CH-211 Organic Chemistry I

Chapter 6: Chemical Reactivity and Mechanisms

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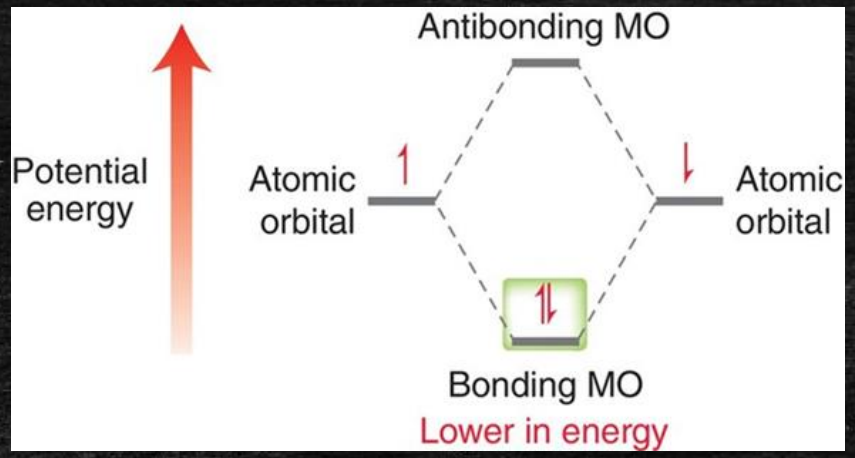
Textbook: Organic Chemistry, D.R. Klein. 4th ed. 2021 John Wiley & Sons, Inc.

Enthalpy

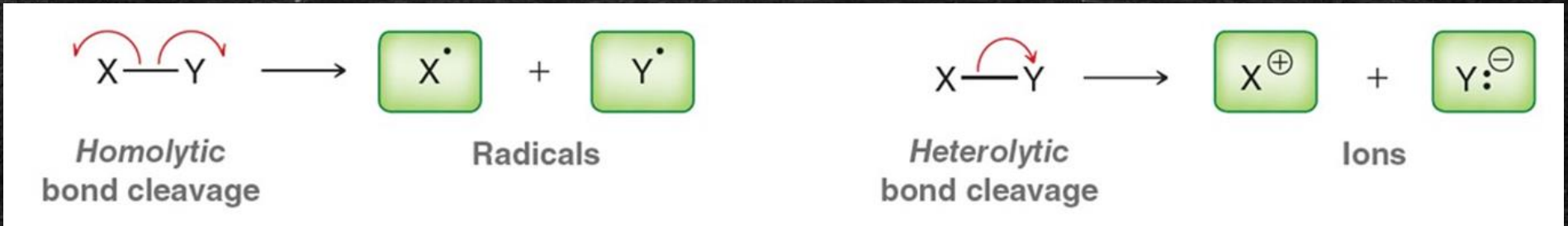
- **Enthalpy** (ΔH or q) is the heat energy exchange between the reaction and its surroundings
- Breaking a bond requires the system to absorb energy



- **The electrons must absorb kinetic energy to overcome the stability of the bond**

Enthalpy (ΔH) / Bond Cleavage

- Bonds can break homolytically or heterolytically



- **Bond dissociation energy** (**BDE**) or Δ*H* for bond breaking corresponds to **homolytic bond cleavage**

Bond Dissociation Energy / Exothermic and Endothermic

- Most reactions involve multiple bonds breaking and forming.
- **Exothermic reaction** – The energy gained by bonds formed exceeds the energy needed for bonds broken

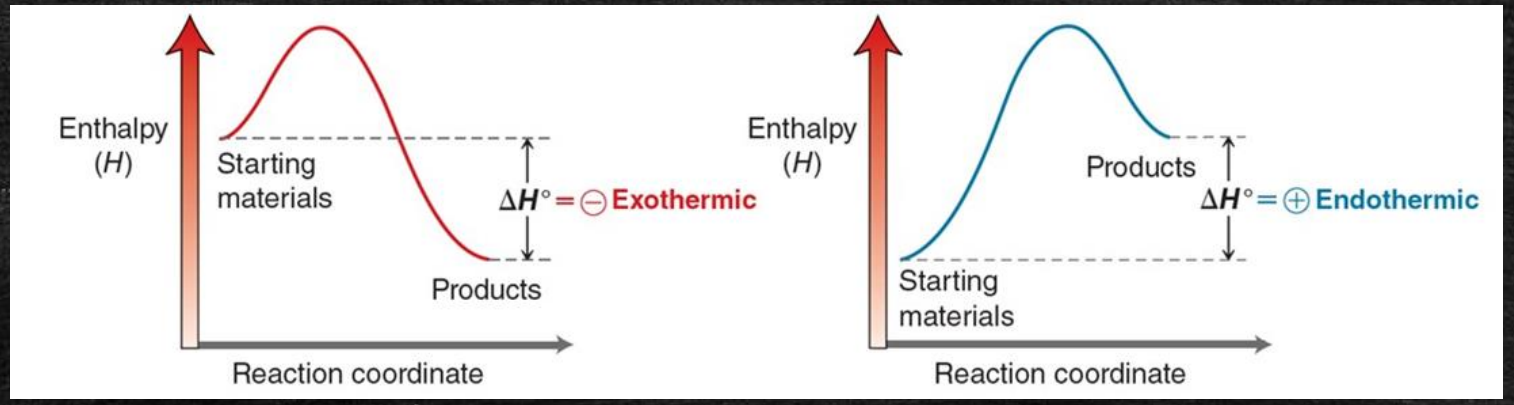
Products more stable than reactants

- **Endothermic reaction** – Energy needed for bonds broken exceeds the stability gained by the bonds formed

Products less stable than reactants

Enthalpy (ΔH) / Energy Diagrams

- Energy diagrams for **exothermic** vs. **endothermic** reactions



- Products lower in energy
- Energy is released as heat (PE converted to KE)
- ΔH ° is negative
- Temp of surroundings increases

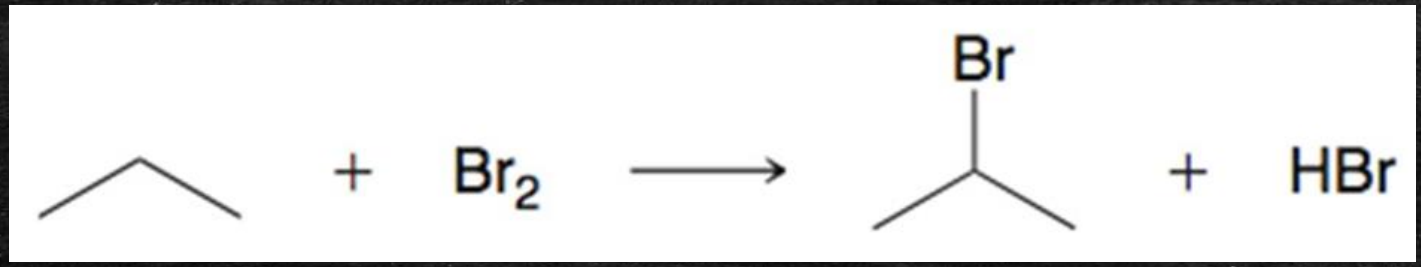
- Products higher in energy
- Energy is consumed (KE converted to PE)
- ΔH ° is positive
- Temp of surroundings decreases

Enthalpy (ΔH) / Sign of ΔH

- The sign (+/–) of ΔH indicates if the reaction is **exothermic** or **endothermic.**
- An **energy diagram** is often used to describe the kinetics and thermodynamics of a chemical reaction
  - Potential energy (PE) is described by the y-axis
  - Reaction progress described by the x-axis (reaction coordinate)
- Practice with SkillBuilder 6.1 – Predicting $\Delta H°$ of a reaction

Enthalpy (ΔH) / Practice

- **Practice the Skill 6.1** – Use BDE's to determine if the following reaction is exothermic ($+\Delta H$) or endothermic ($-\Delta H$)



- ΔH = BDE (bonds broken) – BDE(bonds formed)

  Bonds broken = C—H (397 kJ/mol) and Br—Br (193 kJ/mol)

  Bonds formed = C—Br (285 kJ/mol) and H—Br (368 kJ/mol)

  - ΔH = (397 + 193) – (285 + 368) = **– 63 kJ/mol**

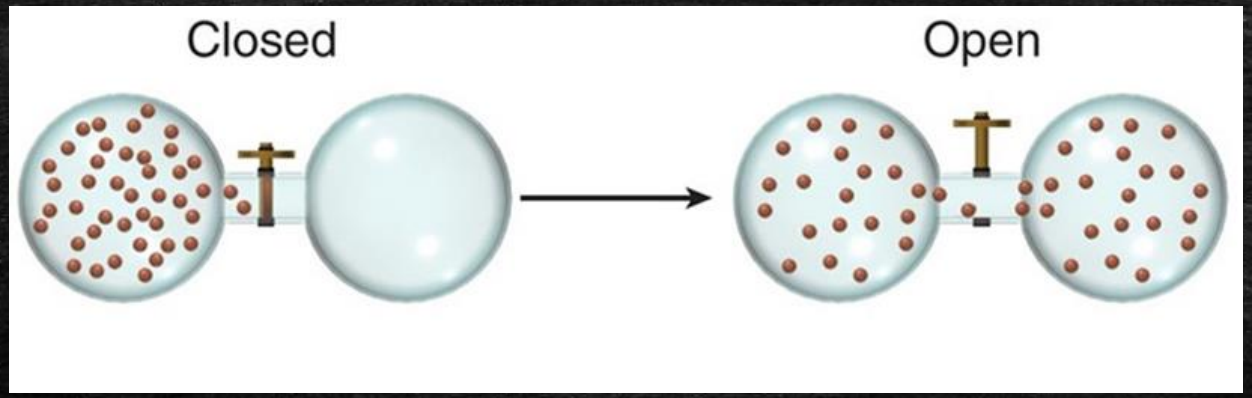
ΔH is negative, so the reaction is exothermic

Entropy (ΔS) / Introduction

- Exothermic and endothermic reactions can occur spontaneously (most reactions are exothermic though).
- Enthalpy (ΔH) and **entropy (ΔS)** must both be considered when predicting whether a reaction will occur.
- Recall that **entropy** can be described as molecular disorder, randomness, or freedom.
- **Entropy** is the number of vibrational, rotational, and translational states the energy of a compound is distributed.

Entropy (ΔS) / Visualization

- Consider why a gas will expand and spread out into an empty container.



- The number of states the molecules spread across increases with increasing volume.
- **More volume** for gas to occupy = **greater entropy**

Entropy (ΔS) / Total Entropy Change

- The total entropy change (ΔS_{tot}) will determine whether a process is spontaneous.

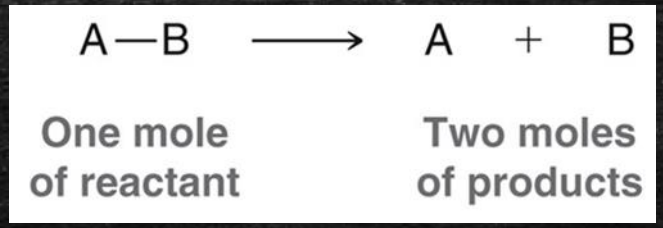
$$\Delta S_{tot} = \Delta S_{sys} + \Delta s_{surr}$$

- For chemical reactions, we must consider the entropy change for both the system (the reaction) and the surroundings (the solvent usually).
- If $\boldsymbol{\Delta S_{tot}}$ is **positive**, the process is **spontaneous.**

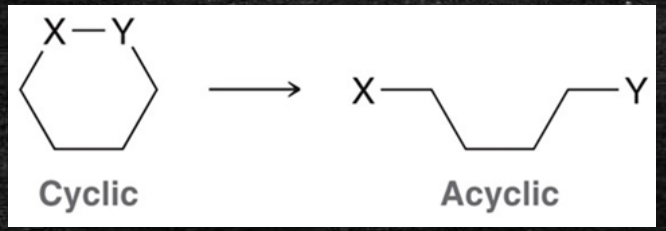
Entropy (ΔS) / Entropy Change of the System

- ΔS_{sys} is affected most significantly by two factors, and will be positive…

1. When there are more moles of product than reactant



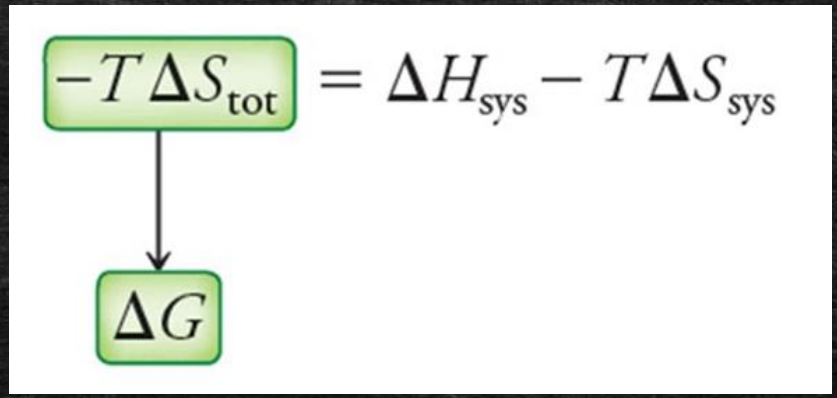
2. When a cyclic compound becomes acyclic



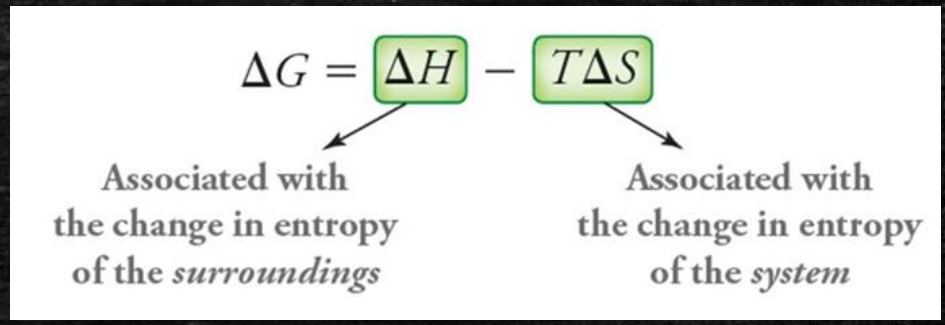
Practice with CONCEPTUAL CHECKPOINT 6.3.

