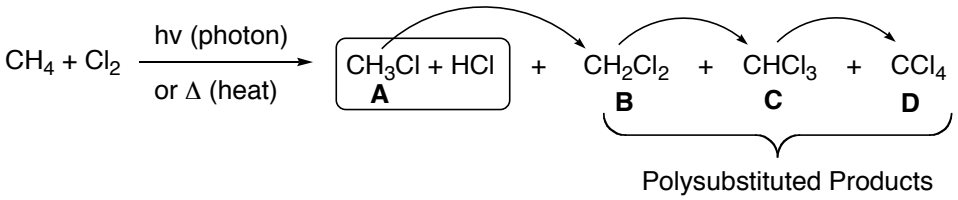
Ch. 4 The Study of Chemical Reactions

4.1 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?

4.2 The Chlorination of Methane: A Case Study



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 Cl_2, is most effective
3. High "quantum yield": one photon can result in conversion of thousands of methane reactant molecules into product molecules
   - Q: if light energy is needed, why isn't one photon needed for each reaction?

ANY MECHANISM MUST BE CONSISTENT WITH EXPERIMENTAL OBSERVATIONS

4.3 The Mechanism: Radical Chain Reaction

Balanced Reaction: $CH_4 + Cl_2 \xrightarrow{hv} CH_3Cl + HCl$

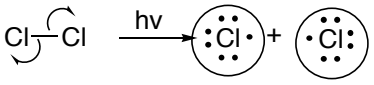
The mechanism must show all bonds broken and made:

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)

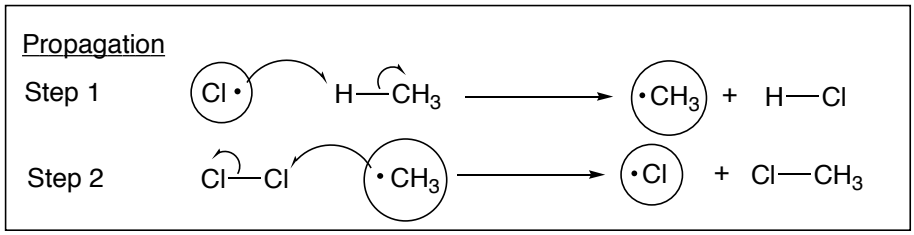
Initiation



"radical" something with an unpaired electron

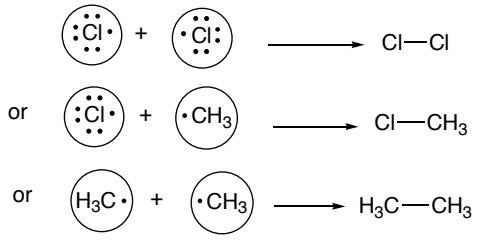
- In a radical initiation step, two reactive radicals form from a nonradical precursor

PROPAGATION



- In each propagation step, one reactive radicals reacts with a nonradical to produce a new reactive radical and a new nonradical.
- Since a reactive radical is reproduced in each step, you always have another reactive radical ready to keep the chain going.
- The chlorine radical produced in step two is the same as the chlorine radical that reacts in step 1.
- 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
- The sum of the two propagation steps is the overall balanced reaction

Termination



Mechanism Notes:

1. "Radical": Something with an unpaired electron.
   - Never satisfy octet rule→ highly unstable and always highly reactive.

2. Initiation is needed to produce a highly reactive radical. But once you've got one, initiation is done.

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.) **"Chain reaction"**

5. The overall reaction is the sum of the two propagation steps
   - When you sum the propagation steps, notice that the methyl radical cancels itself out (what's formed in step one is erased in step 2) and the chlorine radical cancels itself out (what's formed in step two is erased in step 1).

6. Like initiation, termination occurs only occasionally

7. Notice:
   - Initiation: nonradical in → radicals out
   - Each Propagation Step: radical + nonradical → nonradical + radical
   - Any Termination Step: radical + radical → nonradical

4.4, 4.5 Free Energy, Enthalpy, Entropy

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

ΔG: Free Energy: favorable reactions have negative ΔG
ΔH: Enthalpy: heat lost or gained
- ΔH<0 exothermic ΔH>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…

4.6 Bond Energies:

- **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 4.2) 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:

- Given bond energies, be able to rank bond strengths
- Given bond energies, be able to rank radical stabilities
- Given known radical stabilities, be able to predict relative bond strengths
- **Memorize the stability pattern for the halogen radicals**
- **Memorize the bond strength pattern for H-X bonds**
- **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 anion stability, bond energy values reflect radical stability

Problems:

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

2. Which is stronger, CH_3CH_2—Cl or CH_3CH_2—Br?

Why are H-F and C-F bonds stronger than H-I and C-I bonds?

1. **Electronegativity and radical stability: (Remember)**
   - Radicals are short of octet rule → electron poor
   - 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

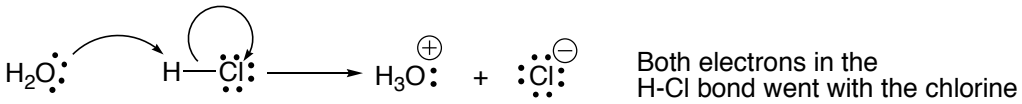
Problem: Rank the probable stability of the following radicals, 1 being most stable and 4 being least stable? (Use electronegativity to guide you…)

$H_3C\bullet$ $H_2N\bullet$ $HO\bullet$ $F\bullet$

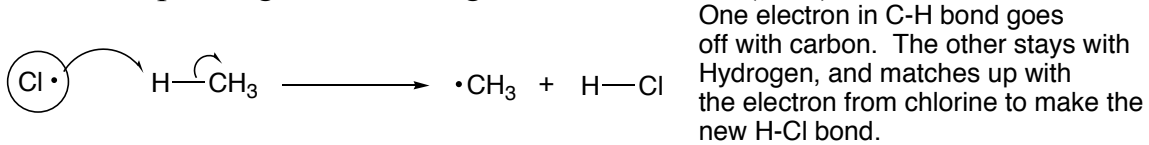
2. Atomic size and orbital overlap:
   - Fluorine is small, and it's orbitals match up well size-wise with H and C resulting in strong overlap and strong bonds.
   - Iodine is big, so it's orbitals don't match up well or overlap so well with H or C resulting in weak bonds.

Two Types of Bond Breaking:

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

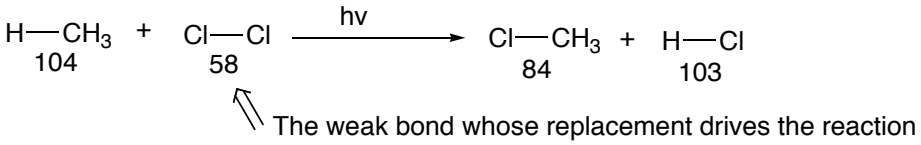


Homolysis: Bond breaks in half so that an electron goes with each atom (rare, but that's the type in this chapter)
- Radicals are involved
- Arrow-pushing involves single-barbed arrows (⌒)



4.7 Calculating Energy Changes

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

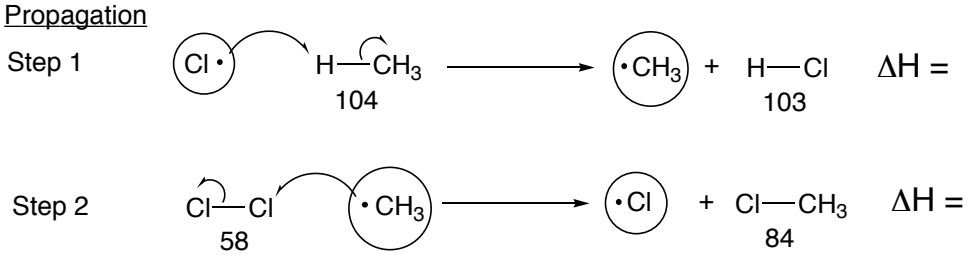


Q1: What is ΔH:

Q2: Is the overall reaction energetically favorable?

Notes:

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



Q1: Which step is better?

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

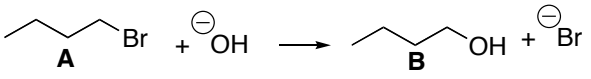
Q3: Note: Can you see what initiation would cost, and why a good chunk of energy is required to make it happen?

4.8 Kinetics, Reaction Rates, and Rate Laws

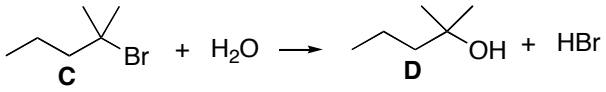
- Lots of reactions with seemingly favorable ΔH energetics don't happen very fast or at all
- We're often really interested in reaction speed ("kinetics"). Not so simple!
- Rate Law: relationship between reactant concentrations and overall rate

General: rate = $k[A]^x[B]^y$

- k is rate constant: each reaction has it's own unique rate constant.
- We will often be able to make qualitative predictions based on structural factors
- "x" and "y" are the "orders" of reactants A and B
- the "overall order" of a reaction = x + y



overall rate law: $r = k[A]^1[{}^{\ominus}OH]^1$ | overall order | individual orders



$r = k[C]^1$

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

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

Q2: If you triple the volume of solvent for reaction two, again without changing the number of moles of reactants, how will it's rate change?

4.9 Activation Energies and Dependence of Rates on Temp

- So, if every reaction has it's own k value, what influences the "k" value?
- Arrhenius Equation: $k = Ae^{-Ea/RT}$
  - A is a constant
  - E_a or E_{act} is the "activation energy"
  - R is the ideal gas constant
  - T is the temperature
- Math: larger E_{act}/RT → smaller k (and slower reaction)
- Math: smaller E_{act}/RT → larger k (and faster reaction)

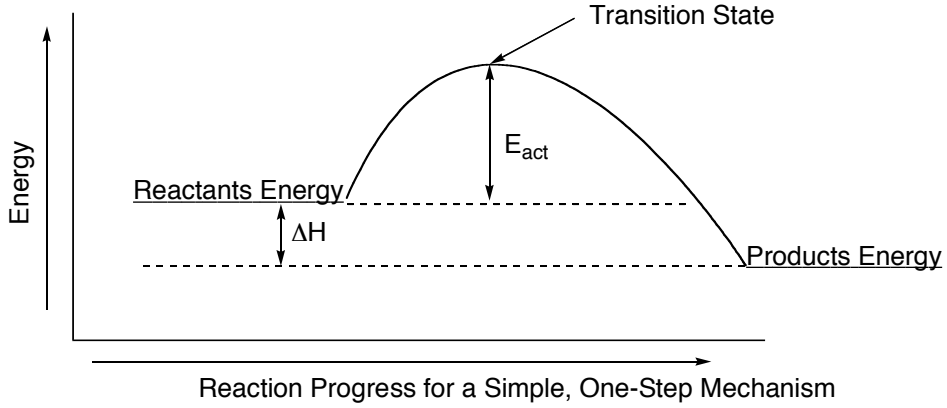
Practical Stuff

Temperature:

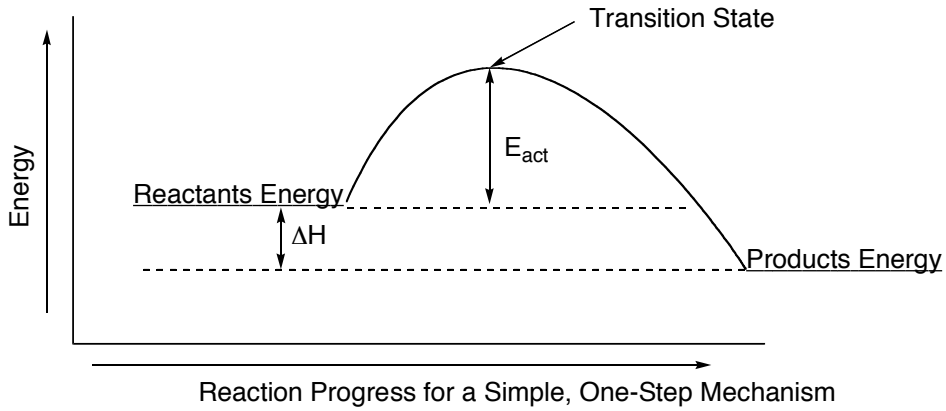
- Higher temp → higher k → faster reaction
- Lower temp → smaller k → slower reaction
- Crude guide: for every 10º rise in temp, the k value and reaction rate will double for an ordinary reaction. (This is super, super, super crude, though…)

Activation Energy: the minimum energy needed for a reaction

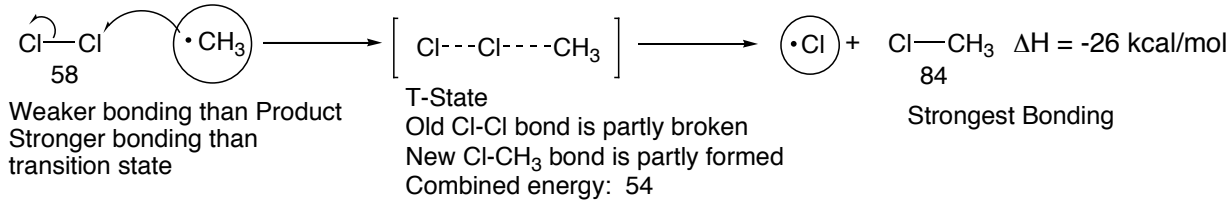
- It's the minimum energy required to cross the energy barrier between reactants and products
- The height of the barrier influences reaction speed.
- Activation barriers explain why many exothermic, energy-favorable reactions don't actually occur at room temperature
- Temperature reflects the average kinetic energy of the molecules; but some are always above average.
- **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} (see Figure 4.2 on p. 140 for a nice picture of this).**



4.10 Transition States



- The transition state is the **highest, worst energy spot** on the road from reactants to products
- The height of the transition state dictates the magnitude of the activation barrier (E_{act}). Thus the T-state has a huge impact on reaction rates.
- Why are T-states so much higher in energy than most products or reactants? And why do reaction with very favorable ΔH often have fairly high T-states?
    - 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.



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

Transition-State Stability/Reactivity Principle: The more stable the transition state, the faster the reaction will be.

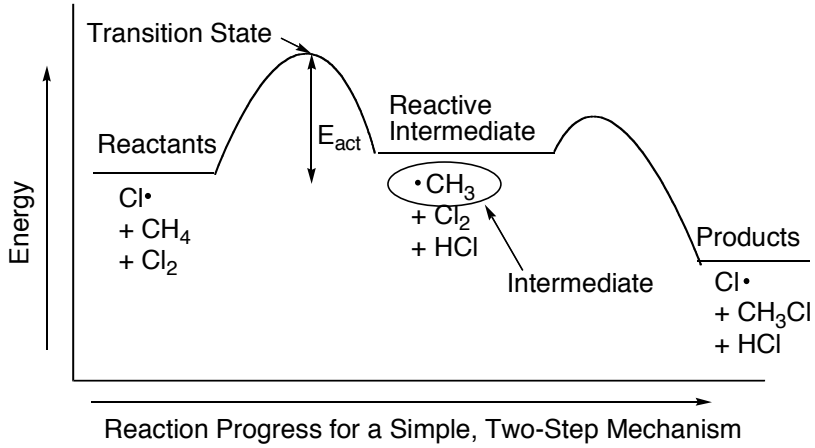
Reactant Stability/Reactivity Principle: The more stable the reactant, the slower it will react.

