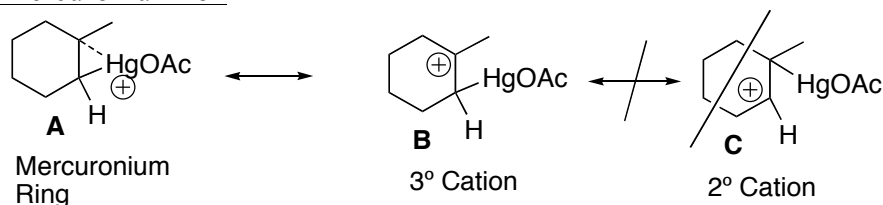
Both participation from structures **A** and **B** are required to explain everything
 * **A** explains why you don't get cation rearrangments, ever: you don't have a free carbocation
 * **A** also explains structure studies, which show that the mercury is weakly bonded to the more substituted carbon
 * **B** helps to explain why water adds to the more substituted carbon, which has extensive positive charge
 * **C** doesn't contribute, isn't really involved

In the real thing, there is a long, very weak and super breakable bond between mercury and the more substituted carbon. The bond to the less substituted carbon is much shorter and stronger.

"π-Complex" Perspective

Electrophilic
⊕HgOAc
Adds

"π-complex"
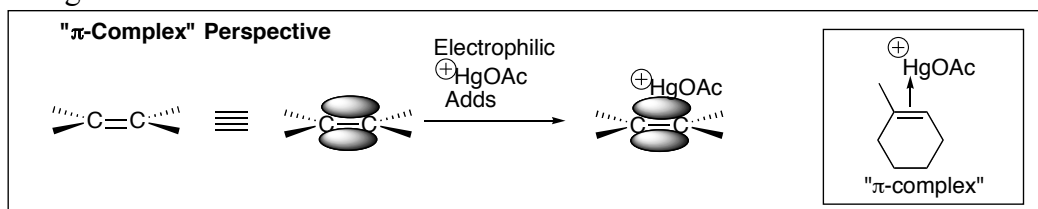
6.11-13   Indirect anti-Markovnikov Addition of H-OH via Hydroboration/Oxidation.
Reaction 5.

Overall pathway:

5

Anti-
Markovnikov

Cis

Not
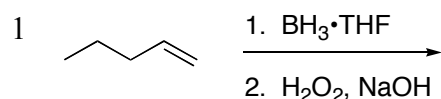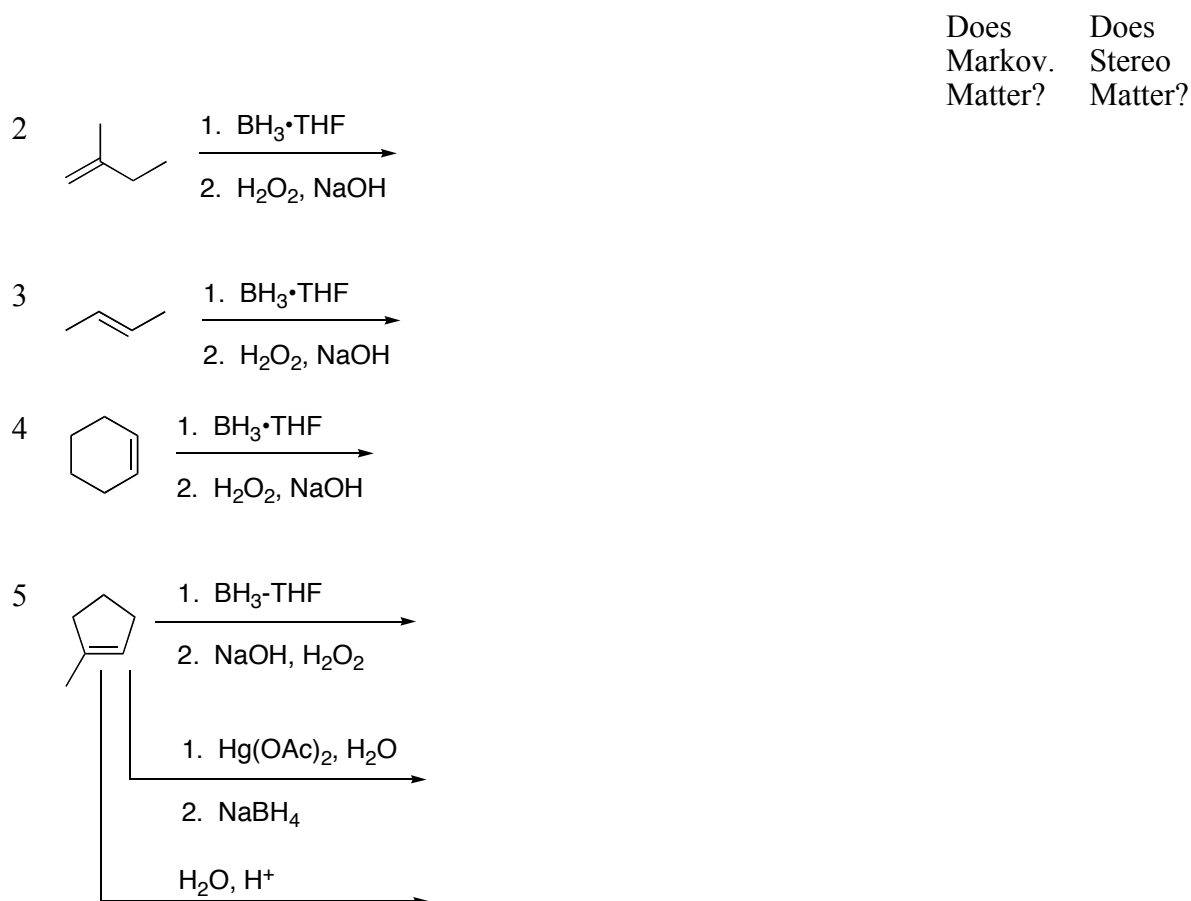responsible

plus

enantiomer
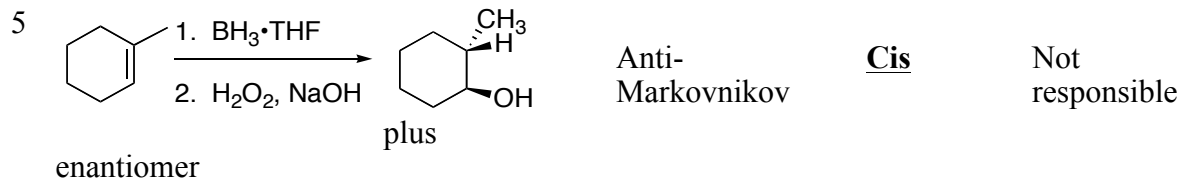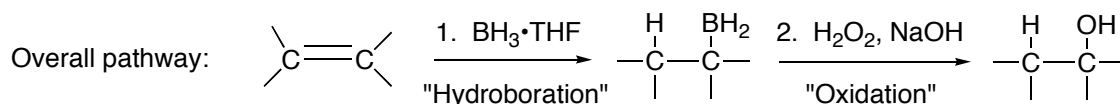
Notes:
1. **Anti-Markovnikov orientation**: the **OH ends up on the less substituted end** of an unsymmetrical alkene; the H adds to the more substituted end
2. **Cis addition. Both the H and the OH add from the same side**.
3. When does cis/trans addition stereochemistry matter?
   o Only when both alkene carbons turn into chiral centers in the product.
   o If one does but not both, then the relative stereochemistry doesn't matter
   o For Markovnikov additions involving H-Br or H-OH, the H usually adds to a carbon that already has an H, so that in the product it is not a stereocenter.
   o In anti-Markovnikov additions, much more common for both carbons to become chiral carbons
4. **Chiral products are Racemic (two enantiomers form) but not optically active**
   o When only one chiral center forms (often in the Markovnikov additions), any chiral product will always be racemic
   o When two chiral centers form, as in the example above, of the four possible stereoisomers, you get only two of them, in racemic mixture.

Cis Addition Enantiomers
Do Form

Trans Addition Enantiomers
Do NOT Form
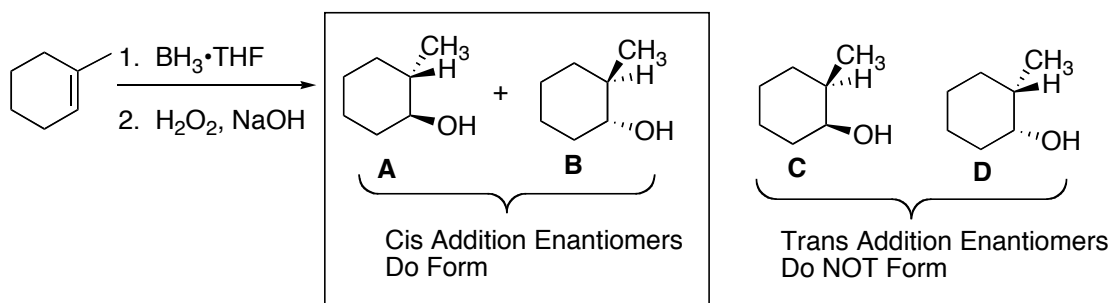
Examples, Predict the Products.

Does
Markov.
Matter?

Does
Stereo
Matter?

1

Does   Does
Markov.   Stereo
Matter?   Matter?

2   1. BH₃•THF
     ⎯⎯⎯⎯⎯⎯⎯⎯→
     2. H₂O₂, NaOH

3   1. BH₃•THF
     ⎯⎯⎯⎯⎯⎯⎯⎯→
     2. H₂O₂, NaOH

4   1. BH₃•THF
     ⎯⎯⎯⎯⎯⎯⎯⎯→
     2. H₂O₂, NaOH

5   1. BH₃-THF
     ⎯⎯⎯⎯⎯⎯⎯⎯→
     2. NaOH, H₂O₂

     1. Hg(OAc)₂, H₂O
     ⎯⎯⎯⎯⎯⎯⎯⎯→
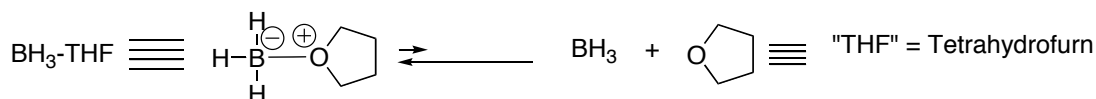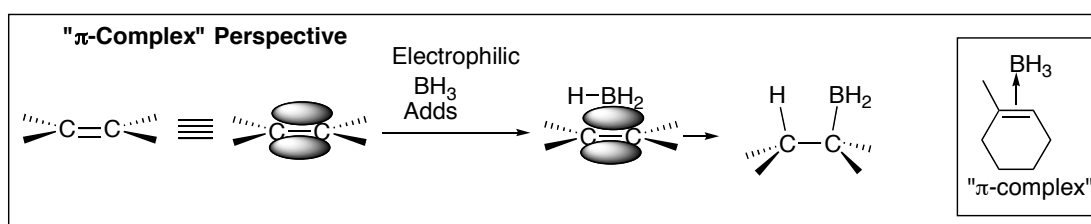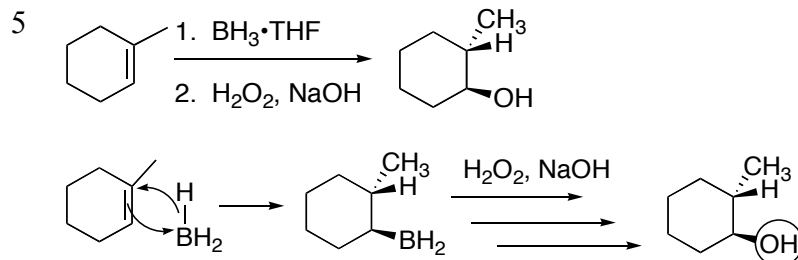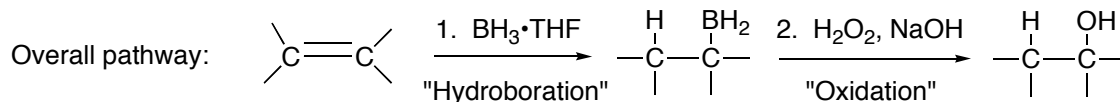   2. NaBH₄

     H₂O, H⁺
     ⎯⎯⎯⎯⎯⎯⎯⎯→

1. Which starting alkenes would produce the following products following
    hydroboration-oxidation? Factor in the stereochemistry of the products in
    considering what starting materials would work.

     1. BH₃-THF
     ⎯⎯⎯⎯⎯⎯⎯⎯→   HO H
     2. NaOH, H₂O₂   Ph
                       H₃C H

     1. BH₃-THF
     ⎯⎯⎯⎯⎯⎯⎯⎯→   H OH
     2. NaOH, H₂O₂   Ph
                       H₃C H
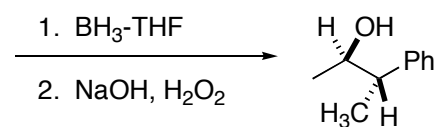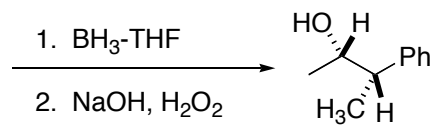
2. Fill in recipes for converting 1-butene into the three derivatives shown.

     ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯→   OH

                              OH
     ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯→

Mechanism (For interest sake. Not for memorization, not for test.)

Overall pathway:

$$\text{C=C} \xrightarrow[\text{"Hydroboration"}]{\text{1. BH}_3\cdot\text{THF}} \quad \overset{\text{H}\quad\text{BH}_2}{-\text{C}-\text{C}-} \xrightarrow[\text{"Oxidation"}]{\text{2. H}_2\text{O}_2,\ \text{NaOH}} \quad \overset{\text{H}\quad\text{OH}}{-\text{C}-\text{C}-}$$

5
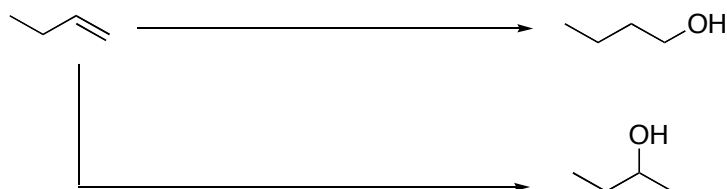
Notes
1. Other recipes (B_2H_6, etc. are common)
2. BH_3-THF is a convenient complex in which the oxygen provides the extra electron pair. But the weak complex provides a small equilibrium amount of free, reactive BH_3
3. Free BH_3 is actually the electrophile
4. Because BH_3 does not have octet rule, the boron is very electrophilic
5. The electrophilic boron originally makes a π-complex, but then you get actual hydroboration via a 4-centered ring
6. The key is that both the boron and the hydrogen enter from the same side of the alkene
   • **concerted addition of B-H across C=C**
   • **cis addition**
7. Why do you get the orientation?
   • the B-H addition actually does follow Markovnikov's rule
      o $H_2B\delta+H\delta-$
      o The B is δ+, the H is δ-, because boron is a semi-metal and less electronegative than hydrogen! The only case this chapter where the hydrogen is δ- rather than δ+
   • Sterics: The Boron end is pretty big, so it prefers to go to the less substituted, less hindered end of the alkene for steric as well as electronic reasons.
8. The NaOH/H2O2 workup is complex and beyond our scope, but replaces the B with OH with complete retention of stereochem
   • the cis stereochemistry established in the hydroboration
   • the oxygen stereo is preserved in the oxidation.

Alkoxymercuration-Demercuration: Markovnikov Addition of H-OR (Reaction 6)

General:

$$\text{C=C} \quad \xrightarrow[\text{2. NaBH4}]{\text{1. Hg(OAc)}_2,\ \textbf{ROH}} \quad \overset{\text{H}\quad\textbf{OR}}{\underset{|\quad\ |}{-\text{C}-\text{C}-}}$$

6

Markovnikov   Stereo: Mech:
None   Not
responsible
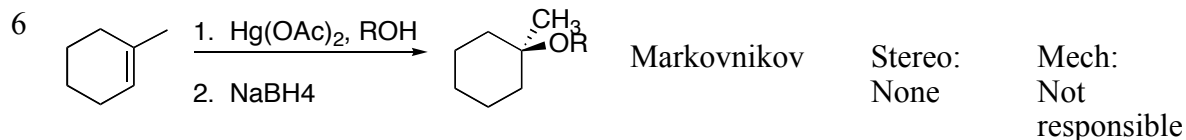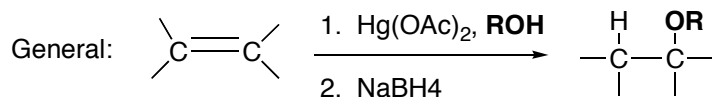
Mechanism
6
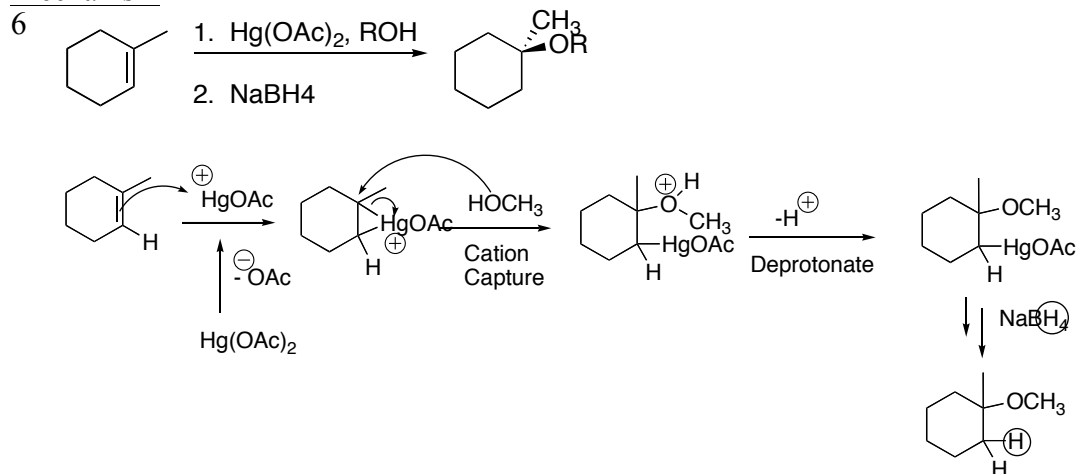
Notes:
1. Everything is the **same as with oxymercuration-demercuration to form an alcohol, except you use an alcohol instead of water**
2. This results in an oxygen with it's spectator carbon chain adding rather than an OH
3. Strong Markovnikov orientation
   • The OR adds to the more substituted end of the alkene
   • The Hydrogen ends up on the less substituted end of the alkene
4. The mechanisms are analogous.

Examples, Predict the Products.

Does   Does
Mark's   Stereo?
Rule
matter?

1

1. Hg(OAc)₂, **CH₃CH₂OH**

2. NaBH4

2

1. Hg(OAc)₂,   (isopropanol)

2. NaBH4
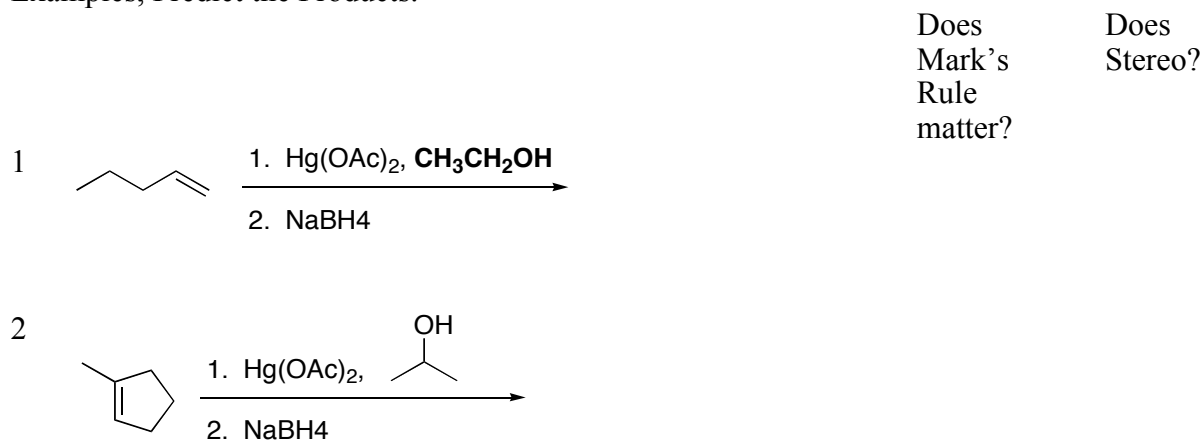
Ether Synthesis: Two Routes
1.   From Alkene and Alcohol: By Oxymercuration/Demercuration
2.   From R-Br and Alkoxide Anion: By S_N2

Multistep Synthetic Design: Design Reactants for the Following Conversions
1.   Note: It is often most strategic to think backward from product to precursor.
2.   Then think back how you could access the precursor from the starting material.
3.   There may sometimes be more than one suitable route.
4.   There will be problems of this style/format on the next test.

1.

2.

3.

4.

5.

6.

7.
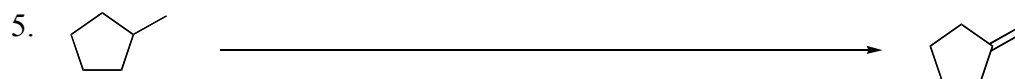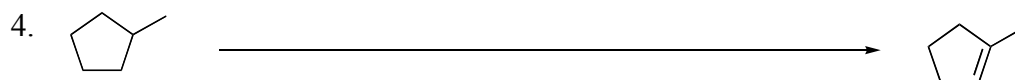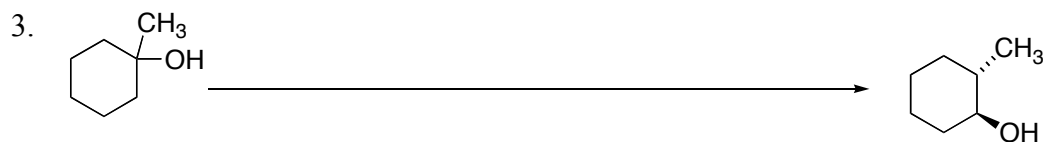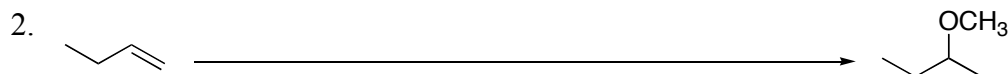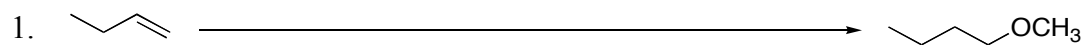
6.1. H-H addition. Catalytic Hydrogenation (Reaction 7)

General: (alkene) $\xrightarrow[\text{(or Pd, or Ni, etc.)}]{\text{H}_2,\ \text{Pt}}$ (alkane product with H H)

7   (cyclohexene with CH₃ and D) $\xrightarrow{\text{H}_2,\ \text{Pt}}$ (cyclohexane with CH₃, H, H, D)

plus enantiomer

Orientation: Stereo: Mech:
None   **Cis**   Not
                           responsible
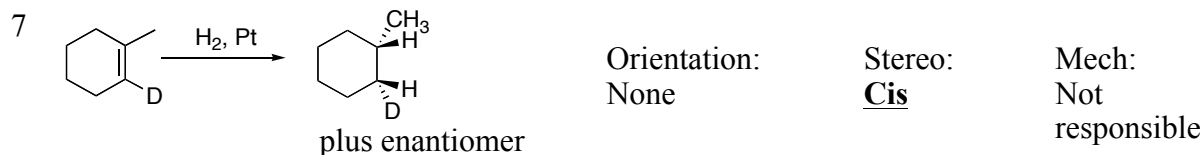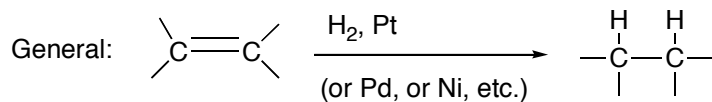
Notes:
1. Since both atoms adding are the same (H), Markovnikov orientation issues don't apply
    • You're adding a hydrogen to both the more and less substituted alkene carbon!
2. Stereochemistry isn't often relevant, but when it is it's **cis**
    • Rarely relevant because if either alkene carbon has even one hydrogen attached, addition of an additional hydrogen will result in an achiral carbon.
3. The reaction is substantially exothermic
4. But some kind of transition-metal catalyst is required to active the otherwise strong H-H bonds.

Examples, Predict the Products.

Does   Does
Mark's   Stereo?
Rule matter?