Gibbs Free Energy (ΔG) / Definition

- Multiply both sides by temperature (*T*)



- **Δ*G*** is the **Gibbs Free Energy.** A **negative** value of Δ***G*** means the reaction is **spontaneous,** and a **positive** value is a **nonspontaneous** reaction.



Gibbs Free Energy (ΔG) / Example

- Consider the following reaction, which is ***spontaneous:***

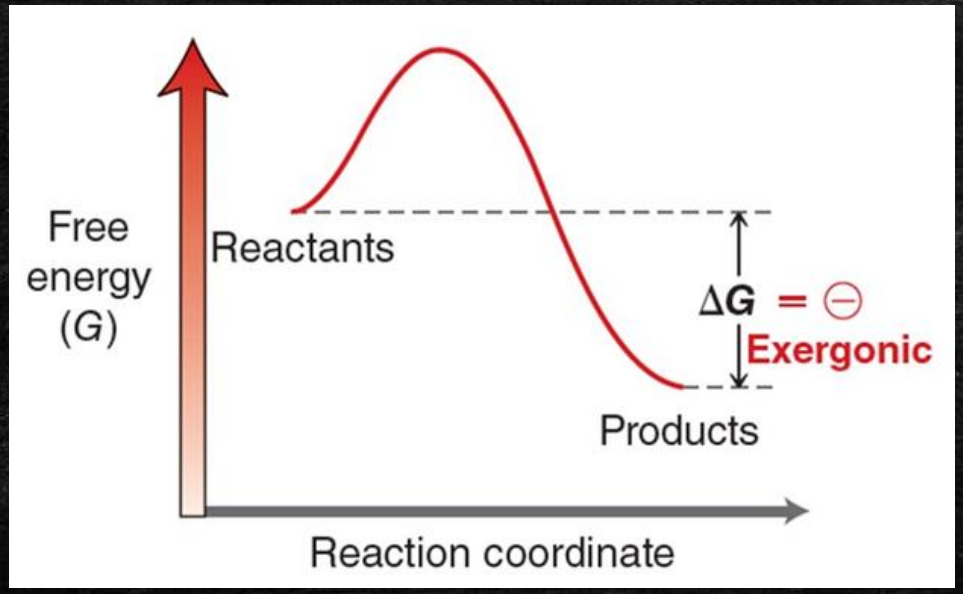
- Since the reaction is **spontaneous,** ΔG must be **negative**

$$\Delta G = \Delta H + (-T\Delta S)$$

  - We also know that $T\Delta S$ will be negative value because entropy is decreasing (2 molecules become 1).
  - So, it must be true that ΔH is a negative value, for ΔG to be negative overall.
  - In other words, the entropy of the surroundings is increasing more than the entropy of the system is increasing.

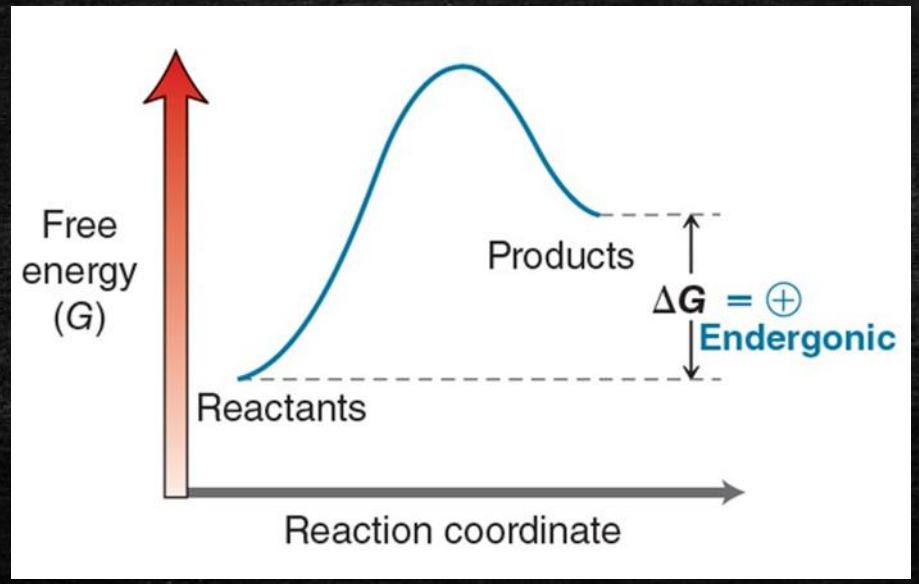
Gibbs Free Energy (ΔG) / Exergonic

- If a process has a negative Δ*G*, the process is spontaneous, and the process is **exergonic**
- Notice that in this energy diagram, the free energy (*G*) is plotted rather than enthalpy (*H*)



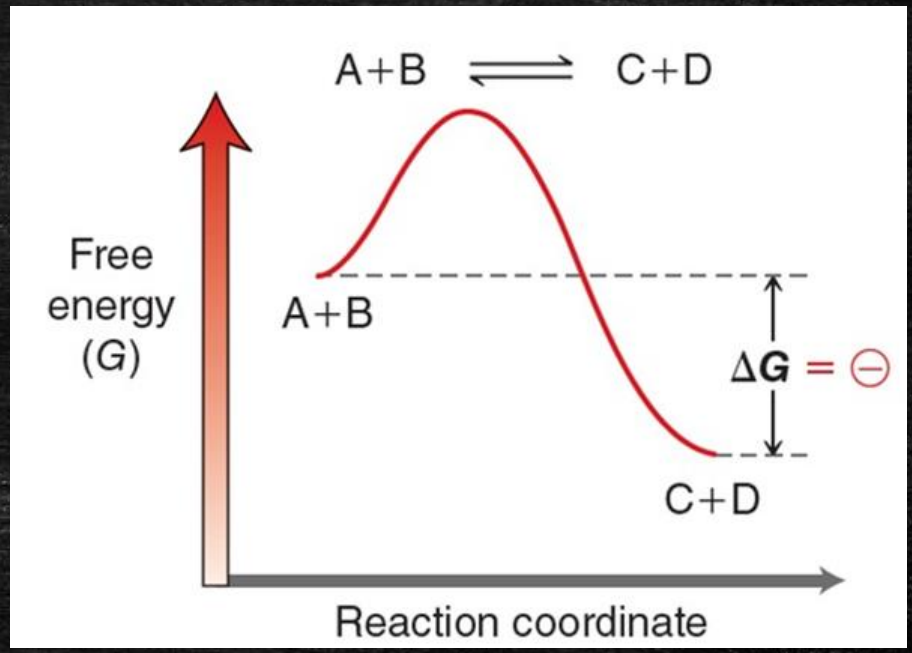
Gibbs Free Energy (ΔG) / Endergonic

- If a process has a positive ΔG, the process is nonspontaneous, and the process is endergonic.
- An endergonic reaction favors the reactants.
- Practice with CONCEPTUAL CHECKPOINT 6.4.



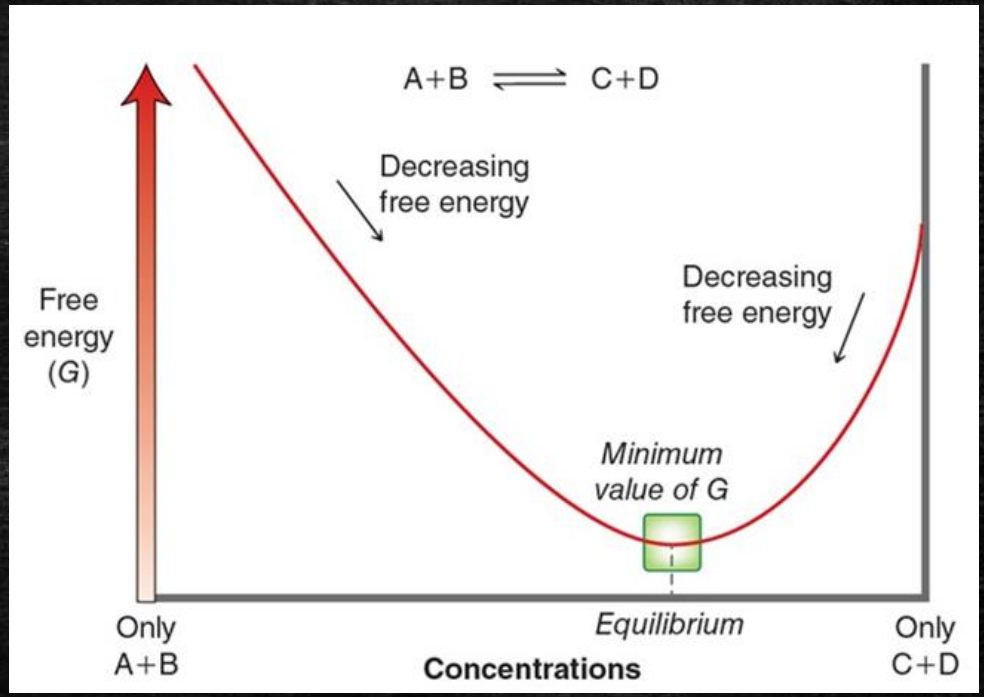
Equilibria / Relation to ΔG

- Consider an exergonic process with a (–) ΔG, which means the products are favored to form (spontaneous).
- An equilibrium will eventually be reached.
- A spontaneous process means there will be more products than reactants.
- The greater the magnitude of a (–) ΔG, the greater the equilibrium concentration of products.



Equilibria / Graphical Representation

- Why doesn't an exergonic process react 100% to give products? Why will some reactants still remain at equilibrium?
- As [A] and [B] decrease collisions between A and B will occur less often
- As [C] and [D] increase, collisions between C and D will occur more often
- Eventually the forward and reverse reaction rates will be equal



Kinetics / No Relation to ΔG

- Recall that a (–) sign for ΔG tells us a process is product favored (spontaneous).
- That does not tell us anything about the rate or kinetics for the process.
- In other words, ΔG says nothing about how fast a reaction will occur.
- Some spontaneous processes are fast, such as explosions.
- Some spontaneous processes are slow such as C (diamond) → C (graphite)… this takes millions of years, even though a spontaneous reaction.

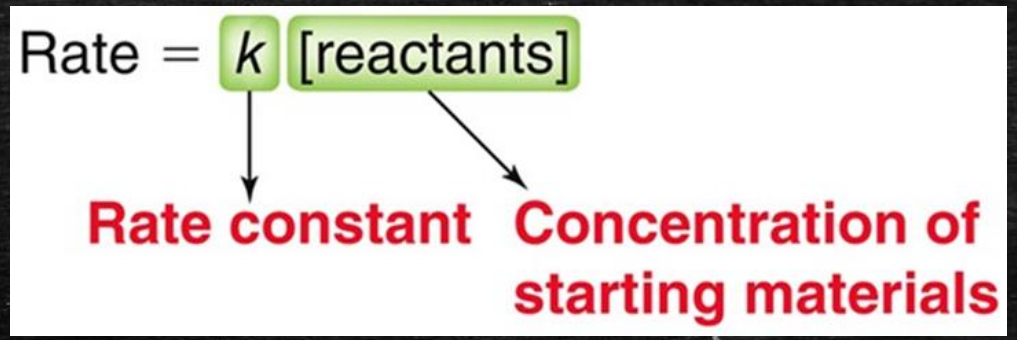
Kinetics / Five Factors

- The reaction rate is a function of the number of molecular collisions that will occur in a given period of time, which is affected by the following factors:

1. The concentrations of the reactants
2. The activation energy
3. The temperature
4. Geometry and sterics
5. The presence of a catalyst

Rate Equations / Rate Law and Reaction Order

- Rate is determined using a rate law:



  - The rate depends on a rate constant, and the concentration of the reactant(s)
  - The degree to which a change in [reactant] will affect the rate is known as the order.