- 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.

Product Stability/Reactivity Principle: The more stable the product, the faster the reaction.

- A more stable product has lower energy. Often the T-state is stabilized/lowered by the same factors that may stabilize the products.

4.11 Rates of Multistep Reactions



- Most reactions involve 2 or more steps with one or more "intermediates" (•CH_3 is the key intermediate in the reaction above)
- An "**intermediate**" is something that forms temporarily, but then rapidly converts into something else. Normally the intermediate is highly reactive and has a very short lifetime. A significant population of intermediate never accumulates.
- The **transition state** for the overall reaction is still the **highest, worst energy spot** on the road from reactants to products
- There is only one transition state for the overall process, no matter how many steps
- The step that goes through the transition state will be the **slowest step** and is often referred to as **the rate-determining step** or the **slow step**.

Practical: To handle rates, identify and only think about the slowest step!!!

Practical: The rate determining step will **always** be the step leading to the worst, least stable intermediate. (•CH_3 < •Cl)

- Therefore the ability to recognize stability patterns for reactive intermediate radicals, cations, and anions is super useful

Product Stability/Reactivity Principle: The more stable the product, the faster the reaction.

- In multistep reactions, **the product that matters kinetically is the product of the rate-determining step. Which is often a reactive intermediate**.
- In order to apply the product stability/reactivity principle in multistep reactions, you'll need to:
  - Know the mechanism. (What is the rate determining step? And what kind of reactive intermediate is produced in that rate-determining step?)
  - Know how structural factors impact the relative stabilities of reactive intermediates. (For example, is a 3º radical better or worse than a 1º radical?)

Reactant Stability/Reactivity Principle: If a reactive intermediate is a reactant in a rate-determining step (rare, but this chapter), knowing stability patterns will help predict speeds.

4.12 Dependence of Halogenation Rates on Halogen

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

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

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

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

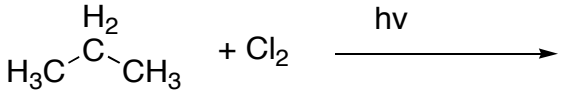
Reactant Stability/Reactivity Principle: The more stable the reactant, the slower it will react.

- The halogen radicals are reactants in the rate determining step.

4.13,14 Selective Halogenations of Higher Alkanes (Higher than Methane)

This is where most of the real problems will come from

A. Chlorination of Propane

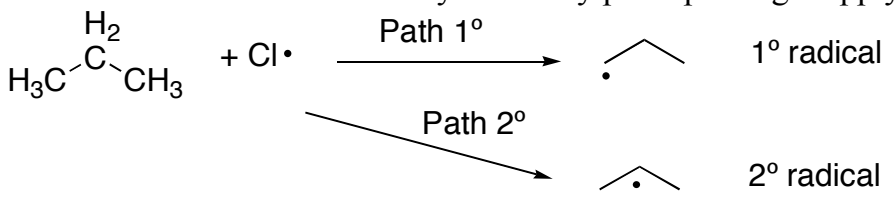


Notes

Reactivity ratio:

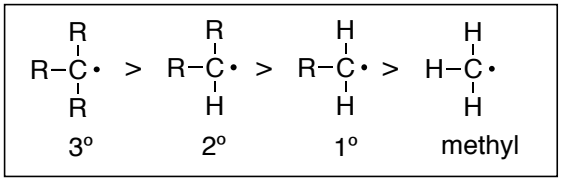
Why are 2º C-H's more reactive than 1º C-H's?

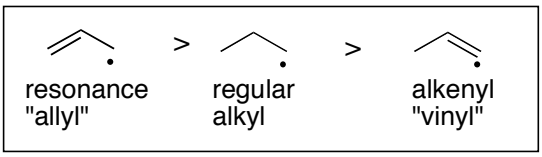
- Think rate determining step
- Think whether some stability/reactivity principle might apply



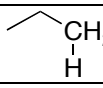
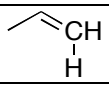
Path 2º is faster than path 1º because path 2º produces a more stable radical product. The path 2º transition-state is stabilized as a result. Product stability/reactivity principle.

B. Free Radical Stability Pattern: 3º > 2º > 1º > methyl Memorize!

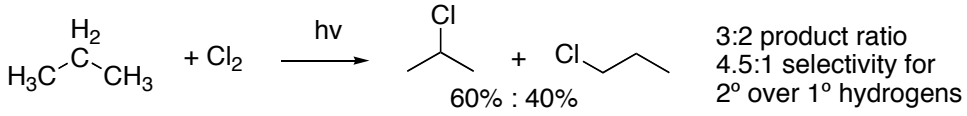


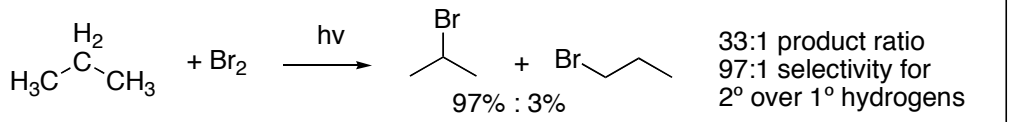


Resonance helps a lot ("**Allylic**")
Being on an alkene is bad ("**Vinylic**")

					H–CH3	
Bond Energy	87	91	95	98	104	111
Class	Allylic	3º	2º	1º	Methyl	vinyl

C. Bromination of Propane





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

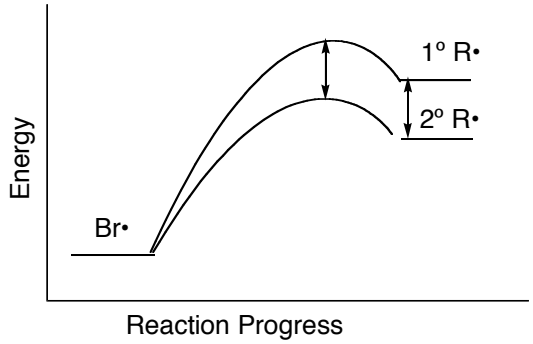
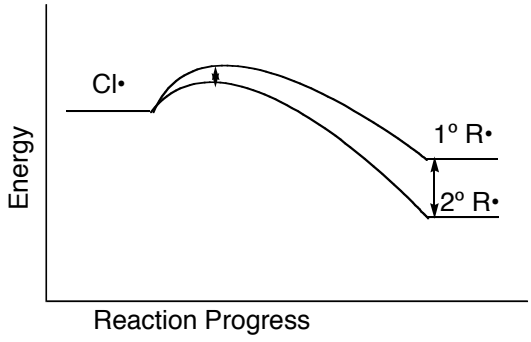
D. Why bromination is so much more selective than chlorination:

Reactant Stability/Reactivity/Selectivity Principle: 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 more stable the reactant, the less reactive it will be and the more selective it will be. (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.)

Application to the Propane Halogenation Situation:

- Br• is more stable than Cl•,

- Therefore Br• is more selective and choosy to make the better 2º radical (leading to 2-bromopropane) rather than the less stable 1º radical (leading to 1-bromopropane).
- Cl• is less stable, and really wants to react. So it doesn't wait around for a weak 2º hydrogen; it often settles for a stronger 1º hydrogen even though it gives an inferior1º 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•

	
• Endothermic • Late transition states • T-states resemble product(s) • 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	• Exothermic • Early transition states • T-states resemble reactant • 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

E. Hammond Postulate:

- For an exothermic step, the T-state is "early" and much resembles reactants
- For an endothermic step, the T-state is "late" and much resembles products

Who Cares?

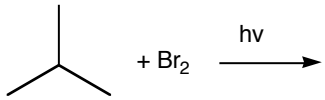
- Transition-states are important! The Hammond postulate helps us to understand what the structure of the transition state is like.
- For most multi-step reactions, the transition-states are late and product-like.
- **For late, product-like transition states, assume that any structural factor that stabilizes the product (of the rate-determining step) will also stabilize the transition state and increase the reaction rate. (This is the basis of the product stability/reactivity principle.)**
- KEY: Remember that you must always be thinking about the products of the rate-determining step, which will routinely be a reactive intermediate that does not appear as a product in the balanced reaction.

Alkane Brominations:

Skills:

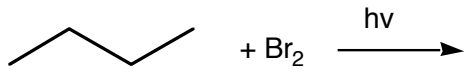
1. Identify all possible monosubstituted products
2. Identify the Major Product
   - Consider all possible radicals. The carbon that gives the most stable radical will be the carbon that gets brominated preferentially.
   - This is true because the rate determining step is the step in which a hydrogen 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.
3. Write the mechanism for chain propagation (with detailed arrows)

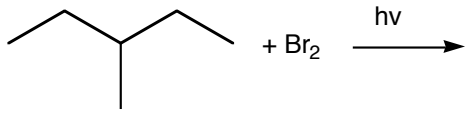
1. Do all three things for:

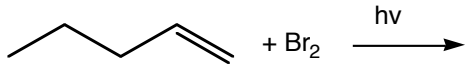


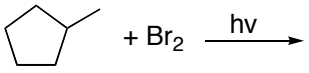
Mechanism

2. Identify the Major Product for each of the following:









4.16 Reactive Intermediates: Stability Patterns

- Shortlived, unstable, highly reactive intermediates
- 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		Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbon Radicals		Allylic > 3º > 2º > 1º > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbanions		Allylic > alkenyl (vinyl, aryl) > methyl > 1º > 2º > 3º	Electron Rich	Nucleophilic/ Basic

Notes

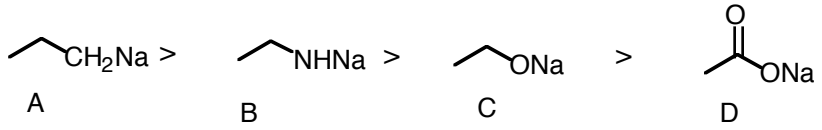
1. Both carbocations and radicals have the same pattern. So you don't need to memorize them twice!
2. Carbanions are almost exactly the reverse, except that being allylic is ideal for both.
3. All benefit from resonance (allylic).
4. Cations and radicals both fall short of octet rule. As a result, they 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

1. **Reactant Stability/Reactivity**: The more stable the reactant, the less reactive it will be. In terms of rates, this means that the more stable the reactant, the slower it will react. (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)

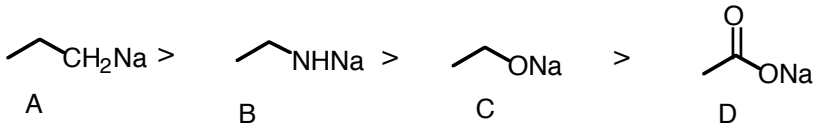
   Key note: Often the "reactant" that's relevant in this context will not be the original reactant of the reaction, but will be the "reactant" involved in the rate determining step.

   - **Basicity**



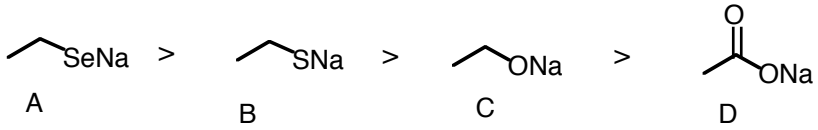
   Why: As anion stability increases from A to D, the reactivity decreases

   - **Nucleophilicity**



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

   - **Nucleophilicity**



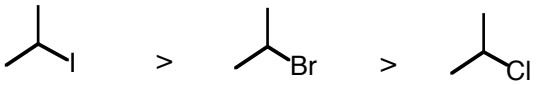
   Why: As anion stability increases from A to D, the reactivity decreases

   - **Reactivity toward alkanes via radical halogenation**

     $F_2 > Cl_2 > Br_2 > I_2$ because $F\bullet > Cl\bullet > Br\bullet > I\bullet$

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

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

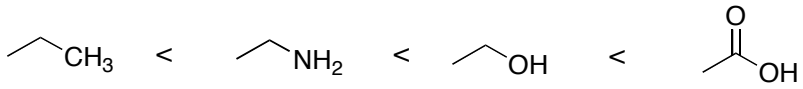


   Why: As carbon-halogen bond stability increases, the reactivity decreases

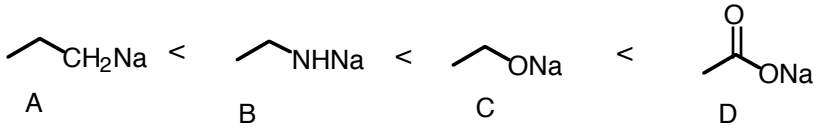
2. **Product Stability/Reactivity**: The more stable the product, the more favorable its formation will be. In terms of rates, this means that the more stable the product, the faster the reaction. (The concept here is that the more stable the product, the more favorable it will be to make that product.)

   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.

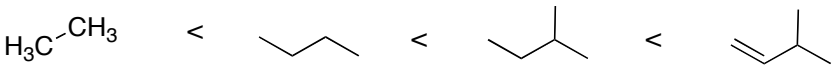
- Acidity



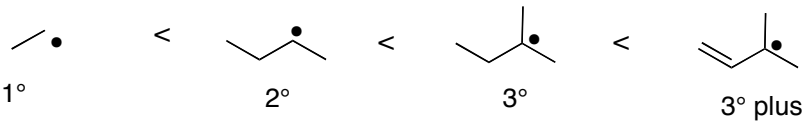
Why: Because as the stability of the anion products increases from A to D, the reactivity of the parent acids increase



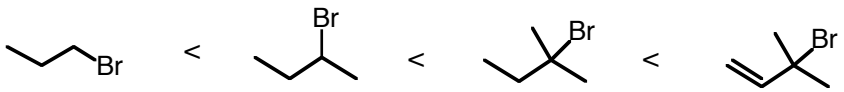
- **Reactivity of alkanes toward radical halogenation**



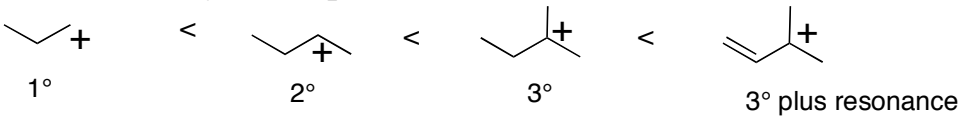
Why: Because as the stability of the radical produced during the rate-determining-step increases, the reactivity of the parent alkane increases



- **S_N1, E1 Reactivity**

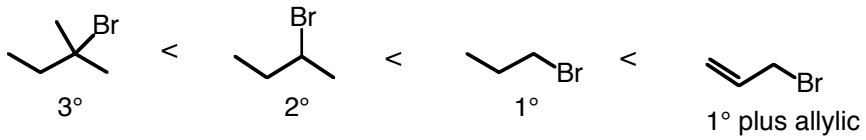


Why: Because as the stability of the cation produced in the rate-determining step increases, the reactivity of the parent halide increases as well



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

   - **S_N2 Reactivity**

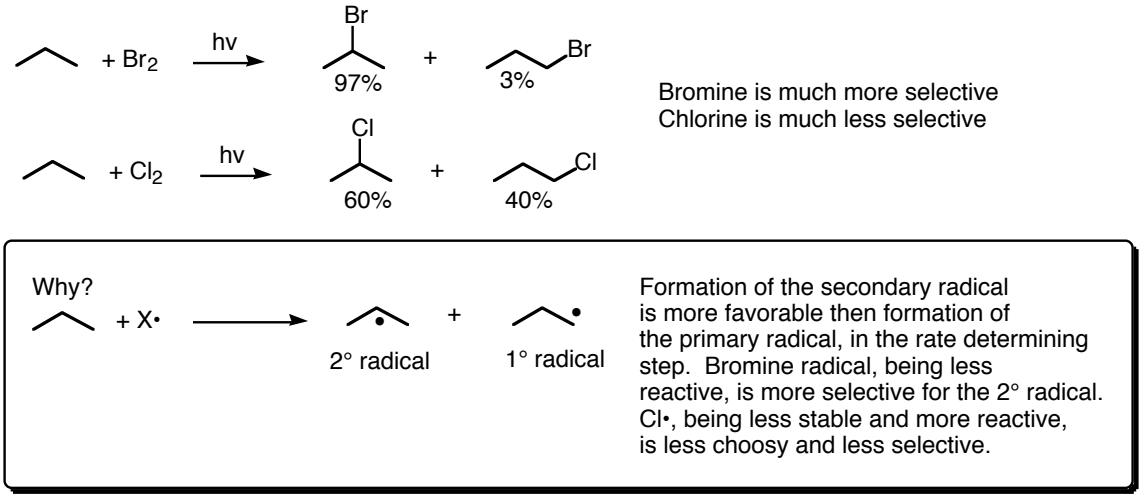


Why: The pattern reflects the relative stability of the transition states. In the case of 3° versus 2° versus 1°, the issue is steric congestion in the transition state. The transition states for the more highly substituted halides are destabilized. In the case of allylic halides, the transition state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

4. **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 more stable the reactant, the less reactive it will be and the more selective it will be. (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.