1   (pent-1-ene) $\xrightarrow{\text{H}_2,\ \text{Pt}}$

2   (2-methyl-2-pentene, Z) $\xrightarrow{\text{H}_2,\ \text{Pt}}$

3   (alkene with D and CH₃) $\xrightarrow{\text{H}_2,\ \text{Pt}}$

4   (1,2-dimethylcyclohexene) $\xrightarrow{\text{H}_2,\ \text{Pt}}$

5   (1-methylcyclohexene) $\xrightarrow{\text{H}_2,\ \text{Pt}}$

6   (1-methyl-2-D-cyclohexene) $\xrightarrow{\text{H}_2,\ \text{Pt}}$
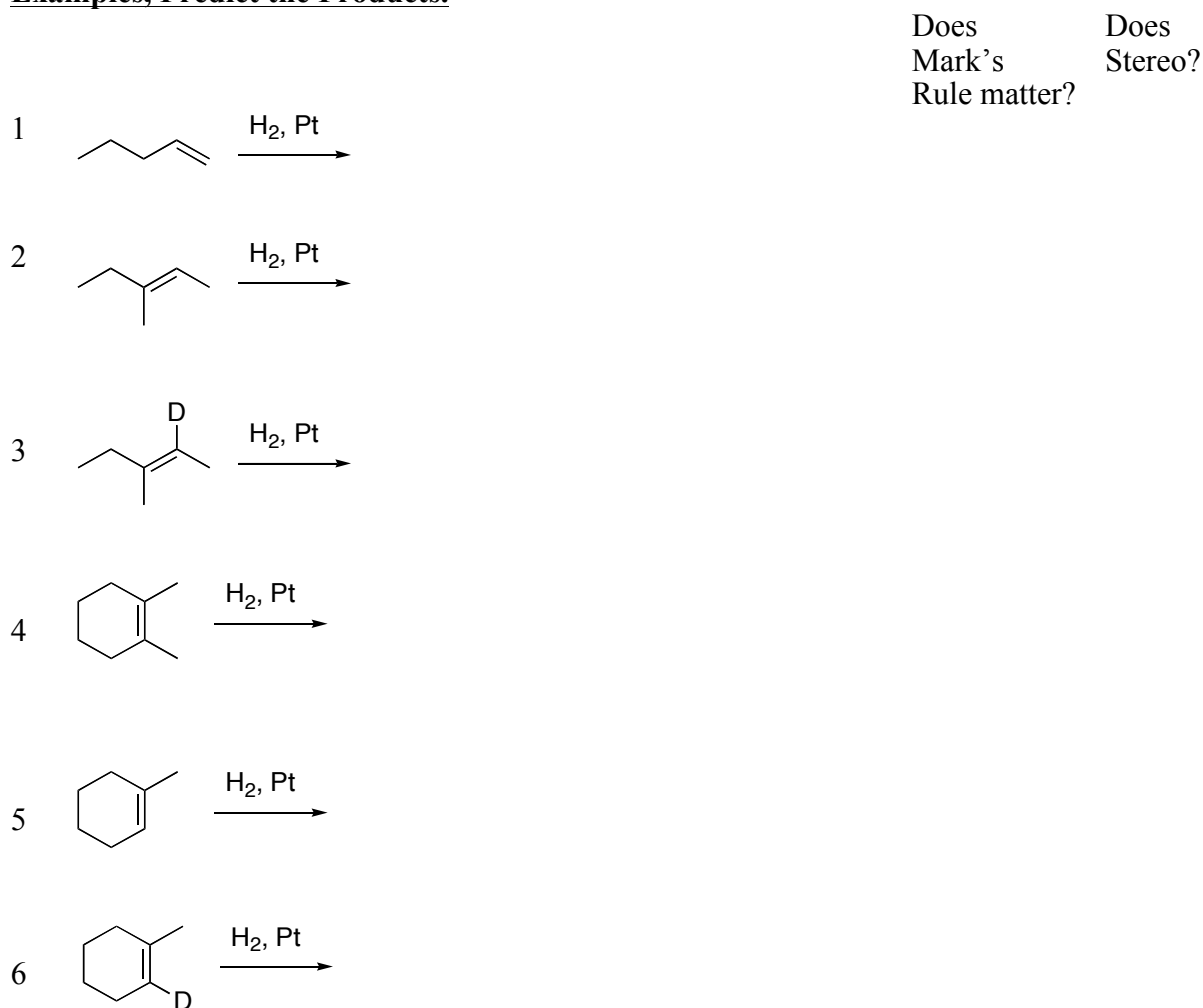
6.14-17 X-X Dihalogen Addition: Trans Addition (Reaction 8)

General:

	Orientation	Stereo	Mechanism
8	None	**Trans**	**Be able to draw completely**

plus enantiomer
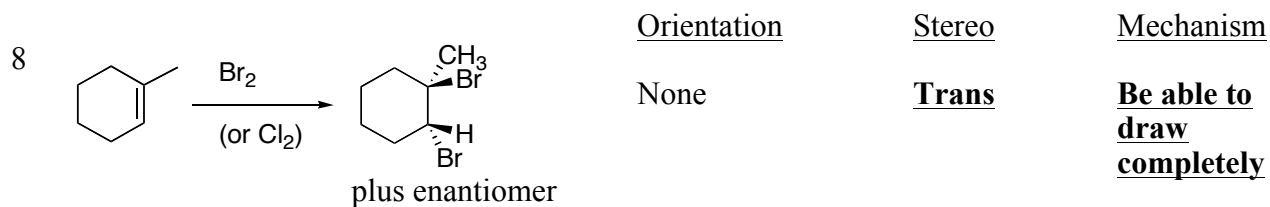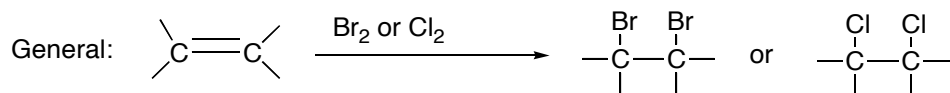
Notes:
1. **Orientation: Non-issue**, since you're adding the same atom to each alkene carbon
2. **Trans addition**
3. **Solvent** matters: to get X-X addition, you need a solvent other than water or alcohol.
    - With water or alcohol, you get different products, see reaction 9

Examples, Predict the Products.

	Does Mark. matter?	Does Stereo?	Chiral?

1   Br$_2$

2   Br$_2$

3   Cl$_2$

4   Cl$_2$

5   Br$_2$

6   Br$_2$
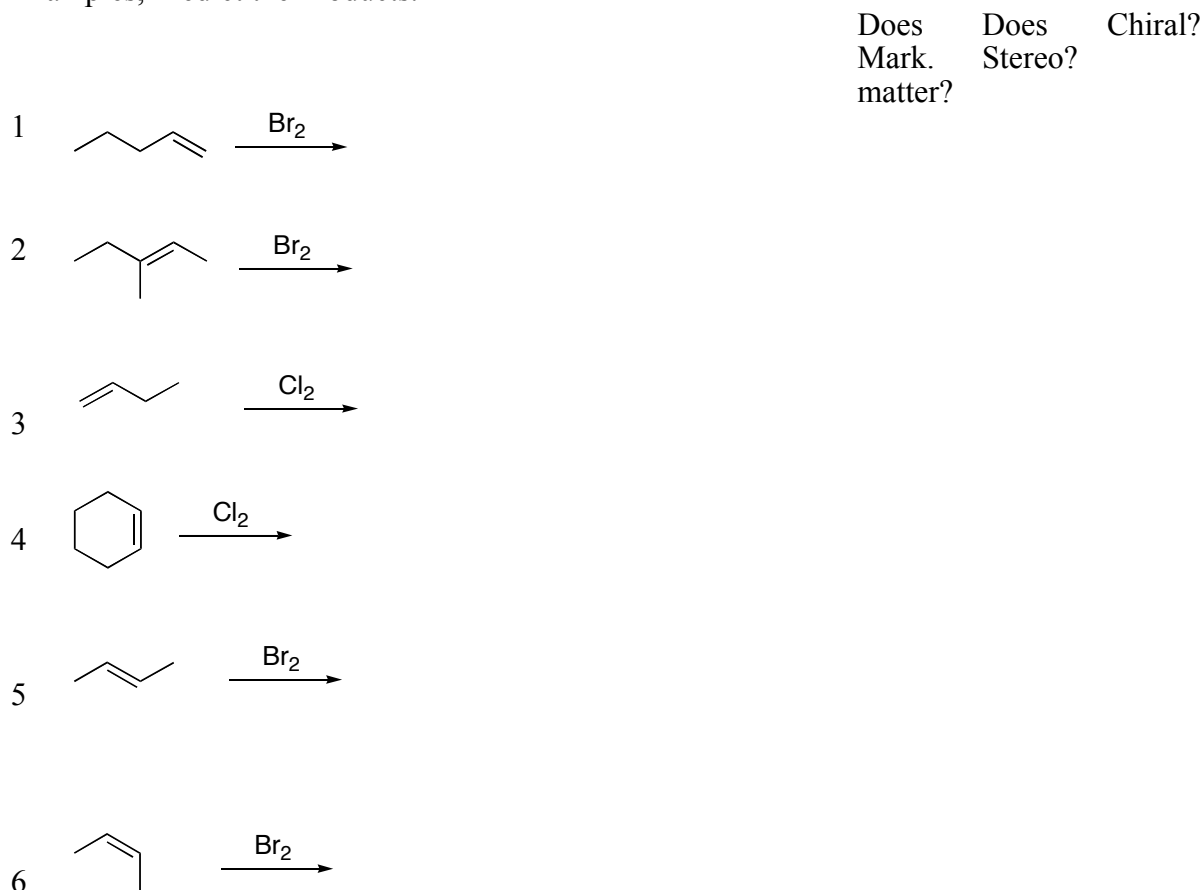
Notes:
1. Cis and trans reactants give different products!
2. For any product (in this and other reactions), be able to identify whether it is chiral or not

Chemical Test for Alkenes: Br_2 in CCl_4 solvent is reddish/brown color. Add a few drops to an unknown organic:

        a. If the color stays reddish/brown → the unknown does not contain any alkenes

        b. If the reddish/brown color goes away → the unknown did have an alkene that is reacting with the bromine

Mechanism (Very important) (6.16)
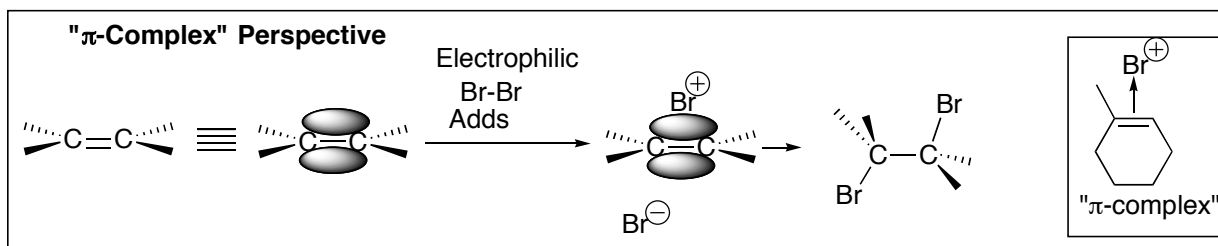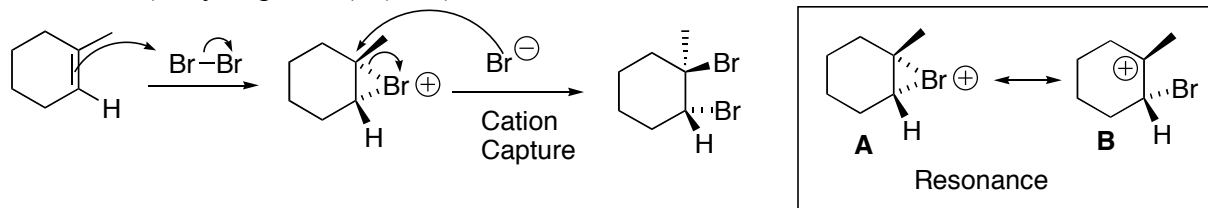
Notes
1. **Cation Formation: Step 1**
2. **Cation capture: Step 2**
3. Br_2 and Cl_2 are exceptionally good electrophiles
4. **The cation that forms is a 3-membered ring**
   - "Bromonium ion"
   - "Chloronium ion"
5. Or, it can be viewed as a π-complex, with a halogen cation sitting on a p-bond
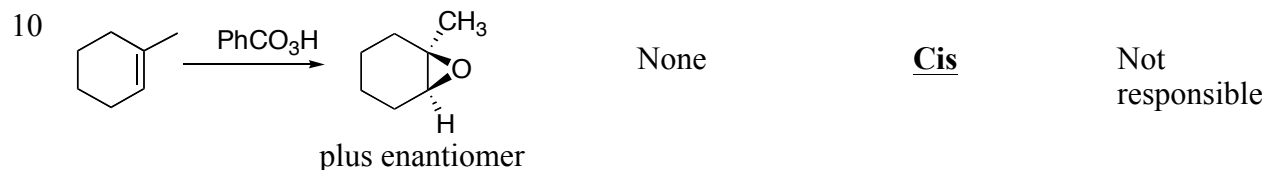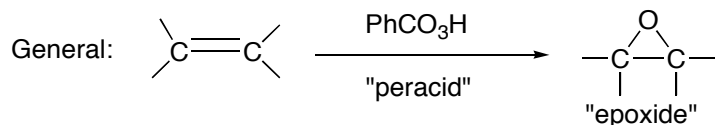6. When the nucleophile captures the cation, it must come in from the opposite face
   - **Backside attack, ala S_N2**
   - **Trans addition results**
7. **The nucleophile actually attacks at the more substituted carbon!**
   - This is contrary to S_N2 expectations!
8. Resonance pictures **A** and **B** help to explain things
   a. The cyclic form **A** explains stereochemistry
   - If acyclic form **B** was all there was, you wouldn't need backside attack and you wouldn't get trans stereochemistry
   b. Form **B** helps explains why the nucleophile attacks the more substituted carbon.
   - Of the two carbons, the more substituted one has the positive charge and is thus more electrophilic, in spite of steric issues.

Solvent Limitation: Solvents that are nucleophilic (water or alcohols…) successfully compete with bromide or chloride in the cation capture step.

Draw the mechanism for:

Br-OH or Cl-OH Addition.   Markovnikov Addition, Trans Addition, to form
"Halohydrins" (reaction 9) (6.17)

General:

$$\text{C=C} \xrightarrow[\text{H}_2\text{O}]{\text{Br}_2 \text{ or Cl}_2} \quad \underset{|}{\overset{\text{Br}}{\text{C}}}-\underset{|}{\overset{\text{OH}}{\text{C}}} - \quad \text{or} \quad \underset{|}{\overset{\text{Cl}}{\text{C}}}-\underset{|}{\overset{\text{OH}}{\text{C}}} -$$

9

	Orientation	Stereo	Mechanism
	Markovnikov	**Trans**	**Be able to draw completely**

plus enantiomer
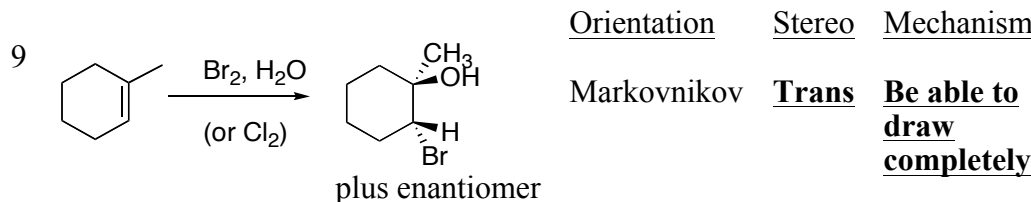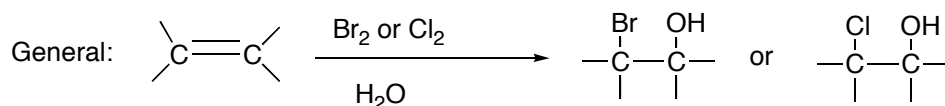
Notes:
1. **Markovnikov Orientation**
   * OH adds to more substituted alkene carbon
   * Br or Cl adds to less substituted alkene carbon
   * This literally follows Markovnikov's Rule, since the relative electronegativity makes for BrOH (or ClOH) is Brδ+(OH)δ-
2. **Trans addition**
3. **Solvent** matters: whenever you see Br$_2$ or Cl$_2$ recipes, check whether there is a water (or alcohol) solvent

Mechanism
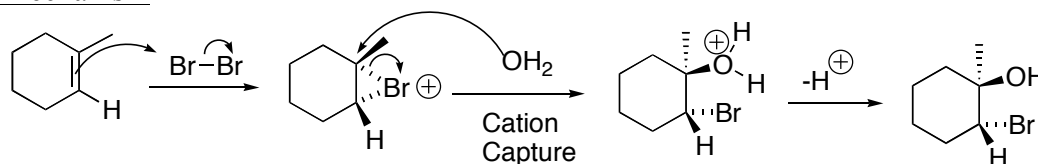
1. 3 Steps:
   * bromonium formation (cation formation)
   * cation capture/nucleophile addition
   * deprotonation (since the nucleophile was neutral)
2. The mechanism is closely analogous to the Br$_2$ or Cl$_2$ additions
3. Water is a better bromonium (chloronium) capture nucleophile than bromide (or chloride) anion
   * The large population of water molecules in the solvent give it a statistical advantage
   * When the bromide anion forms in step one, it is initially formed on the wrong side of the bromonium. It needs to swim around to the opposite side in order to attack. Usually water has already captured the cation before then.
   * Water really is inherently a better electron donor than bromide anion. This is why in water a proton goes onto water to make hydronium ion rather than going onto bromide to make covalent HBr
4. Notice that the water attacks the **more substituted** carbon of the bromonium (chloronium) ion

Alcohol Reactions
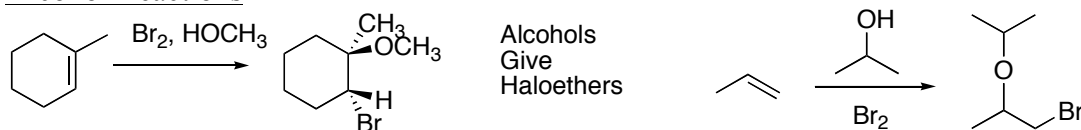
Draw the mechanism for the following reaction:

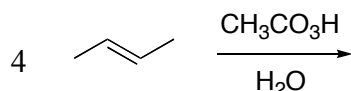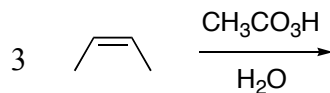$$\text{Br}_2 \quad / \quad \text{H}_2\text{O}$$

Examples, Predict the Products.

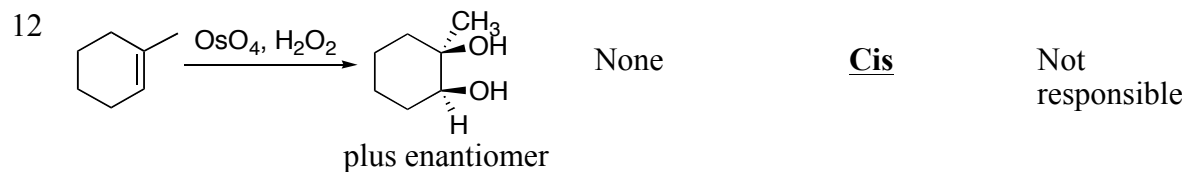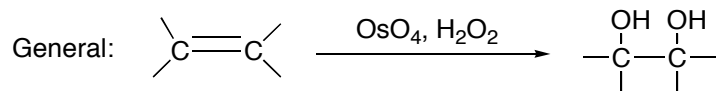|	Does Mark. matter?	Does Stereo?	Chiral?

1   Br_2

Br_2 / H_2O

2   Br_2

Br_2 / H_2O

3   Cl_2 / H_2O

5   Br_2 / H_2O

6   Br_2 / H_2O
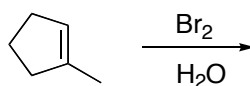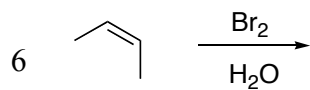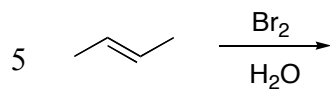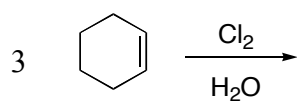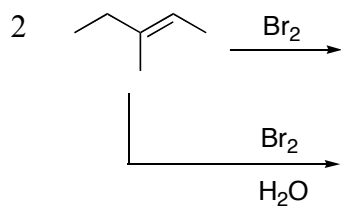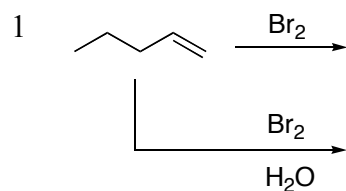
6.19 Epoxidation. Addition of one Oxygen (Reaction

General:

$$\ce{C=C ->[PhCO3H][\text{"peracid"}] epoxide}$$

"peracid"

"epoxide"

10

PhCO₃H → CH₃ / O / H

plus enantiomer

None   **Cis**   Not
responsible

Notes:
1. No orientation issues, since the same oxygen atom connects to both bonds
2. Cis addition: both oxygen bonds come from the same direction

Mechanism: No test Responsibility

ONE
STEP!
No
ions

Ph

Carbonyl-hydrogen
Hydrogen-bonded reactant
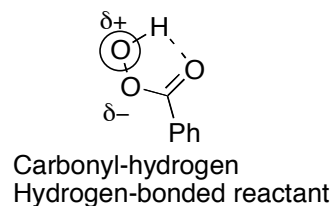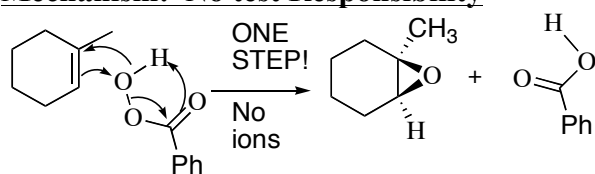
a. Any peracid with formula RCO₃H has an extra oxygen relative to a carboxylic acid.
b. Any peracid can deposit the extra oxygen onto the p-bond to make the epoxide
c. No ions are actually involved, because the leaving group is the neutral carboxylic acid
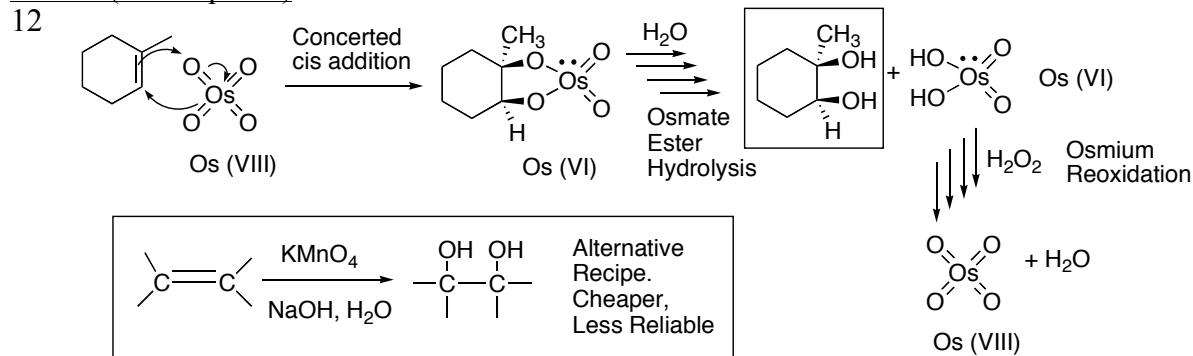
Examples, Predict the Products.

	Does Mark. matter?	Does Stereo?	Chiral?

1   PhCO₃H →

2   PhCO₃H →

3   PhCO₃H →

4   PhCO₃H →
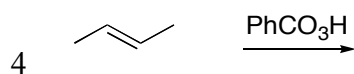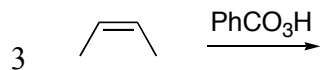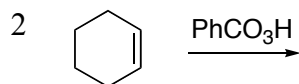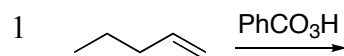
15.4,5 Trans OH-OH addition. Epoxidation in water. The initially formed epoxide undergoes Acid-Catalyzed Ring Opening. Reaction 11. (15.5)

General:

CH_3CO_3H / H_2O

OH OH

11

CH_3CO_3H / H_2O

CH_3
OH
H
OH
plus enantiomer
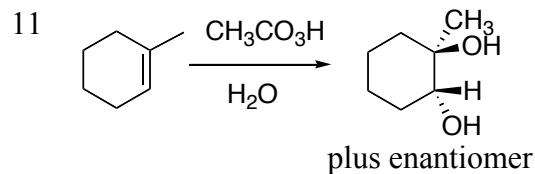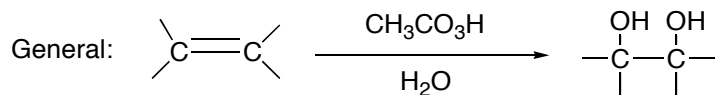
None

Trans

Be able to draw acid-catalyzed epoxide hydrolysis

Examples, Predict the Products.
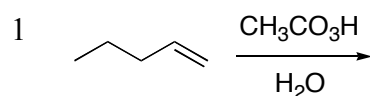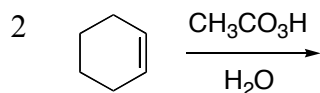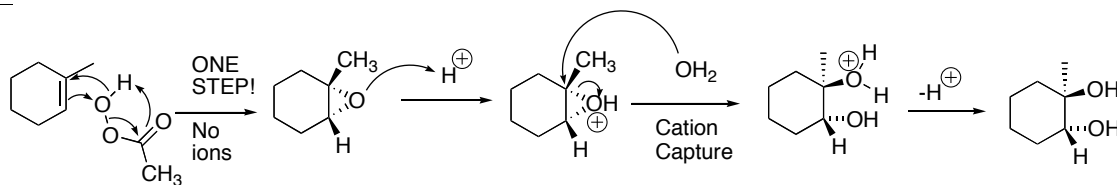
Does Mark. matter?	Does Stereo?	Chiral?