Kinetics / First, Second, Third Order

- The order of a reaction is represented by x and y as follows

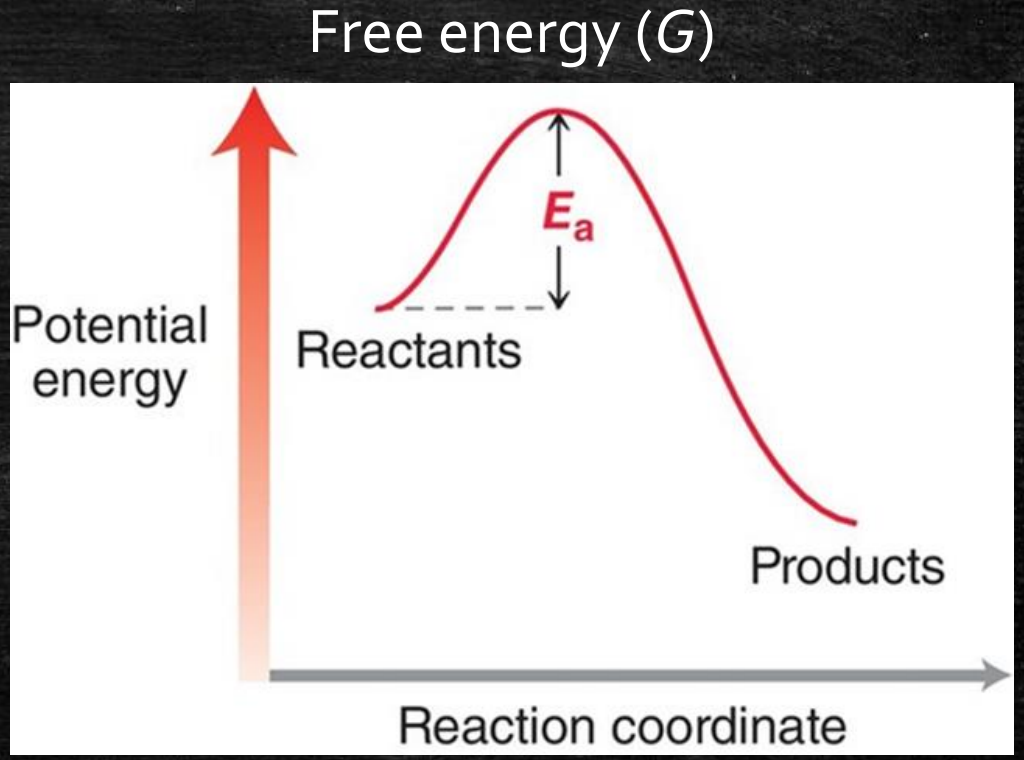
$$\text{Rate} = k[A]^x[B]^y$$

$\text{Rate} = k[A]$	$\text{Rate} = k[A][B]$	$\text{Rate} = k[A]^2[B]$
First order	**Second order**	**Third order**
If [A] is doubled rate is doubled	**If [A] is doubled rate is doubled**	**If [A] is doubled rate is quadrupled**

Factors Affecting the Rate Constant / Activation Energy, Concept

1. **Activation Energy** (E_a) – The energy barrier between reactants and products

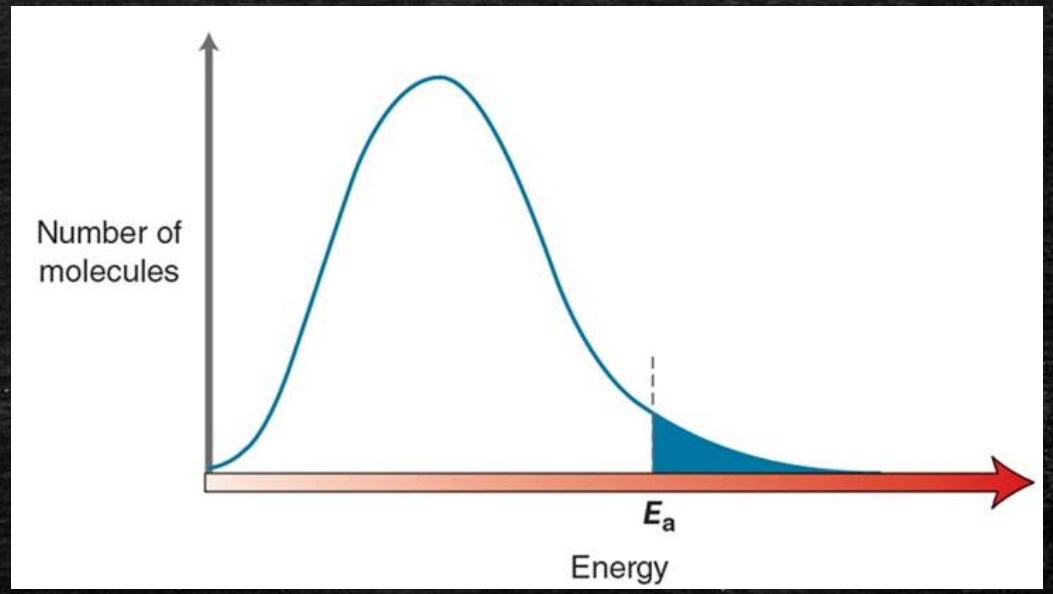
- E_a is the minimum amount of energy required for a molecular collision to result in a reaction



Factors Affecting the Rate Constant / Activation Energy, Elaboration

1. Activation Energy (E_a) – The energy barrier between reactants and products

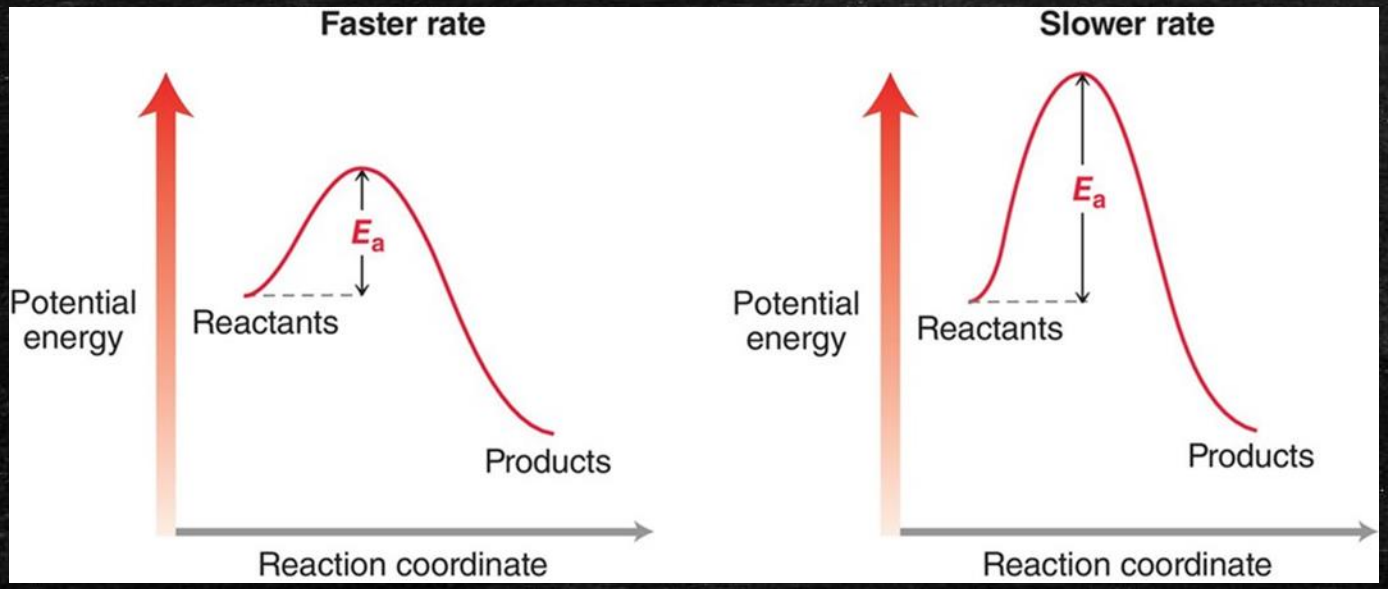
- As E_a increases, the number of molecules possessing enough energy to react decreases.



Factors Affecting the Rate Constant / Activation Energy, Relation to Rate

1. **Activation Energy** (E_a) – The energy barrier between reactants and products

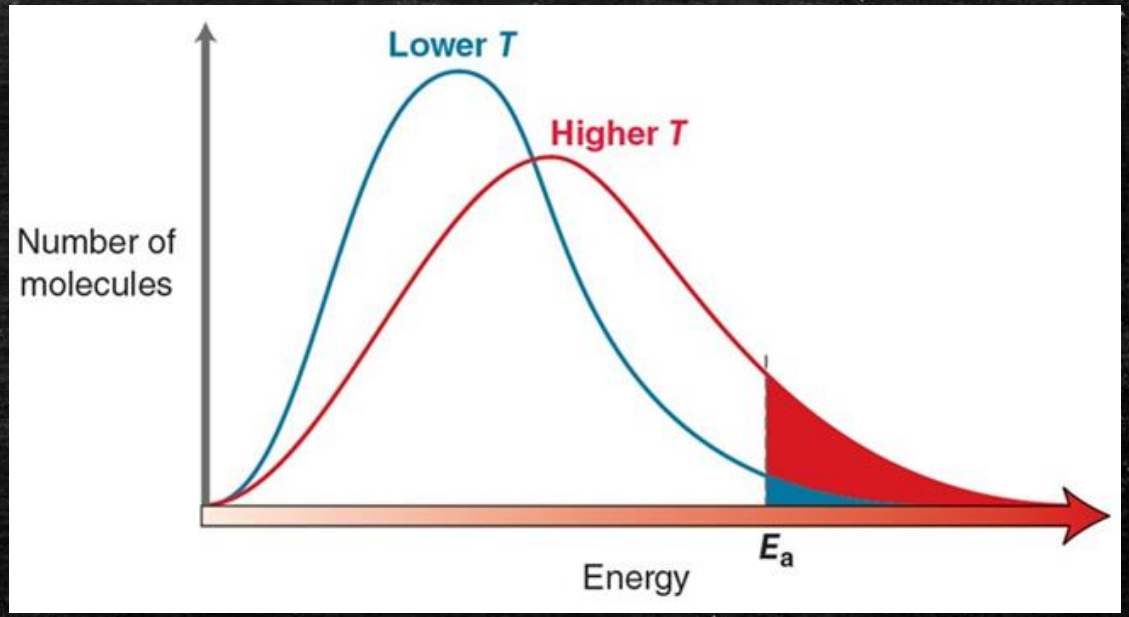
- ***The lower the activation energy, the faster the rate***



Factors Affecting the Rate Constant / Temperature

2. **Temperature** (T) – Raising temperature will result in a faster rxn.

- At higher *T*, molecules have more kinetic energy.
- **At higher *T*, more molecules will have enough energy to produce a reaction**



Factors Affecting the Rate Constant / Sterics

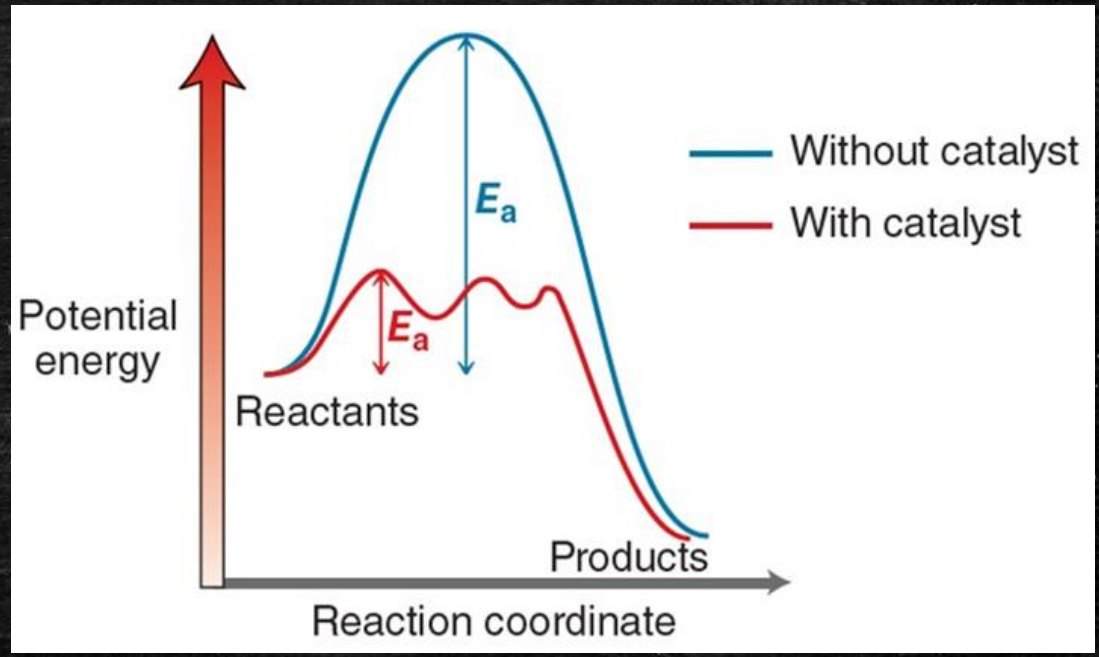
3. **Steric Considerations** – Steric hindrance, and the geometry of a compound, affects the rate of reaction

- When molecules collide, they must have the correct *orientation* for bonds to be made/broken.
- If the *reactive conformation* of a compound is high energy, it will spend less time in that conformation, and so the probability of collision resulting in a reaction is low.
- This will be further explored in Chapter 7.