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



Ch. 5 Stereochemistry

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

5.2 Chirality

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.

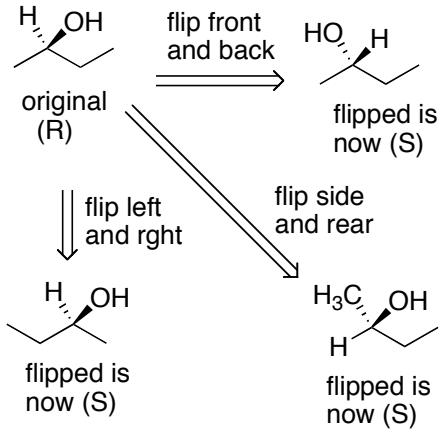
enantiomers-Two molecules that are mirror images of each other but are different and are not superimposable on each other.

- 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. flipping something on a side (could be the left side or the right side) with the hashed position in back

Flipping any two attachments inverts the stereochemistry



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

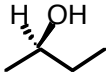
Recognizing Chiral Molecules: Key is to look for chiral carbons/stereocenters

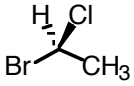
1. If **zero** chiral carbons → molecule is **achiral**
2. If **one** chiral carbons → molecule is **chiral**
3. If **two** (or more) chiral carbons → molecule may be **chiral or achiral**
    a. if it has no plane of symmetry under any conditions, it is chiral.
    b. If it has a plane of symmetry (in one conformation or drawing perspective) → achiral
    c. if a molecule has ≥2 chiral carbons but is achiral with a plane of symmetry, it is called a **meso** compound
    d. 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.

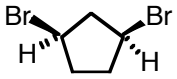
1. Classify as Chiral or Achiral

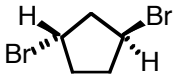
a. 

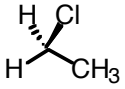
b. 

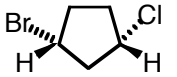
c. 

d. 

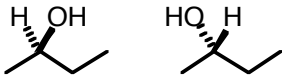
e. 

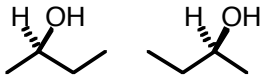
f. 

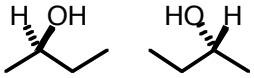
g. 

h. 

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

a. 

b. 

c. 

d. 

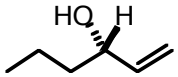
e. 

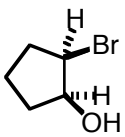
f. 

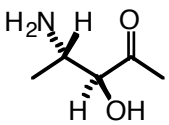
f. 

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. 

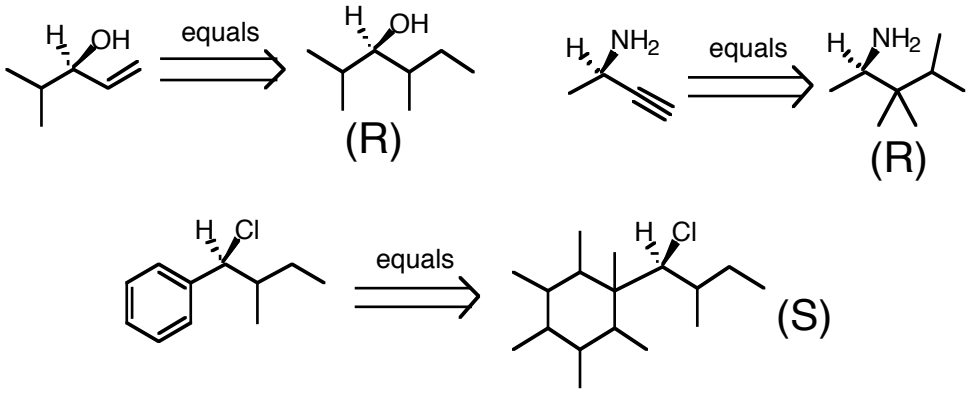
b. 

c. 

d. 

5.3 **R/S Classification for Chiral Carbons**

1. Assign Priority of Atoms/Groups attached to a tetrahedral stereocenter (1 highest, 4 lowest)
    a. For different elements, higher atomic number takes priority
        - Halogen > Oxygen > Nitrogen > Carbon > Hydrogen
    b. In case of carbon versus carbon ties: Differentiate at nearest point of difference
        1. A carbon with a heteroatom attached beats one without
        2. For carbons with no heteroatoms, one with more H's loses to one with less
            - 3º carbon > 2º carbon > 1º carbon > CH_3
    c. Handling double bonds and triple bonds
        - A carbon with more H's again loses to one with fewer
        - Double or triple bonds are treated as if each of the bonds has extra C's attached



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

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

4. If the low priority group 4 (normally H) is to the left or to the right, exchange it with the group in the back (hashed), and trace the path on the resulting figure.
    a. If the path in the redrawn picture goes clockwise (R), the original stereocenter is (S)
    b. If the path in the redrawn picture goes counterclockwise (S), the original stereocenter is (R)

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

5.4,5 Enantiomers and How They Differ

- Enantiomers have indistinguishable properties in most ways:
  - Melting points
  - Boiling points
  - Solubility
  - Density
  - Chemical reactivity towards achiral reactants.

Enantiomers Differ in 2 Ways

1. Reactivity with Chiral Chemicals (Section 5-5) (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 5-4) (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

Two Ways to Be Optically Inactive

1. If the solution has no chiral molecules present, or
2. If the solution has a 50/50 mixture of chiral enantiomers (a "racemic mixture")

- **Note: While to be "optically active" does indicates the presence of chiral molecules, to be "optically inactive" does not prove the absence of chiral molecules! It only means that there is no excess of one enantiomer over the other!**

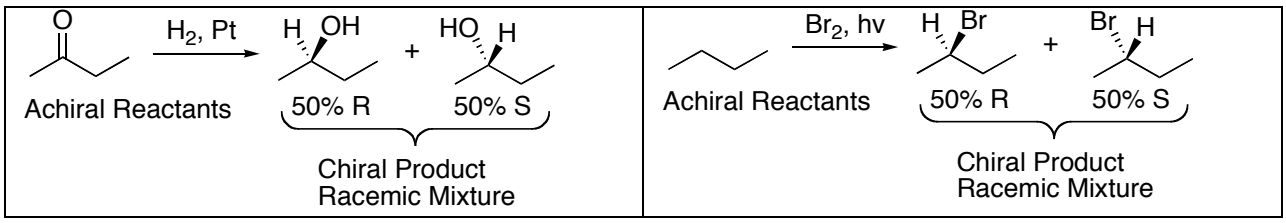
Q: Classify each of the following as "optically active" or "optically inactive"

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

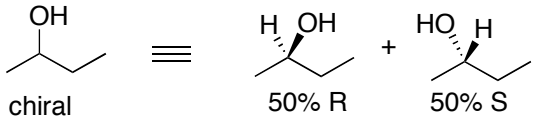
5.6 Racemic Mixtures

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

1. Most reactions that produce chiral molecules provide a racemic, 50/50 mixture of enantiomers



2. For chiral molecules, assume a racemic mixture unless told otherwise



5.7 Enantiomeric Excess ("ee") and Optical 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.

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

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

2. 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

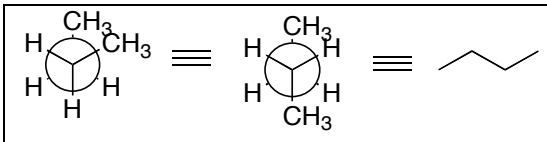
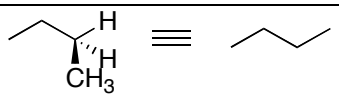
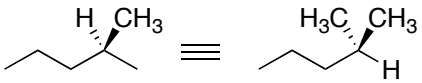
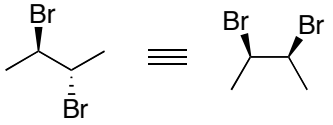
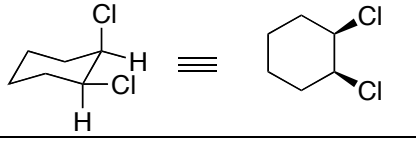
3. If a solution has a 50/50 mixture of (R)- and (S)-2-bromobutane, what would be the enantiomeric excess and the optical purity?

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

5.8 Chirality and Conformations

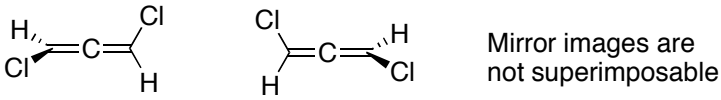
- Avoid conformational pictures, which may deceptively give the appearance of chirality

If any conformation or drawing of a molecule has a symmetry plane, it is achiral

5.9 Freaks: Chiral Compounds without Chiral Carbons: Not Tested

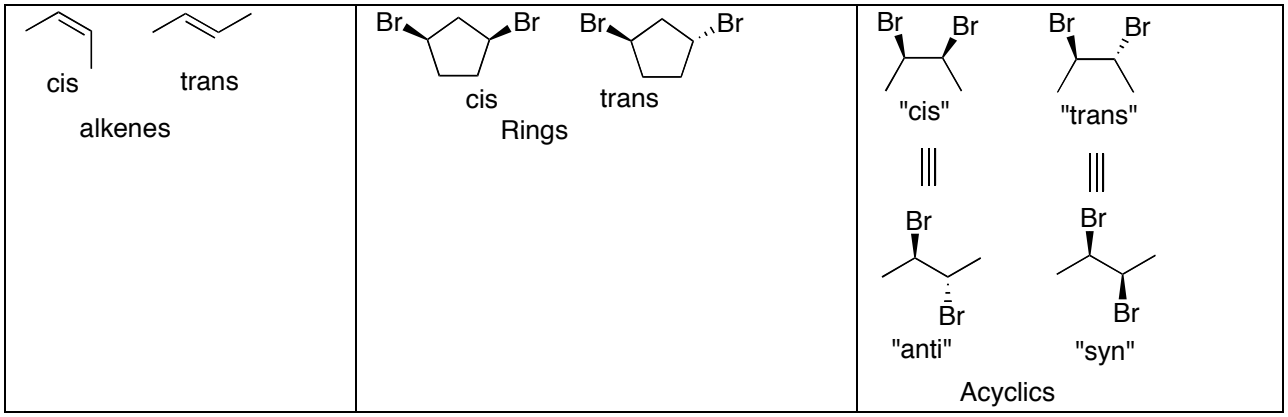
Ex: Allenes



Mirror images are not superimposable

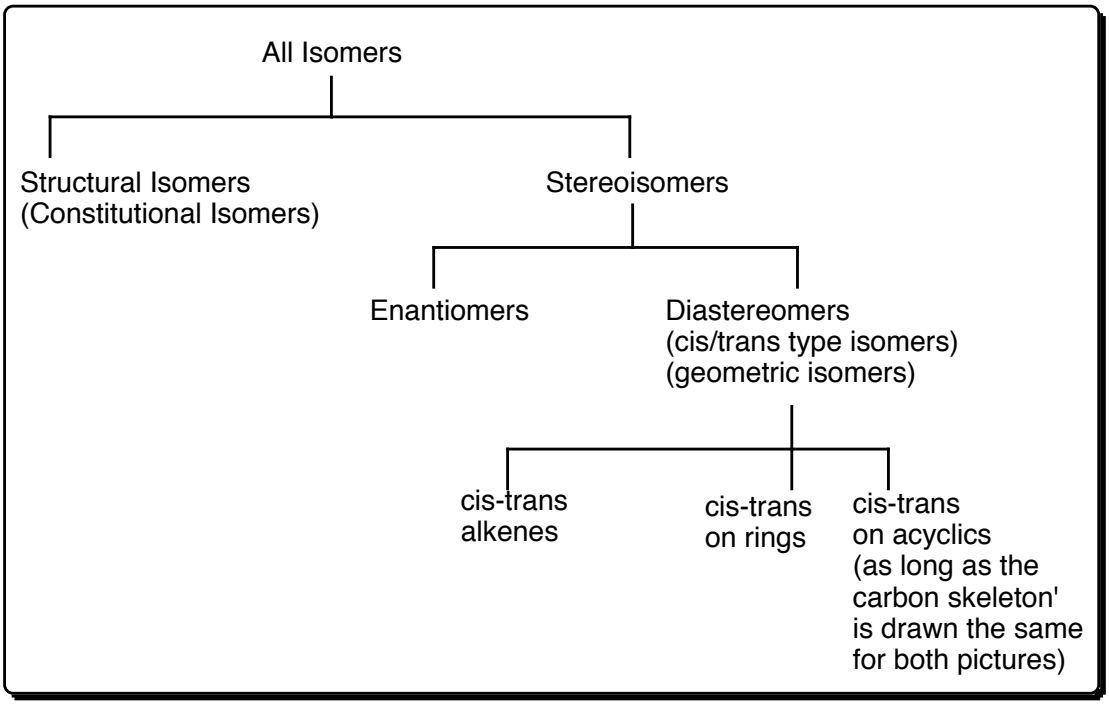
5.10 Fischer Projections: Not Tested Now. A Fischer Projection Handout is included on the website (http://www.mnstate.edu/jasperse/), for future reference.