1   CH_3CO_3H / H_2O

2   CH_3CO_3H / H_2O

3   CH_3CO_3H / H_2O

4   CH_3CO_3H / H_2O

Mech
11

ONE STEP! No ions

CH_3

$H^{\oplus}$

CH_3 OH_2

Cation Capture

$-H^{\oplus}$

OH
OH
H

Notes:
1. The nucleophile (water) attacks from the more substituted end of the protonated epoxide
   - More δ+ charge there
   - The C-O bond to the more substituted end is much weaker
2. The nucleophile adds via S_N2-like backside attack. Inversion at the top stereocenter, but not the bottom, explains the trans stereochemistry.

15.4,5 Cis OH-OH addition. Catalytic Osmylation. Reaction 12. (15.5)

General:

$C=C$ →(OsO$_4$, H$_2$O$_2$)→ OH OH / —C—C—

12

(cyclohexene with CH$_3$) →(OsO$_4$, H$_2$O$_2$)→ CH$_3$, OH, OH, H product
plus enantiomer

None   **Cis**   Not responsible

Examples, Predict the Products.

		Does Mark. matter?	Does Stereo?	Chiral?

1   (pent-1-ene) →(OsO$_4$, H$_2$O$_2$)→

2   (cyclohexene) →(OsO$_4$, H$_2$O$_2$)→
     →(CH$_3$CO$_3$H / H$_2$O)→

3   (cis-2-butene) →(OsO$_4$, H$_2$O$_2$)→
     →(CH$_3$CO$_3$H / H$_2$O)→

4   (trans-2-butene) →(OsO$_4$, H$_2$O$_2$)→

Mech: (Not required)

12

(cyclohexene with CH$_3$) + OsO$_4$ (Os (VIII)) →Concerted cis addition→ osmate ester (Os (VI)) →H$_2$O, Osmate Ester Hydrolysis→ diol product (CH$_3$, OH, OH, H) + HO–Os–OH (Os (VI)) →H$_2$O$_2$, Osmium Reoxidation→ OsO$_4$ (Os (VIII)) + H$_2$O

Alternative Recipe. Cheaper, Less Reliable:
$C=C$ →(KMnO$_4$ / NaOH, H$_2$O)→ OH OH / —C—C—

Stereochemically complementary methods

		Skills:
CH_3CO_3H/H_2O	trans	1. Given starting material and product, provide reagent
OsO_4/H_2O_2	cis	2. Given product and reagent, what was the starting material?

1. **Given starting material and product, provide reagent. Consider stereo.**
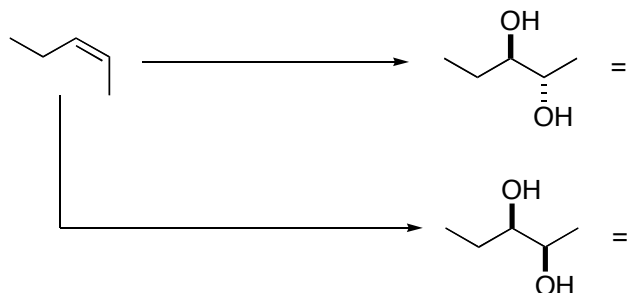
2. **Stereochemistry Problems. Given product + reagent, what was the starting alkene?**
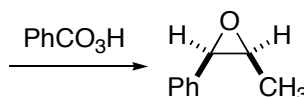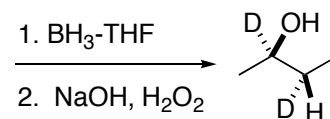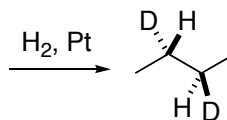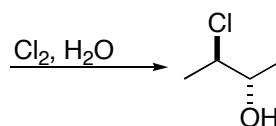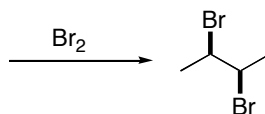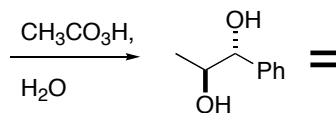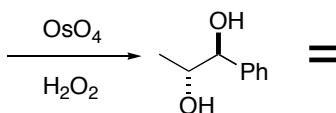
6.20 Ozonolysis. Cleavage of Alkenes. Reaction 13

General:

13

None   None   Not responsible
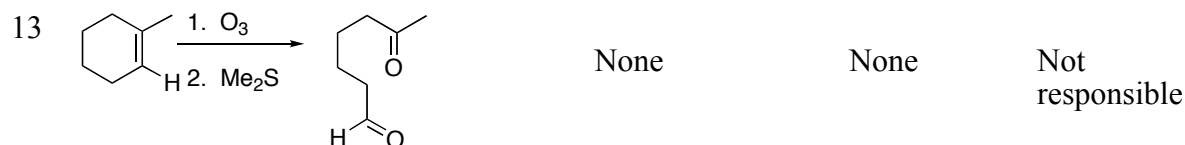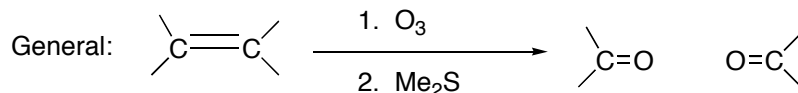
Note: H-bearing alkene carbon
ends up as aldehyde.

Notes
1. Double bond gets sliced in half, gives two corresponding carbonyls per alkene
2. Alkene bonds and nothing else are oxidized.
3. **Get ketones and/or aldehydes and/or formaldehyde**
4. **Zn often used in workup step two instead of dimethylsulfide**
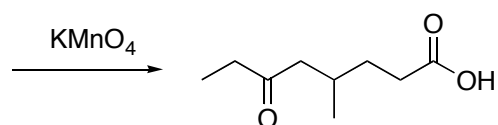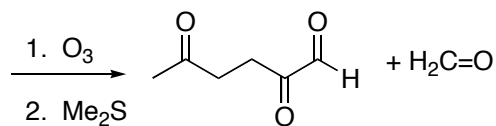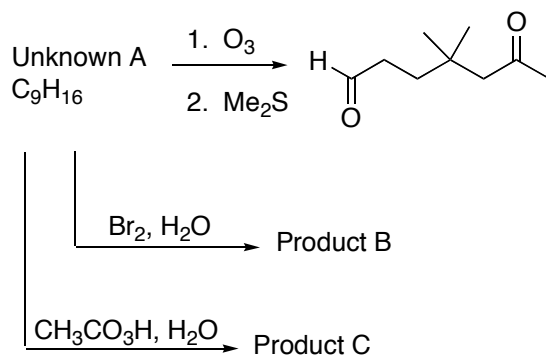
Oxidative Cleavage of Alkenes by Permanganate. Reaction 14

General:

14

None   None   Not responsible
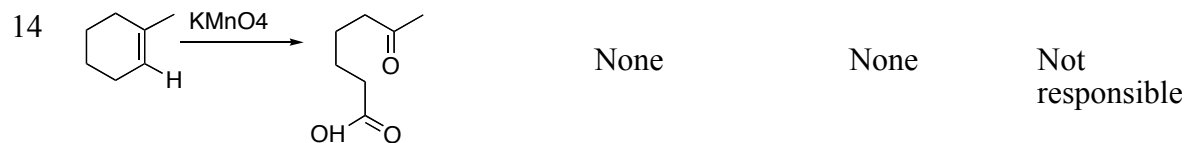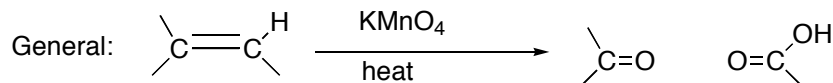
H-bearing alkene carbon
ends as carboxylic acid

Notes
1. Double bond gets sliced in half, gives two carbonyls per alkene
2. Alkene C-H bonds are also oxidized to C-OH bonds.
3. **Get ketones and/or carboxylic acids and/or carbonic acid.**

1

2

3

4.   1. O₃   KMnO₄
        ←————————   ————————→
                    2. Me₂S

1. **Identify reactants.**

                            1. O₃   + H₂C=O
                    ————————→
                            2. Me₂S

                            KMnO₄
                    ————————→

2. **Identify A, B, and C.**

                            1. O₃
        Unknown A   ————————→
        C₉H₁₆   2. Me₂S

                    Br₂, H₂O
                    ————————→   Product B
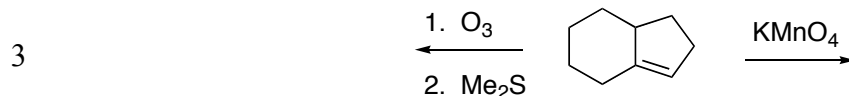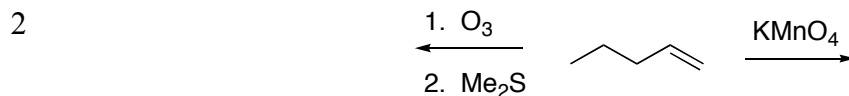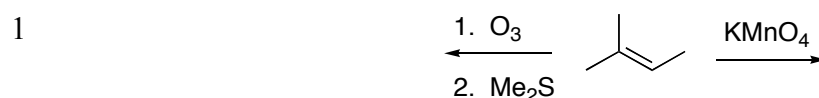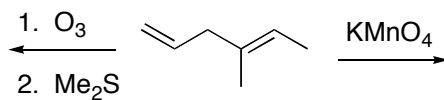
        CH₃CO₃H, H₂O
        ————————————→   Product C

Review Problems.
3. **"Roadmap format". Identify products A-D.**

            Br₂, hv   NaOH
        ————————→   A   ————————→   B

                                                Br₂, CH₃OH

                                                C
                    NEt₃
        D   ←————————
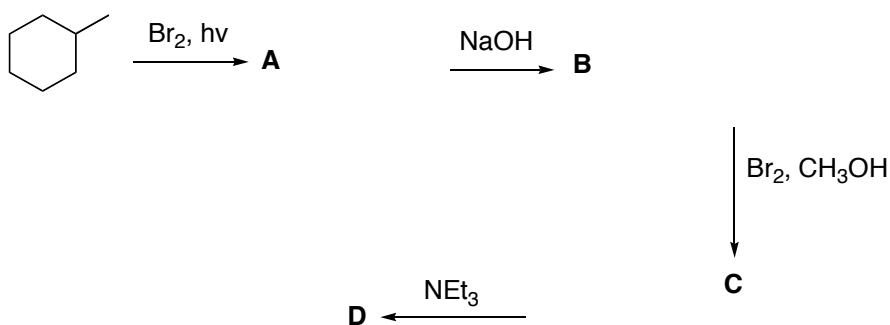
1. Design a synthetic plan for the following conversions. (Several on test)

a.

b.

c.

d.

e.

f.
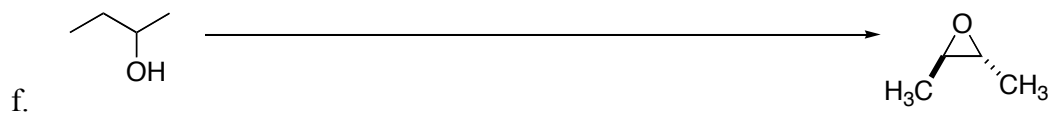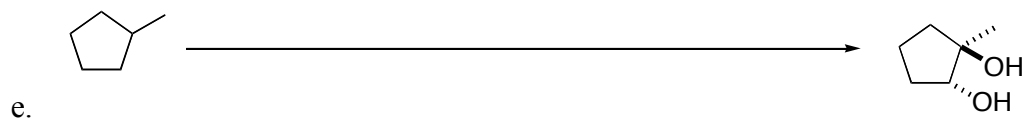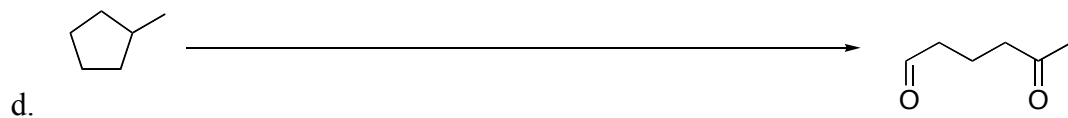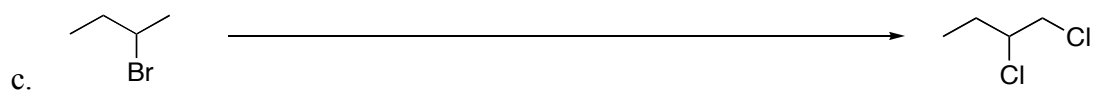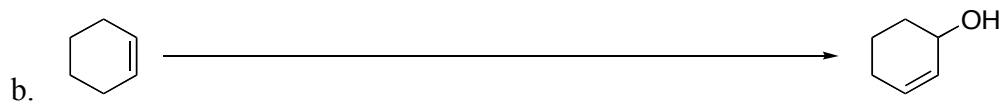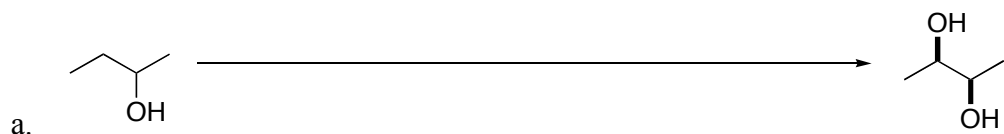
1. What is a structure for C_3H_6, if it reacts with Br_2?

Elements of Unsaturation Problems

2. What is a structure for $C_5H_{10}O$, if it does <u>not</u> react with H_2/Pt, but does react with H_2SO_4 to give 2 different isomeric alkenes C_5H_8?
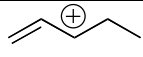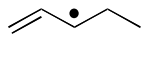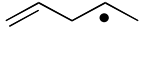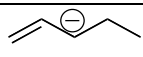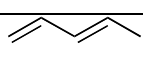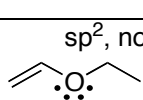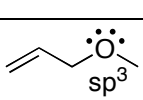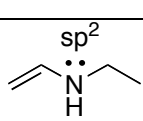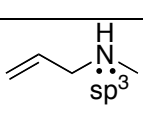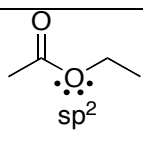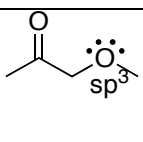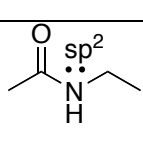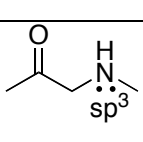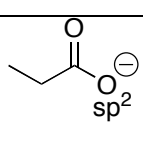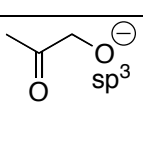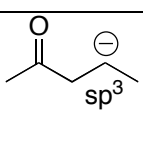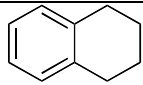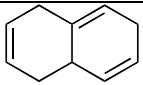
3. What is a possible structure for C_5H_8, if it reacts with H_2/Pt to give C_5H_{10}?

4. Identify products **A-C**.

HBr,
$\longrightarrow$ **A**
Peroxides

$\downarrow$ NaOCH₂CH=CH2

B

1. BH₃-THF
C $\longleftarrow$

2. NaOH, H₂O₂
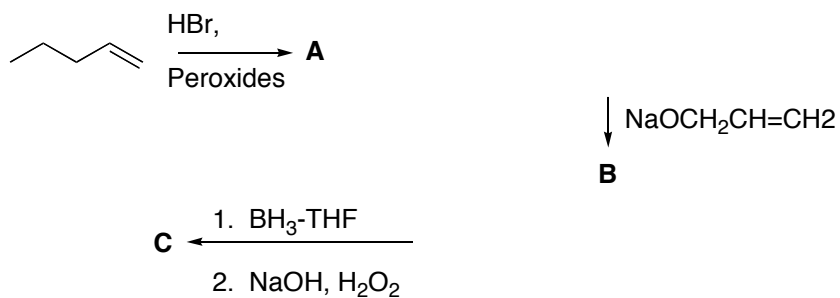
Ch. 10 Conjugation and Allylic Systems

The General Stabilization Effect of Conjugated/Allylic Systems (Section 10.2,3,7,9,10)

		Conjugated (more stable)	Isolated (less stable)	Notes:
1	Cations			
2	Radicals			
3	Anions			
4	Dienes			
5	Ethers	sp^2, not sp^3!!	sp^3	An N or O next to a double bond becomes sp^2. An isolated N or O is sp^3
6	Amines	sp^2	sp^3	
7	Esters	sp^2	sp^3	
8	Amides	sp^2	sp^3	Very special, chapter 25, all of biochemistry, proteins, enzymes, etc.
9	Oxyanions (Carboxylates)	sp^2	sp^3	Very special, chapter 18
10	Carbanions (Enolates)	sp^2	sp^3	Very special, chapter 20
11	Aromatics			Very special, chapters 11 + 12

Conjugation: Anything that is or can be sp^2 hybridized is stabilized when next to π bonds.
  • oxygens, nitrogens, cations, radicals, and anions

Notes:
1. Any atom that can be sp^2 will be sp^2 when next to a double bond
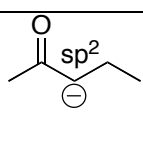2. "Conjugation" is when sp^2 centers are joined in an uninterrupted series of 3 or more, such that an uninterrupted series of p-orbitals is possible
3. Any sp^2 center has one p orbital

Impact of Conjugation

4. **Stability:** Conjugation is **stabilizing** because of p-orbital overlap (Sections 10.10)
    *   Note: In the allyl family, **resonance = conjugation**

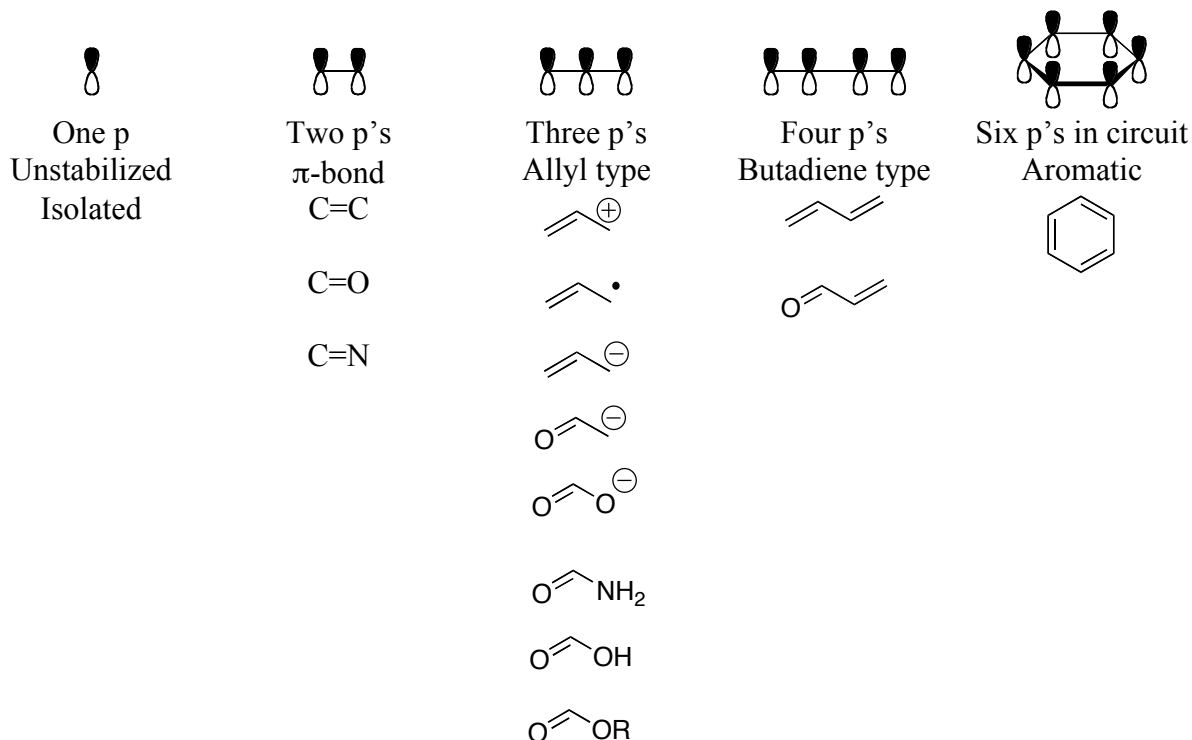| One p Unstabilized Isolated	Two p's π-bond	Three p's Allyl type	Four p's Butadiene type	Six p's in circuit Aromatic
	C=C			
	C=O			
	C=N			

5. **Reactivity:** Conjugation-induced stability impacts **reactivity** (Sections 15.4-7)
    *   If the **product** of a rate-determining step is stabilized, the reaction rate will go **faster** (product stability-reactivity principle)
        o   Common when allylic cations, radicals, or carbanions are involved
    *   If the **reactant** in the rate-determining step is stabilized, the reaction rate will go **slower** (reactant stability-reactivity principle)
        o   Why aromatics are so much less reactive
        o   Why ester, amide, and acid carbonyls are less electrophilic than aldehydes or ketones

6. **Molecular shape** (Sections 15.3, 8, 9)
    *   The p-orbitals must be aligned in parallel for max overlap and max stability
    *   The sp^2 centers must be coplanar
        All four sp^2 carbons must be flat for the p's to align
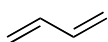
7. **Bond Length:** Bonds that look like singles but are actually between conjugated sp^2 centers are **shorter** than ordinary single bonds

• In amides, esters, and acids, the bond between the carbonyl and the heteroatom is shortened
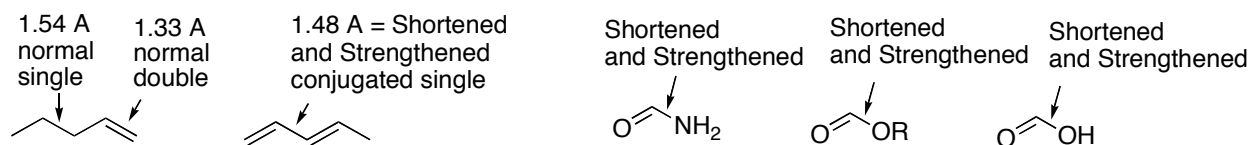
8. **Bond Strength:** Bonds that look like singles but are actually between conjugated sp^2 centers are **stronger** than ordinary single bonds
9. **Bond Rotation Barrier:** Bonds that look like singles but are actually between conjugated have much larger rotation barriers than ordinary single bonds
    • Because in the process of rotating, the p-overlap and its associated stability would be temporarily lost
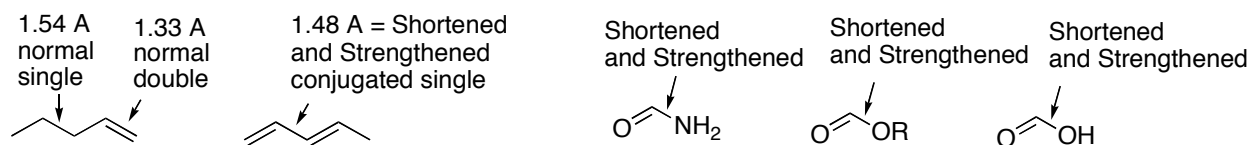
10. **Hybridization:** Conjugated sp^2 atoms have both sp^2 and p orbitals. You should always be able to classify the hybridization of **lone pairs on nitrogen and oxygen**.
    • **Isolated** oxygens or nitrogens: sp^3 atom hybridization, sp^3 lone-pair hybridization, and tetrahedral, 109º bond angles
    • **Conjugated nitrogens**: sp^2 atom hybridization, **p lone-pair hybridization (needed for conjugation)**, and 120º bond angles
    • **Conjugated oxygens**: sp^2 atom hybridization, **one p lone-pair hybridization** (needed for conjugation), **one sp^2 lone-pair**, and 120º bond angles
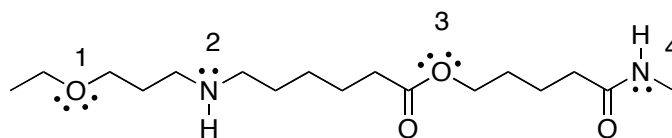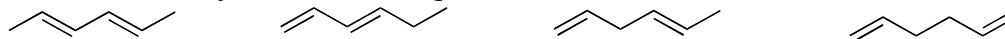

Atom	O-1	N-2	O-3	N-4
Isolated vs. Conjugated				
Atom Hybridization				
Lone-Pair(s) Hybridization				
Bond Angles				

Diene Stability and the Stability of other Acyclic Systems with 2 Elements of Unsaturation (10.8-11)

Q1: Rank the stability of the following dienes:

Stability Factors for Simple Dienes:
1. Isolated versus Conjugated: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.