Catalysts and Enzymes

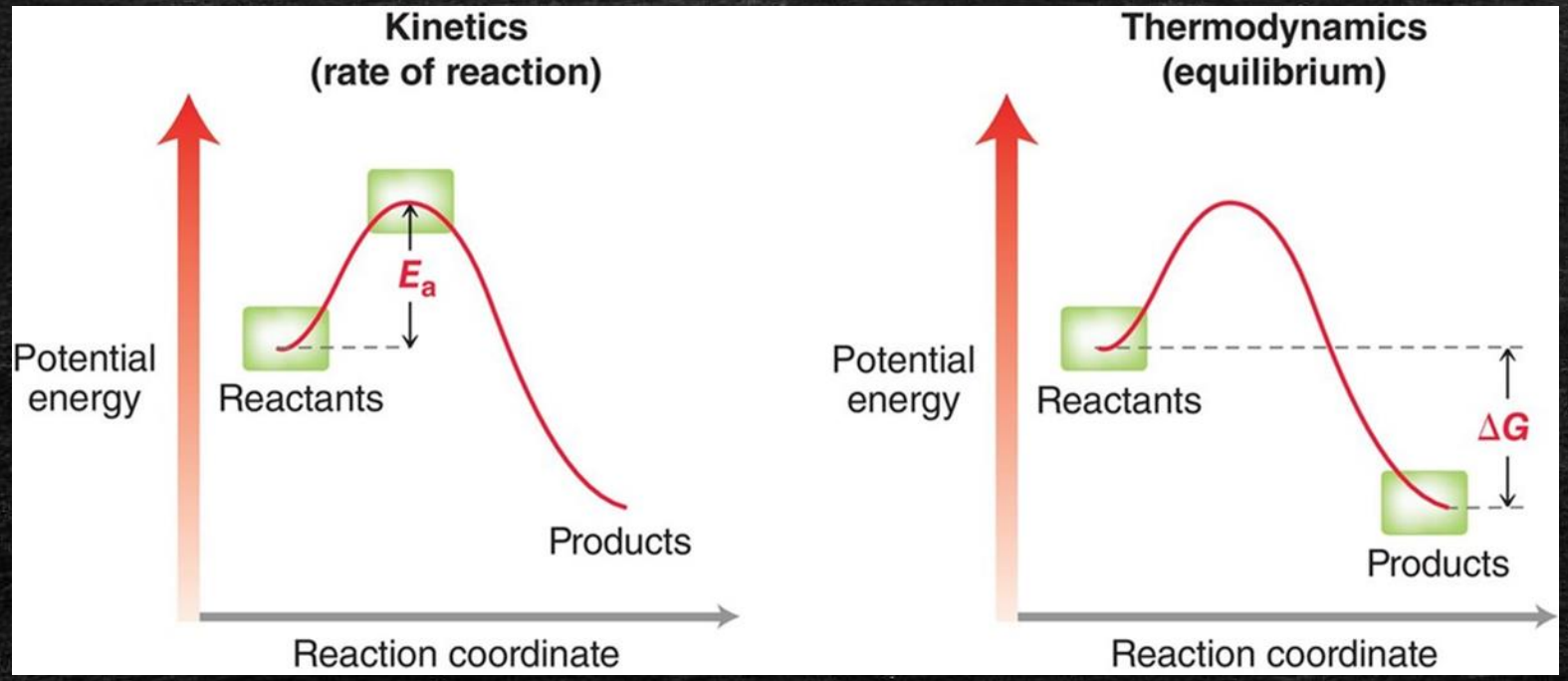
4. Catalyst – speeds up the rate of a reaction without being consumed

- Enzymes are catalysts
- Catalyst provides an alternate, and faster pathway of reaction
- **Catalysts lower the activation energy**

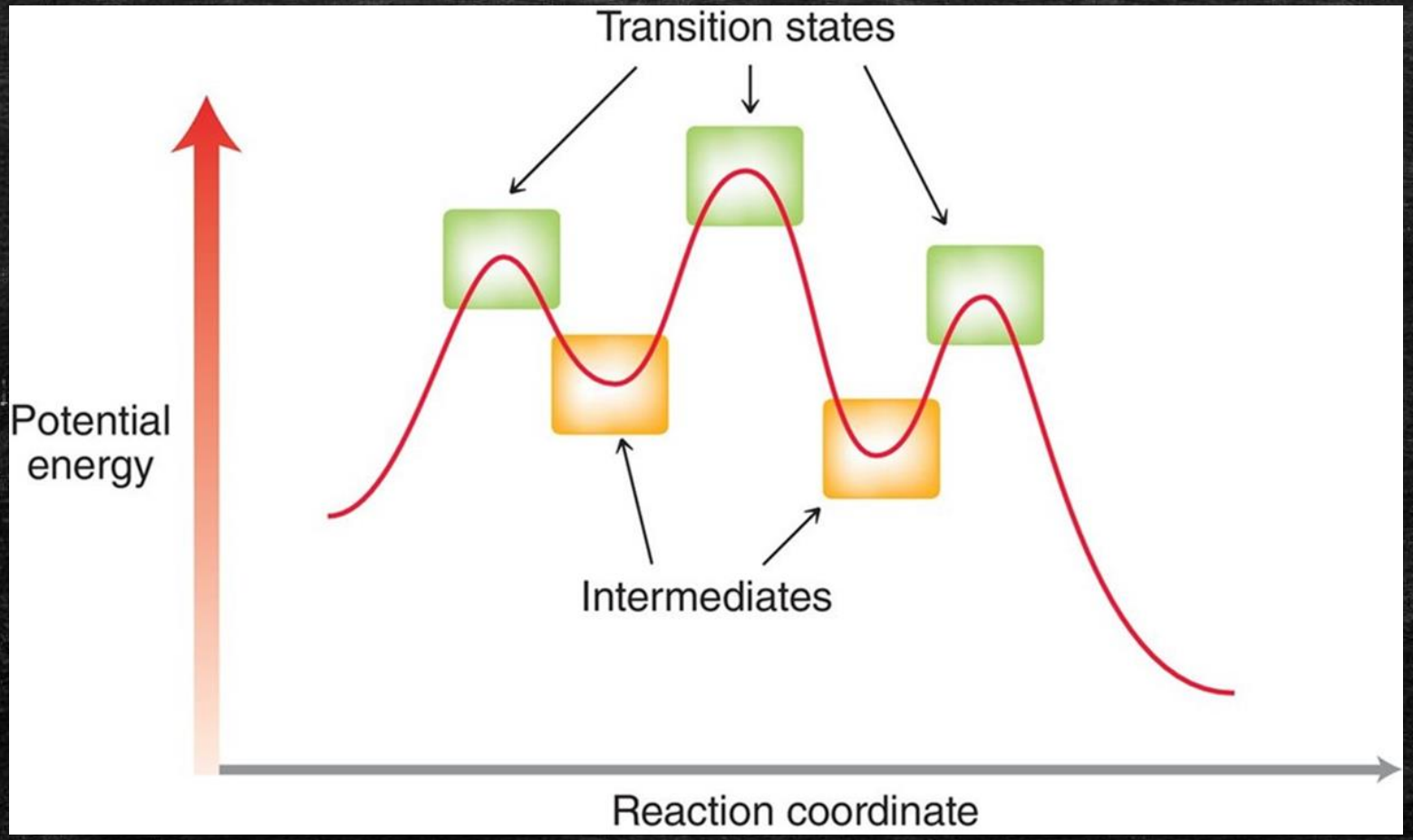


Reading Energy Diagrams

- Recall that **kinetics** and **thermodynamics** are completely different concepts

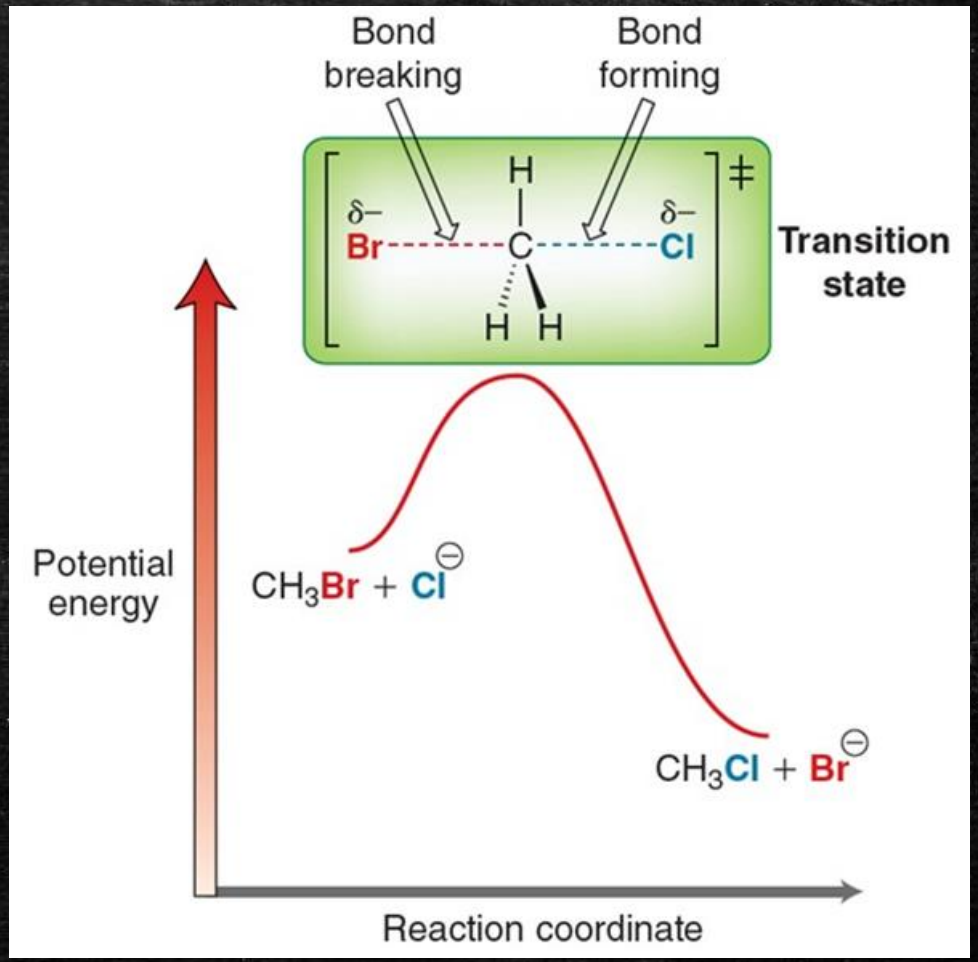


Transition States vs. Intermediates / Introduction



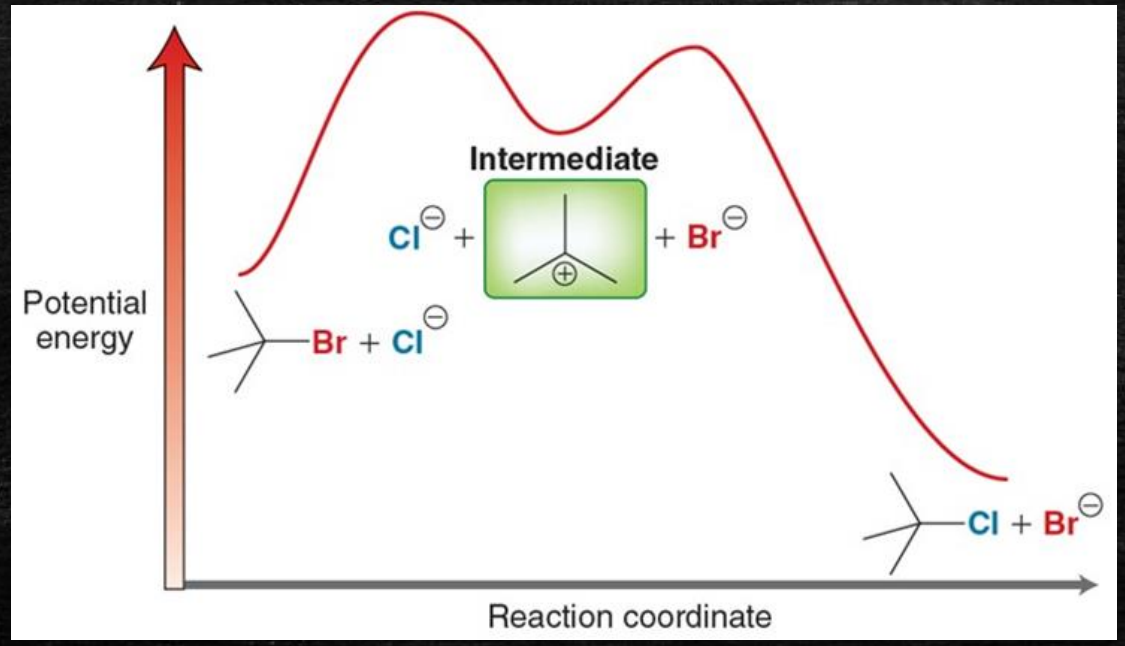
Transition States vs. Intermediates / What is Not Observable?

- A **transition state** is the high energy state a reaction passes through
- **Transition states** are fleeting; they <u>cannot</u> be observed
- On an energy diagram, **transition states are energy maxima,** and represent the transition as bonds are made and/or broken



Transition States vs. Intermediates / What is Observable?