5.11 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



5-12 Molecules with ≥2 Chiral Carbons

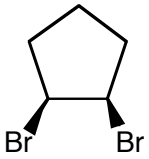
- **Rule: The maximum number of potential stereoisomers = 2^n (n = number of chiral carbons)**
- Remember: If a molecule can be drawn with a plane of symmetry, then it is achiral and it's mirror image will be the same as the original.
- If one possible isomer is achiral, then you won't get the maximum number of unique stereoisomers because two of them will be identical mirror images
- **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:

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

5-13 **Meso Compounds**

- **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

- 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

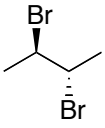
1. Problem:
   a. Draw all unique stereoisomers of 2,3-dibromobutane.
   b. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers.
   c. Identify each picture as chiral or achiral (meso)

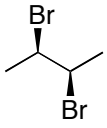
2. Draw all unique stereoisomers of 2,3-dibromopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

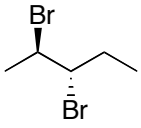
3. Draw all unique stereoisomers of 2,4-dibromopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

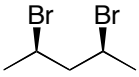
4. Draw all unique stereoisomers of 2,4-dibromocyclopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

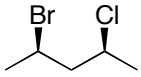
5. Identify each picture as chiral or meso

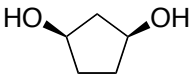
a. 

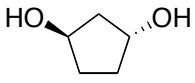
b. 

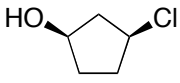
c. 

d. 

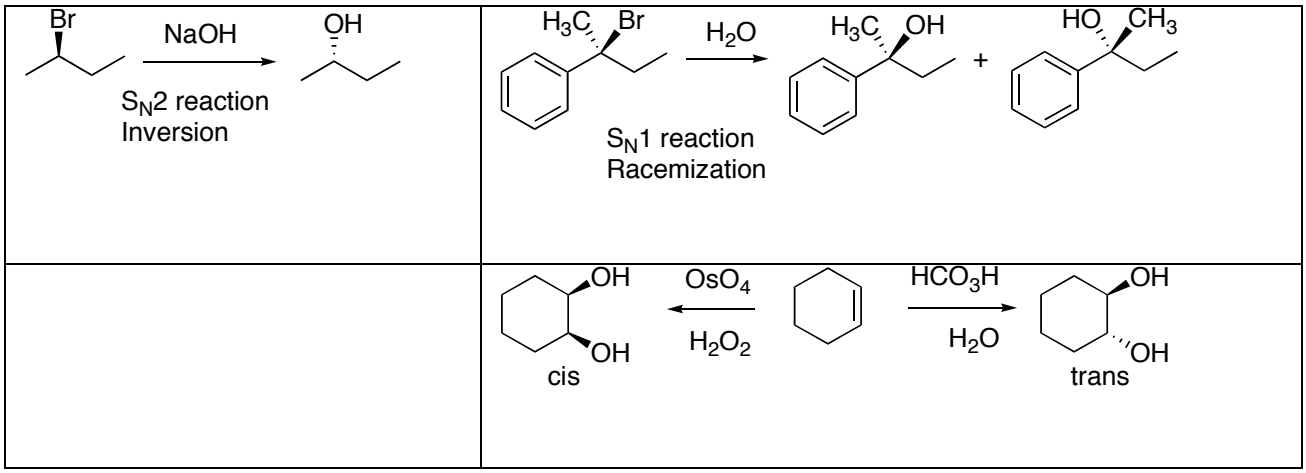
e. 

f. 

g. 

h. 

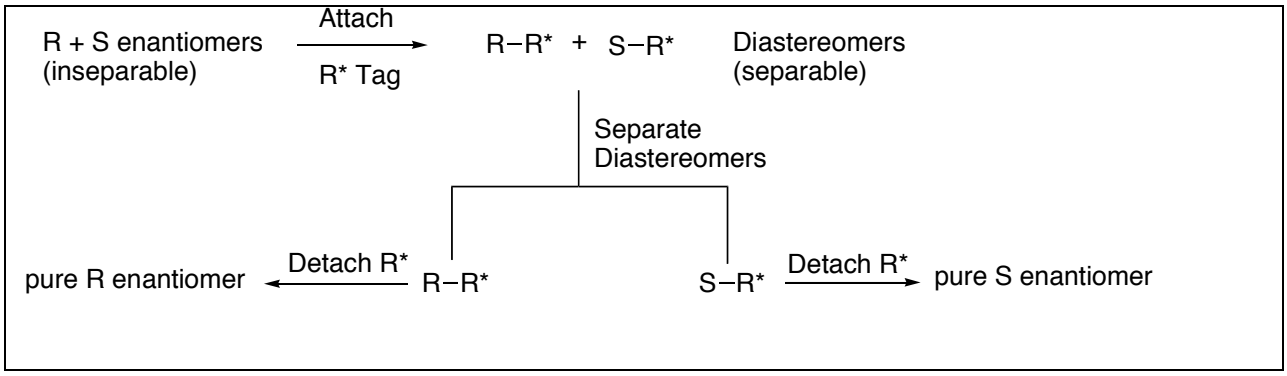
5.14 Absolute and Relative Configuration
Absolute: (R) or (S)
Relative: Comparison between 2 molecules or 2 chiral carbons (even if we don't know absolute)



- Relative stereochemistry is often an important feature in mechanisms and product predictions

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

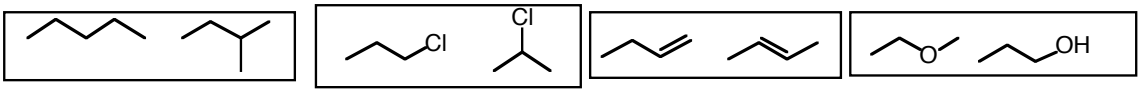
5.16 Separation of Enantiomers via Diastereomers
- Enantiomers can be separated by temporary attachment to an optically active thing → resulting in separable diastereomers → chop attachment following separation



Chem 350 Chapter 5 Stereochemical Terminology Summary
Terms and Definitions

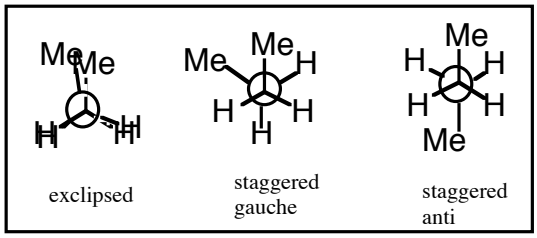
Classification of Isomers
isomers-different compounds with the same molecular formula.

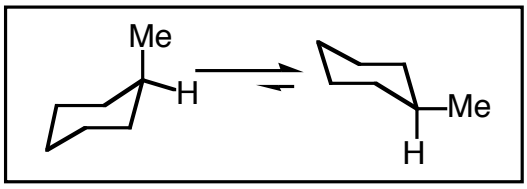
structural isomers (or constitutional isomers)-isomers that have their atoms connected in a different order.



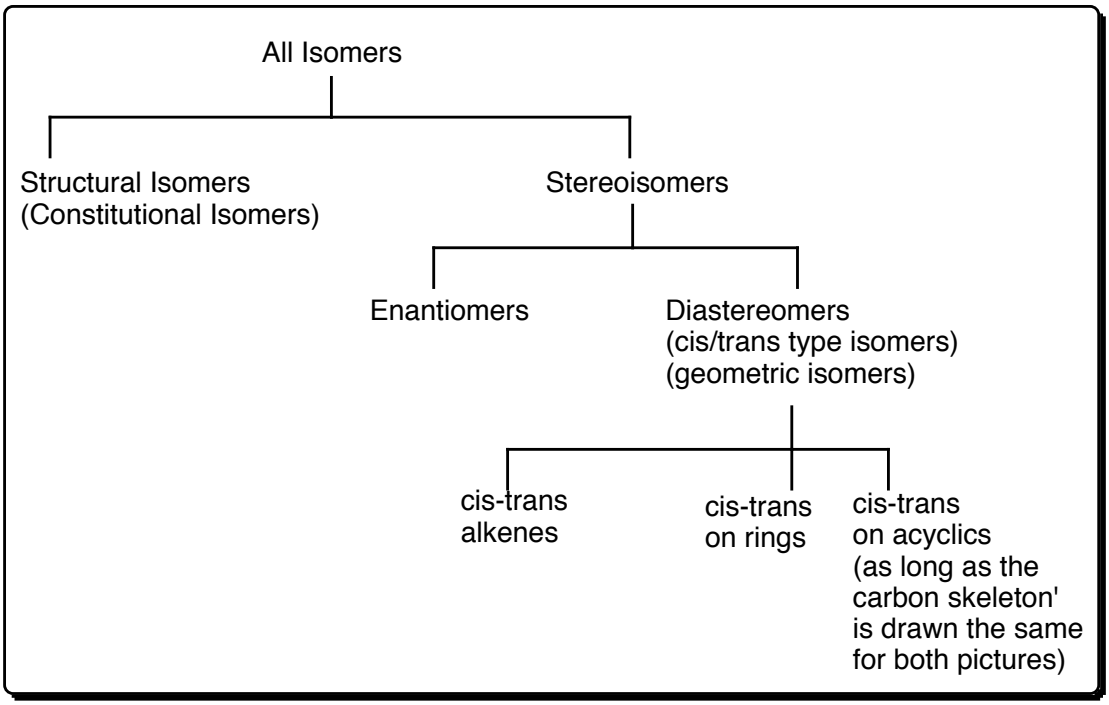
stereoisomers (or configurational isomers)-isomers in which atoms are joined in the same order but differ in the way their atoms are arranged in space. Stereoisomers are subdivided into two categories: **enantiomers** and **diastereomers**.

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.





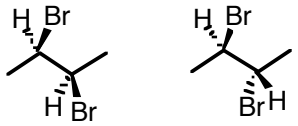
Summary: Types of Isomers



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 optically active.

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.

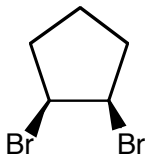
chiral carbon (or stereocenter or asymmetric carbon atom)-an atom bearing groups such that interchange of 2 of the groups produces a stereoisomer. Any tetrahedral atom that has four different attached groups is a chiral carbon.

- 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.

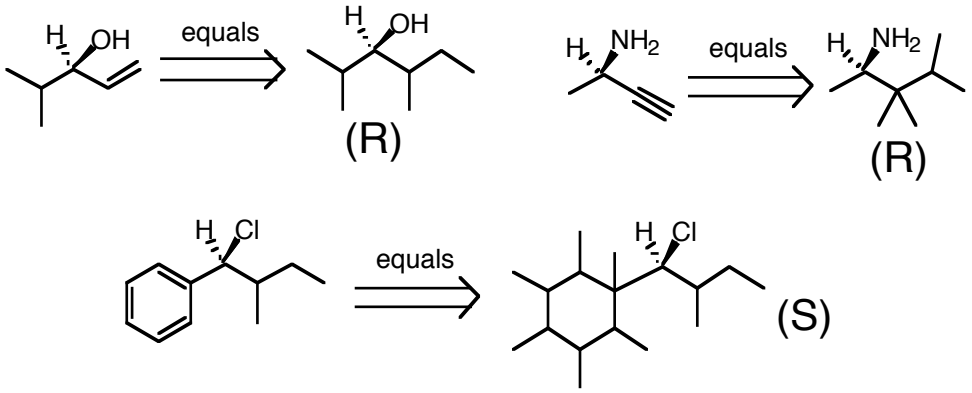
meso compound-an achiral, optically inactive molecule that contains tetrahedral stereocenters (usually two). Both of the Br-bearing carbons in cis-1,2-dibromocyclopentane are stereocenters, but the molecule itself has a plane of symmetry and is achiral.



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. For different elements, higher atomic number takes priority
        - Halogen > Oxygen > Nitrogen > Carbon > Hydrogen
    b. In case of carbon versus carbon ties: Differentiate at nearest point of difference
        1. A carbon with a heteroatom attached beats one without
        2. For carbons with no heteroatoms, one with more H's loses to one with less
            - 3º carbon > 2º carbon > 1º carbon > CH_3
    c. Handling double bonds and triple bonds
        - A carbon with more H's again loses to one with fewer
        - Double or triple bonds are treated as if each of the bonds has extra C's attached



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

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

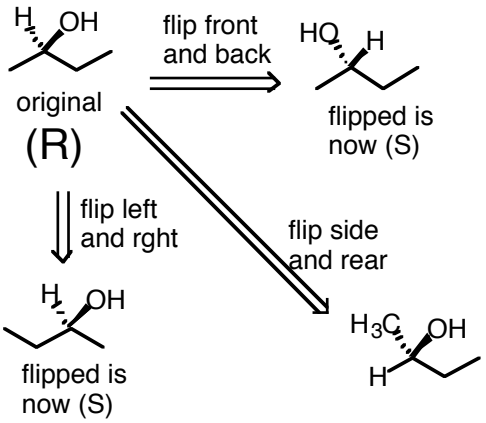
4. If the low priority group 4 (normally H) is to the left or to the right, exchange it with the group in the back (hashed), and trace the path on the resulting figure.
    h. If the path goes clockwise, the stereocenter is (S)
    i. If the path goes counterclockwise, the stereocenter is (R)

5. 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

Flipping any two attachments inverts the stereochemistry



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**
    e. if it has no plane of symmetry under any conditions, it is chiral.
    f. If it has a plane of symmetry (in one conformation or drawing perspective), then it is achiral
    g. if a molecule has ≥2 chiral carbons but is achiral with a plane of symmetry, it is called a **meso** compound
    h. 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

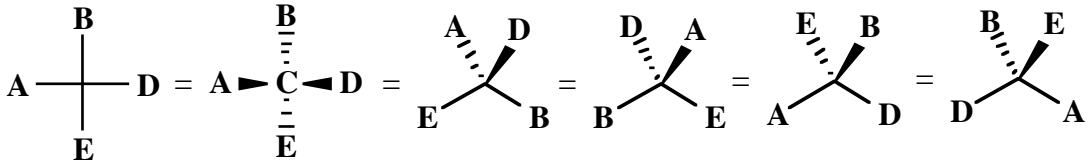
optical purity = [observed rotation/rotation of pure enantiomer] x 100

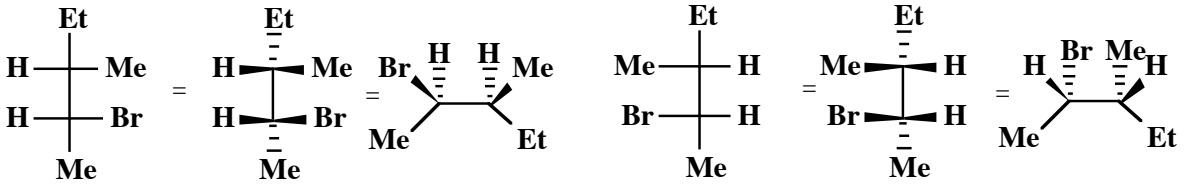
Note: Enantiomeric excess and optical purity values are exactly the same, but are used depending on the experimental method of measurement. Enantiomeric excess is used when you determine the mole/mole ratio of enantiomers by NMR or some other method; optical purity is used when you use optical rotation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

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

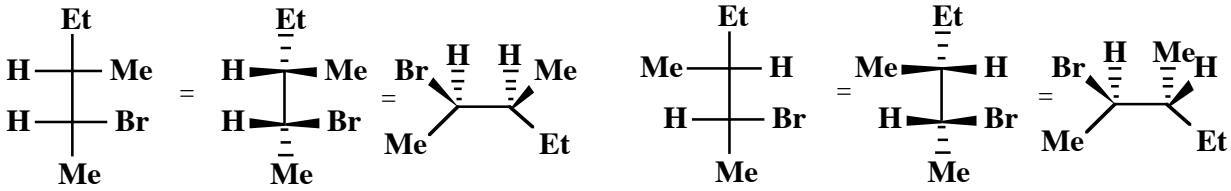
Fischer Projections

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.