Stability Patterns for Regular Dienes versus Other Systems with 2 elements of unsaturation
3. **Allenes** = "Cumulated Dienes": **Less stable than dienes or alkynes**
   - in allenes, the central carbon is sp rather than sp^2 hybridized

$$\overset{\text{sp}}{\underset{\downarrow}{}}$$
$$H_2C=C=CH_2$$

4. **Alkynes**: **Less stable than dienes, but more stable than allenes**.
   As for alkenes and dienes, more substituted alkynes are more stable less substituted alkynes

Q2: Rank the stability of the following isomers:
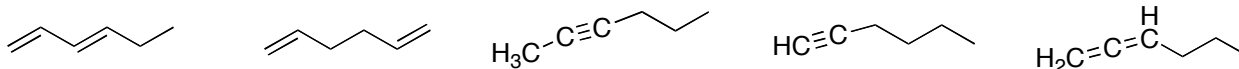
Q3:   Rank the amount of heat produced if the isomers above were hydrogenated? Burned?

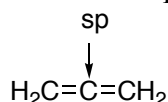**Stability of Allylic/Benzylic (Conjugated) Cations (10.1,2)**

Stability Factors for Cations:
1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.
    *   Conjugation/allylic is more important than the substitution pattern of an isolated cation (i.e. 1° allylic > 3° isolated)

Q1: Rank the stability of the following cations?
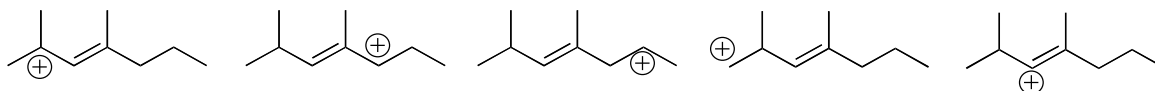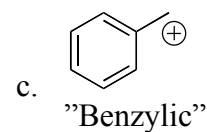
Q2: Rank the stability of the following alkene cations?

Allylic Cations, Resonance, and Allylic Symmetry/Asymmetry

a.   b.   c.

"Benzylic"
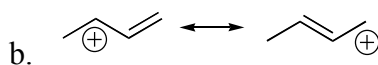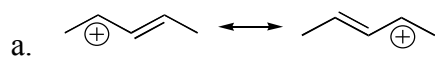
1. Two resonance structures each (at least)
2. Charge is delocalized, shared
3. Allylic cations can be symmetric or asymmetric
4. When an allylic cation is asymmetric, it's helpful to evaluate which form would make a larger contribution to the actual hybrid
    *   Cation substitution is more important than alkene substitution

Q3: For above cations, identify as symmetric or asymmetric.

Q4: For the following cations:
     a.   identify which are allylic (would have a resonance structure).
     b.   For those that are allylic, identify which are symmetric vs. asymmetric?
     c.   For any asymmetric allylic cations, draw the resonance structure
     d.   For any asymmetric allylic cations, identify which resonance structure would
         make the larger contribution to the actual resonance hybrid

1.

2.

3.

4. Ph

5.

6.

7.

8.

9.

10.
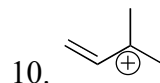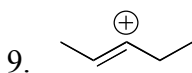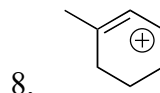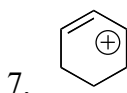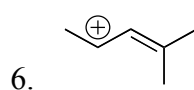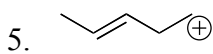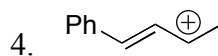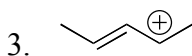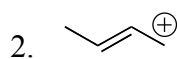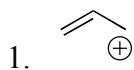
Impact of Allylic Cation Resonance on Reaction Rates and on Whether One or Two Products Form (S$_N$1 Reactions (10.3)

1. **Rates**: Resonance/conjugation stability enhances rates when cation formation is rate-determining

2. **One Product or Two?** Product mixtures result if an allylic cation is asymmetric.
    *   two unequal resonance structures can lead to two products (structural isomers).

3. **Product Distribution**
    *   When two isomeric products can form, consider two things:
        1. Which product is more stable?
            *   This will impact "product stability control" = "thermodynamic control" = "equilibrium control"
            *   To assess product stability, focus on the alkene substitution
        2. Which resonance form of the cation would have made a larger contribution?
            *   This will often favor "kinetic control", in which a product which may not ultimately be the most stable forms preferentially
4. **Position of Cation Formation**: When a conjugated diene is protonated, consider which site of protonation would give the best allylic cation.

Q1: Key: Think about the cation! For the bromides A-C:
a. Draw the cation intermediates.
b. If an allylic cation is involved, recognize as symmetric or asymmetric.
c. Rank the reactivity of the three bromides.
d. Draw the product or products. Be clear to notice whether you'd get one isomer or two.
e. If two products are possible, identify which is more stable (the "thermodynamic product") based on product alkene stability.
f. For the asymmetric allylic cation, identify which resonance structure makes a larger contribution to the resonance hybrid. Does this lead to the "thermodynamic" (more stable) product, or to the "kinetic" (less stable) product?
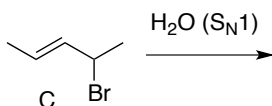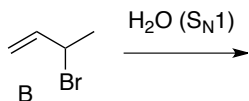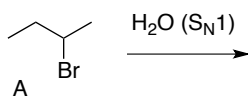
Impact of Allylic Cation Resonance on Addition of H-X to Conjugated Dienes.
- Notes on predicting products when H-X adds to a diene.

Questions/Issues to Deal With When Predicting Product(s).
1. Always protonate first on an outside rather than inside carbon.
   - This will give an allylic rather than isolated cation
2. Is the diene symmetric or asymmetric?
   - If it's symmetric, it doesn't matter which outside carbon you add to first.
   - If it's asymmetric, then protonating at different ends will likely give allylic cations of unequal stability. Thus you should decide which protonation site will give the best allylic cation.
3. Is the allylic cation (once you have protonated) symmetric or asymmetric?
   - If it's symmetric, you'll get one structural isomer.
   - Is it's asymmetric, you'll get two structural isomers.

Question 2: Key: Think about the cation! For the dienes A-C,
a. Draw the cation intermediates.
b. If an allylic cation is involved, recognize as symmetric or asymmetric.
c. Rank the reactivity of the three bromides.
d. Draw the product or products. Be clear to notice whether you'd get one isomer or two.
e. If two products are possible, identify which is more stable (the "thermodynamic product") based on product alkene stability.
f. For the asymmetric allylic cation, identify which resonance structure makes a larger contribution to the resonance hybrid. Does this lead to the "thermodynamic" (more stable) product, or to the "kinetic" (less stable) product?
g. When two products form, classify each as a "1,2" or "1,4" product

1.0 H-Br

A

1.0 H-Br

B

1.0 H-Br

C
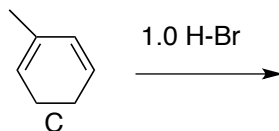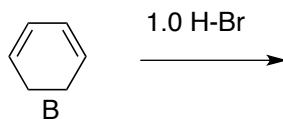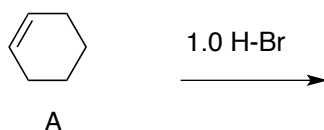
Sections 10.13,14   **1,2 vs. 1,4 Addition to Conjugated Dienes: "Kinetic" vs. "Thermodynamic" Control**
1. **"Thermodynamic Control" = "Product-Stability Control" = "Equilibrium Control"**
    ▪ This is when **the most stable** of two possible **products** predominates.
        o **Use Alkene Stability to identify which product is more stable.**
        o The most stable product will be preferred if either:
            ▪ The two products can equilibrate, or
            ▪ The more stable product involves a more stable transition state
2. **Kinetic Control:** If **the less stable** of two possible products predominates.
    ▪ This will always require that for some reason the less stable product forms via a better transition state (transition-state stability/reactivity principle). Common reasons:
        o Charge distribution in an allylic cation or radical.
        o Proximity of reactants. In an H-X addition to a diene, often the halide anion is closer to the "2" carbon than to the "4" carbon of the allylic cation.
        o Steric factors. (Why bulky E2 base give less stable Hoffman alkenes.)
3. **Temperature Factor**: When allylic halides are produced, the "thermodynamic" product increases at higher temperature due to equilibration.

Example:

1,2- vs 1,4 Addition Product:

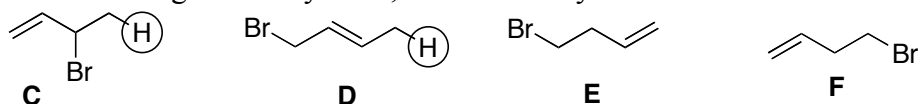|		
at -80°C	80% (major)	20% (minor)
at +40°C	15% (minor)	85% (major)

More/Less stable:

Mech (and why)

What about the following? Do they form, and if not why not?

More H-X to Conjugated Dienes Practice
1. Draw the mechanism, including both resonance structures for the best allylic cation.
2. Predict the products for the following reaction.
3. Identify each product as 1,2 or 1,4 product.
4. Identify which product is the "thermodynamic" product, and which might be the "kinetic".
5. One product **X** is the major product at low temp, but the other product **Y** is major at higher temperatures. Assign "**X**" and "**Y**" to the appropriate products.

1.0 D−Br
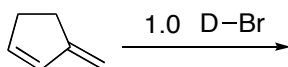
Review on predicting products when H-X adds to a diene.
1. Always protonate first on an outside rather than inside carbon.
   - This will give an allylic rather than isolated cation
2. Is the diene symmetric or asymmetric?
   - If it's symmetric, it doesn't matter which outside carbon you add to first.
   - If it's asymmetric, then protonating at different ends will likely give allylic cations of unequal stability. Thus you should decide which protonation site will give the best allylic cation.
3. Is the allylic cation (once you have protonated) symmetric or asymmetric?
   - If it's symmetric, you'll get one structural isomer.
   - Is it's asymmetric, you'll get two structural isomers.

Mixtures of 1,2 and 1,4 addition also occur when dihalogens (Br$_2$, Cl$_2$) add to dienes
Q2: Draw the major products when the diene above reacts with Br$_2$. Which would you expect to be the "thermodynamic" product?

10.5,6 Allylic/Benzylic Radicals and Allylic Halogenation
Stability Factors for Radicals:
1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
2. Substitution: More highly substituted are more stable.
    • Conjugation/allylic is more important than the substitution pattern

Impact of Radical Resonance on Reactivity and Product Formation: Allylic Radical
Bromination is Fast!
1. **Rates**: Allylic bromination is fast.
2. **Position of Radical Formation: Allylic positions react.**
3. **Product Distribution A:**   Unequal allylic positions can each lead to products.
4. **Product Distribution B:** Asymmetric allylic radicals product two bromide isomer.

**Review on predicting products in allylic radical brominations.**
1. Is the alkene symmetric or asymmetric?
    • If it's symmetric, it doesn't matter which allylic carbon you convert to a radical.
    • If it's asymmetric, then you can remove a hydrogen from different allylic sites and
      make different allylic radicals, each of which can lead to products.
2. For each allylic radical, is it symmetric or asymmetric?
    • If it's symmetric, it will lead to one structural isomer bromide.
    • Is it's asymmetric, it will lead to two structural isomer bromides.
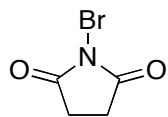
"**NBS**" = N-Bromosuccinimide = More commonly used than Br_2/hv for
allylic/benzylic radical brominations. Maintains dilute [Br_2], absorbs HBr.
Prevents Br_2 or HBr from undergoing ionic addition to alkenes. More
convenient to weigh out (solid). Some mechanistic complexity. Often
higher yields.

Practice Problems
a. Draw the radical intermediates, including resonance structures
b. Ranks the reactivity of **A**, **B**, and **C**.
c. Draw the product or products for the following reactions

NBS
peroxides

A

NBS
peroxides

B

NBS
peroxides

C
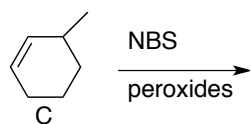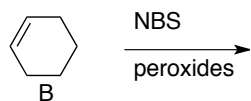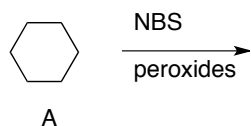
10.7 Allylic Anions

1. Allylic anions are stabilized, just as are cations and radicals

2. Anion stability impacts acidity

 • when something neutral functions as an acid, it releases H^+ and produces an anion

Question 1: Compare the acidity of cyclpentene to cyclopentane. One is a quintillion times more acidic than the other. Which is it, and why?

Question 2: Compare the acidity of acetone, 2-methylpropene, and 2-methylpropane
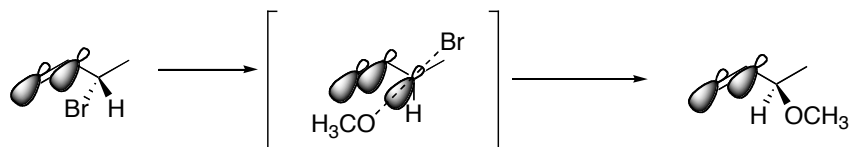
Section 10.3   Allylic Halides and S$_N$2 Reactions. Allylic Systems Are Really Fast

Ex.

Slow, and contaminated by competing E2

80% yield

NaOCH$_3$

15 min

100% yield

Fast and Clean
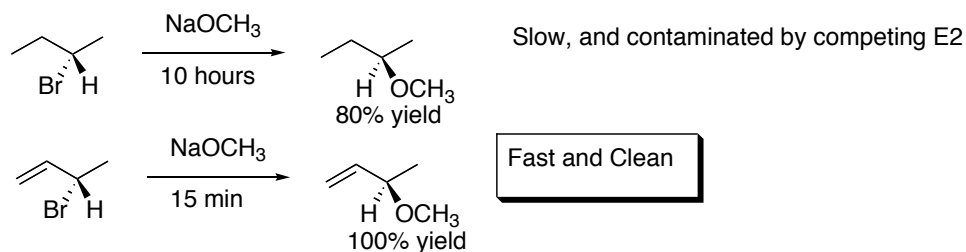
Why? Because the backside-attack transition-state is stabilized by conjugation!
(Transition state-stability-reactivity principle).

1. Neither the product nor the reactant has conjugation, so it's hard to see why conjugation should apply
2. However, in the 5-coordinate T-state the reactive carbon is sp^2 hybridized
    ▪ the nucleophile and the electrophile are essentially on opposite ends of a temporary p-orbital.
3. That transient sp^2 hybridization in the transition-state is stabilized by π-overlap with the adjacent p-bond.
4. This stabilization of the transition-state lowers the activation barrier and greatly accelerates reaction

Key Application: RMgBr can do Clean S$_N$2 Reactions on 1° Allylic Bromides
▪ RMgBr carbanionic nucleophiles can't do good S$_N$2's on normal 1° or 2° allylic bromides because of competing elimination and single-electron-transfer reactions.
▪ But they work well on allylic halides

1

2

3
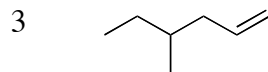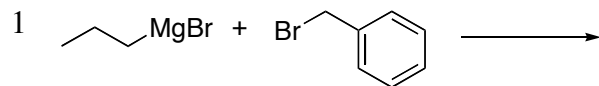
Retrosynthesis.
Make from bromides
that began with 4 or fewer carbons

Note: When thinking backwards, identify the allylic carbon and the next carbon removed from the alkene. Those will be the two carbons that were linked.

Sections 10.16 Molecular Orbitals and Conjugation (not for test)

Molecular Orbital Summary Sheet

Anti-bonding Orbitals

Non-bonding Line

Bonding Orbitals

E=O
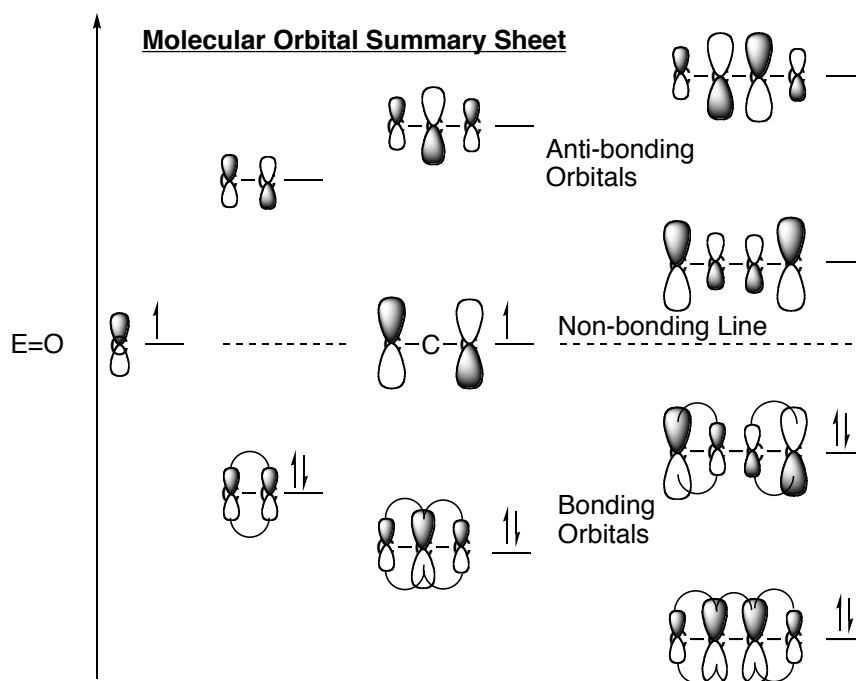
Observations:
1. Shown are an isolated radical, a double bond, an allyl radical, and butadiene.
2. "**MO**" = "**M**olecular **O**rbital"
3. MO's lower/stabler in energy than the non-bonding line are referred to as "bonding MO's", while those that are higher (less stable) in energy are called "antibonding MO's"
4. The number of π MO's equals the number of contributed π (p) orbitals. (One p in gives one MO. Two p's in gives two MO's. Three p's in gives three MO's. Four p's in gives four MO's. Etc.)
5. Any bonding MO is mirrored by an antibonding MO, whose energy is as high above nonbonding as the bonding MO is above it.
6. Thus the sum energies of the MO's (ignoring electron occupancy) equals 0.
7. However, not all MO's are occupied by electrons. Electron occupancy proceeds from the lowest MO's up. And it's the energies of the electrons that determine the molecular energy. Thus explains why it's energetically profitable for a molecule to be conjugated. CONJUGATING THE P ORBITALS LOWERS THE ENERGIES OF THE ELECTRONS AND THUS IS STABILIZING.
8. The **h**ighest **o**ccupied **m**olecular **o**rbital is called the "**HOMO**", and the **l**owest **u**noccupied **m**olecular **o**rbital is called the "**LUMO**". These are also referred to as the Frontier Molecular Orbitals (**FMO**'s). The frontier molecular orbitals are the orbitals involved as nucleophiles or electrophiles in reactions. If electrons are donated (nucleophile), they will come from the HOMO. If electrons are accepted (electrophile), they will go to the LUMO. Thus the energies and shapes of the HOMO/LUMO are really important.
9. The lowest MO keeps getting lower and lower (more and more stable). But, the energy level of the HOMO does **not** get progressively lower. Notice that the diene HOMO is higher than the simple alkene HOMO.
10. Notice that not all atoms have the same sized p-orbitals in the FMO's. When reactions happen, atoms with the big p-lobes are the ones that react.
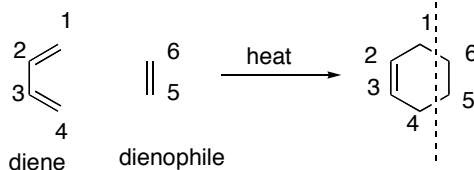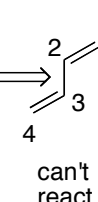
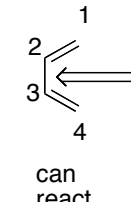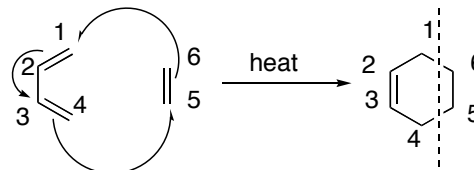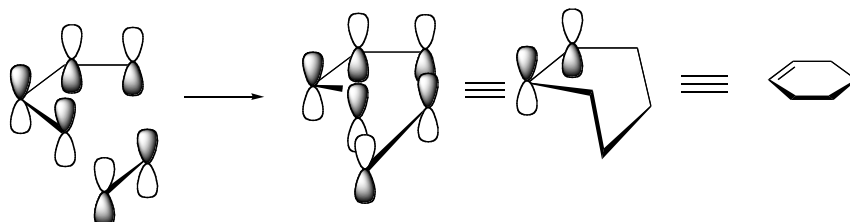Molecular Orbitals For Allylic Cations, Radicals, and Anions
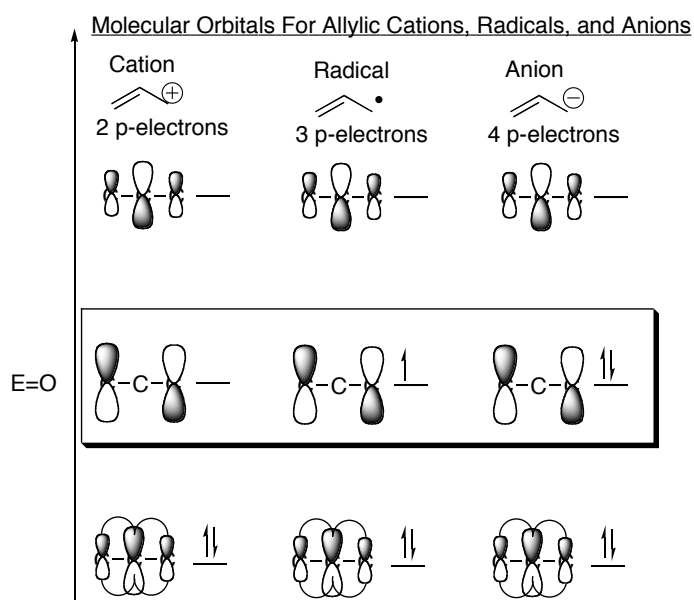
11. For allylic systems, notice that the energies and shapes of the MO's stay the same.

12. However, the occupancy does change. An allylic cation has two π-electrons, an allylic radical has three, and an allylic anion has four. Thus the key reactive middle MO goes from empty (strongly electrophilic) to full (strongly nucleophilic) across the series.

13. The MO picture tells the same story that resonance pictures show: there is no reactivity on the central carbon, but the outside carbons are the ones that react, whether in an allylic cation, radical, or anion.
   ▪ MO theory explains this with the orbital lobes
   ▪ Resonance theory explains this with

14. Sometimes MO can explain things that the simpler resonance theory can't.

15. In an actual reaction, the HOMO and LUMO interact
   • As usual two orbitals in produce two new orbitals (molecular orbitals) out.
   • The electrons end up lower in energy: more stable
   • MO fact: the closer the HOMO and LUMO are to each other in energy, the more favorable and profitable the reaction will be
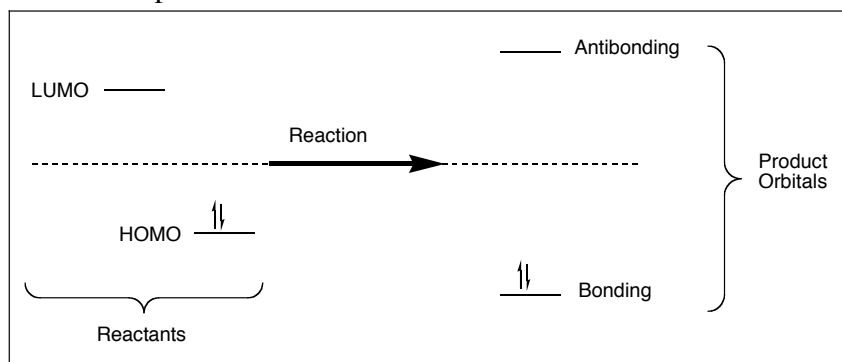
Section 10.15-17   The Diels-Alder Reaction. The Reaction of Conjugated Dienes (Dienes) with Electron-Poor Alkenes (Dienophiles) to make Cyclohexenes.