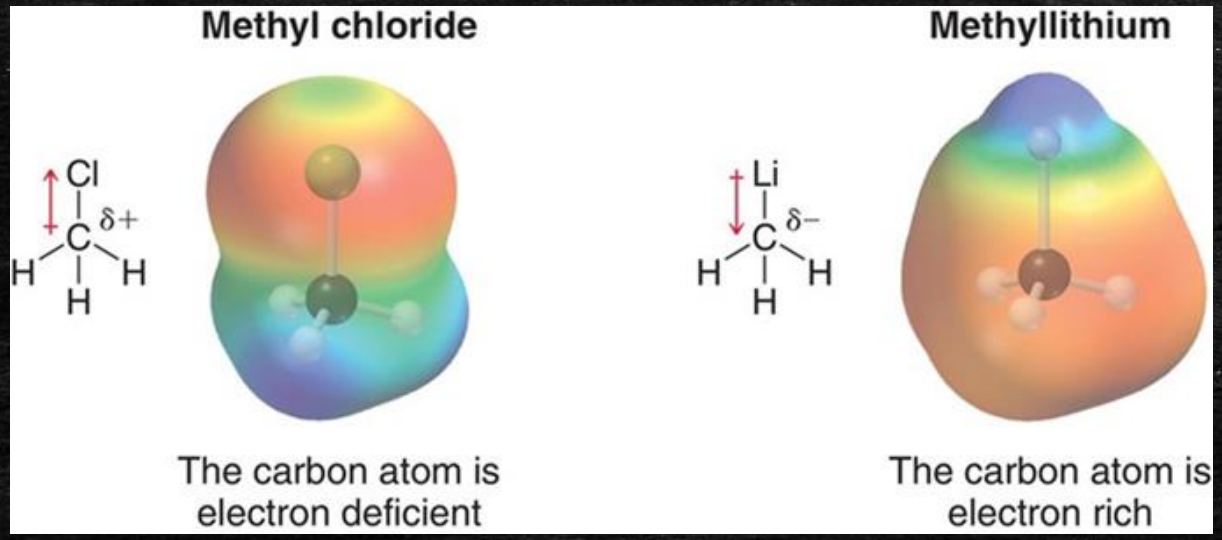
- An **intermediate** is an intermediate species formed during the course of a reaction. They are **energy minima** on the diagram.
- **Intermediates** are observable. They are an actual chemical species that exists for a period of time before reacting further.



Nucleophiles & Electrophiles / Overview

- **Polar reactions** – involve ions as reactants, intermediates, and/or products
  - **Negative charges** attracted to **positive charges**
  - **Electron-rich species** attracted to **electron-deficient species**

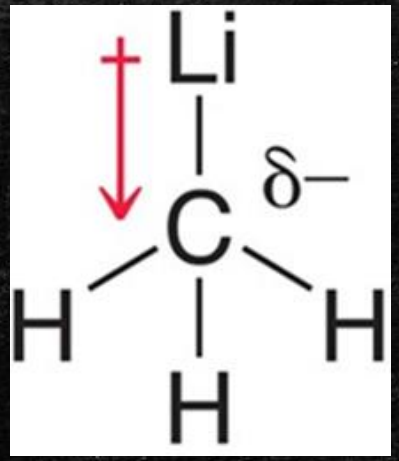
The carbon is electrophilic

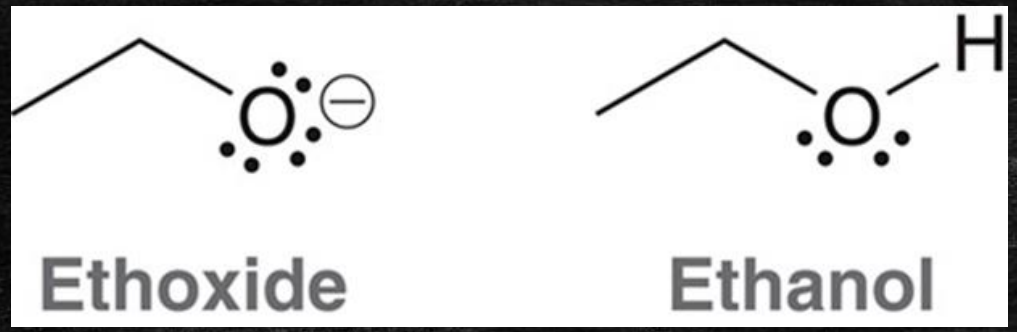


The carbon is nucleophilic

Nucleophiles

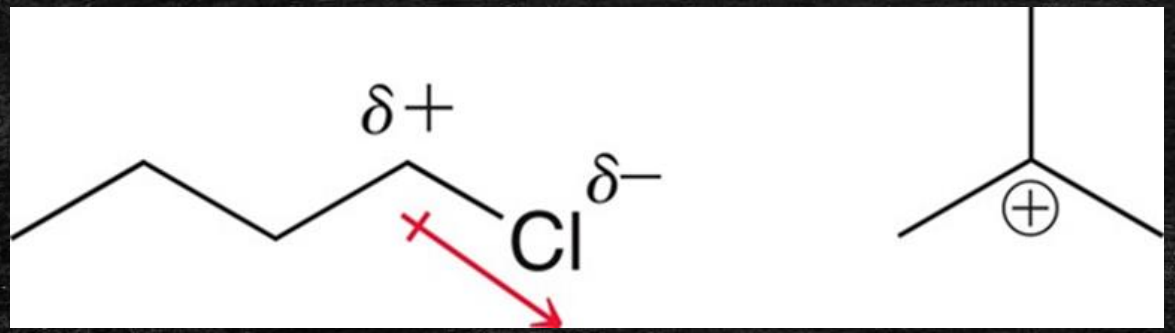
- **Nucleophile** – electron-rich species, can **donate a pair of electrons**
  - Nucleophiles are **Lewis bases**
  - More polarizable nucleophile = stronger nucleophile

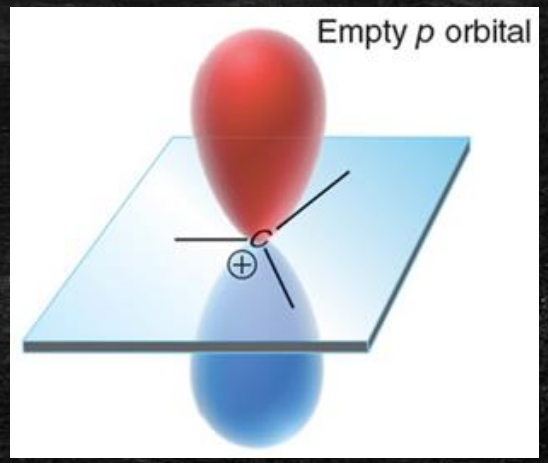




Electrophiles

- **Electrophile** – electron-deficient species, can **accept a pair of electrons**
  - Electrophiles are **Lewis acids**
  - **Carbocations** and **partially-positive** atoms are electrophilic

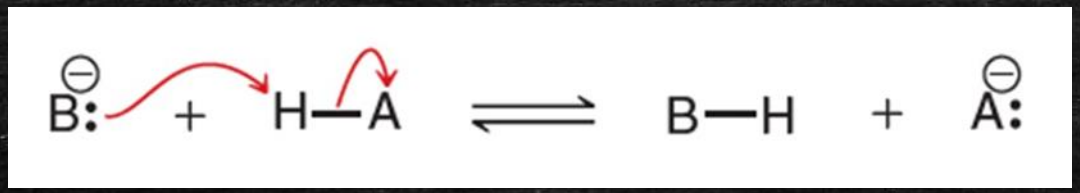




Practice with SkillBuilder 6.2 – Identifying Nucleophilic and Electrophilic Centers.

Mechanisms and Arrow Pushing

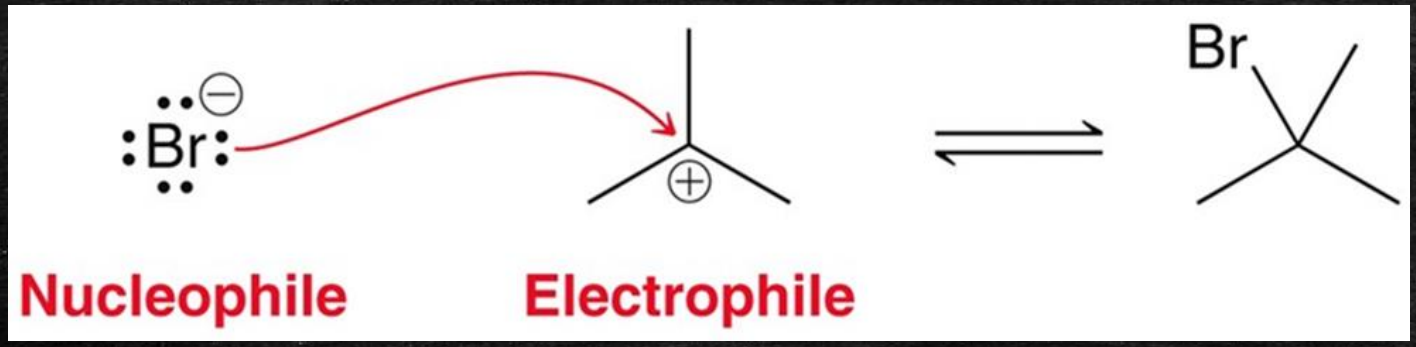
- **Curved arrows** are used to **show how electrons move** as bonds are breaking and/or forming
  - *Recall their use in acid-base reactions*



- There are four main ways that electrons move in **polar reactions**
  1. Nucleophilic Attack
  2. Loss of a Leaving Group
  3. Proton Transfers (Acid/Base)
  4. Rearrangements

Nucleophilic Attack / One-Arrow Example

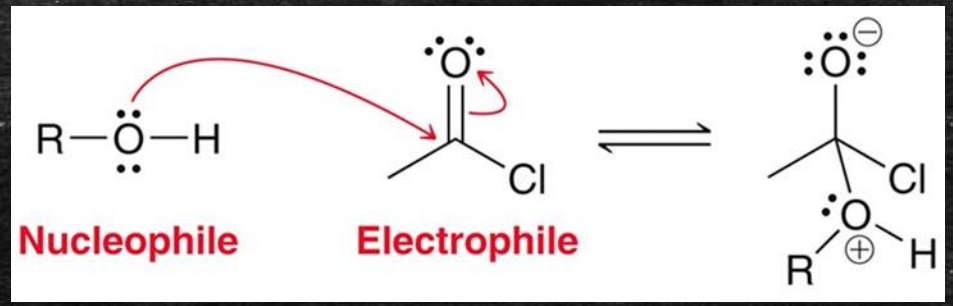
1. **Nucleophilic attack** - nucleophile attacking an electrophile



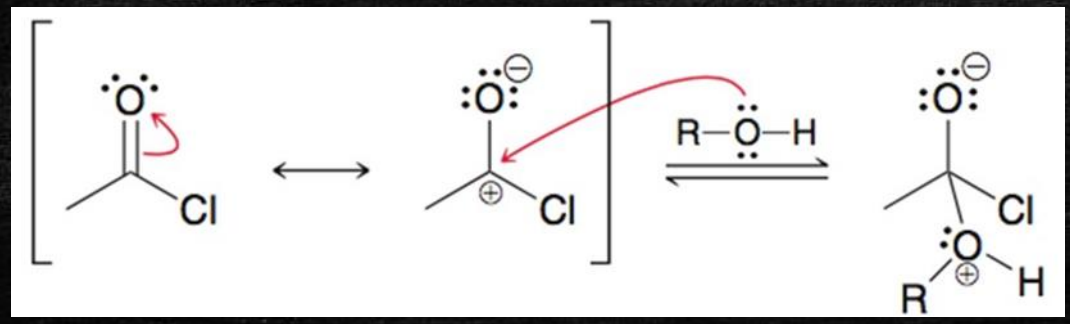
- The tail of the arrow starts on the electrons (– charge)
- The head of the arrow ends on a nucleus (+ charge)
- The electrons end up being sharing rather than transferred

Nucleophilic Attack / Two-Arrow Example

1. **Nucleophilic attack** may require more than one curved arrow

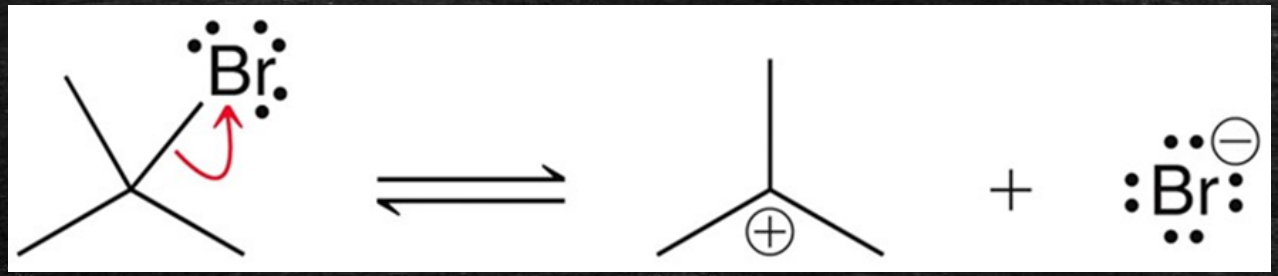


- The alcohol (nucleophile) attacks a carbon with a δ+ charge.
- *The second arrow could be thought of as a resonance arrow.*