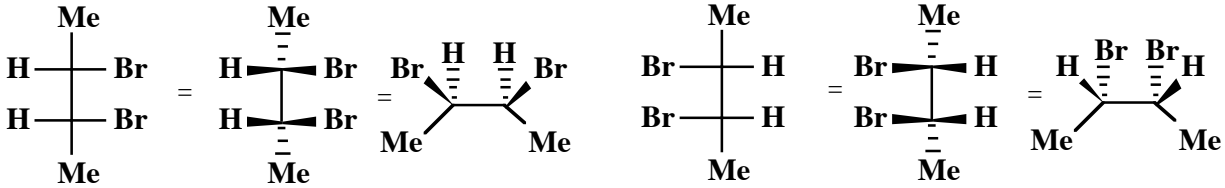




The two structures shown above are enantiomers



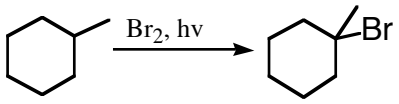
The two shown here are diastereomers.



The two shown here are not stereoisomers; they are "meso compounds", because there is a plane of symmetry.

Chem 350 Jasperse Ch. 6 Summary of Reaction Types, Ch. 4-6, Test 2

1. Radical Halogenation (Ch. 4)



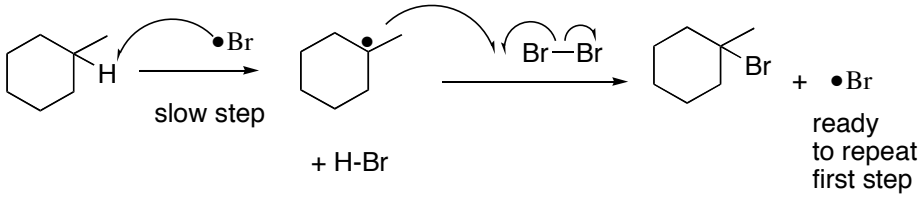
resonance stabilized>3°>2°>1°>alkenyl

Recognition: X_2, hv

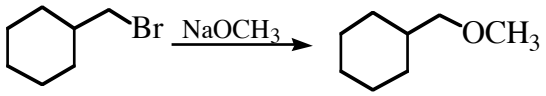
Predicting product: Identify which carbon could give the most stable radical, and substitute a Br for an H on that carbon.

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

Mech: Radical. Be able to draw propagation steps.



2. S_N2 Substitution



S_N2: 1°>2°>3°> alkenyl

Any of a large variety of nuclophiles or electrophiles can work.

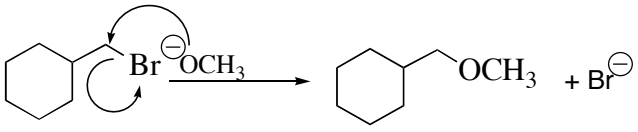
Recognition: A. Anionic Nucleophile, and
B. 1° or 2° alkyl halide

(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

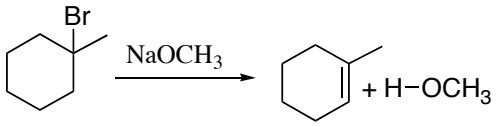
Stereochemistry: Leads to Inversion of Configuration

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

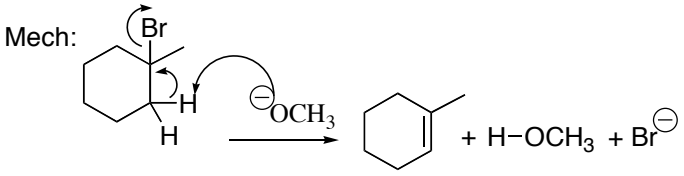


S_N2: 1°>2°>3°> alkenyl

3. E2 Reactions.



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.)

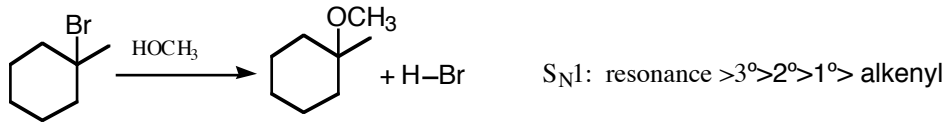
Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7)

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.

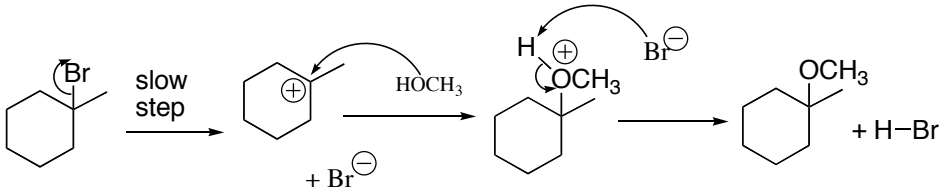
Stereochemistry: Anti elimination. The hydrogen on the neighbor carbon must be trans/anti.

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

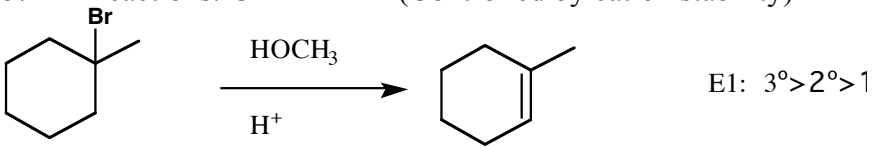
4. S_N1 Reactions.



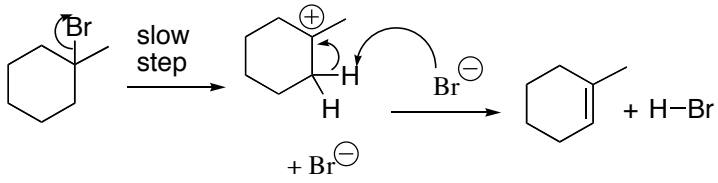
Recognition: A. Neutral, weak nucleophile. No anionic nucleophile/base, and
B. 3° or 2° alkyl halide. (Controlled by cation stability).
(1° alkyl halides undergo S_N2 instead. For 2° alkyl halides, S_N1 is often accompanied by variable amounts of E1.)
Predicting product: Remove halide and replace it 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° (Controlled by cation stability)



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.



Sorting among S_N2, S_N1, E2, E1: How do I predict?

Step 1: **Check nucleophile/base**.

- If **neutral**, then **S_N1/E1** → mixture of both
- If **anionic**, then **S_N2/E2.**

Step 2: If **anionic**, and in the **S_N2/E2**, then **Check the substrate**.

- 1° → **S_N2**
- 2° → **S_N2/E2 mixture.** Often more **S_N2**, but not reliable…
- 3° → **E2**

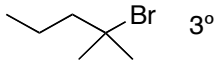
Ch. 6 Alkyl Halides: Nucleophilic Substitution and Elimination

6.1,2 Classification, Nomenclature

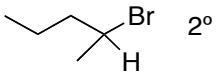
A. General Classification

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

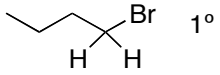
B. 1º, 2º, 3º Classification



3º



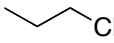
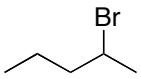
2º



1º

C. Systematic Naming: x-Haloalkane (test responsible) (Include number!)

D. Common Naming: "alkyl halide" (not tested)

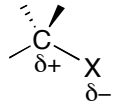
Structure	Formal Name	Common Name
		
		
		Isopropyl iodide

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

6.3 Uses:

- solvents
- anesthetics
- refrigerants
- pesticides
- **reactants**

6.4 Structure:

A. Polar		

B. Weak Bonds, Breakable

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

6.5 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)

6.6 Preparation of Alkyl Halides

- Review: R-H + Br_2 → RBr + HBr (under photolysis, Ch. 4)
- We will learn other preparations in chapters 8 and 11

6.7 Basic Overview/Preview of Alkyl Halide Reactions: Substitution (S_N2 or S_N1) or Elimination (E2 or E1)

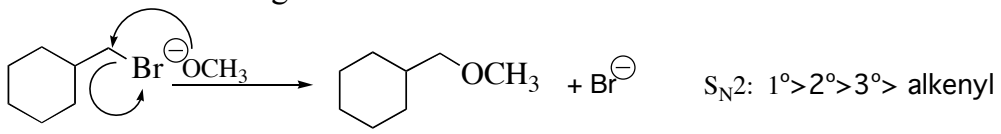
- Because R-X bonds are weak, halides are good leaving groups.

A. Substitution

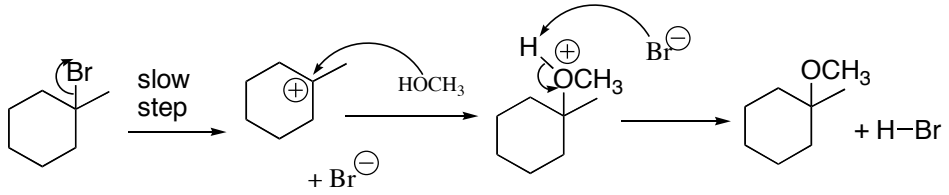
R-X + NaZ or HZ → R-Z + NaX or HX
Anion or neutral

2 Variants

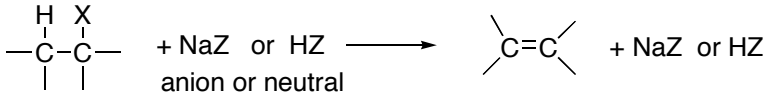
1. S_N2:
   - Anionic nucleophile
   - The R-X bond breaking is simultaneous with R-Z bond formation



2. S_N1:
   - Neutral nucleophile
   - The R-X bond breaks first to give a carbocation in the rate determining step; formation of the R-Z bond comes later

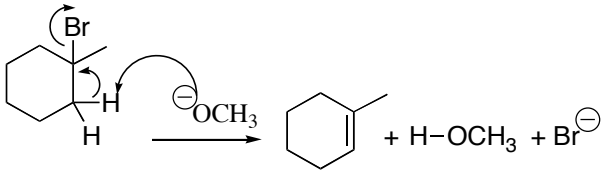


B. Elimination

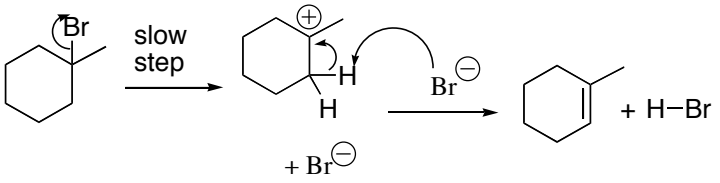


<u>2 Variants</u>

1. E2:
   - Anionic base
   - The R-X and C-H bond breaking is simultaneous with C=C bond formation

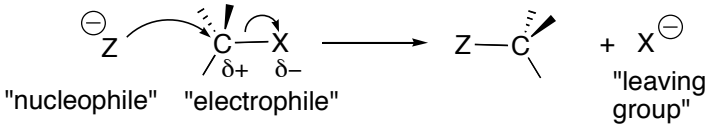


2. E1:
   - Neutral base
   - The R-X bond breaks first to give a carbocation in the rate determining step. C-H bond cleavage and C=C bond formation comes later

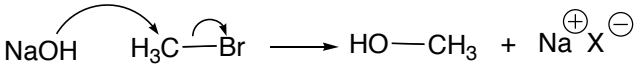


6.8 The S_N2 Reaction

General:

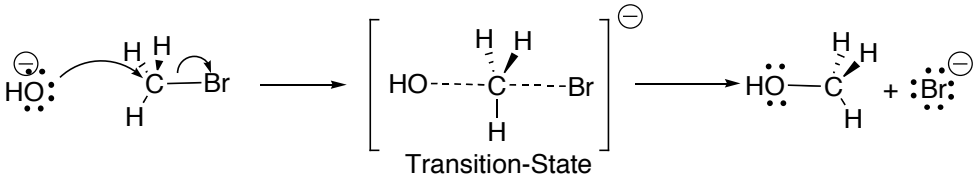


Example, with test-level mechanism:



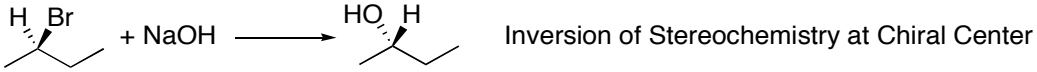
- double-barbed arrows (electron pairs move)
- Na^+ is a spectator

More Detailed Mechanism:



Notes:

- Simple, concerted one-step mechanism. No intermediates.
- The anion needs to be very reactive and thus not too stable. Normally **ANIONIC NUCLEOPHILE**.
- Both nucleophile and electrophile are involved in the rate determining step.
- Rate = $k[anion]^1[R\text{-}X]^1$
- 2nd order rate law is why it's called S_N2: **S**ubstitution$_{\text{Nucleophilic}}$**2**nd order
- The nucleophile attacks opposite side from the leaving group.
- This "backside attack" (or opposite side attack) results in inversion of stereochemistry when a chiral, 2º R-X is involved



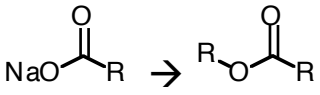
- The **transition state** involves a 5-bonded, trigonal bipyramidal carbon that **is more cluttered** than either the original tetrahedral reactant or the final tetrahedral product
- Steric crowding in the transition-state makes the reaction very, very, very sensitive to steric factors
    - For the electrophile R-X: CH_3-X > 1º R-X > 2º R-X > 3º R-X for steric reasons
    - For the nucleophile it also helps to be smaller rather than larger

6.9 Generality of S_N2 Reactions

-many kinds of nucleophiles, give many products

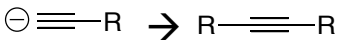
R-X + NaOH → R-OH Alcohols

R-X + NaOR → R-O-R Ethers

R-X +  Esters

R-X + KI → R-I Iodides

R-X + NaCN → R-CN Nitriles

R-X +  Alkynes

Etc.