Quick Overview Summary

|	
1.	
2.	s-cis diene conformational requirement: The diene must be locked or be able to single-bond rotate it's way into the "s-cis" conformation in order to react
3.	Rate Factors 1. Dienophile ▪ activated by electron withdrawing groups ("W" or "EWG") for electronic reasons 2. Diene: ▪ Deactivated by substituents that make it harder or less stable to exist in the s-cis conformation. This is true when a diene alkene has a Z-substituent. ▪ Steric factors equal, activated somewhat by electron donating groups ("D" or "EDG")
4.	Concerted Mechanism All bond making and breaking happens at once: *3 π-bonds break *2 σ-bonds and 1π-bond form The diene is really the "nucleophile" (HOMO) The dienophile is really the "electrophile" (LUMO)
5.	Orbital Picture
6.	Product Prediction Highlights ▪ Try to match up the 4 diene and 2 dienophile carbons with the product o The product double bond will be between C2 and C3 of the diene ▪ Substituents are spectators ▪ 1,4/1,2 Rule: when asymmetric dienes react with asymmetric dienophiles o Match δ- end of nucleophilic diene with δ+ end of electrophilic dienophile ▪ For disubstituted dienophiles: o cis-substituents end up cis, and trans-substituents end up trans

A. The General Diels-Alder Reaction
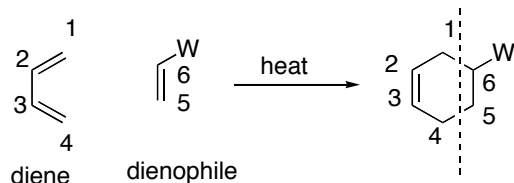
diene   dienophile

1. **Electronics**: The diene HOMO reacts with the dienophile LUMO
    - Effectively the diene is the nucleophile and the dienophile functions as the electrophile
2. The **dienophile** usually **needs an electron-withdrawing attachment** ("W") (at least one)
    - This makes the dienophile more electrophilic
   - Electron Withdrawing Groups to Memorize:

- Keys:
    - The atom that is connected to the alkene has δ+ charge
    - Anything with a double-bond to a heteroatom tends to have this
        - C=O, C≡N, N=O, S=O

Q1/example: Rank the reactivity of the following alkenes as dienophiles. The actual relative reactivity ratios are 50,000 : 1,000 : 1. Huge differences.
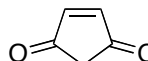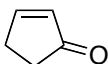
Q2: Rank the reactivity of the following dienophiles:
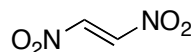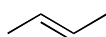
3. **Energetics**:
    - **Bonds broken**: 3 π bonds
    - **Bonds made**: 2 σ bonds, 1 π bond
    - **Enthalpy:** The net replacement of 2 π bonds (weaker) with 2 σ bonds is normally **strongly enthalpy favored**
    - **Entropy:** The high required organization of the concerted transition state makes the reaction **entropy disfavored**.
    - Heat normally required to overcome entropy

4. **Simple Mechanism (Good enough for test)**
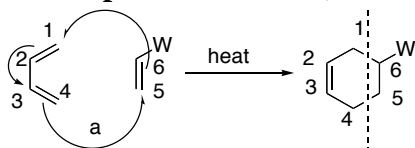
Concerted: All bond making and breaking happens at once
-three arrows show each of the three p-bonds breaking and the three new bonds forming
-the arrow "a" from the diene to the dienophile is really key

5. **Orbital Picture**
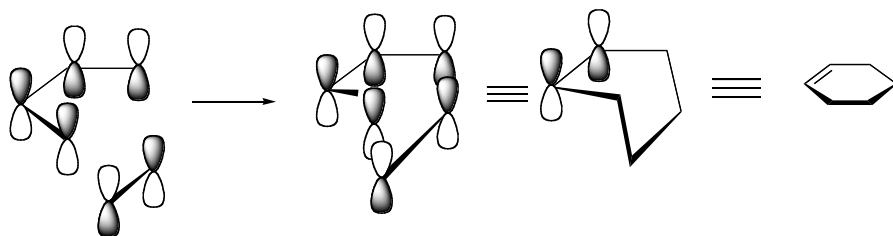
a. the p orbitals on the dienophile overlap with the p-orbitals on C1 and C4 of the diene
b. the overlapped p orbitals from the diene and dienophile end up being σ bonds in product
c. the leftover p orbitals on C2 and C3 end up overlapping to give the π bond in product
d. the diene must be in the s-cis conformation; in the zigzag s-trans layout, can't react
e. Not tested: perfect HOMO/LUMO orbital symmetry match (Section 15.12)

B. Predicting Products When the Diene or the Dienophile (or both) is Symmetric
1. Always make a cyclohexene 6-ring product
2. Number the diene from 1-4, and identify those four carbons in the product ring.
3. A double bond in the product will always exist between carbons 2 and 3.
4. Any substituents on the diene or dienophile are spectators: they will be attached to the same carbons at the end.
- Beware of cyclic dienes
- Beware of dienes that are drawn in their zigzag s-trans form, but could react following rotation into an s-cis form

<u>Noteworthy</u>
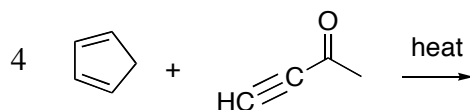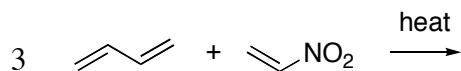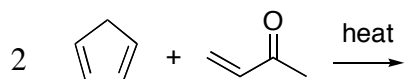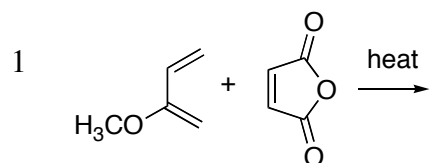
C. Stereochemistry: For Cis- or Trans- **Disubstituted Dienophiles**
- Both carbons of a disubstituted dienophile usually turn into stereocenters.
1. **Cis in → cis out**: If two substituents on the **dienophile** are cis to begin with, they will still have a cis relationship on the product cyclohexene
2. **Trans in → trans out**: If two substituents on the **dienophile** are cis to begin with, they will still have a cis relationship on the product cyclohexene
- **Note**: this is for the **dienophile only**. The diene alkenes may also have substitution such that one or both diene double bonds are cis or trans, but the "cis-in-cis-out" guideline does not apply to the diene.
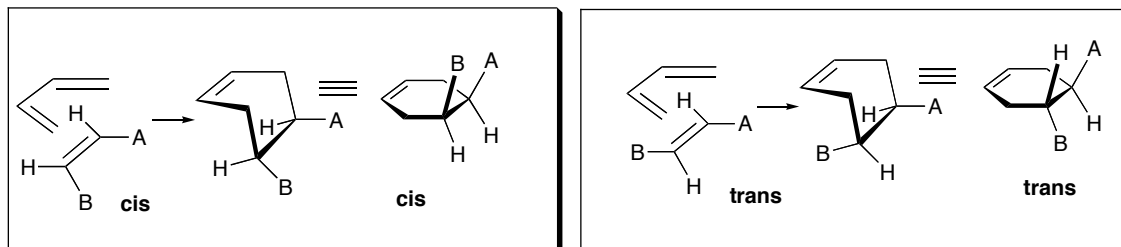
- **Why**: Because of the concerted mechanism. The diene is basically doing a concerted "cis" addition to the dienophile. The attachments on the dienophile never have opportunity to change their position relative to each other.

1

2

3

4

5
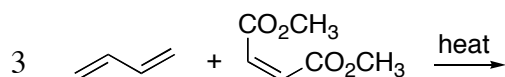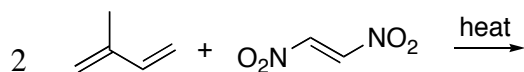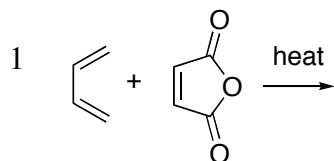
D. Structural Factors for **Dienes**

1. s-cis (cisoid) diene conformational requirement: The diene must be locked "s-cis" or be able to single-bond rotate it's way into the "s-cis" (cisoid) conformation in order to react

"transoid" or "s-trans"
-relative to the **s**ingle bond

"cisoid" or "s-cis"
-meaning that it's "cis" relative to the **s**ingle bond
-even though the single bond is capable of rotation

can't react   can react

Why? Because the concerted, p-orbital overlap mechanism is impossible from s-trans.

s-cis: p-orbital overlap possible

s-Trans

overlap no good

Would need to make an impossible 6-ring with trans alkene!
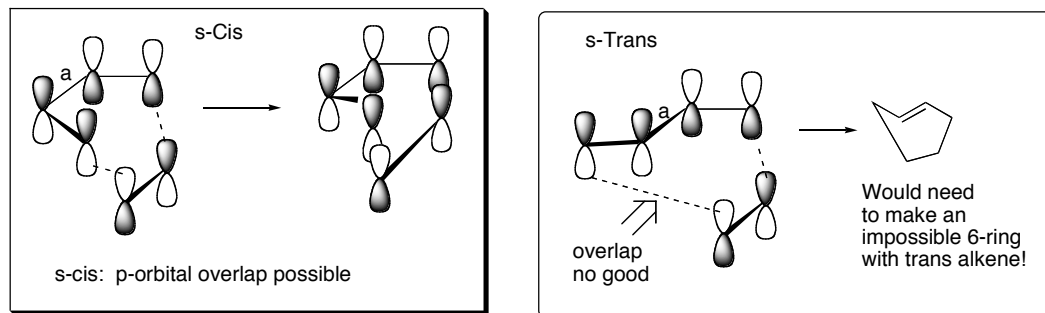
*   Normally the s-cis conformation is less stable than the s-trans conformation (sterics).
*   Only the minor fraction of a diene in the s-cis conformation is able to react
*   The larger the equilibrium population in the s-cis conformation, the greater the reactivity

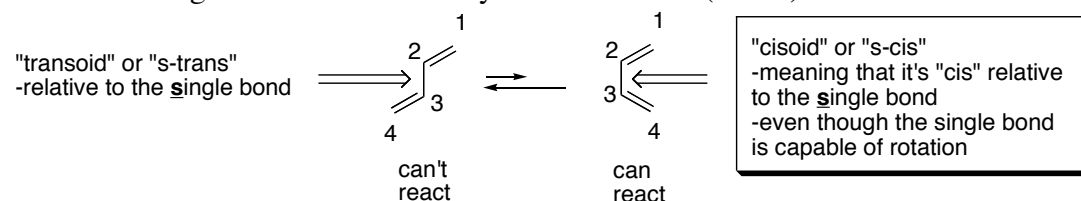2. For an acyclic diene, a "Z" substituent on either (or both) of the diene alkenes causes major steric problems for the s-cis conformation, reduces the equilibrium population of s-cis diene, and thus reduces Diels-Alder reactivity

Q1: For the dienes **A-Z**, circle the letters for those that are in a reactive s-cis conformation.
Q2: For the acyclic dienes **C-Z**, identify any double bonds the are E or Z.
Q3: Match acyclic dienez **C-Z** with the alternate s-cis/s-trans form shown below.
Q4: For the dienes **A-E**, try to rank their probable Diels-Alder reactivity based on the probable relative population of their s-cis conformations. (or match: $100\%, 3\%, 001\%$, $0.000001\%, 0\%$)
Q5: Try to redraw **D** and **E** into their s-cis forms

A   **B**   **C**   **D**   **E**   **W**   **X**   **Y**   **Z**
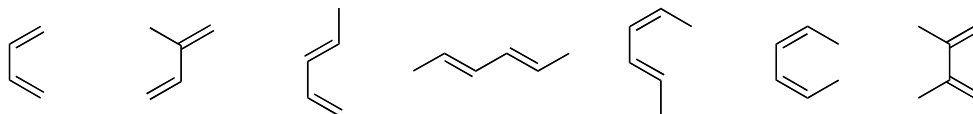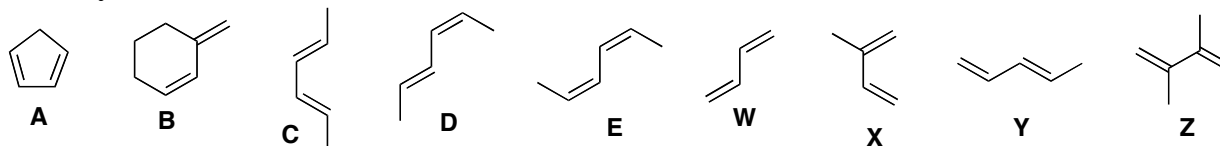
3. When steric factors are not a problem (in other words, when not in a "Z" position), electron donating groups ("D" or "EDG") have a mild activating effect
   - OR, NR₂, R (memorize)
   - Why: The diene functions as the nucleophile. A donor makes the diene more electron rich and thus more nucleophilic.

Rank the reactivity:

E. Stereochemistry: For **Dienophiles with Substituents on C1 and/or C4** (Not test responsible)

- Need to convert diene into s-cis conformation, then envision the transition state
- The "inside" (Z) substituents on C1/C4 end up "up" (cis); the "outside" (E) substituents on C1/C4 end up "down" (and cis to each other); inside/outside attachments on C1/C4 end up trans

F. Predicting Products When **Both Diene and Dienophile are Asymmetric** (****)

Q. Circle the symmetric dienes or dienophiles

Dienes

Dienophiles

- Any monosubstituted diene or monosubstituted dienophile is asymmetric
- You can be trans and still symmetric
- Symmetry requires equal attachments on: C1+C4, C2+C3 (dienes), C5+C6 (dienophile)

If either component is symmetric, you don't have structural isomer issues.

Same

Same

1. If both ends of diene are the same, it doesn't matter which adds to which end of dienophile
2. If both ends of dienophile are the same, it doesn't matter which adds to which end of diene

If both components are asymmetric: two structural isomers are possible; one dominates.
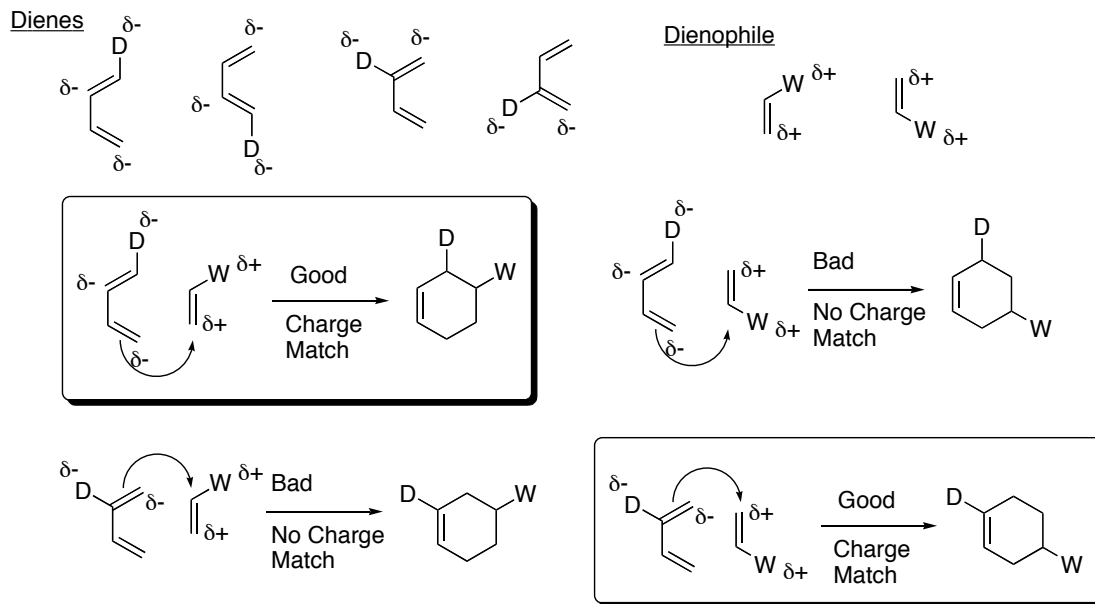
major
1,4 relationship
(para-like)

major
1,2 relationship
(ortho-like)

not formed
1,3 relationship
(meta-like)

not formed
1,3 relationship
(meta-like)

*** A 1,2 or 1,4 relationship is always preferred over a 1,3 relationship, if possible   ***

- Although ortho/meta/para terms don't really correctly apply to cyclohexenes, many students remember this is an "**ortho/para preferred**" rule, to avoid number confusion
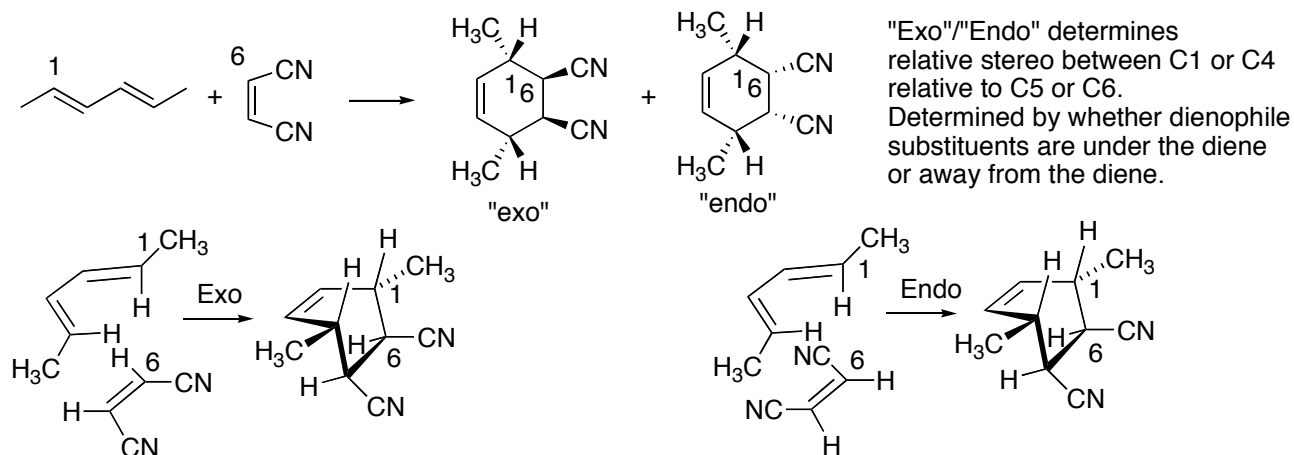
Explanation for Structural Isomer Selectivity in Addition of Asymmetric Dienes to Asymmetric Dienophiles: Electronics

- Donors function as electron rich ($\delta-$); withdrawers function as electron poor ($\delta+$)
- $\delta-$ or $\delta+$ partial charges are shared on **alternating atoms** (ala allylic) over π-systems
- For an asymmetric diene, one of the two terminal carbons ends up $\delta-$ and nucleophilic
- For an asymmetric dienophile, one of the alkene carbons ends up $\delta+$ and electrophilic.
- Matching the $\delta-$ diene terminus with the $\delta+$ dienophile carbon gives major structural isomer.

Dienes   Dienophile

Good Charge Match

Bad No Charge Match

Bad No Charge Match

Good Charge Match

| 1 | H₃CO diene + OCH₃ dienophile (acrylate) | heat | |
2	diene + methyl vinyl ketone	heat	
3	2,3-dimethylbutadiene-type + NO₂ vinyl	heat	
4	diene + NO₂ vinyl	heat	
5	H₃CO diene + enone	heat	
6	isoprene + cyclopentenone	heat	

G. Endo/Exo Stereochemistry: Relative stereochemistry when both diene and dienophile generate stereocenters. (This will involve **Dienophiles with Substituents on C1 and/or C4)** (Not test responsible)

"Exo"/"Endo" determines relative stereo between C1 or C4 relative to C5 or C6. Determined by whether dienophile substituents are under the diene or away from the diene.

1. In the exo product, the relative stereochemistry at C1-C6 is trans.
2. In the endo product, the relative stereochemistry at C1-C6 is cis.
3. The difference results from how the dienophile lays out under the diene.
    *   In the exo case, the dienophile substituent extends away from the diene, while the dienophile hydrogens extend underneath the diene. (Sterically preferable)
    *   In the endo case, the dienophile substituent extends under the diene, while the dienophile hydrogens extend away from the diene. (Some electronic advantage.)

Ch. 16 Aromatic Compounds

16.1-5 Structure and Unique Properties of Benzene

C_6H_6

A ⟷ **B** ≡ **C**
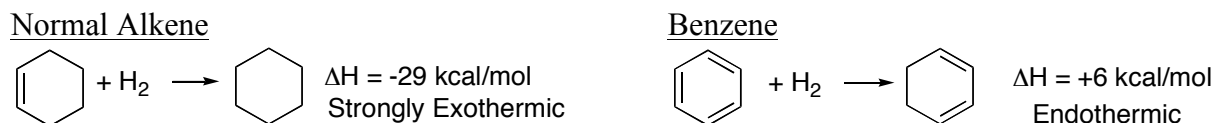
2 Resonance Structures
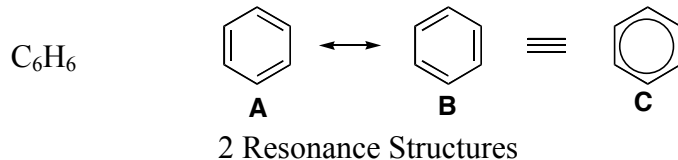
Facts to Accommodate
1. 4 elements of unsaturation
2. All C-C bonds are same length, not alternating (contrary to expectation based on structure **A**)
3. Only 1 isomer of 1,2-dibromobenzene (contrary to expectation based on structure **A**)
4. Unlike alkenes, does <u>not</u> undergo addition reactions (contrary to expectations based on **A**)
5. Extreme stability indicated by combustion or hydrogenation tests

|	H_2/Pt	Br_2	HBr	BH_3	$Hg(OAc)_2$/H_2O	Etc.
D	Reacts	Reacts	Reacts	Reacts	Reacts	
A	No Reaction	No Reaction	No Reaction	No Reaction	No Reaction	
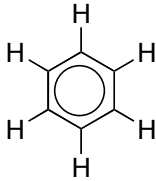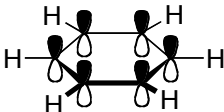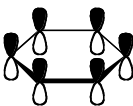
Hydrogenation: Measurement Tests for the Extraordinary Stability of Benzene

Normal Alkene

+ H_2 ⟶ ΔH = -29 kcal/mol
Strongly Exothermic

Benzene

+ H_2 ⟶ ΔH = +6 kcal/mol
Endothermic

*   Hydrogenation is normally very exothermic, but not for benzene
*   The less favorable hydrogenation reflects **greater stability**
*   The stability difference is over 30 kcal/mol: huge
    o   Butadiene gains <4 kcal/mol of stability from it's conjugation

16.3,4 Benzene Molecular, Structural Details, and Molecular Orbitals

1. Some different pictures of benzene

	H, H, H, H, H, H		
a) Simplest **b) Ideal for mechanisms**, helps keep track of the electrons	Illustrates: a) delocalization of b) equivalence of bonds d)<u>complete planarity</u>	**a) Easy to see π-system** b) Helps explain why the C-C bonds are all the same	**a) Easy to see the π-system**, undistracted by the hydrogens

2. Notes on Pictures and Structural Features
1. All 6 carbons are sp^2, with one p orbital each
2. 120º angles, so all 6 carbons and each of their attached hydrogens are all co-planar.
3. Perfectly flat.
4. Perfect 120º angles, no angle strain whatsoever
5. Complete symmetry
6. Each C-C bond is equal in length and strength
7. Each C-C bond is longer than a normal double but shorter than a normal single bond

Normal Bond Lengths:	C-C: 1.54A	C=C: 1.34 A	Benzene CC: 1.39A

- "1.5" bonds, as we see from resonance.

8. 6 π -electrons are delocalized throughout the ring.
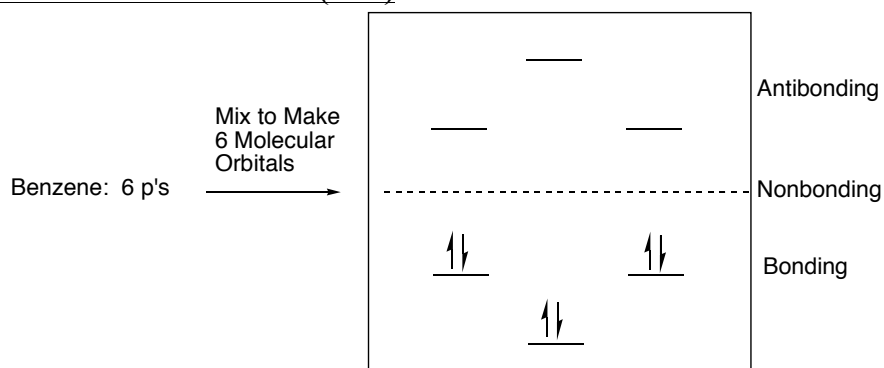   - Complete racetrack
9. Resonance delocalization, stabilization
10. Note: not all "π racetracks" are stabilized
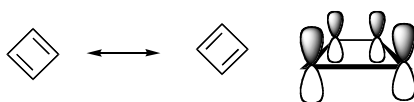
No extra stability
Actually somewhat destabilized

3. Molecular Orbital for Benzene (11.5)

- All and only the bonding molecular orbitals are completely filled. Special stability
- But how can you know what the molecular orbitals will look like for other rings?