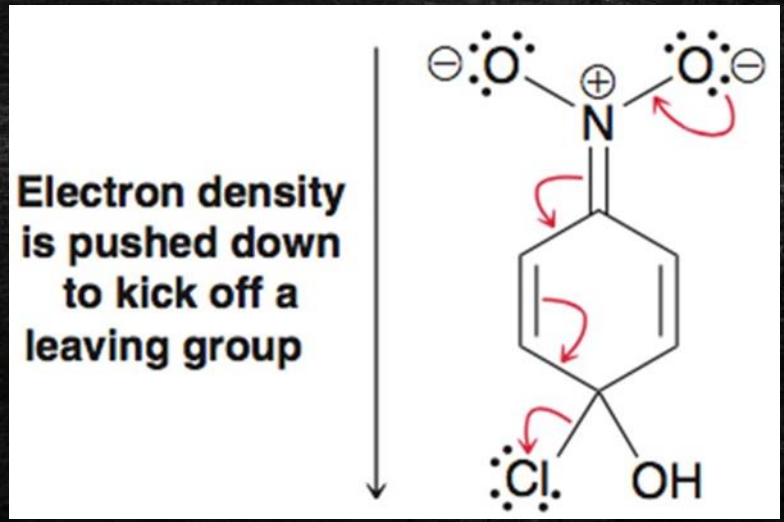


Loss of a Leaving Group

2. Loss of a leaving group – heterolytic bond cleavage, an atom or group takes the electron pair

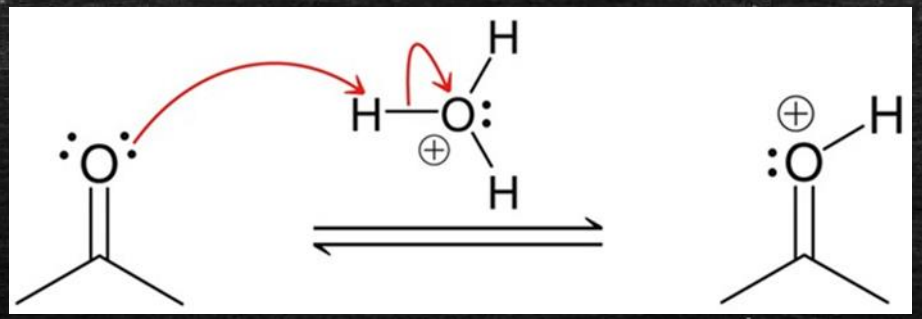


It is common for more than one curved arrow be necessary to show the loss of a leaving group:

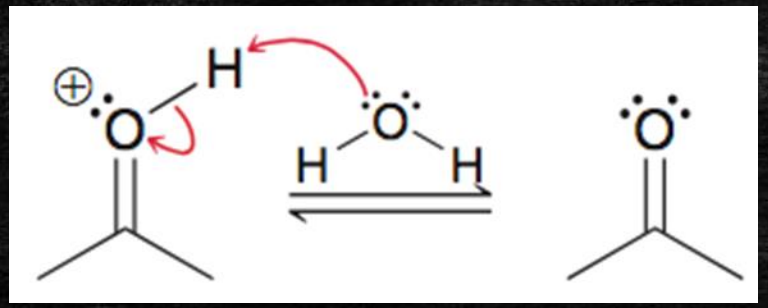


Proton Transfers / Overview

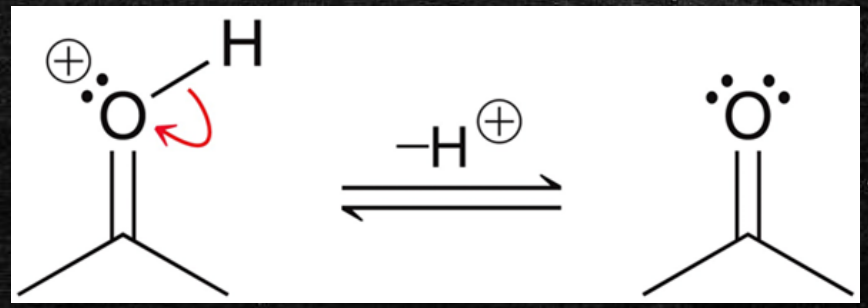
3. Proton transfer - recall (from chapter 3) that proton transfer requires two curved arrows



- The deprotonation of a compound is sometimes shown with just a single arrow and "–H+" above the rxn arrow.

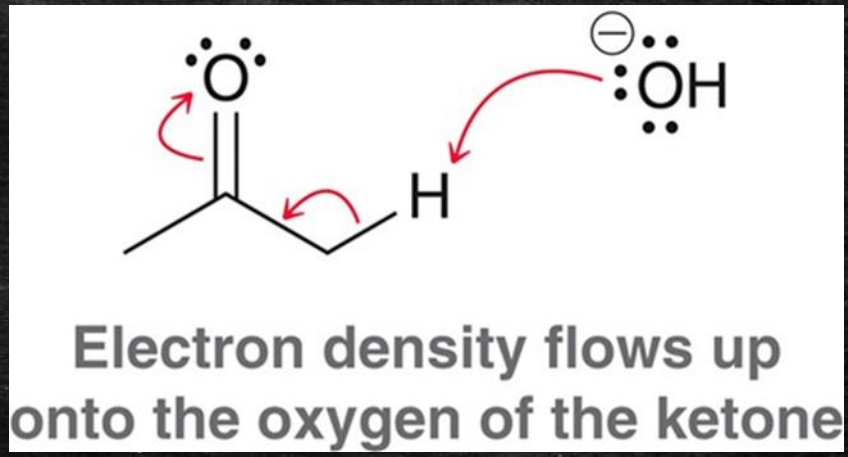


or

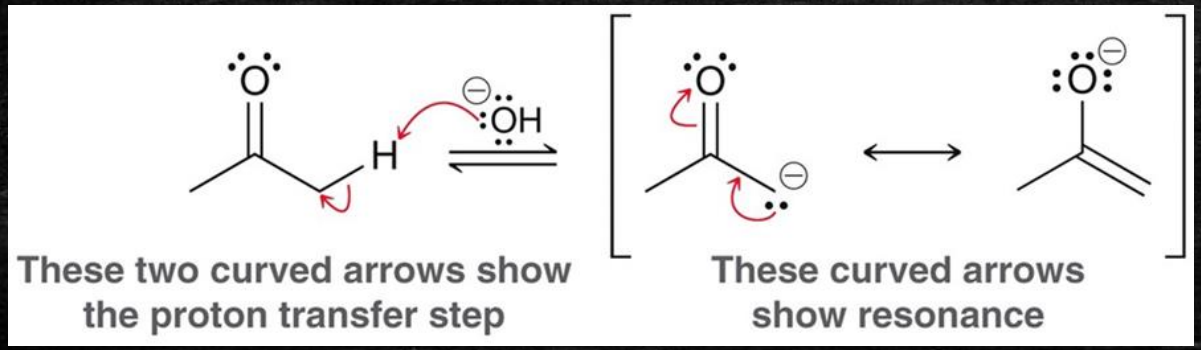


Proton Transfers / Distinct from Resonance

- Multiple arrows may be necessary to show the complete electron flow when a proton is exchanged

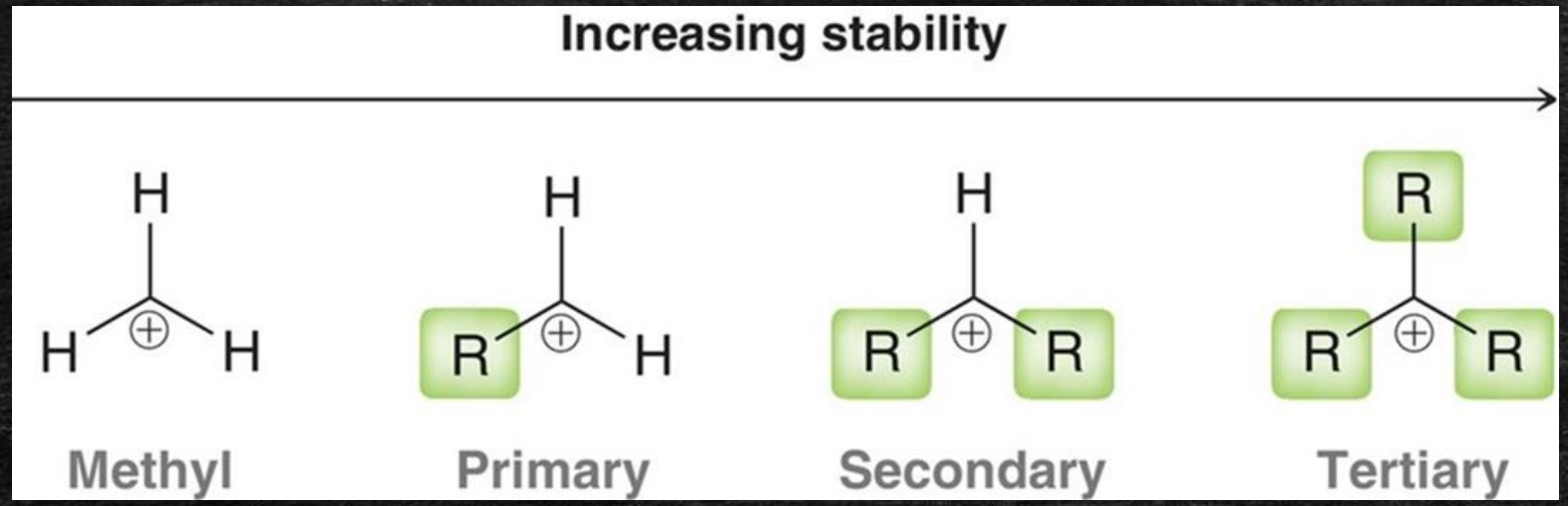


- Such electron flow can also be thought of as a proton transfer combined with resonance



Rearrangements / Carbocation Stability

- **Hyperconjugation** explains the carbocation stability trend below

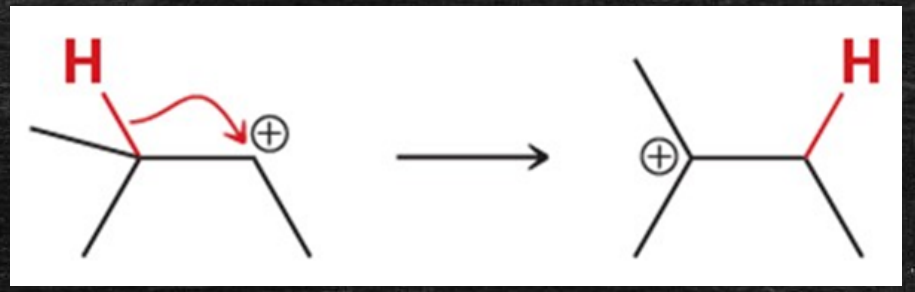


- Increasing the substitution increases the stability of a carbocation, due to the increasing number of adjacent sigma bonds aligned with the empty *p*-orbital.

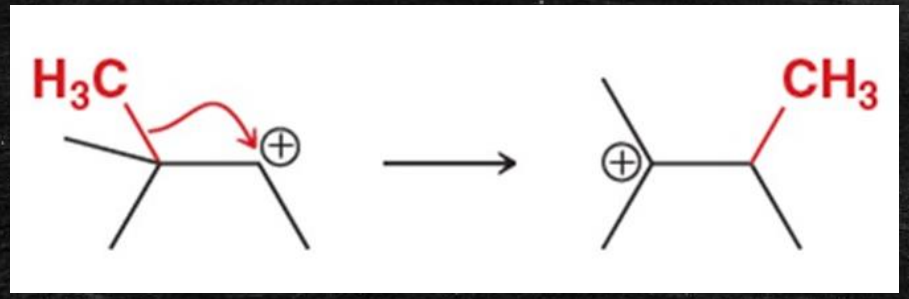
Rearrangements / Two Types

4. Rearrangements - Two types of carbocation rearrangement are common

- 1,2-hydride shift



- 1,2-methide shift

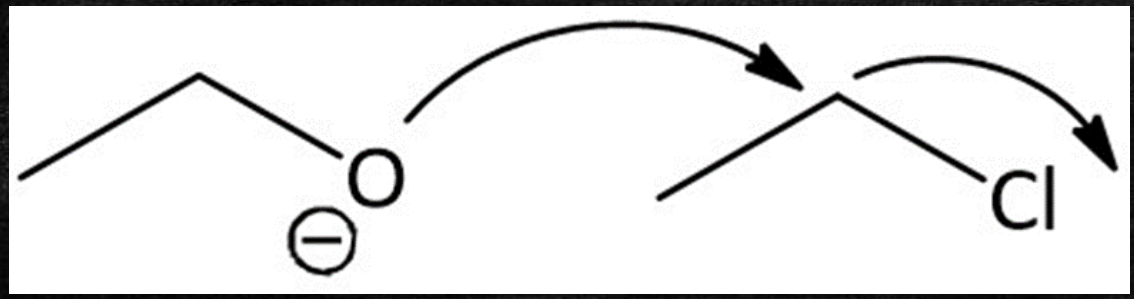


- Shifts can only occur from an adjacent carbon.
- Shifts only occur if a more stable carbocation results