Notes

- Most nucleophiles are **ANIONS**
- Various oxygen anions are good to make alcohols, ethers, or esters
- Halogen exchange useful route to iodides (more valuable and less accessible)
- There are a few neutral nucleophiles (not for test): nitrogen family

Predicting Products for S_N2 Reactions

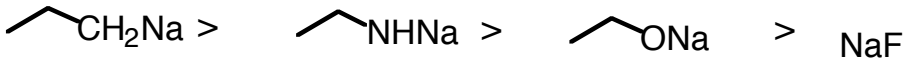
1. Don't change the structure for the carbon skeleton
2. **Put the nucleophile in exactly the spot where the halide began…**
3. Unless the halide was attached to a **chiral** center; in that case invert the configuration for the product
   - If the halide was "wedged", the nucleophile should be "hashed"
   - 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

6.10, 6.11 Structural Factors that Impact S_N2

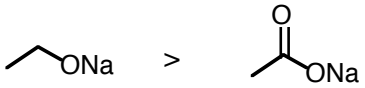
1. Nucleophile
   a. Anion versus Neutral: Should be **ANIONIC**

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

      1) -anion nucleophilicity decreases across a **horizontal row** (electronegativity factor)



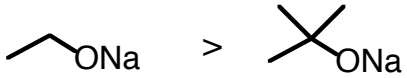
      2) -anion nucleophilicity decreases when an anion is stabilized by **resonance**



      3) -anion nucleophilicity increases down a **vertical column**

NaSeH > NaSH > NaOH

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

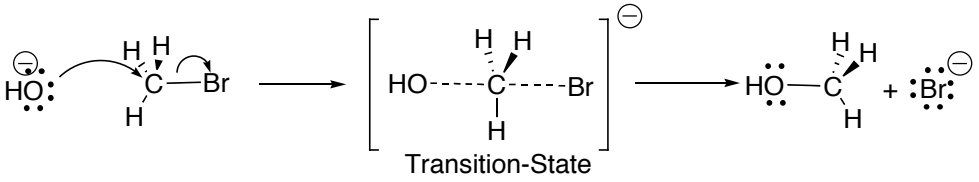


2. Electrophile
   - **Substrate: Allylic > 1º > 2º > >> 3º, alkenyl, aryl**
     - **3º and alkenyl, aryl never do S_N2**
     - transition-state stability-reactivity principle
     - Steric clutter in the transition state explains the 1º > 2º > >> 3º pattern
     - Allylic benefits from a complex orbital 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)

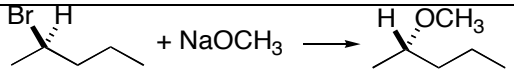
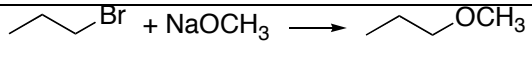
   - **Leaving Group: R-I > R-Br > R-Cl**
     - reactant stability-reactivity principle
     - weaker bonds break faster

6.12 Inversion of Stereochem in S_N2

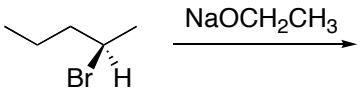
In the mechanism, the nucleophile attacks from the "backside" or opposite side from the leaving group → inverts configuration

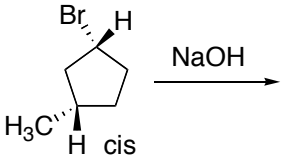


- Inversion occurs mechanistically in **every** S_N2 reaction
- But inversion is chemically relevant **only** when a chiral carbon is involved

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

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



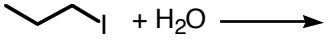


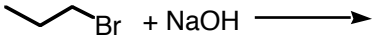
Two Standard Proofs for S_N2 mechanism:
- Inversion of configuration on a chiral carbon
- 2nd order rate law

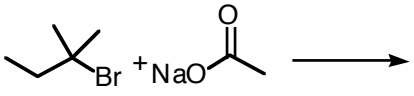
Predicting Products for S_N2 Reactions
1. Don't change the structure for the carbon skeleton
2. **Put the nucleophile in exactly the spot where the halide began…**
3. Unless the halide was attached to a **chiral** center; in that case invert the configuration for the product
   - If the halide was "wedged", 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

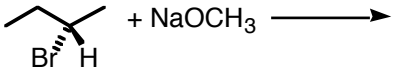
S_N2 Problems: For each of the following

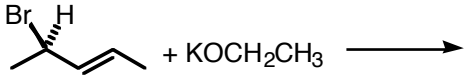
a. Identify whether or not an S_N2 reaction would take place?
b. If not, why not?
c. For those that could undergo S_N2 substitution, draw in the product.

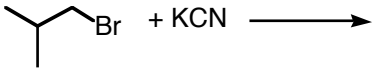
1. 

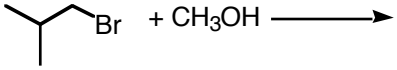
2. 

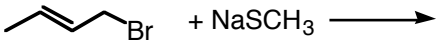
3. 

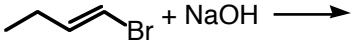
4. 

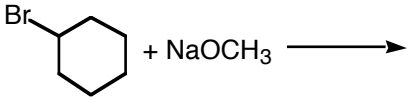
5. 

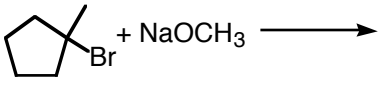
6. 

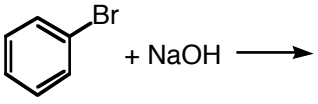
7. 

8. 

9. 

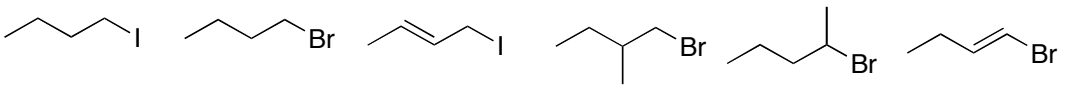
10. 

11. 

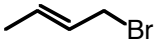
12. 

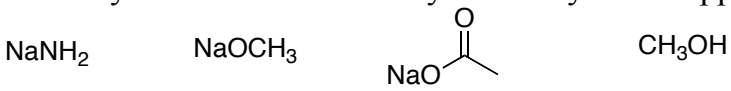
More S_N2 Problems

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:

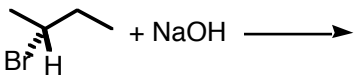
2. Rank Reactivity toward  (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

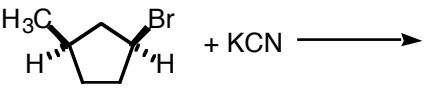


Issues:

3. What nucleophile should you use to accomplish the following transformations?

4. Draw the Products, Including Stereochemistry. (Stereochemistry will matter for S_N2 and S_N1 reactions anytime the haloalkane is 2º)





Issue:

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

Issues:

6.13 S_N1 = **S**ubstitution$_{\underline{N}\text{ucleophilic}}$**1**st Order = "Solvolysis"

Dramatic difference in mechanism, rates, structure dependence, and stereochemical outcome (compared to S_N2)

General: R-X + Z-H → R-X + HX
neutral

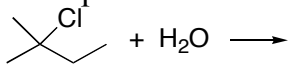
Neutral, **non-anionic** nucleophiles do the substitution

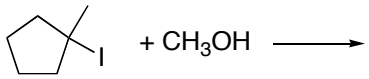
- Often this is just the solvent (H_2O, ROH, RCO_2H are common)
  - For this reasons, these reactions are often called "solvolysis" reactions
- Heat is often required
- Acid is sometimes used to accelerate S_N1 reactions

Predicting Products for S_N1 Reactions

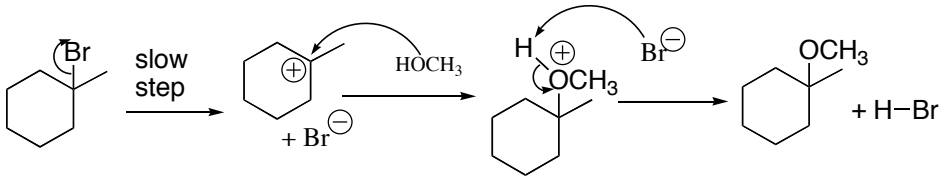
1. Don't change the structure for the carbon skeleton
2. Connect "R" and "Z", while taking the halide off of the electrophile and H off of the nucleophile
3. Unless the halide was attached to a **chiral** center, a **racemic mixture** will result
4. Maintain the integrity of the spectator attachments

Examples:





3-Step Mechanism



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

Notes:

1. Carbocation formation is key
2. Rate = k[R-X] → First order
3. Rate does not depend on concentration of nucleophile
4. See cations, not anions. Acidic, not basic conditions. Neutral, not anionic nucleophile.
5. Charge and atoms must balance in step 2. Thus, the oxygen retains the hydrogen.
6. Oxygen eventually loses the H, but only in step 3.
7. 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

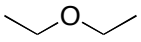
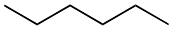
Electrophile

1. Substrate: Allylic > 3º > 2º > > 1º > alkenyl, aryl
   - Resonance is huge
   - alkenyl, aryl never do S_N2, 1º only with $AgNO_3$
   - product stability-reactivity principle: in the rate-determining step, the more stable the product **cation**, the faster it will form
   - In terms of 1º, 2º, 3º, S_N1 and S_N2 have exactly opposite patterns

2. Leaving Group: R-I > R-Br > R-Cl
   - reactant stability-reactivity principle: in the rate determining step, the weaker the C-X bond, the faster it will break
   - This pattern is the same as for S_N2

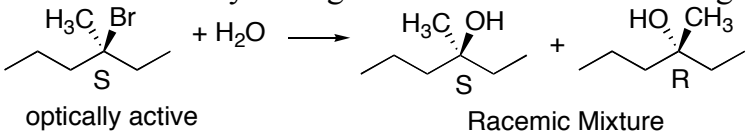
3. $AgNO_3$ Helps
   - Ag+ helps strip the halide off in step one

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

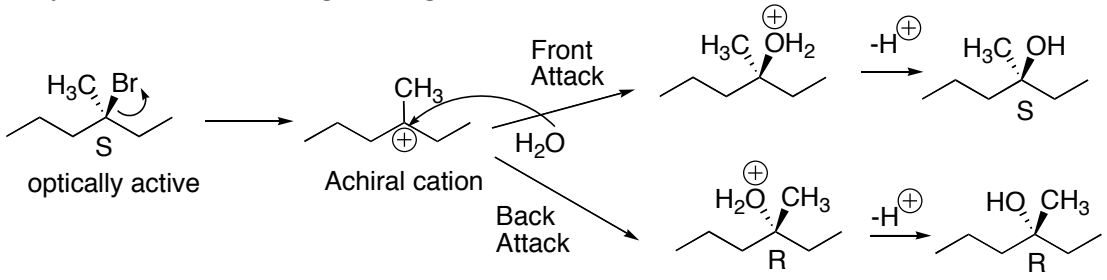
Solvent Polarity:					
Solvent	H_2O	CH_3OH			
Relative Rate	8000	1000	1	0.001	0.0001

6.14 S_N1 Stereo: Racemization

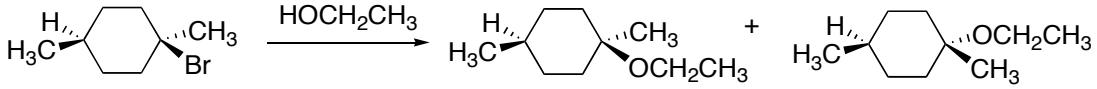
Original stereochemistry is forgotten at the carbocation stage, get racemic R/S mixture



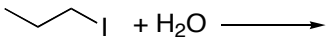
Why? Carbocation forgets original stereo:

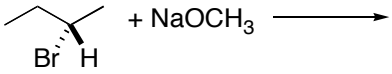


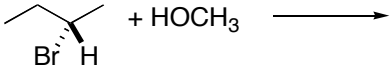
Ex.

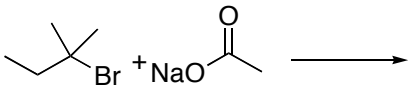


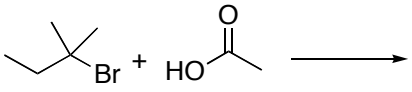
S_N1 Problems: For the following, which are and aren't S_N1 candidates? If not, why not? What would be the product if they are S_N1 candidates?

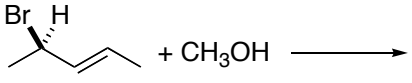
1. 

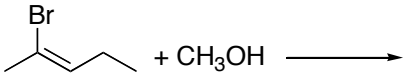
2. 

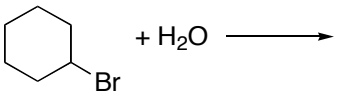
3. 

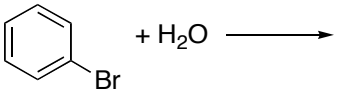
4. 

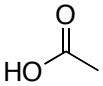
5. 

6. 

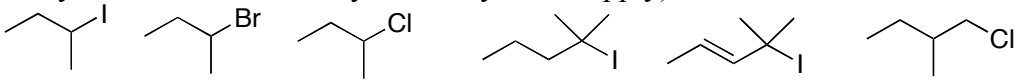
7. 

8. 

9. 

10. Rank Reactivity towards 

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



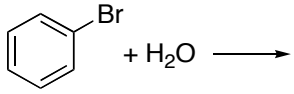
Issues:

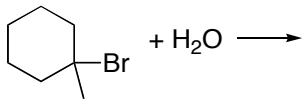
6.16 Comparing S_N2 vs S_N1

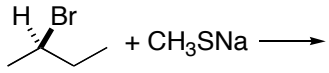
		S_N1	S_N2
1	**Nucleophile**	**Neutral, weak**	**Anionic, strong**
2	**Substrate**	**3º R-X > 2º R-X**	**1º R-X > 2º R-X**
	Allylic effect…	Allylic Helps	Allylic helps
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	K[RX]	k[RX][Anion]
6	Stereochemistry (on chiral, normally 2º R-X)	Racemization	Inversion
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never

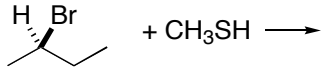
1. Identify as S_N1 or S_N2 or No Reaction. Draw the Product(s), if a reaction occurs.

a. 

b. 

c. 

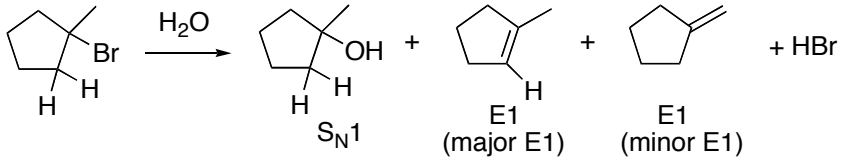
d. 

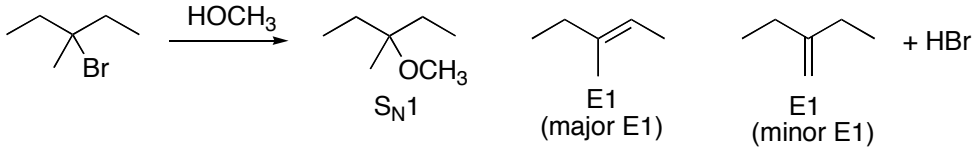
e. 

2. Which fit S_N1, which fit S_N2?
   a. Faster in presence of silver nitrate?
   b. Faster in water than in hexane?
   c. 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?
   d. By 4-fold?
   e. 2-bromobutane reacts faster than 1-bromobutane?
   f. 2-bromobutane reacts slower than 1-bromobutane?

6-17 E1 Elimination Reactions

Examples:

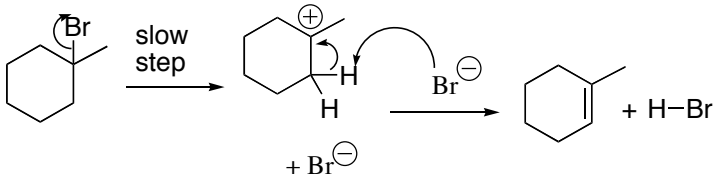




Notes

- 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



- Step 1: Carbocation Formation. THIS IS THE SLOW STEP
  - Therefore the rate is controlled by cation stability! Just like S_N1!
  - Benefits from exactly the same factors that speed up S_N1 (3º > 2º, RI > RBr, polar solvent, etc..)
- Step 2: Deprotonation from a carbon that neighbors the cation (and the original halogenated carbon)
  - Draw bromide as base for simplicity
  - 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. 3º or 2º alkyl halide. (Controlled by cation stability).