**Frost Diagram/Polygon Rule:** (11.19) For a **complete ring** of **sp^2 centers**,
1. Draw the ring/polygon with a vertex down, basically inside what would be a circle
2. Each apex represents a molecular orbital
3. A horizontal line through the middle of the ring provides the non-bonding reference point
4. Populate the MO's as needed depending on how many π-electrons are available

Molecular Orbital Rules for a cyclic π-system:
1. If all and only bonding molecular orbitals are occupied→ good ("aromatic")
2. If any nonbonding or antibonding MO's are occupied, or if any bonding MO's are not completely occupied → bad, poor stability ("antiaromatic")
   - Below nonbonding line → bonding
   - Above nonbonding line → antibonding
   - On nonbonding line → nonbonding

Practice Problem
1. Draw the MO's for 3-, 4-, 5-, and 6-membered cyclic π systems.
2. Fill in the orbitals and circle the following as good=stable=aromatic or not.
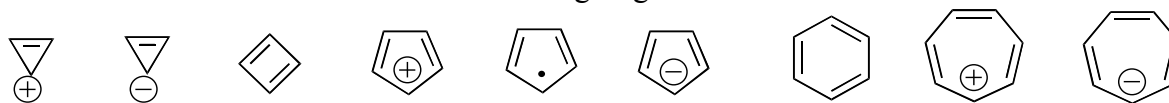
(3)   (4)

----

(5)   (6)

NOTE: 5-, 6-, 7-, and 8-membered rings all end up with 3 molecular orbitals below the non-bonding line

(11.19) **Aromatic, Antiaromatic, Nonaromatic**. **Huckel's Rule**: For a **planar**, **continuous ring** of **p-orbitals**, (sp^2 all around):

- If the number of π-electrons = 2,6,10 etc. (4N + 2) → AROMATIC, STABILIZED
- If the number of π-electrons = 4,8,12 etc. (4N) → Anti-aromatic, destabilized

- Why: the 4N+2 rule always goes with favorable Frost diagrams: bonding and only bonding MO's are always filled.

- Generality: Huckel's Rule applies for cycles, bicycles, ionic compounds, and heterocycles.
a. Cycles (one-ring)   b. Polycycles (2 or more)   c. Ionic rings   d. Heterocycles

Practice Problems: Classify each of the following as Aromatic (circle them) or not. For those that aren't, are there any that are Antiaromatic? (square them)

Keys:
1. Do you have an uninterrupted sp^2 ring?
2. Apply Huckel's Rule: Do you have 2,6,10 etc. π electrons?
3. Applying Huckel's Rule requires that you can accurately count your π-electrons. Be able to count:
   - Anions: contribute 2 π-electrons
   - Cations: contribute 0 π-electrons
   - Heteroatoms (O or N): can provide 2 π-electrons if it helps result in aromatic stability.

Note: For those that are not aromatic, why not?
1. Lacks cyclic sp^2 ring   2. Lacks Huckel's rule electron count
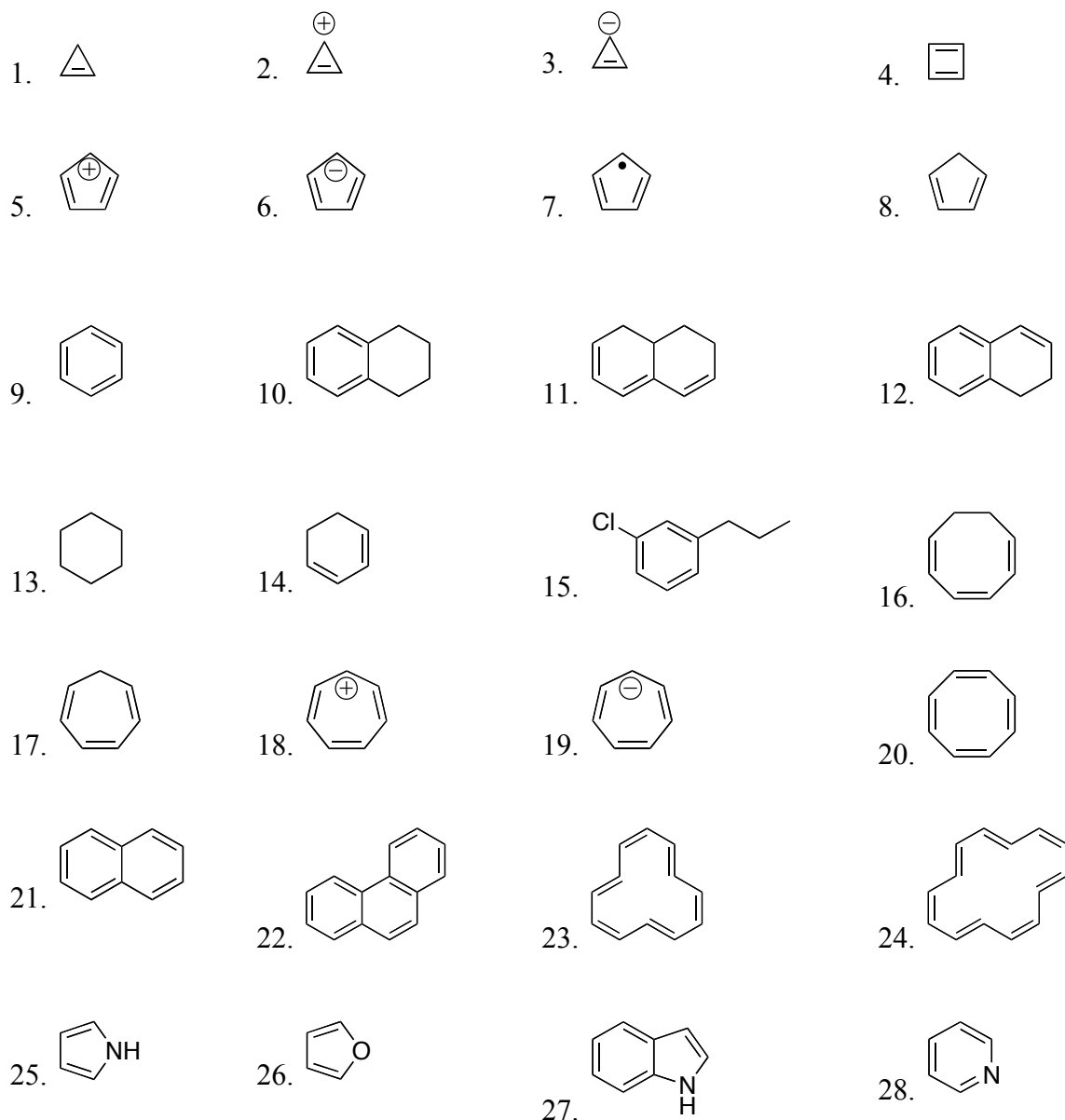
(11.21) Aromatic Ions
* 3 common, important Aromatic Ions

Problem 1: The following substrates have widely differing reactivity toward **H₂O solvolyis**. (The fastest is more than a million times faster than 2nd fastest, and the slowest more than a hundred times slower than the second slowest). Rank the reactivity. (Key: What kind of reaction would happen, and what determines reactivity?)

Br   Br   Br   Br
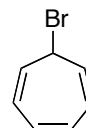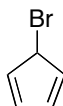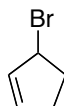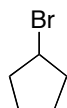
Problem 2: The following have enormous differences in **acidity**. (10^{-20}, 10^{-42}, 10^{-50}, 10^{-56})
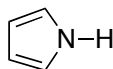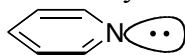Key:

H   H   H   H
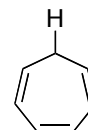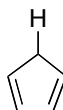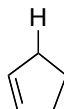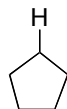
(11.22,23) Heterocyclic Aromatics. Memorize 3.

|		
Pyridine	**Pyrrole**	**Furan**

N-hybridization: sp^2
N-lone-pair: sp^2
N-basicity: reasonably normal

The lone pair is not used in the π-system; the sp^2 points in plane of paper, and has normal basicity.
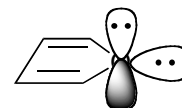
N-hybridization: sp^2
N-lone-pair: p
N-basicity: Nonbasic

The lone pair is used in the π-system and is counted toward the 6 electrons for Huckel's rule. Because the lone pair is p, pyrrole is nonbasic.
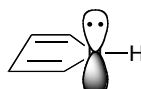
O-hybridization: sp^2
O-lone-pairs: one p, one sp^2

The p lone pair is used in the π - system and is needed to get the 6 electrons needed for Huckel's rule. But the sp^2 lone pair is in the plane of the ring, extending straight out.
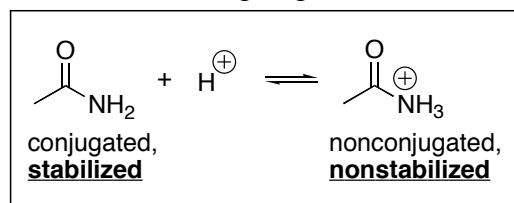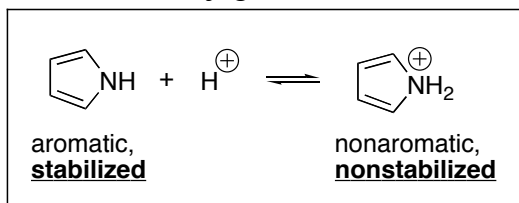
Nitrogens: Atom hybridization, Lone-Pair hybridization, and Basicity
- Amine nitrogens are normally basic, but not when the N-lone pair is p-hybridized
- Rule: If a nitrogen lone pair is p (used in conjugation) → nonbasic
- Nitrogen lone-pair basicity: $sp^3 > sp^2 >>> p$

| Situations	N-Atom	N-Lone Pair	N-Basicity
1. Isolated	sp^3	sp^3	Normal
2. Double Bonded	sp^2	sp^2	Normal (a little below, but not much)
3. Conjugated (not itself double bonded, but next to a double bond)	sp^2	p	Nonbasic

Why are p-lone pairs so much less basic?
- Because conjugation/aromatic stability in the reactant is lost upon protonation.

aromatic,
stabilized

nonaromatic,
nonstabilized

conjugated,
stabilized

nonconjugated,
nonstabilized

Problem: For each nitrogen, classify:
a) hybridization of the Nitrogen atom
b) hybridization of the Nitrogen lone-pair
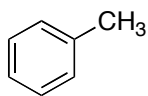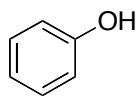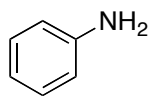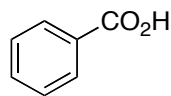c) basicity of the Nitrogen (basic or nonbasic)

1.

2.

3.

4.
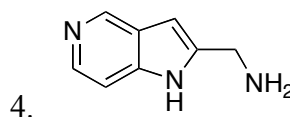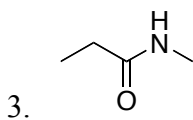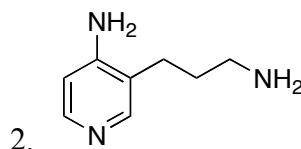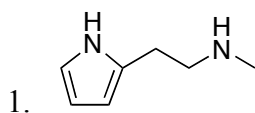
(11.7) Polycyclic Aromatics (needn't memorize names)

napthalene

anthracene

phenanthrene
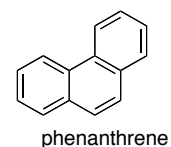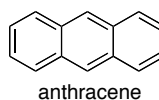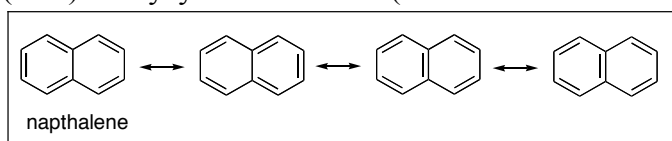
(11.6,22) AROMATIC NOMENCLATURE

1. **Memorize** Special Names.
- Six Special Monosubstituted Names You Must **Memorize**
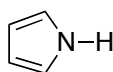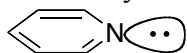
Toluene   **Phenol**   **Aniline**   **Benzoic Acid**   **Nitrobenzene**   **Anisole**

- Three Special Heterocyclic Common Names You Must **Memorize**

Pyridine   Pyrrole   Furan

N-hybridization: sp^2	N-hybridization: sp^2	O-hybridization: sp^2
N-lone-pair: sp^2	N-lone-pair: p	O-lone-pairs: one p, one sp^2
N-basicity: reasonably normal	N-basicity: Nonbasic	

The lone pair is not used in the π-system; the sp^2 points in plane of paper, and has normal basicity.

The lone pair is used in the π-system and is counted toward the 6 electrons for Huckel's rule. Because the lone pair is p, pyrrole is nonbasic.
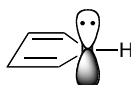
The p lone pair is used in the π - system and is needed to get the 6 electrons needed for Huckel's rule. But the sp^2 lone pair is in the plane of the ring, extending straight out.

2. Mono-substituted benzenes, if not one of the special memory names: use "benzene" as core name

3. Di- or polysubstituted aromatics
   a. If one of the "special" memory names can be used, use that as the core name and number with the special substituent on carbon 1.
   b. Special Terms:
      - "ortho" or o-   1,2 relationship
      - "meta" or m-   1,3 relationship
      - "para" or p-   1,4 relationship

1.   2.   3.
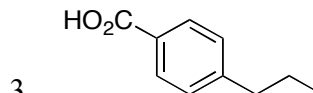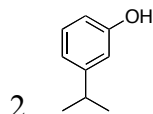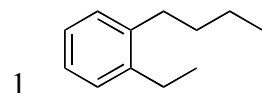
5. Di- or polysubstituted aromatics
   c. If one of the "special" memory names can be used, use that as the core name and number with the special substituent on carbon 1.
   d. Special Terms:
      - "ortho" or o-   1,2 relationship
      - "meta" or m-   1,3 relationship
      - "para" or p-   1,4 relationship

4.

5.

6.
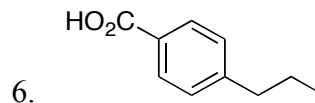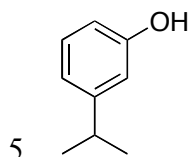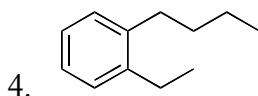
6. As a substituent, benzene is named "phenyl"
   - "phenyl" = C6H5- = a benzene group attached to something else, named as a substituent

phenyl group ─Something Else

OH
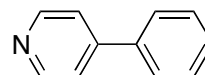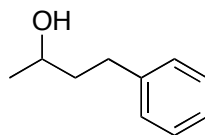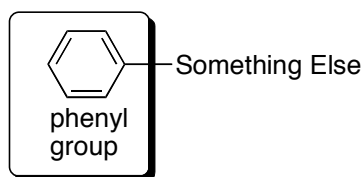
7. Three Shorthands for phenyl

Br

PhBr C_6H_5Br

Br

8. "Benzyl" = PhCH₂

Cl   OH   NH₂   OH
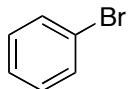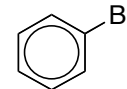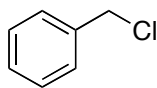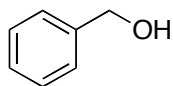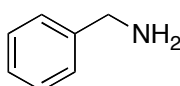
benzyl   benzyl   benzyl
chloride   alcohol   amine
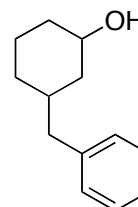
3-benzylcyclohexanol

Some Complex Aromatics in Nature

1. Amino Acids. 3 of 22 amino acids found in human proteins are aromatic

Tryptophan   Phenylalanine   Tyrosine
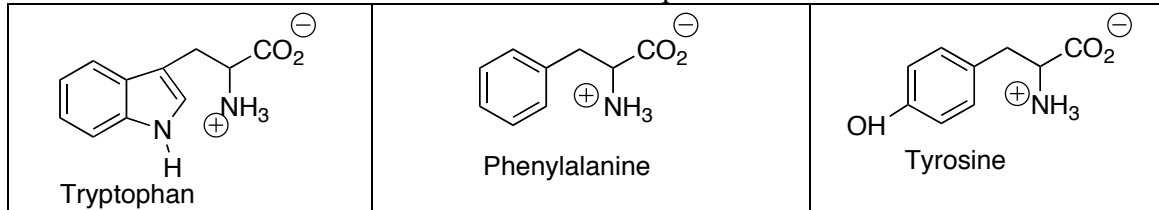
- "Essential"-have to eat them, since body can't make the benzene rings

2. Nitrogen Bases: Purine, Pyrimidine, Imidazole.
   - Nitrogen Bases Purine, Pyrimidine, Imidazole. Substituted derivatives of purine and pyrimidine are the stuff of DNA and RNA. The basicity of their nitrogens is crucial to genetics, replication, enzymes, and protein synthesis.

Purine   Pyrimidine   Imidazole
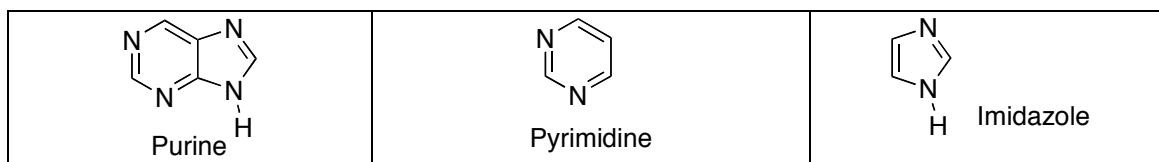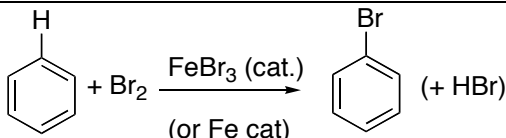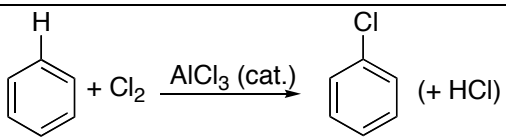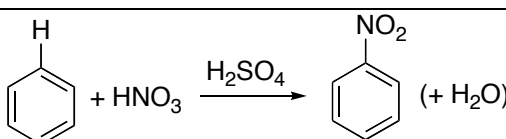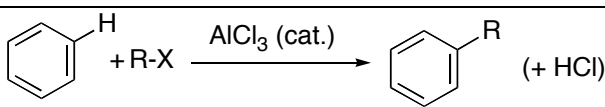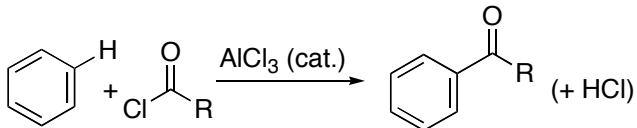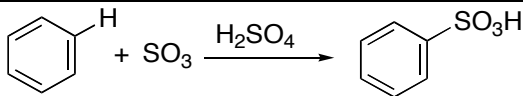
3. Nitrogen Bases: Purine, Pyrimidine, Imidazole. Nicotinamide Adenine Dinucleotide (NAD+) and NADH. Important Redox reagents.
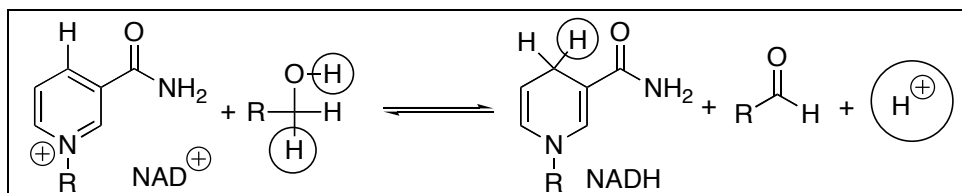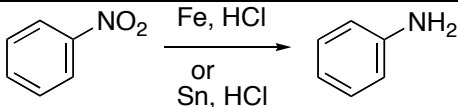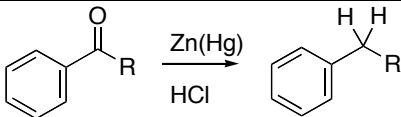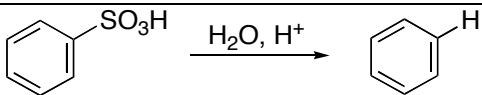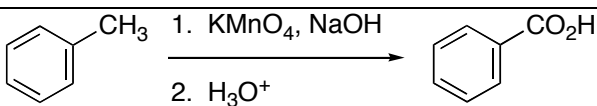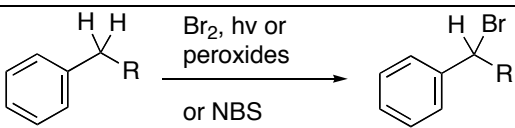
4. Polychlorinated Biphenyls (PCB's). High stability as insulators, flame-retardants make them so stable that they are hard to get rid of!
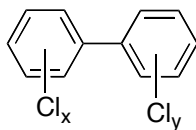
5 Major Electrophilic Aromatic Substitution Reactions

		Activating/ Deactivating	Ortho/Para Or Meta Directing	Book
1	H ⟨benzene⟩ + Br$_2$ →(FeBr$_3$ (cat.)) (or Fe cat) Br ⟨benzene⟩ (+ HBr)	Deactivating	Ortho/Para	12.5
	H ⟨benzene⟩ + Cl$_2$ →(AlCl$_3$ (cat.)) Cl ⟨benzene⟩ (+ HCl)	Deactivating	Ortho/Para	
	The halides are unique in being deactivating but ortho/para directing. All other o/p-directors are activating, and all other deactivating groups are m-directors. **Mech required**			
2	H ⟨benzene⟩ + HNO$_3$ →(H$_2$SO$_4$) NO$_2$ ⟨benzene⟩ (+ H$_2$O)	Deactivating	Meta	12.3
	The product can be reduced to Ar-NH$_2$ by Fe/HCl or Sn/HCl. Nitration/Reduction provides an effective way to introduce an NH$_2$ group. Reduction converts m-directing NO$_2$ group into an o/p-directing NH$_2$ group. **Mech required.**			
3	H ⟨benzene⟩ + R-X →(AlCl$_3$ (cat.)) R ⟨benzene⟩ (+ HCl)	**Activating**	Ortho/para	12.6
	a. Restricted to 3°, 2°, or ethyl halides. 1° halides suffer carbocation rearrangements. b. Since product is more active than starting material, polyalkylation is often a serious problem. c. Fails with strongly deactivated benzenes. **Mech required.**			
4	H ⟨benzene⟩ + Cl—C(=O)—R →(AlCl$_3$ (cat.)) C(=O)R ⟨benzene⟩ (+ HCl)	Deactivating	Meta	12.7
	a. The product can be reduced to -CH$_2$R by Zn(Hg)/HCl. b. The acylation-reduction sequence provides an effective way to introduce a 1° alkyl group. **c.** Reduction converts meta-directing acyl group into an ortho/para-directing alkyl group. **Mech required.**			
5	H ⟨benzene⟩ + SO$_3$ →(H$_2$SO$_4$) SO$_3$H ⟨benzene⟩	Deactivating	Meta	12.4
	The sulfonyl group is a useful para-blocking group, since it can later be removed upon treatment with H$_2$O/H$^+$. **No mech required.**			

5 Major Aromatic Support Reactions

		Activating/ Deactivating	Ortho/Para Or Meta Directing	Book
6	NO_2 → NH_2 Fe, HCl or Sn, HCl	Activating	Ortho/Para	21.9
	▪ Reduction converts meta-director into an ortho-para director. ▪ Fe, Sn, or several other reducing metals can work.			
7	O‖—R → H H—R Zn(Hg), HCl	Activating	Ortho/Para	12.8
	▪ Clemmensen reduction converts meta-director into ortho-para director. ▪ Acylation (#4) followed by Clemmensen Reduction (#7) is the standard method for introducing a 1° alkyl group. (Direct alkylation with a 1° alkyl halide, reaction #3, fails due to cation rearrangement problems…)			
8	SO_3H → H H_2O, H^+	------	------	12.4
	▪ The sulfonyl group is a useful and reversible para-blocking group, since it can be temporarily put on (reaction 5) but then can be removed later upon treatment with H_2O/H^+ (reaction 8). ▪ The sulfonation/other reaction/desulfonation sequence is crucial for clean ortho-substitution of an o/p director.			
9	CH_3 → CO_2H 1. $KMnO_4$, NaOH 2. H_3O^+	Deactivating	Meta	11.12
	▪ Oxidation converts ortho/para-director into a meta-director. ▪ Side alkyl chains longer than methyl can also be oxidized to benzoic acid in the same way, although more time and heat is required. ▪ For test purposes, just writing $KMnO_4$ will be OK. But the real reaction requires a basic solution for the $KMnO_4$ to work, so an acidic workup step is actually required to isolate the neutral carboxylic acid.			
10	H H—R → H Br—R Br_2, hv or peroxides or NBS	------	------	10.5, 11.11, 11.14
	▪ Bromination occurs via free-radical mechanism. ▪ It is selective for substitution at the benzylic position because the benzylic radical intermediate is resonance-stabilized. ▪ Note: keep distinct $Br_2/FeBr_3$ from Br_2/peroxides! ▪ Product is subject to S_N2 substitutions (benzylic bromides are especially good) and E2 eliminations with bulky bases. ▪ "NBS" is N-bromosuccinimide, which functions just like Br_2/peroxides, but avoids competing reactions caused by Br_2 and HBr.			