Drawing Curved Arrows / Where They Start

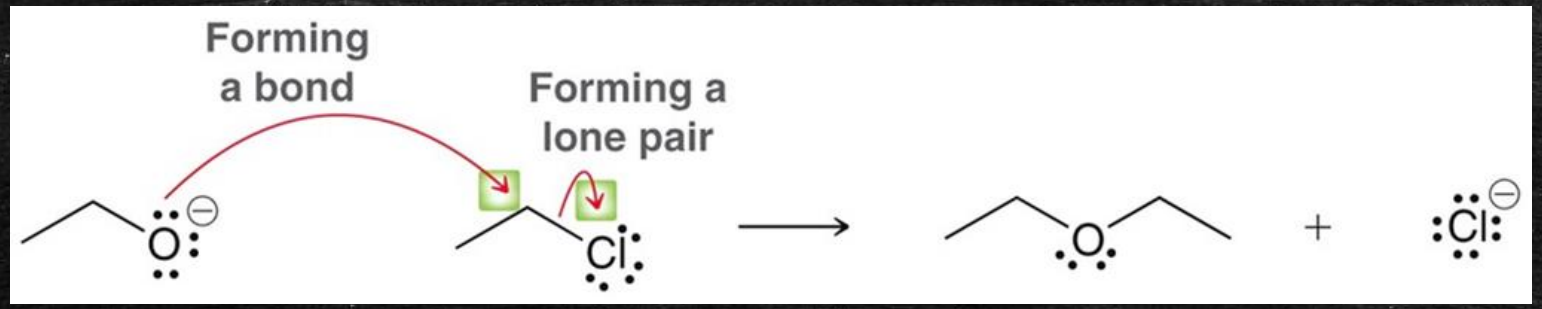
1. The curved arrow starts on a **pair of electrons** (a **shared pair** in a bond, or a **lone pair**)

- The second arrow shown below is drawn incorrectly

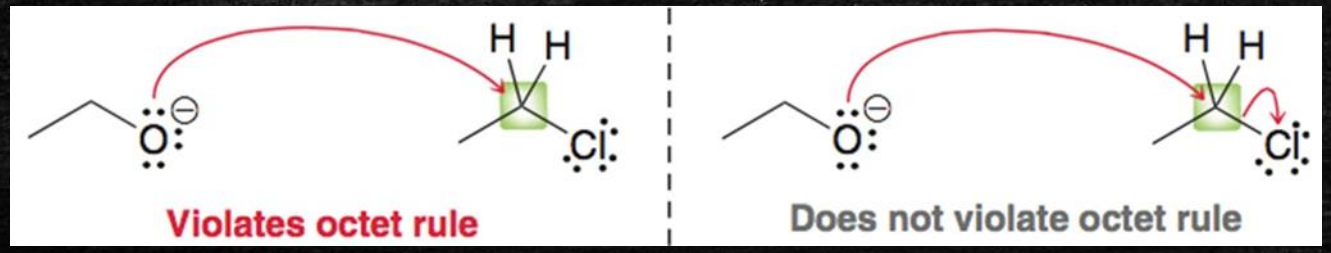


Drawing Curved Arrows / Where They Terminate

2. The head of a curved arrow shows either the formation of a bond, or the formation of a lone pair

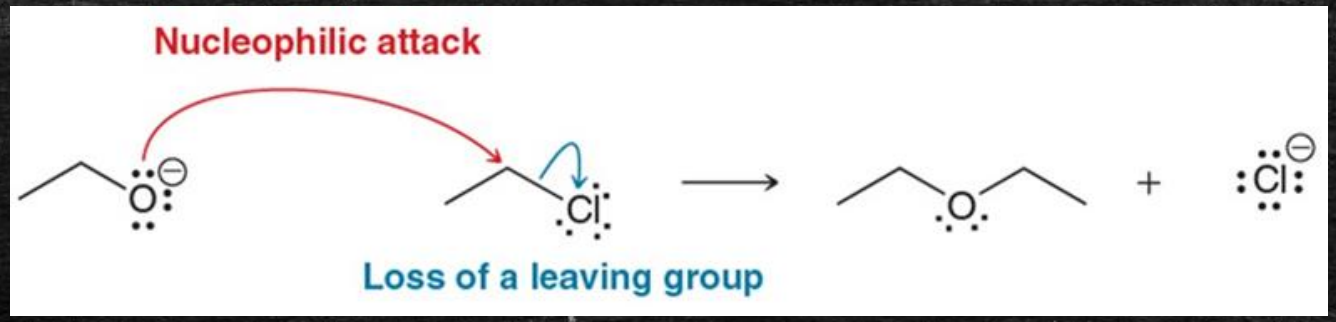


3. The head of a curved arrow can never show carbon forming more than 4 bonds

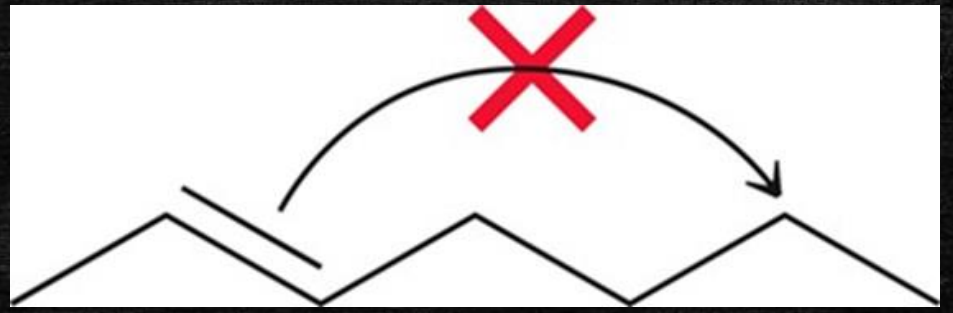


Drawing Curved Arrows / Summary

4. Any curved arrow drawn should describe one of the 4 patterns discussed thus far.



- The arrow below is unreasonable. It violates the octet, and doesn't match one of the 4 patterns

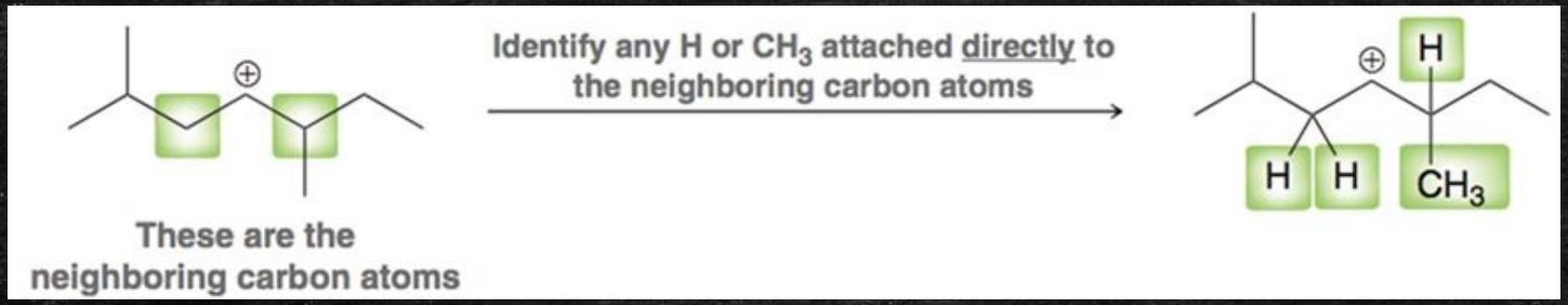


Practice with SkillBuilder 6.5 – Drawing Curved Arrows.

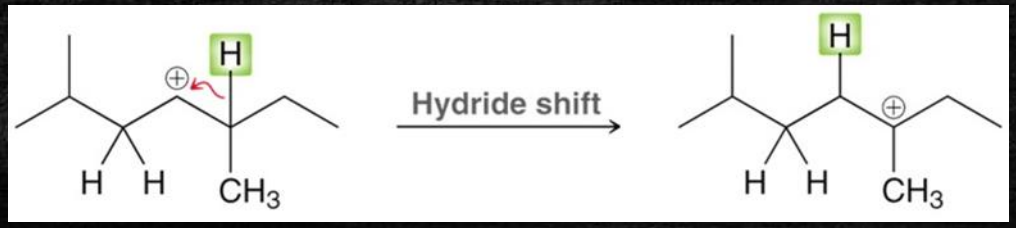
Carbocation Rearrangements / Considerations

- When you encounter a carbocation, you must consider if **rearrangement** will occur

1. Identify H atoms and/or methyl groups on neighboring carbon atoms



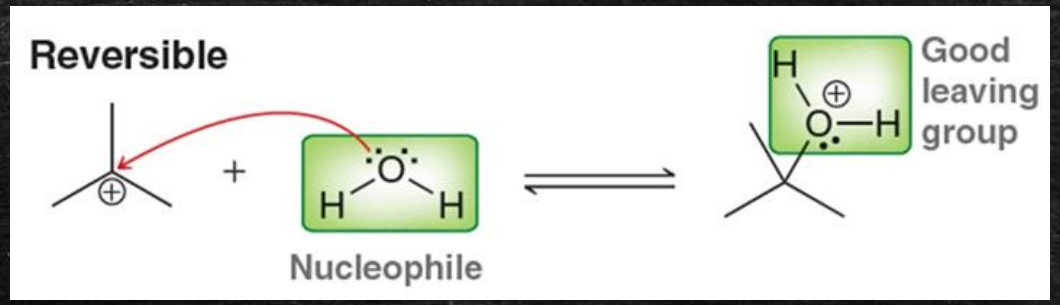
2. Determine if the shifting of one of these groups give a more stable carbocation



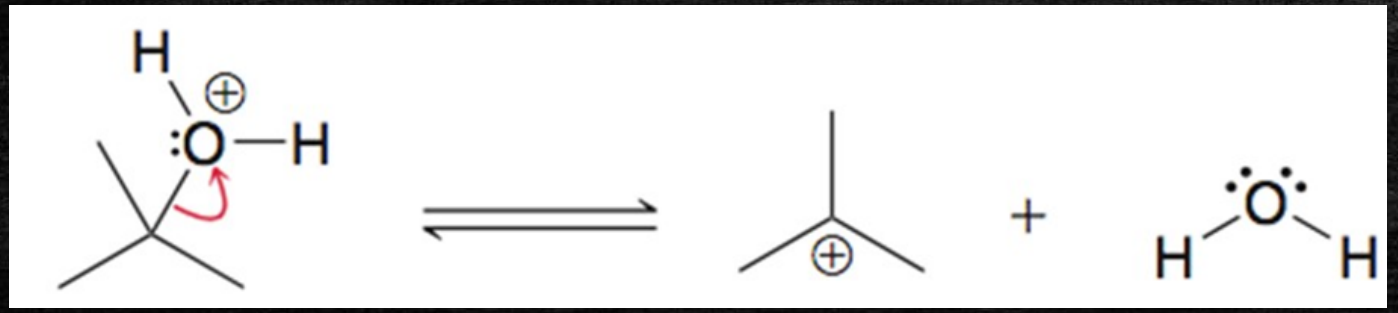
More stable, tertiary carbocation can form

Reversible and Irreversible Reaction Arrows / Attacking Nucleophile is a Good Leaving Group

- If the **attacking nucleophile is also a good leaving group**, it will be a **reversible attack**

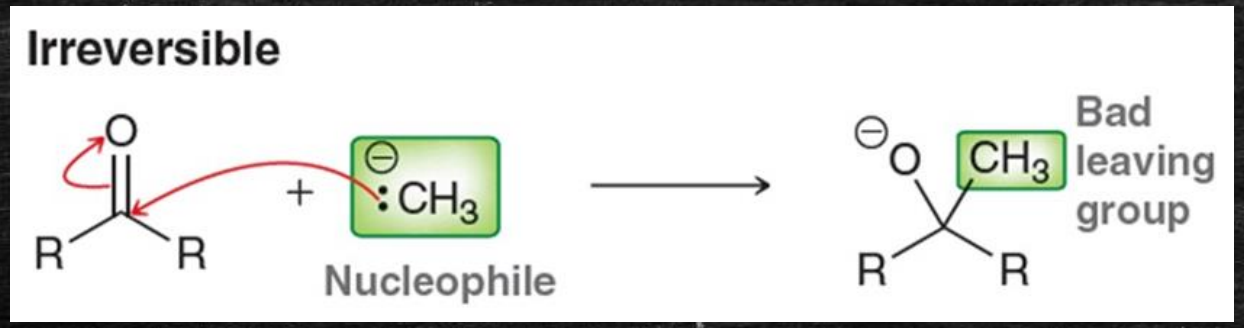


- The reverse process occurs at an appreciable rate

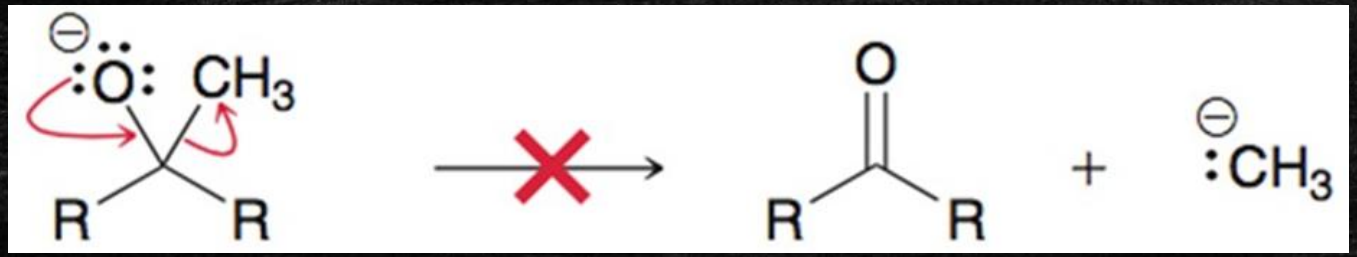


Reversible and Irreversible Reaction Arrows / Attacking Nucleophile is a Poor Leaving Group

- If the attacking nucleophile is a poor leaving group, it will essentially be an irreversible attack