(For 2º alkyl halides, E1 is often accompanied by variable amounts of S_N1.)

Orientation: The most substituted alkene forms

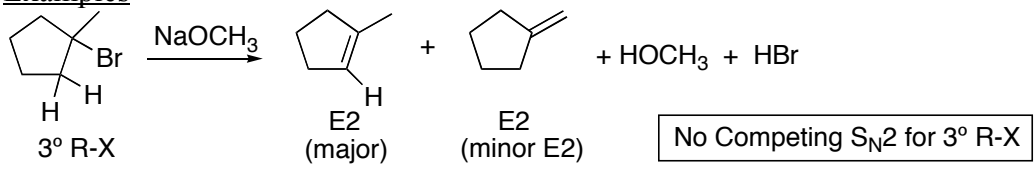
Predicting the major product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.

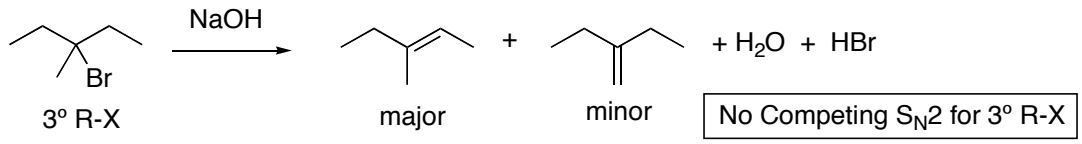
Stereochemistry: Not an issue. The eliminating hydrogen can be cis or trans. .

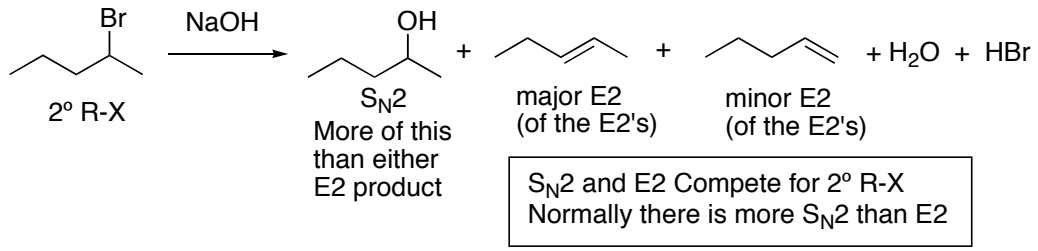
Mech: Stepwise, 2 steps, via carbocation. Be able to draw completely.

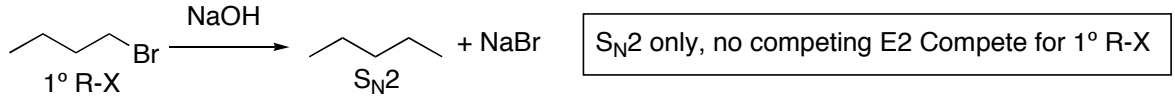
6-19 E2 Reaction (2nd Order, Under Anionic/Basic S_N2 type Conditions)

Examples





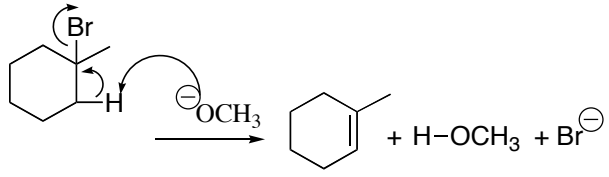




Notes

- E2 happens with **anionic nucleophiles/bases**, when S_N2 is hindered
- Reactivity: 3º R-X > 2º R-X.
  - 1º R-X and vinyl or aryl halides do not undergo E2.
- 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



- anionic. Anion base gets things started.
- 2nd order rate law. Rate = $k[R\text{-}X]^1[\text{anion base}]^1$
- 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_N2 instead. For 2º alkyl halides, E2 is often accompanied by variable amounts of S_N2.)

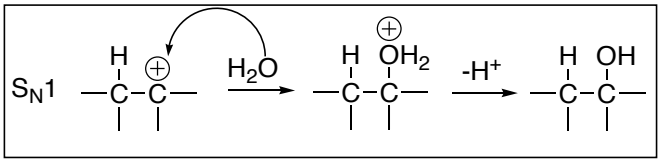
Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7)

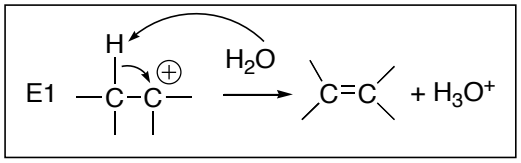
Predicting product: Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans, however.

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

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

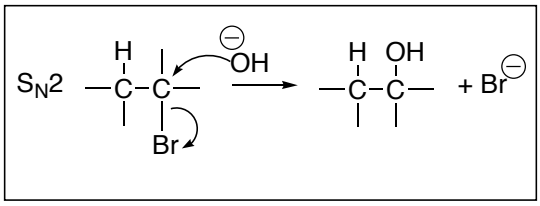
S_N1 vs E1

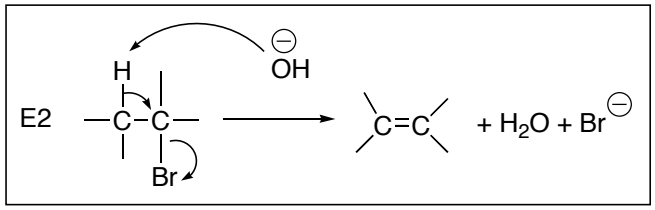




- Both satisfy the carbocation. They just meet it's bonding need with different electrons.

S_N2 vs E2

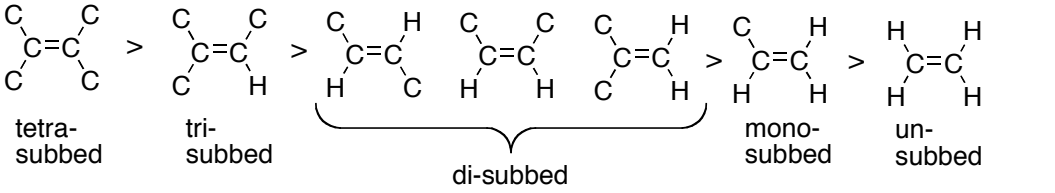


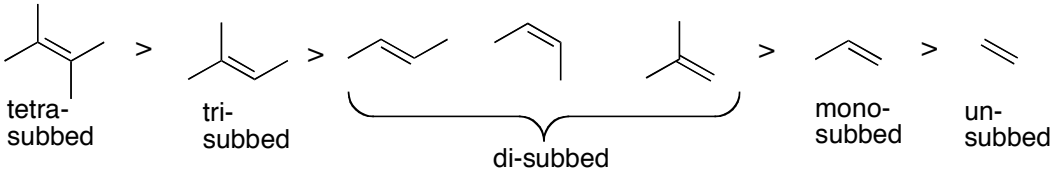


- Both provide an electron pair to displace the C-Br bond pair. They just use different electrons.
- Both involve the anion. It's called the nucleophile in the S_N2, the base in the E2.
- The S_N2 involves a crowded transition state, and thus is strongly impacted by steric factors. The E2 does not have any steric problems (and in fact alleviates them).
- The difference in steric profile explains why for S_N2, 1º > 2º > 3º, but that for E2, the reactivity of 3º is just fine.

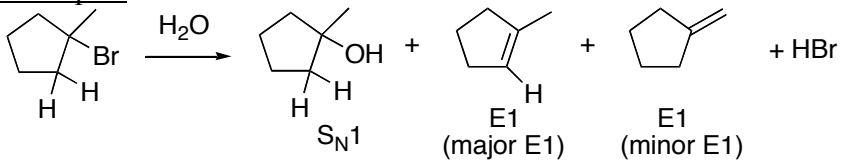
6-18 Zaitsev's Rule: When E1 or E2 elimination can give more than 1 structurally isomeric alkene, **the more highly Carbon-substituted alkene form will predominate over a less highly carbon-substituted alkene**.

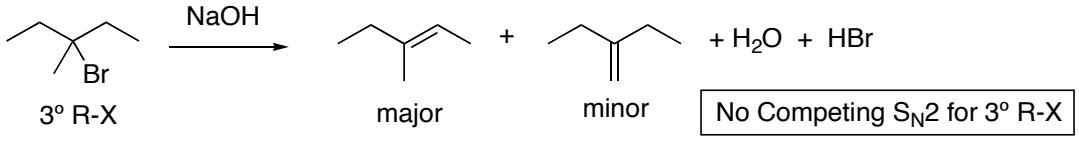
- **The fewer H's on the product alkene the better.**
  - Every Alkene has four attachments. The fewer of these that are H's, the better.
  - When pictures are drawn in which the H's are not shown, the more highly substituted alkenes turn out to be the best.
- Why? Product Stability-Reactivity Rule. Alkenes with more C's and fewer H's attached are more stable.
- Alkene Stability is shown below: tetra- > tri- > di- > mono- > unsubstituted
  - 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 3º > 2º > 1º stability pattern for cations and radicals

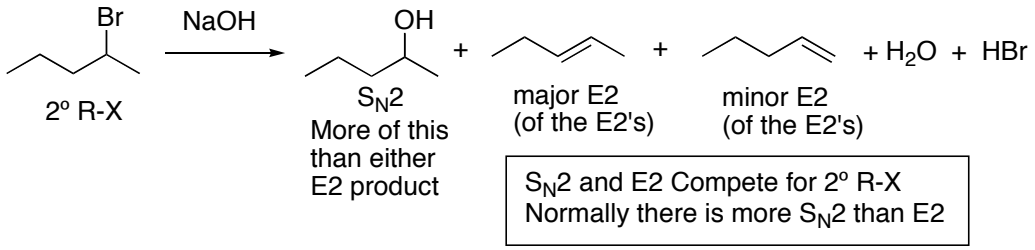




Examples

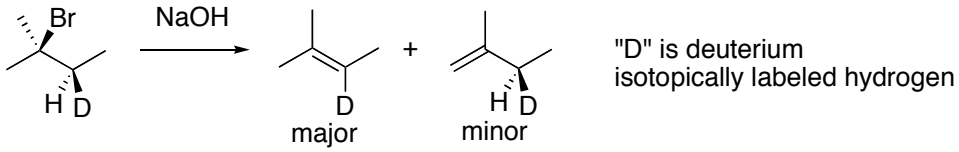




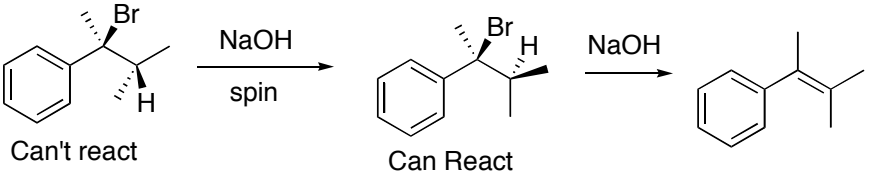


6-20 Stereochemistry of E2 Eliminations

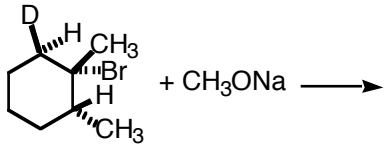
- For E2 (not for E1) C-H and C-X bonds must be in the same plane (**coplanar**)
- The halogen and the hydrogen being removed must be **trans** to each
- Why?
  - Due to orbital overlap requirements.
  - In the concerted E2 mechanism, the electrons from the hydrogen must essentially come in backside to the leaving halide
    - just as in backside-attack S_N2 mechanism

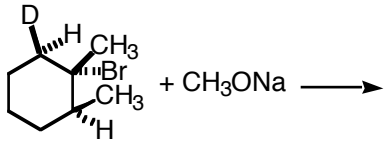


- Sometimes, a molecule will need to single-bond spin into an eclipsed conformation to enable it to do a trans-elimination.



- Eliminations in **Cyclic Compounds** are Often impacted by the Trans Requirement

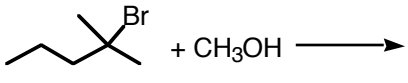


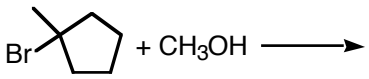


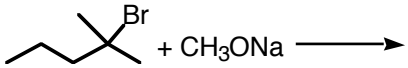
6.21 Comparing E2 vs E1

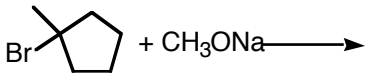
		E1	**E2**
1	**Nucleophile/Base**	**Neutral, weak, acidic**	**Anionic, strong, basic**
2	Substrate	3º R-X > 2º R-X	3º RX > 2º RX > 1º RX
	Allylic effect…	Allylic Helps	Non-factor
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	K[RX]	k[RX][Anion]
6	Stereochemistry	Non-selective	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)

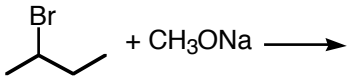
Elimination Problems: Draw the major Elimination Product for the following Reactions. Classify as E1 or E2. (There may be accompanying S_N2 or S_N1 material, but to whatever degree elimination occurs, draw the major product.)

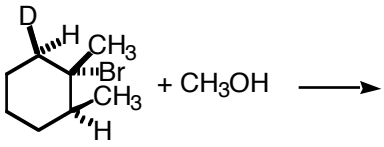
1. 

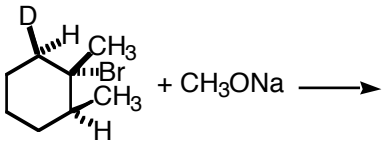
2. 

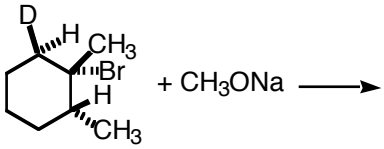
3. 

4. 

5. 

6. 

7. 

8. 

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

Step 1: **Check nucleophile/base**.

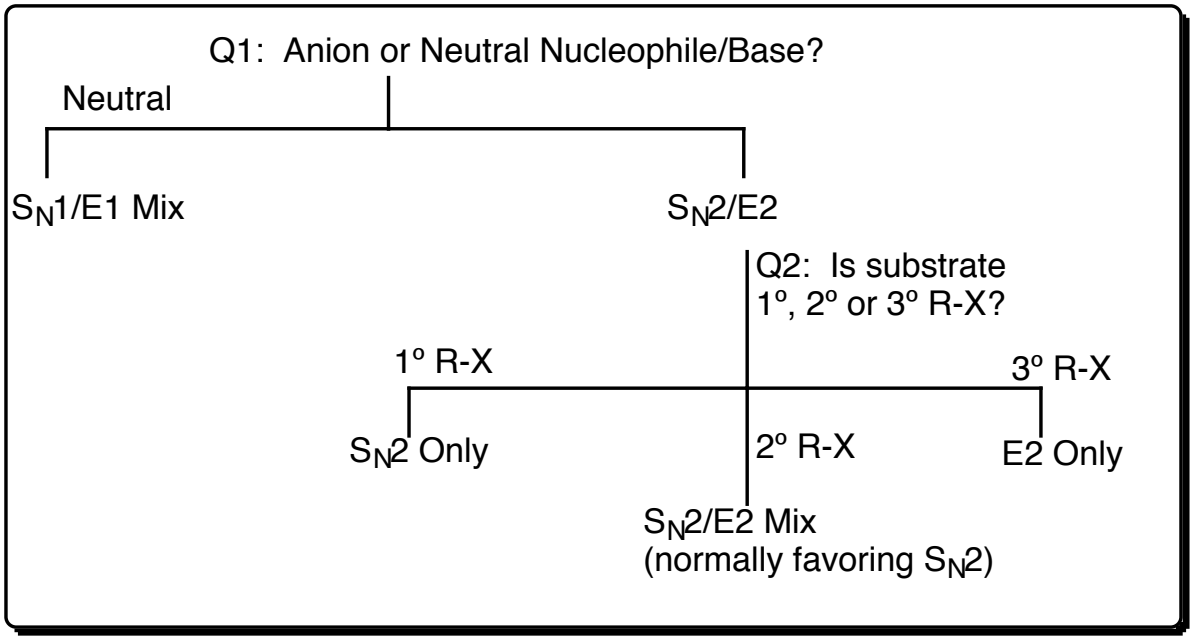
- If **neutral**, then **S_N1/E1** → mixture of both
- If **anionic**, then **S_N2/E2.**

Step 2: If **anionic**, and in the **S_N2/E2** pool, then **Check the substrate**.