Section 12.1, 2 Electrophilic Aromatic Substitution

General Mechanism for Electrophilic Aromatic Substitution
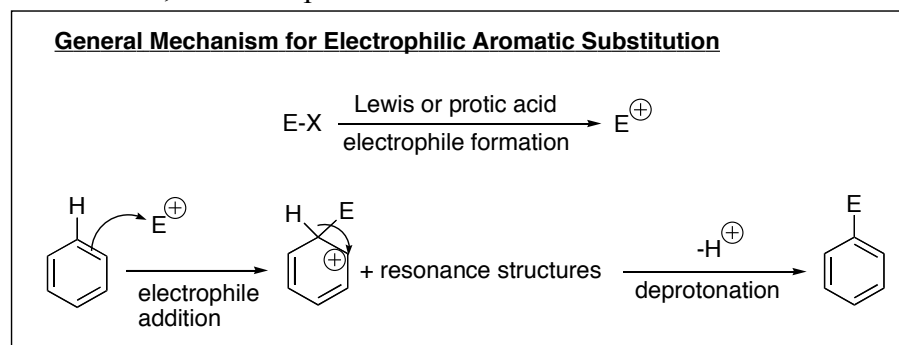
1. The **addition step**, generating the carbocation, is the **rate-determining** step
2. Any extra **substituents that stabilize the carbocation will make the reaction faster** (the product stability-reactivity principle). And vice-versa…
    ▪ **Electron-donating groups** will stabilize carbocations and accelerate (**activate**)
    ▪ **Electron-withdrawing groups** that destabilize carbocations will decelerate (**deactivate**)
3. As shown below, the **positive charge is shared by resonance** over three carbons: the carbons that are **ortho and para** relative to the carbon where the electrophile actually adds
    ▪ Positive charge does not appear at either of the positions meta to where the electrophile adds
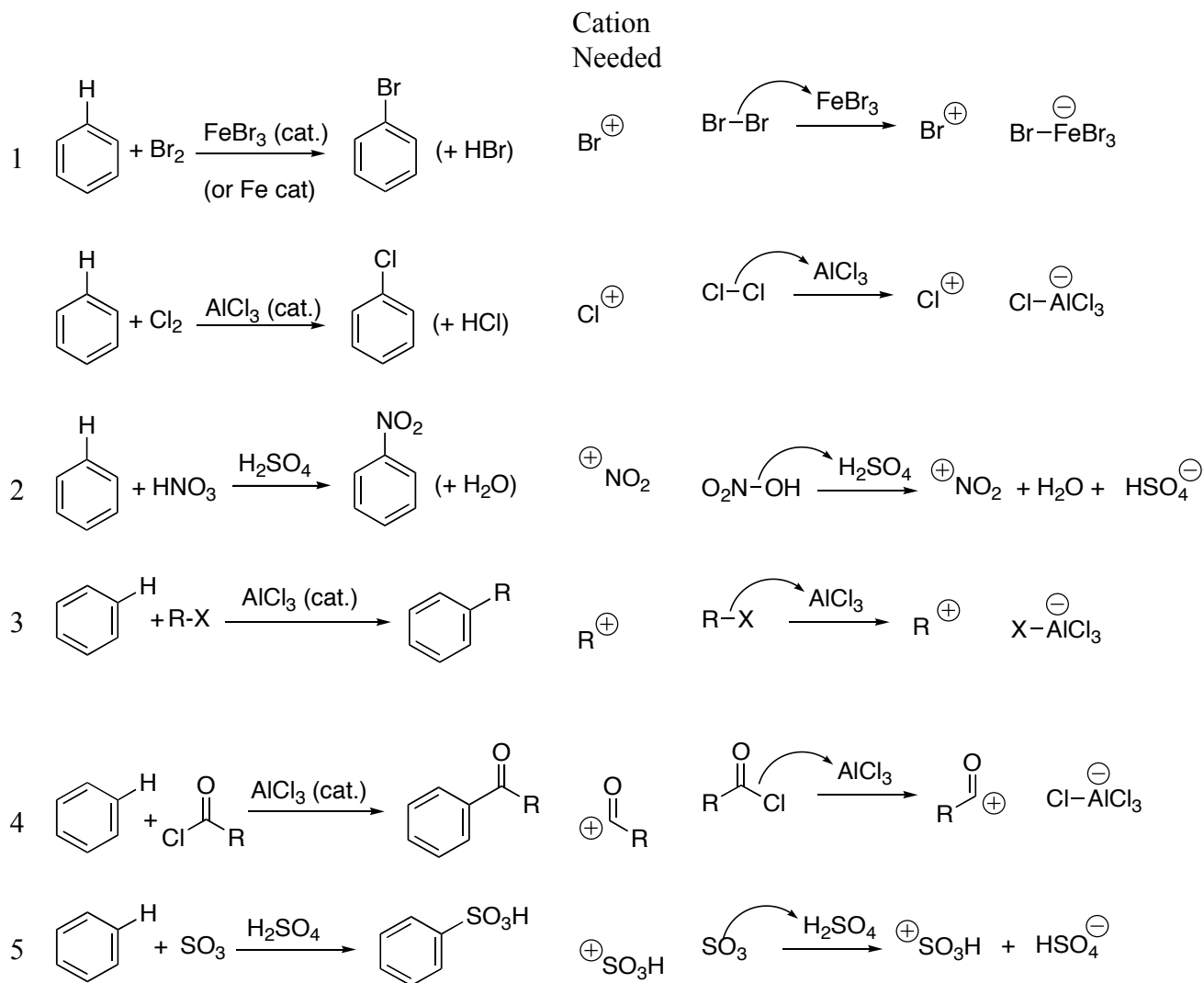4. If a substituent is ortho or para relative to the carbon where the electrophile actually adds, the substituent will be next to a positive charge in one of the three resonance structure, and will have a large electronic effect, for good (donors) or bad (withdrawers)
    ▪ If a substituent is an electron donor (cation stabilizer), it will be very beneficial if the electrophile adds ortho or para relative to the substituent. Therefore ortho or para addition will be much faster than meta addition.
        ➢ **Thus electron donors (cation stabilizers) function as ortho/para directors.**
    ▪ If a substituent is an electron withdrawer (cation destabilizer), it will be very harmful if the electrophile adds ortho or para relative to the substituent. Therefore ortho or para addition will be much slower than meta addition.
        ➢ **Thus electron withdrawers (cation destabilizers) function as meta directors.**
        o Note: meta directors are meta directors not because meta addition is especially good; rather, it's because meta isn't nearly as bad as ortho or para addition, so meta addition is the best option available. But keep in mind that it still is slower than normal.

Three Resonance Structures for Every Electrophilic Aromatic Substitution
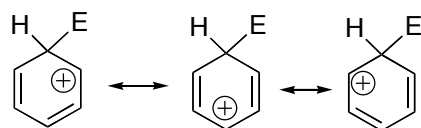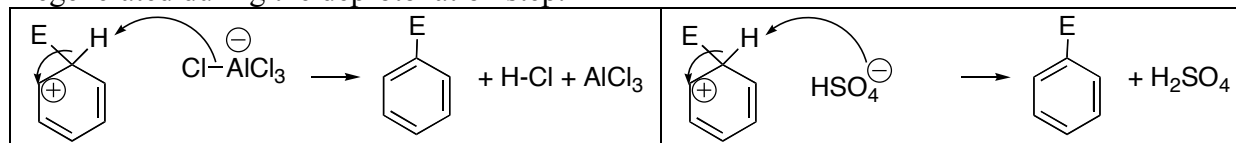

▪ A substituent that's good for one of these cation forms (donor) is good for the addition:
    o This results in activation (kinetics)
    o and ortho/para addition (orientation)
▪ A substituent that's bad for one of these cation forms (withdrawer) is bad for the addition:
    o This results in deactivation (kinetics)
    o And meta addition (orientation)

Formation of the Active Electrophiles
1. In each case, the cationic form of the thing that adds must be generated
2. The arrow pushing in the E+ generation always involves an arrow going from the cation precursor to the Lewis or Bronsted acid
3. For class, we will focus on sulfuric acid as Bronsted acid, and $AlCl_3$ or $FeBr_3$ as Lewis acids
    ▪ But in an actual synthesis lab, other Bronsted or Lewis acids are available and may sometimes provide superior performance.

Cation
Needed

1. benzene + Br_2 → $FeBr_3$ (cat.) (or Fe cat) → bromobenzene (+ HBr)

$Br^{\oplus}$ $Br-Br$ → $FeBr_3$ → $Br^{\oplus}$ $Br-\overset{\ominus}{F}eBr_3$

2. benzene + Cl_2 → $AlCl_3$ (cat.) → chlorobenzene (+ HCl)

$Cl^{\oplus}$ $Cl-Cl$ → $AlCl_3$ → $Cl^{\oplus}$ $Cl-\overset{\ominus}{A}lCl_3$

(Row labeled 2) benzene + HNO_3 → H_2SO_4 → nitrobenzene (NO_2) (+ H_2O)

$\overset{\oplus}{N}O_2$ O_2N-OH → H_2SO_4 → $\overset{\oplus}{N}O_2$ + H_2O + $HSO_4^{\ominus}$

3. benzene + R-X → $AlCl_3$ (cat.) → benzene-R

$R^{\oplus}$ $R-X$ → $AlCl_3$ → $R^{\oplus}$ $X-\overset{\ominus}{A}lCl_3$

4. benzene + $\underset{Cl}{\overset{O}{\underset{}{R}}}$ → $AlCl_3$ (cat.) → benzene-C(=O)-R

$\overset{\oplus}{\underset{R}{C}}=O$ (acylium) $R-\overset{O}{C}-Cl$ → $AlCl_3$ → $R-\overset{O}{C}{}^{\oplus}$ $Cl-\overset{\ominus}{A}lCl_3$

5. benzene + SO_3 → H_2SO_4 → benzene-SO_3H

$\overset{\oplus}{S}O_3H$ SO_3 → H_2SO_4 → $\overset{\oplus}{S}O_3H$ + $HSO_4^{\ominus}$

Note: The **acids** really need be used in only **catalytic** quantities. The active acids are regenerated during the deprotonation step.

E-H arenium + $Cl-\overset{\ominus}{A}lCl_3$ → E-benzene + H-Cl + $AlCl_3$ E-H arenium + $HSO_4^{\ominus}$ → E-benzene + H_2SO_4

Additions to Substituted Benzenes. The Effect of Substituents on Reactivity Rates and the Position of Substitution. (12.9-14)

Three Issues
1. Activators versus Deactivators
2. Electron Donors versus Electron Withdrawing Groups
3. Ortho-Para directors versus Meta Directors

Fact: The rate determining step is the cation addition step
▪ The transition state much resembles the carbocationic product of that step
▪ What's good for the cation is good for the reaction rate (product stability-reactivity principle)
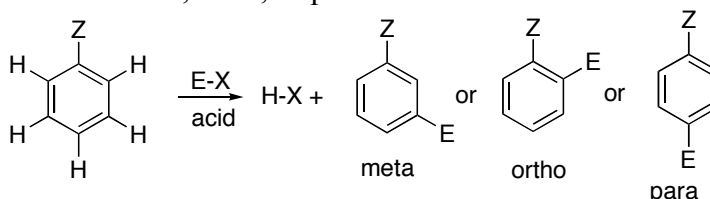
Cation stabilizers = **electron donors** → good for cations → good for rates = **activators**
Cation destabilizers = **electron withdrawers** → bad for cations → bad for rates = **deactivators**

Problem: Rank the reactivity towards HNO_3/H_2SO_4 (The fastest is 25 times faster than the middle, the slowest one is less than $1/100^{th}$ as fast as the middle.)
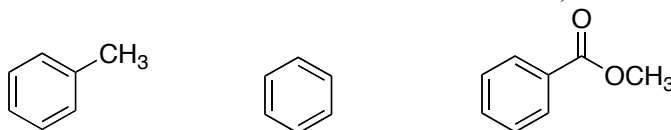
Position of Substitution: When an electrophile adds to a substituted benzene, does it add Ortho, Meta, or Para to the pre-existing substituent? Ortho-para directors versus Meta Directors
▪ When an electrophile adds to a substituted benzene, it can potentially come in at three different positions: ortho, meta, or para

| | Cation-stabilizing donors are **ortho-para** directors |
| | For an ortho-para director, **para predominates for steric reasons** |
| | Cation-destabilizing withdrawers are **meta directors** |

The Situation with an Electron **Donor**/Cation Stabilizer (Ortho-Para Director) (Section 12.12)
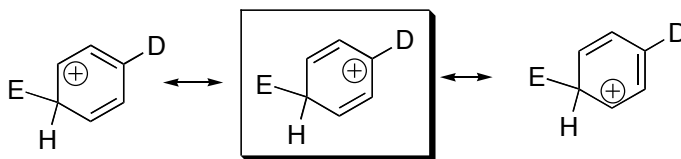
Ortho
Addition
Relative to a
Donor
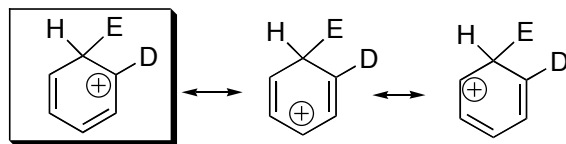
Boxed form is especially good electronically.
Ortho addition often has some steric destabilization.

Meta
Addition
with a
Donor
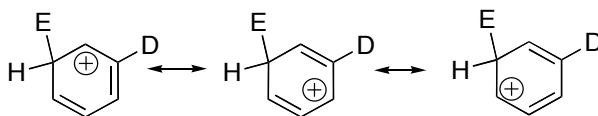
None of the three resonance forms benefits from the electron donor.

Para
Addition
Relative to a
Donor

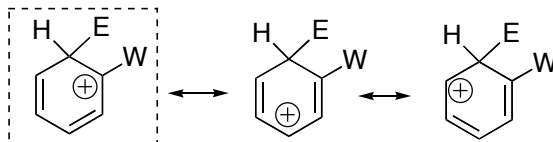**Boxed resonance form is especially benefitted electronically.**

Summary: **Electronic Factor**: An electron donor (cation stabilizer) is especially beneficial electronically when the electrophile adds ortho or para relative to the donor.
- **Thus donors are ortho/para directors.**

Steric Factor: Ortho addition relative to the donor is always destabilized somewhat by steric interactions. Thus, when addition para relative to the donor does not involve any steric interactions, (usually but not always the case), para addition is faster than ortho addition.
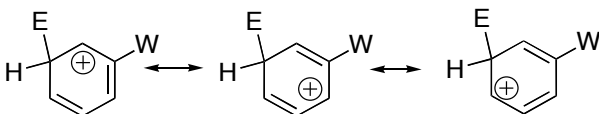
The Situation with an Electron **Withdrawer**/Cation Stabilizer (Ortho-Para Director) (12.13)

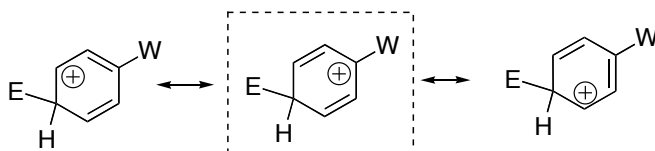Ortho
Addition
Relative to a
Withdrawer

Boxed form is especially bad electronically.

Meta
Addition
Relative to a
Withdrawer

None of the three resonance forms suffers badly from the electron donor.

Para
Addition
Relative to a
Withdrawer

**Boxed form is especially bad electronically.**

Summary: An electron withdrawer (cation destabilizer) is especially harmful electronically when the electrophile adds ortho or para relative to the withdrawer. Thus withdrawers are meta directors. Not because meta is that good; it's just not as bad as ortho or para.
- Note: Meta is still deactivated somewhat, it's just not as slow as ortho or para addition.

Halogenation Reactions (12.5)

1   + Br_2 →(FeBr₃ (cat.)) (or Fe cat) (+ HBr)   Deactivating   Ortho/Para   17.2

 + Cl_2 →(AlCl₃ (cat.)) (+ HCl)   Deactivating   Ortho/Para   17.2
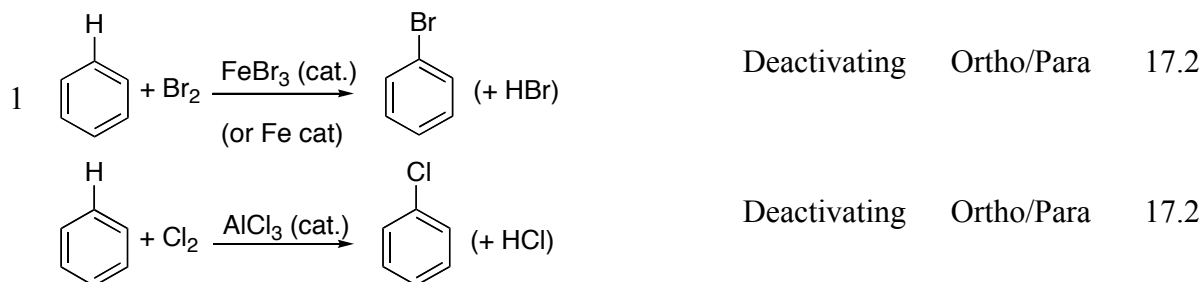
- Note: In the presence of Br_2, Fe metal is converted directly into $FeBr_3$, so sometimes Fe rather than $FeBr_3$ is used
- Many other Lewis acids can accomplish the same reactions

Draw the products for the following reactions.

1   + Br_2 →(FeBr₃ (cat.))

2   + Cl_2 →(AlCl₃ (cat.))
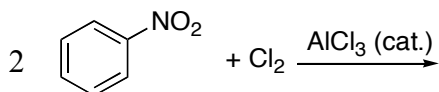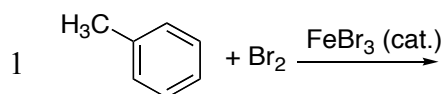
3 Draw the mechanism for the first reaction above.
   - Identify the slow step.
   - Draw in all three resonance structures for the cation.
   - Circle the best resonance structure.

4 Even minor products form via mechanisms.   Draw the mechanism for formation of ortho-bromotoluene from toluene.

Tips:
- Always draw the hydrogen on the reacting carbon
- For resonance structures, keep substituent, key H, and adding group in each picture
- Never draw the + charge on the tetrahedral center
- At the cation stage, make sure you never draw a double bond to the tetrahedral center (that would make 5 bonds!)

Seeing the Mechanism and Resonance Structures from Different Perspectives
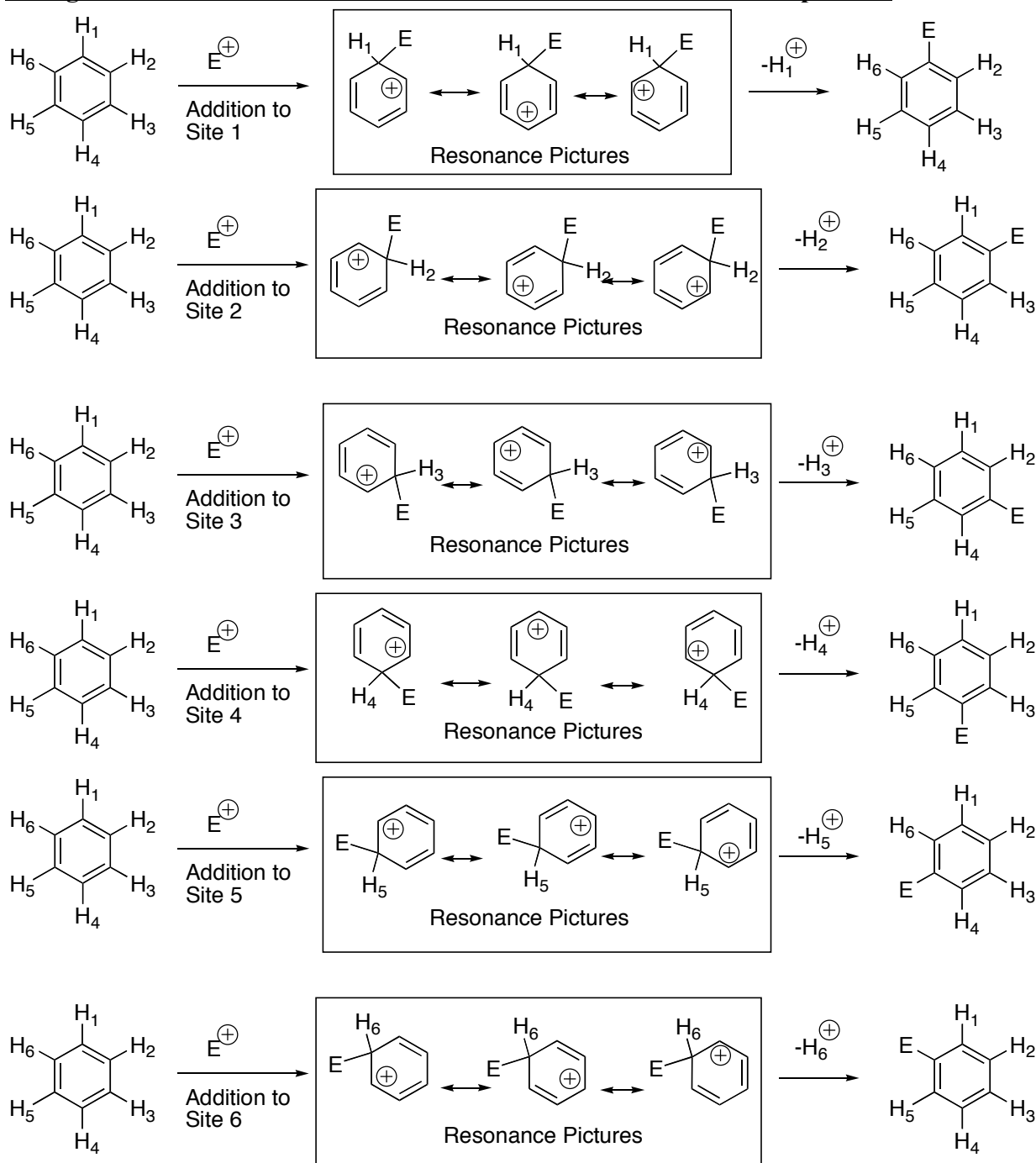
NOTES:
1. These focus on drawing the resonance structures and seeing how the positive charge is delocalized in the cation.
2. Notice that regardless of which position the electrophile adds to, the positive charge still ends up delocalized onto the positions ortho and para **relative to the site of addition**
3. Notice that the site of addition does <u>not</u> have positive charge
4. Notice that the hydrogen that is lost is from the same carbon where the electrophile adds, not from an ortho carbon

## 4 Classes of Substituents: Memorize! (Sections 12.9-14)

Donating?	Memorize the list	Activating/Deactivating	Directing Effect
	OH, OR, NH$_2$, NHR, NR$_2$	Strong Activators	Ortho/para directors
	R, Ar	Weak Activators	Ortho/para directors
	Cl, Br	Weak Deactivators	Ortho/para directors
	Carbonyl, NO$_2$, CN, SO$_3$H	Strong Deactivators	Meta directors

Note: Halogens are a special case that are ortho-para directors despite being deactivating
Otherwise, the following pattern is general:
- Activator = ortho-para director (and vice versa, with exception of halides)
- Meta director = deactivator (and vice versa, with exception of halides)

Special Resonance/Conjugation with Oxygen and Nitrogen Substituents
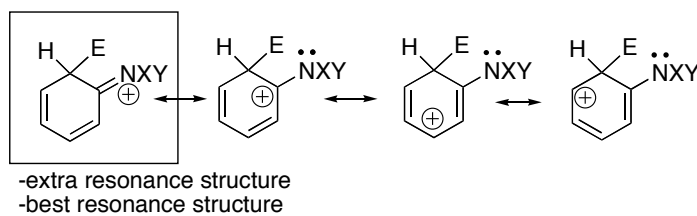
Ortho
Addition
Relative to an
Oxygen Donor
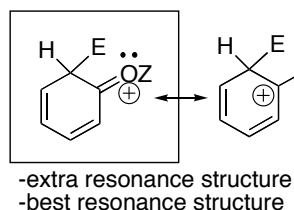
-extra resonance structure
-best resonance structure

Boxed resonance form is especially benefitted electronically.