- 1º → **S_N2**
- 2º → **S_N2/E2 mixture.** Often more **S_N2**, but not reliable…
- 3º → **E2**

Notes:

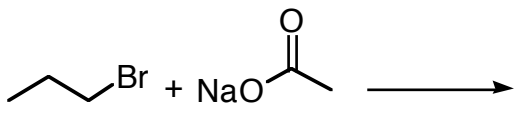
1º R-X	S_N2 only	No E2 or S_N1/E1 (cation too lousy for S_N1/E1; S_N2 too fast for E2 to compete)
3º R-X	E2 (anionic) or S_N1/E1 (neutral/acidic)	No S_N2 (sterics too lousy)
2º R-X	mixtures common	

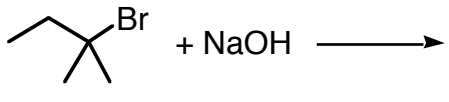


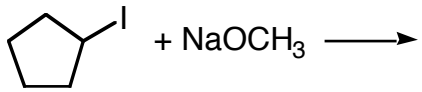
- Note: Aryl and Vinyl Halides will not undergo **any** of these types of reactions.
- If you see Br_2/hv type recipe, then you're back in the chapter 4 world of radical halogenation

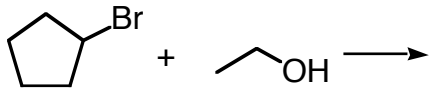
For each mixture,

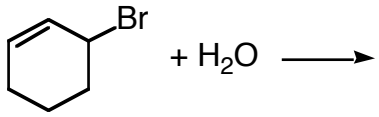
- Classify the Type of Reaction (or "no reaction")
- Draw the <u>major</u> product. (Or both a substitution and elim product..)

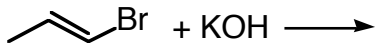
1. 

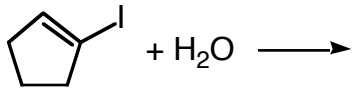
2. 

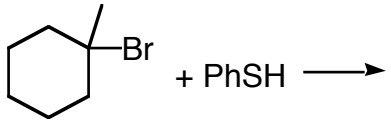
3. 

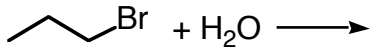
4. 

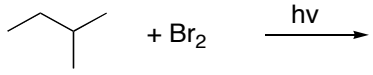
5. 

6. 

7. 

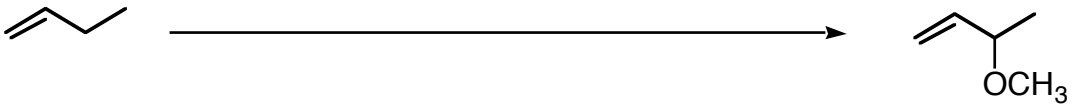
8. 

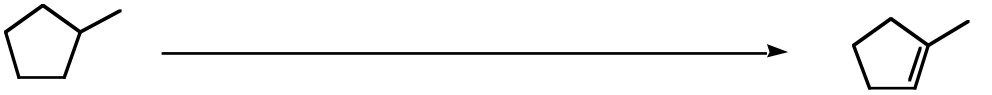
9. 

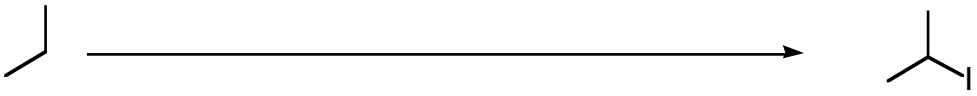
10. 

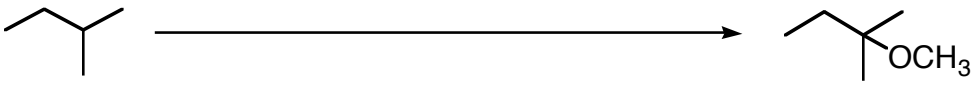
Design Synthetic Plans for converting the starting materials into the target molecules.

- In each case, **more than one chemical operation will be required**.
- Strategy: R-H → R-Br (via bromination) → Substitution product (via S_N2) or alkene (via E2)

1. 

2. 
(no substitution side product)

3. 

4. 

(some alkene would accompany this product)

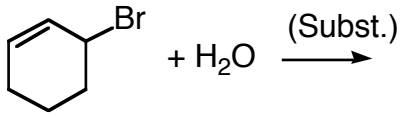
Keys:

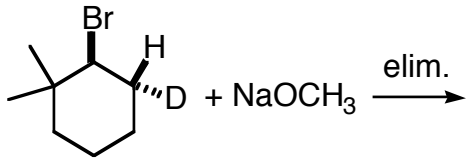
- These can't be done directly, in a single operation
- Each sequence ends up increasing the number of functional groups in the ultimate product.

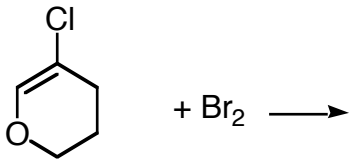
- **The key reaction for increasing the functionality**: R-H →

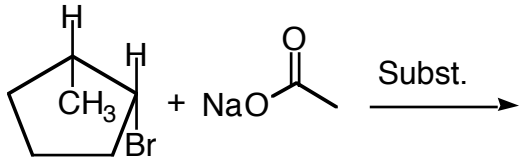
- Once you're converted the starting material to an you can interconvert that functional group into something else by substitution, or into an alkene by elimination

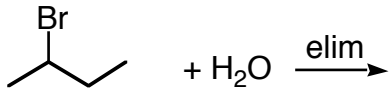
Draw the **mechanism** for formation of the major product in each of the following reactions. In some cases where both elimination and substitution might compete, the problem specifies whether to draw the substitution or elimination mechanism.

1. 

2. 

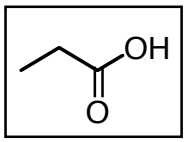
3. 

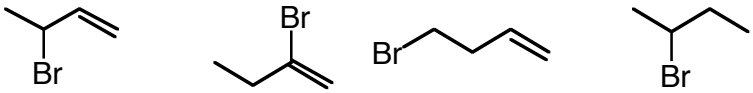
4. 

5. 

Rank the Reactivity of the chemicals shown toward the thing in the box. Keys:

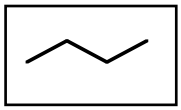
- Identify the type of reaction that would be involved
- Think about the rate-determining step and how reactant or product or transition-state stability would influence the rate.

1. 

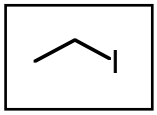


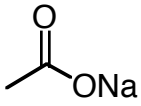
2. Br_2, hv

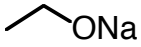
$H_3C–CH_3$  

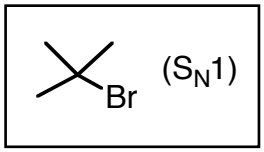
3. 

Cl• Br• I•

4. 

CH_3OH 

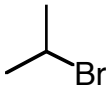


5. 

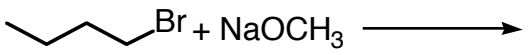
Solvent: Pentane 

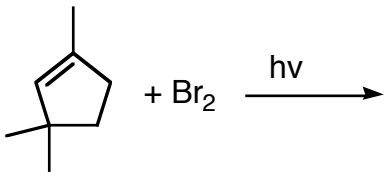
H_2O

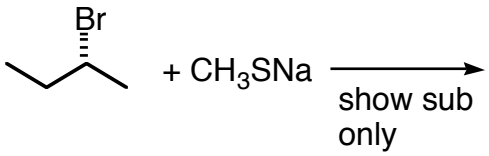
6. NaOH

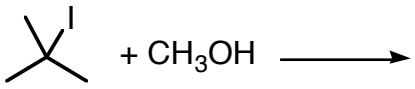


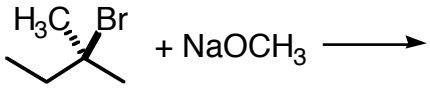
Give the Major Product(s) for each of the following. If it's likely to give a mixture of both substitution and elimination, just draw the substitution product. Designate stereochemical outcomes when stereochemistry is relevant (2º substrates).
Key: Try to recognize what type of reaction will happen first.

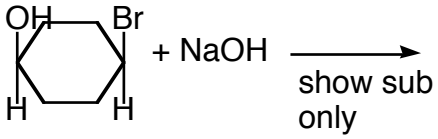


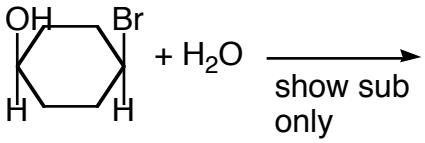


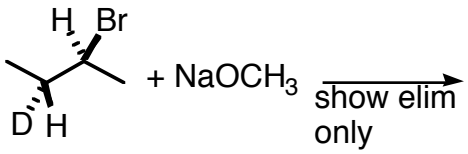






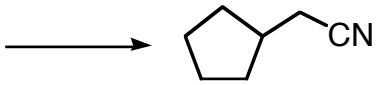






Provide Reactants for the Following (One of the Starting Chemicals must be an R-Br)

1



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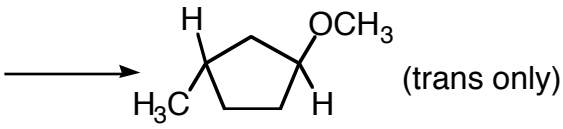
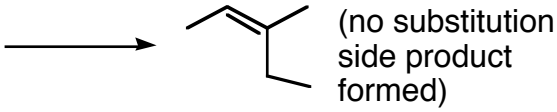


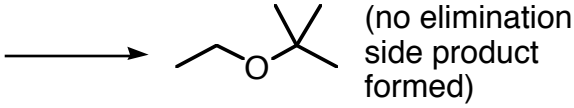
(trans only)

3



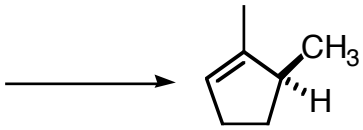
(no substitution side product formed)

4



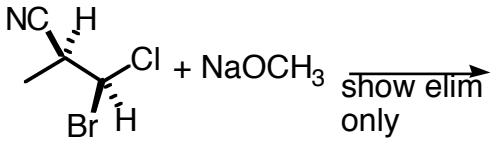
(no elimination side product formed)

5



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

6.



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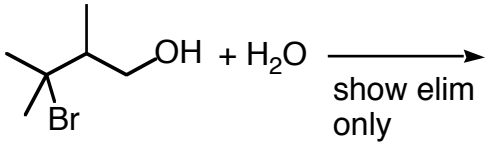
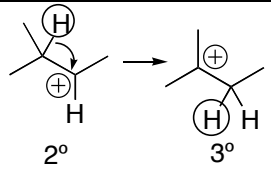
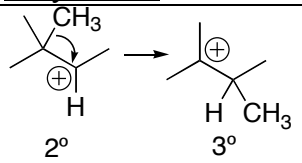
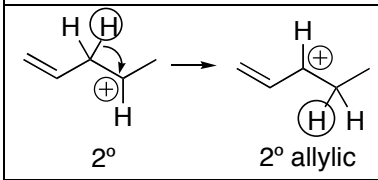
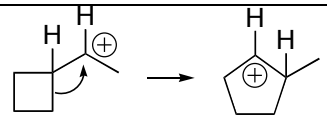
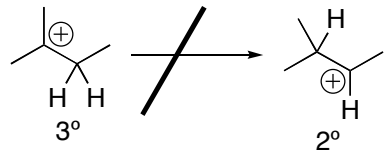
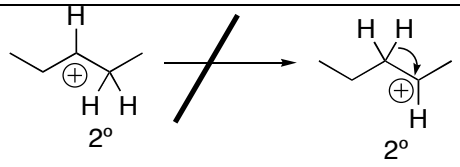


6-15 Cation Rearrangements (and their impact in S_N1 and E1 reactions)

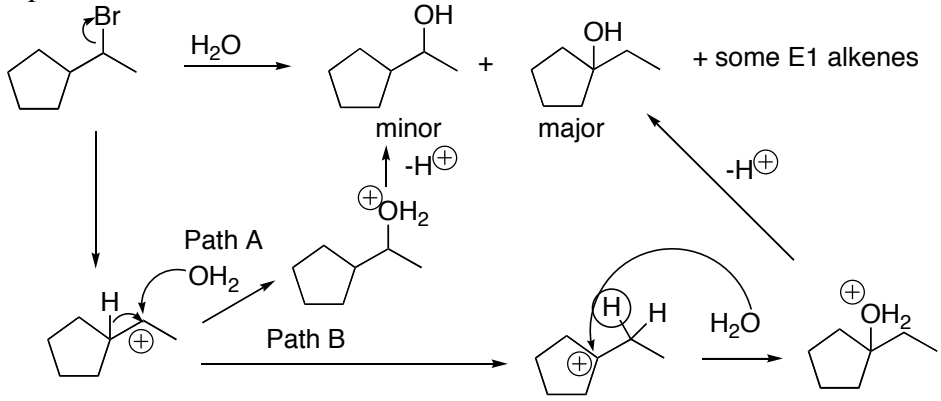
1. Carbocations are very unstable, and sometimes rearrange to other carbocations that are more stable.
2. A rearrangement requires that a superior cation will result. Four cases:
   - 2º → 3º
   - non-allylic → allylic
   - strained ring → unstrained or less strained ring
   - 1º cation → 2º or 3º cation (rare, since 1º cations are hard to make and pretty rare)

Hydride Shifts		Alkyl Shifts
		
		

3. Two processes for cation rearrangement:
   - Hydride shift (an H jumps over)
   - Alkyl shift (a carbon jumps over)
4. The resulting rearranged cation must always be on a carbon directly adjacent to the original
5. Cation rearrangement does not occur if you start with a pretty good cation in the first place.
   - Thus, most cation mechanisms that start with 2º or 3º cations don't undergo rearrangement because rearrangement does not lead to improved cation stability

Why Bother? No Stability Gain, No Motive, **Won't Happen**			
			

Examples in SN1



- Product mixture results from competition between Path A and Path B.