The two electrons in the extra bond come from an oxygen lone pair.

This is why oxygen is such a strong donor.

Ortho
Addition
Relative to an
Nitrogen Donor

-extra resonance structure
-best resonance structure

Boxed resonance form is especially benefitted electronically.

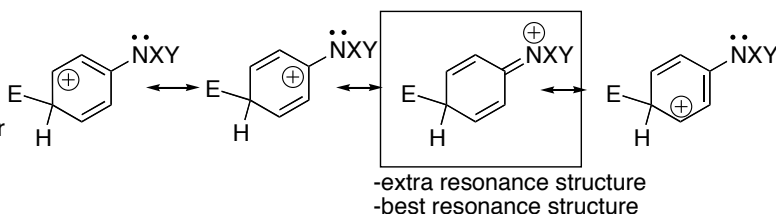**The two electrons in the extra bond come from a nitrogen lone pair.**

This is why nitrogen is such a strong donor.

Para
Addition
Relative to a
Oxygen Donor

-extra resonance structure
-best resonance structure
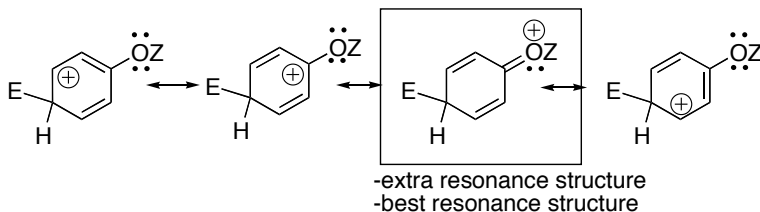
-Boxed form is best
-The two electrons in the extra bond come from a nitrogen lone pair.

Para
Addition
Relative to a
Nitrogen Donor

-extra resonance structure
-best resonance structure

-Boxed form is best
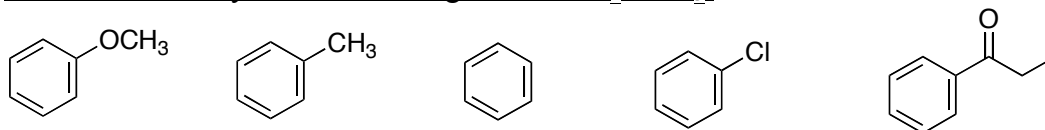**-The two electrons in the extra bond come from a nitrogen lone pair.**

Halogens. Special Case: Weak Deactivators, but still ortho-para directors.

Explanation (not for test):   Halogens are both withdrawers (based on their electronegativity) but also donors (through resonance/conjugation/π-donation)
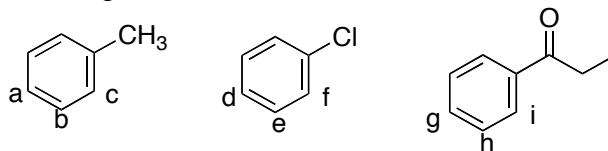
- Withdrawers, because of the polarized, electronegative C-X bond
- Donors via the π-conjugation
- The withdrawing effect is stronger, thus they are overall deactivators, whether ortho, meta, or para
- The π-conjugation only benefits with ortho-para addition
- Because of the conjugation/resonance factor, ortho-para addition isn't as destabilized as meta addition.

Electronegativity withdrawer
(through sigma bond)
σ-Withdrawer

Conjugation/resonance donor
Through lone-pair π-system
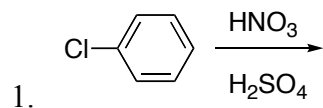π-Donor
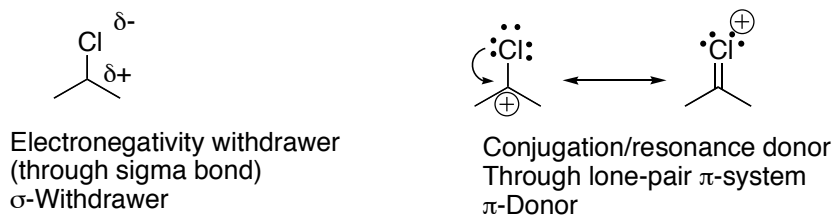
Rank the reactivity of the following towards $Br_2/FeBr_3$.

Shown are 9 different sites for possible addition. Rank all 9, from most to least reactive.

**Nitration Reaction (12.3)**

2	H ⬡ + HNO$_3$ $\xrightarrow{H_2SO_4}$ NO$_2$ ⬡ (+ H$_2$O)	Deactivating	Meta	17.3
6	⬡NO$_2$ $\xrightarrow[\text{Sn, HCl}]{\text{Fe, HCl} \\ \text{or}}$ ⬡NH$_2$	Activating	Ortho/Para	19.21

Draw the major product.

1.
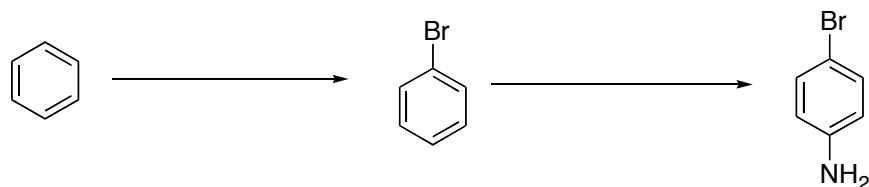Cl—⟨benzene ring⟩ $\xrightarrow[\text{H}_2\text{SO}_4]{\text{HNO}_3}$

2. Anisole is more than 1000 times faster than benzene. Draw the mechanism, including all of the resonance structures for the cation intermediate in the p-bromination of anisole, and circle the "best" resonance structure.
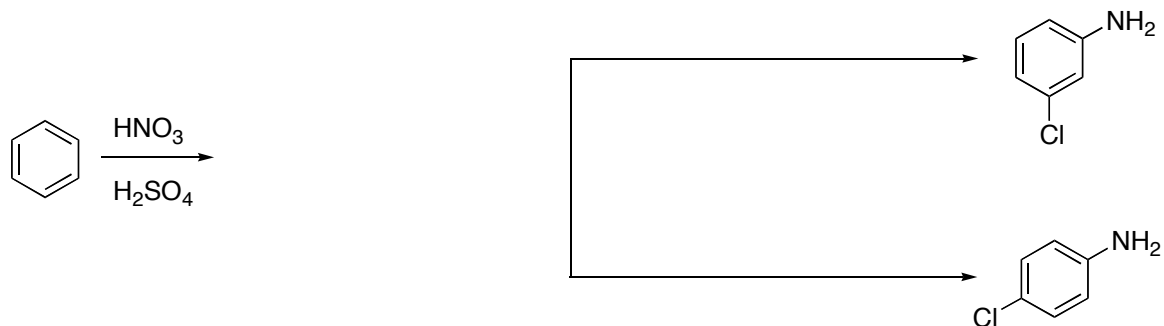
H_3CO—⟨benzene ring⟩ $\xrightarrow[\text{H}_2\text{SO}_4]{\text{HNO}_3}$
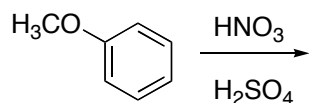
2-Step Route to Add NH_2:   1) HNO_3, H_2SO_4 2) Fe, HCl
- at nitro stage, Nitrogen is a meta director
- at amino stage, Nitrogen is an ortho-para director

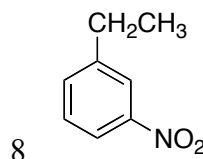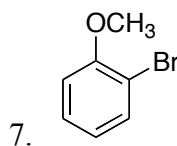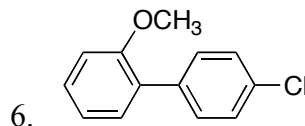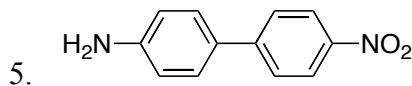3. Provide the reagents for the following transformation.
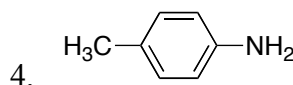
⟨benzene⟩ ⟶ ⟨benzene with Br⟩ ⟶ ⟨benzene with Br and NH₂ para⟩

4. Design synthetic routes for the following transformations.

⟨benzene⟩ $\xrightarrow[\text{H}_2\text{SO}_4]{\text{HNO}_3}$ ⟶ ⟨benzene with NH₂ and Cl (meta)⟩

⟶ ⟨benzene with NH₂ and Cl (para)⟩
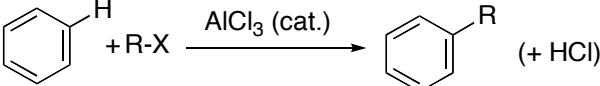
Rules for Additions to Disubstituted/Polysubstituted Aromatics (12.5)
1. Effects are additive if both direct to the same spot
2. If there is a conflict of interest, the more activating group controls the outcome
   ▪ You need to know the relative activating/deactivating strengths!
3. Steric considerations: if two substituents have a 1,3 (meta) relationship, addition in between (to give a 1,2,3 relationship) is prohibitively slow for steric reasons

For each of the following, imagine what would happen if a mono-nitration took place. Would there be one main product, or more than one? If so, where?

1.

2.

3.

4.

5.

6.

7.

8.
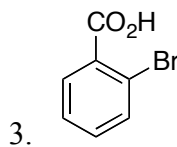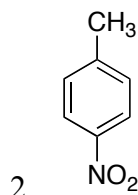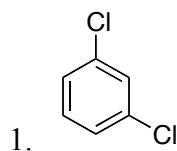
Section 12.6. Friedel-Crafts Alkylation

3	(benzene) + R-X →(AlCl₃ (cat.)) (benzene)-R (+ HCl)	**Activating**	Ortho/para

a. Restricted to 3°, 2°, or ethyl halides. **1° halides suffer carbocation rearrangements**.
b. Since product is more active than starting material, **polyalkylation is often a problem**.
c. Fails with strongly deactivated benzenes.
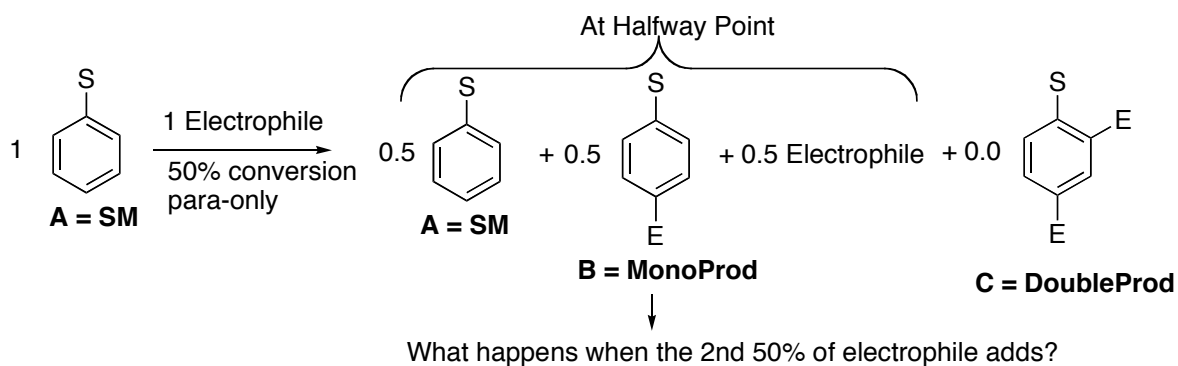
Mech required.

Other Sources of Carbocations:

▪ $ROH + H_2SO_4$

▪ $ROH + BF_3$

▪ $Alkene + H^+$

Draw the Major Product and Mechanism for the Following (Assume a single substitution)

5.
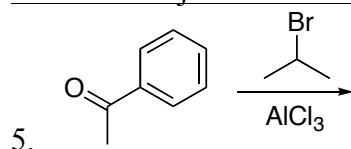
Problem: Activating or Deactivating Effect by a Newly Added Substituent. Polysubstitution vs. Clean Monosubstitution. A thought exercise.

At Halfway Point

1   1 Electrophile
    50% conversion
    para-only

A = SM

0.5   A = SM   + 0.5   B = MonoProd   + 0.5 Electrophile   + 0.0   C = DoubleProd

What happens when the 2nd 50% of electrophile adds?

Case:	If: (hypothetically)	Activating/Deactivating Effect of Added Group "E"	Amount of A	Amount of B	Amount of C
1	Product "**B**" " is much **more** reactive than SM "**A**"	Activating			
2	Product "**B**" " is much **less** reactive than SM "**A**"	Deactivating			
3	Product "**B**" " is **equally reactive** to SM "**A**"	No Effect			

Polyaddition Notes:
1. When a deactivator is added, monosubstitution is easy.
   ▪ The adduct is always deactivated relative to the starting material
   ▪ Most of the best aromatic substitutions add deactivators
2. When a donor is added, polysubstitution can be a factor.
   ▪ Electronically, the adduct will be more reactive than the starting material.
3. Some solutions to polyaddition.
   a. Perhaps di- or tri-addition is a good and desirable thing.
   b. Use a huge excess of your aromatic starting material.
      ▪ Benzene, toluene, or anisole for example, are cheap and can be used as solent.
      ▪ The probability of an electrophile reacting with an adduct molecule may be statistically modest if there are thousands of times as many solvent starting materials available
   c. Steric suppression. Often steric reasons can reduce the reactivity of the adduct.
      ▪ Frequently the only available sites might be ortho to something or other, and experience at least some steric interactions
      ▪ This may be increased with bulky electrophiles/substituents, as if often the case with 2° or 3° alkyl groups

Practice Problem: Assume each of the following are treated with $(CH_3)_2CHBr$ (iPrBr) and $AlCl_3$. For each of the following:
   a. draw the product of the first substitution
   b. Draw the product of the second substitution (in other words, if the first product reacts again.)
   c. In every case, the second substitution will have some electronic advantage (because you just added an activator/donor.) But in which cases will the second substitution have a steric disadvantage?
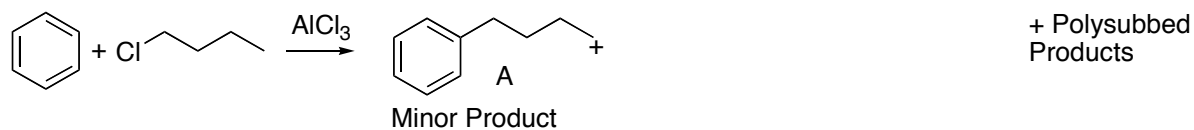
a.

b.

c.
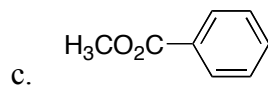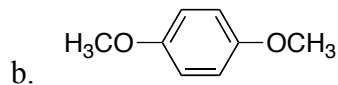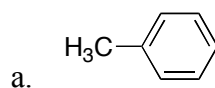
2-Step Route to Add 1° Alkyl: 1) RCOCl, AlCl₃   2) Zn(Hg), HCl
- ▪ at acyl stage, acyl carbon is a meta director
- ▪ at alkyl stage, alkyl is an ortho-para director

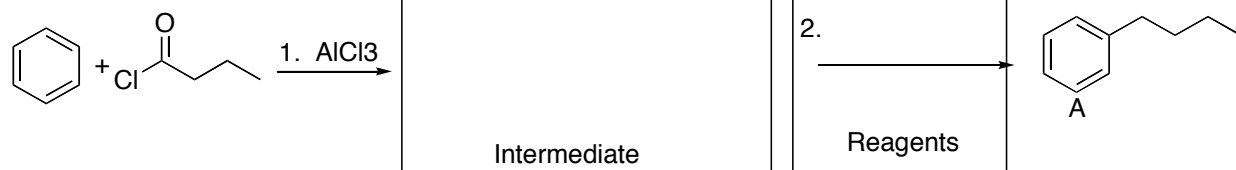6. Fill in the blanks for the following reactions

Method 1: Direct F-C Alkylation

+ Polysubbed
Products

A
Minor Product

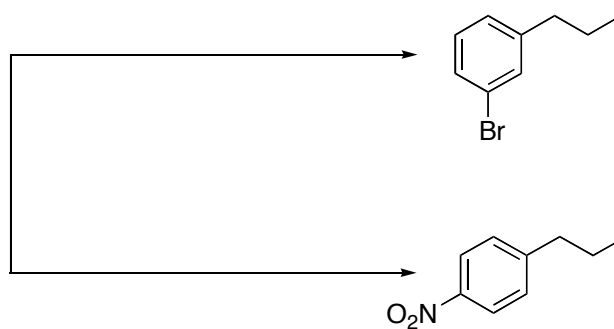Major Monosubbed Product

Method 2: F-C Acylation/Reduction

Intermediate
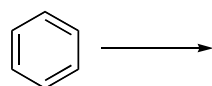
2.

Reagents

A

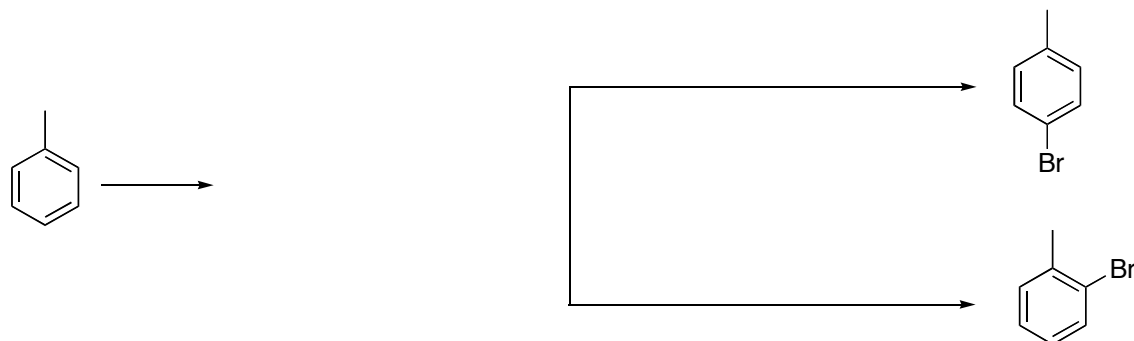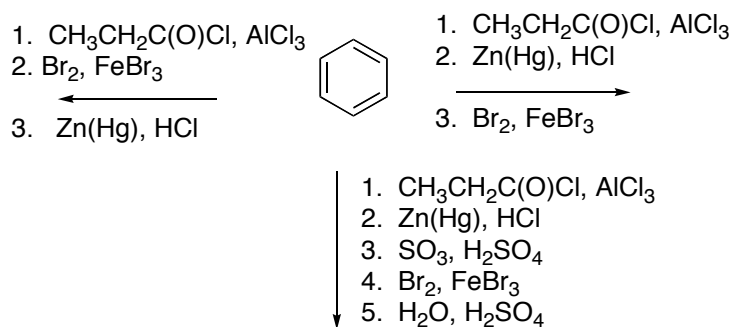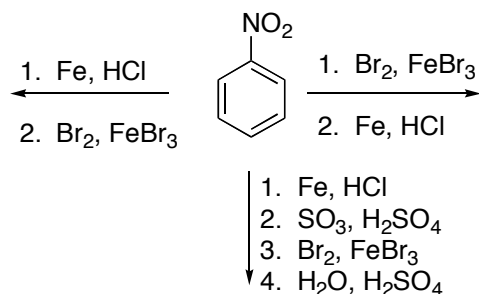7. Design pathways for the following syntheses:

Sulfonylation/Reaction/Desulfonylation: 1. SO_3, H_2SO_4 2. Whatever 3. H_2O, H_2SO_4
- Ideal procedure for when you have an ortho/para director, but you want an electrophile to end up ortho rather than para

8. Design pathways for the following syntheses:

9. Draw the products for the following reactions:

1. Fe, HCl
2. Br_2, $FeBr_3$

1. Br_2, $FeBr_3$
2. Fe, HCl

1. Fe, HCl
2. SO_3, H_2SO_4
3. Br_2, $FeBr_3$
4. H_2O, H_2SO_4

1. $CH_3CH_2C(O)Cl$, $AlCl_3$
2. Br_2, $FeBr_3$

3. Zn(Hg), HCl

1. $CH_3CH_2C(O)Cl$, $AlCl_3$
2. Zn(Hg), HCl

3. Br_2, $FeBr_3$

1. $CH_3CH_2C(O)Cl$, $AlCl_3$
2. Zn(Hg), HCl
3. SO_3, H_2SO_4
4. Br_2, $FeBr_3$
5. H_2O, H_2SO_4

Oxidation of toluene methyl group (or other alkyl side chains): $KMnO_4$ (11.12)
-   The original alkyl group is an activating ortho-para director
-   The resulting carboxylic acid is a deactivating meta director

10. Draw the outcomes for the following reaction sequences.

1. $KMnO_4$, KOH   CH₃   1. Br_2, $FeBr_3$

2. Br_2, $FeBr_3$ 2. $KMnO_4$, KOH

1. SO_3, H_2SO_4
2. Br_2, $FeBr_3$
3. H_2O, H_2SO_4
4. $KMnO_4$, KOH
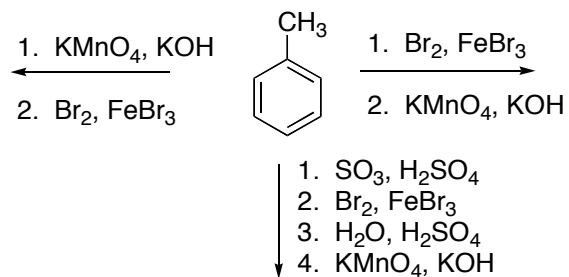
Benzylic Bromination Provides a Useful Functional Group:
  ▪ Treatment with many anions results in S$_N$2 substitution
  ▪ Treatment with bulky bases results in E2 elimination → vinyl benzenes

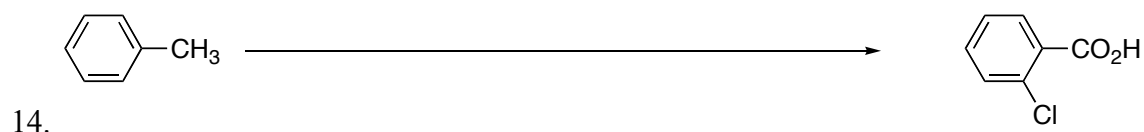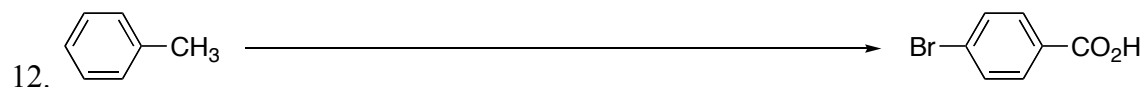11. Design pathways.
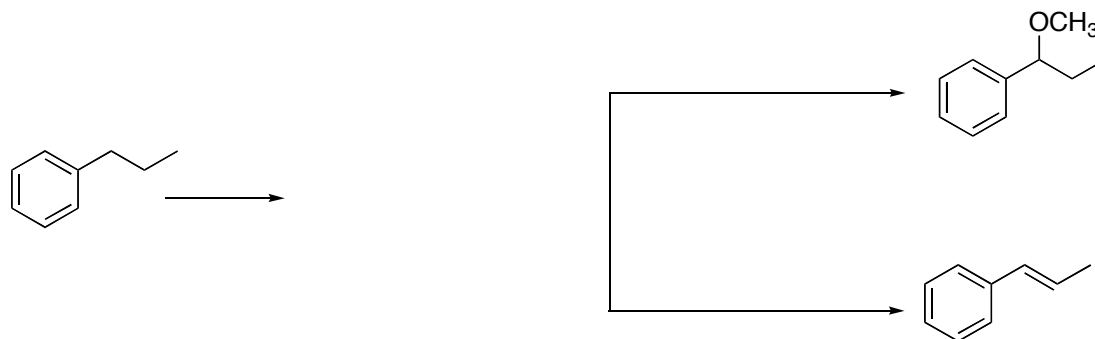
Synthetic Planning: To make multisubstituted aromatics, choose sequence with care!

If:	Make From:
Para Disubbed	An ortho-para director (a donor)
Meta Disubbed	A meta director (a strong, deactivating withdrawer)
Ortho Disubbed	An ortho-para director **and** para position blocked using the sulfonation/desulfonation trick

Design Syntheses for the Following:

12.

13.

14.

Design Syntheses for the Following:

15.

16.

17.

18.

19.