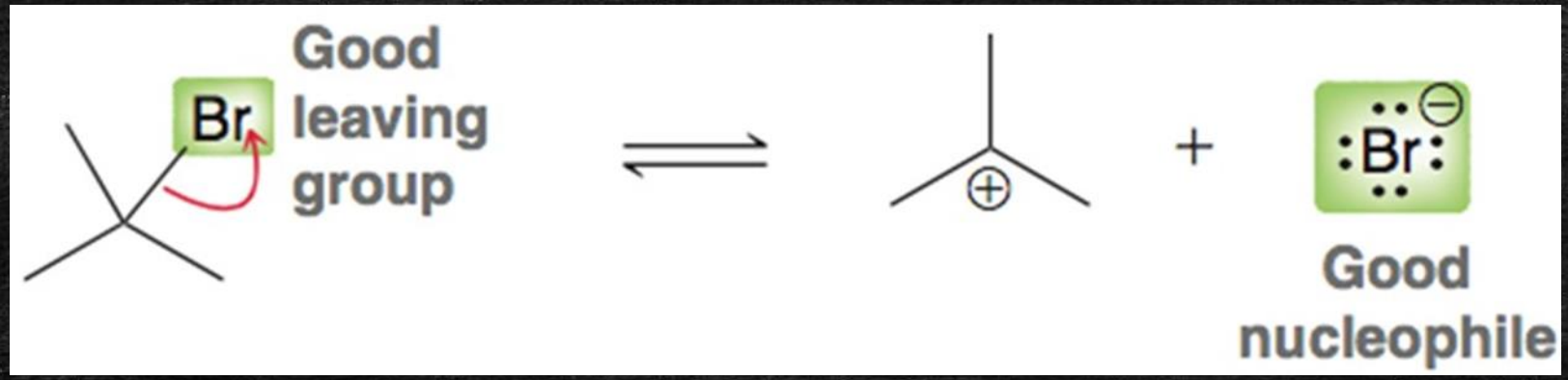


- The reverse reaction does not occur



Reversible and Irreversible Reaction Arrows / Loss of a Good Leaving Group

- The loss of a leaving group is virtually always reversible



- Most of the leaving groups encountered can act as nucleophiles

Reversible and Irreversible Reaction Arrows / Carbocation Rearrangements

- Carbocation rearrangements are generally irreversible

- **Thermodynamically**, there is **no driving force** for a more stable carbocation to rearrange to a less stable one.

CH-211 Organic Chemistry I

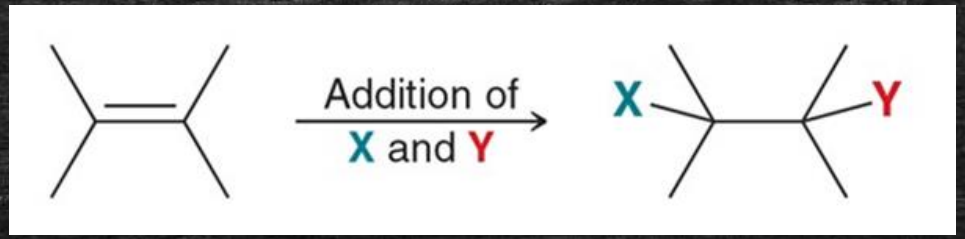
Chapter 8: Addition Reactions of Alkenes

By Ilari Filpponen

Textbook: Organic Chemistry, D.R. Klein. 4th ed. 2021 John Wiley & Sons, Inc.

Introduction to Addition Reactions / Common Types

Addition is the opposite of elimination



C=C π bond is converted to **two new sigma bonds**

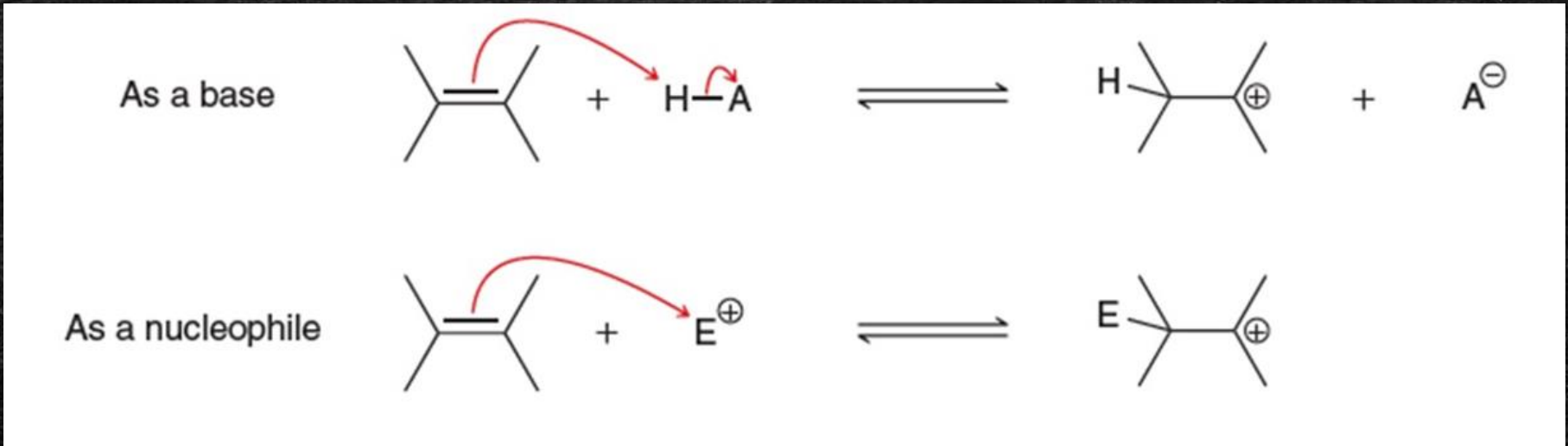
Table 8.1 some common types of addition reactions

TABLE 8.1 SOME COMMON TYPES OF ADDITION REACTIONS

TYPE OF ADDITION REACTION	NAME	SECTION
Addition of H and X → H–C–C–X	*Hydrohalogenation* (X = Cl, Br, or I)	8.5
Addition of H and OH → H–C–C–OH	*Hydration*	8.8
Addition of H and H → H–C–C–H	*Hydrogenation*	8.9
Addition of X and X → X–C–C–X	*Halogenation* (X = Cl or Br)	8.10
Addition of OH and X → HO–C–C–X	*Halohydrin formation* (X = Cl, Br, or I)	8.10
Addition of OH and OH → HO–C–C–OH	*Dihydroxylation*	8.11, 8.12

Introduction to Addition Reactions / Description

- The **π bond** is an **electron-pair donor**



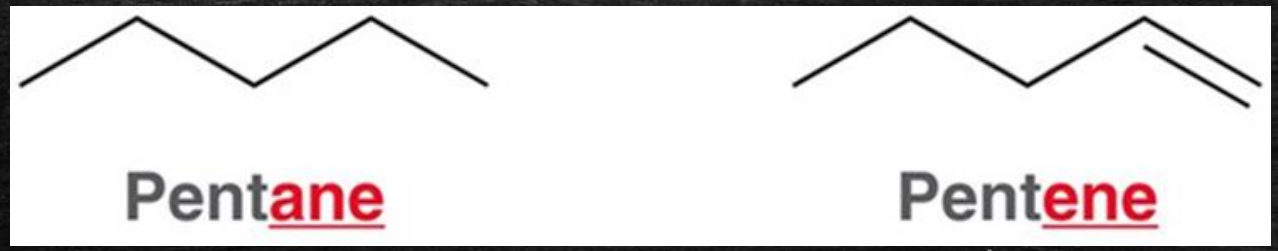
Alkene Nomenclature / Steps

- Alkenes are given IUPAC names using the same procedure to name alkanes, with minor modifications

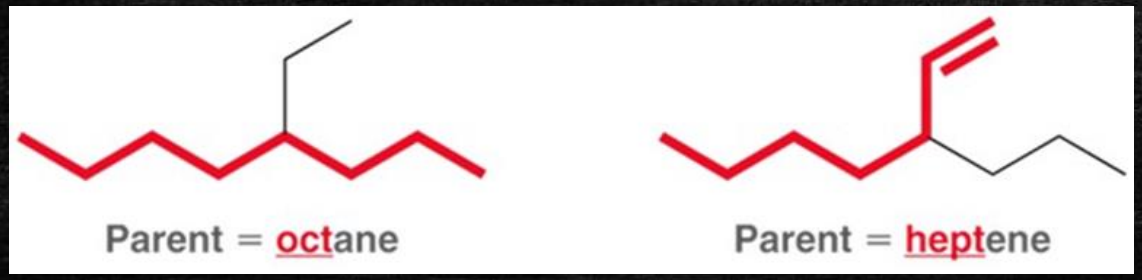
1. Identify the parent chain, which includes the C=C double bond.
2. Identify and name the substituents.
3. Assign a locant (and prefix if necessary) to each substituent. Give the C=C double bond the lowest number possible.
4. List the numbered substituents before the parent name in alphabetical order. Ignore prefixes (except iso) when ordering alphabetically.
5. The C=C double bond locant is placed either just before the parent name or just before the -ene suffix.

Alkene Nomenclature / Step One

1. Identify the parent chain, which must include the C=C double bond.
   - The name of the parent chain ends in -ene rather than -ane.

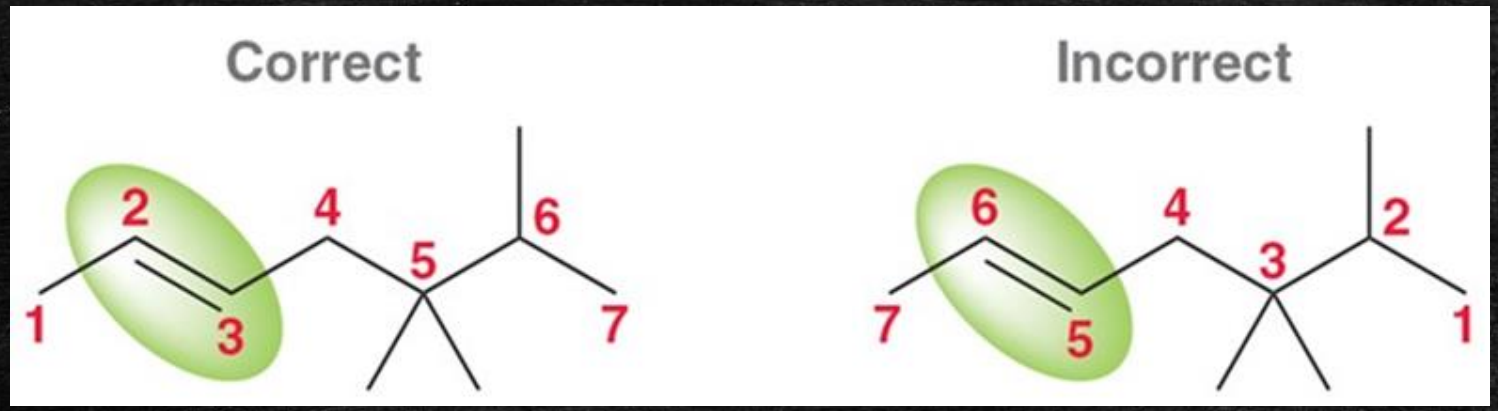


- The parent chain must include the C=C double bond.



Alkene Nomenclature / Steps Two and Three

2. Identify and name the substituents.
3. Assign a locant (and prefix if necessary) to each substituent. Give the C=C double bond the lowest number possible.

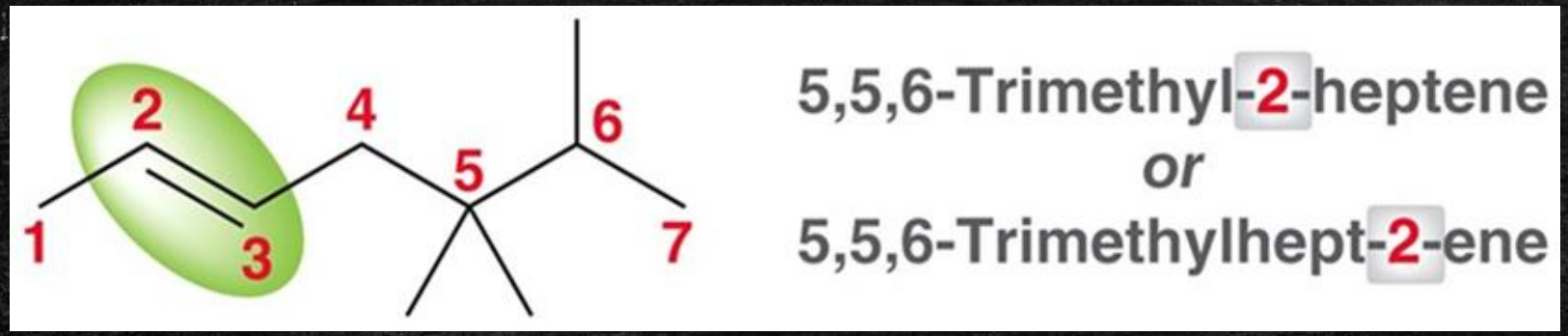


- The locant of the double bond is a single number, and is the number indicating where the double bond *starts*. The alkene above is located at the "2" carbon.

Alkene Nomenclature / Steps Four and Five

4. List the numbered substituents before the parent name in alphabetical order. Ignore prefixes (except iso) when ordering alphabetically.

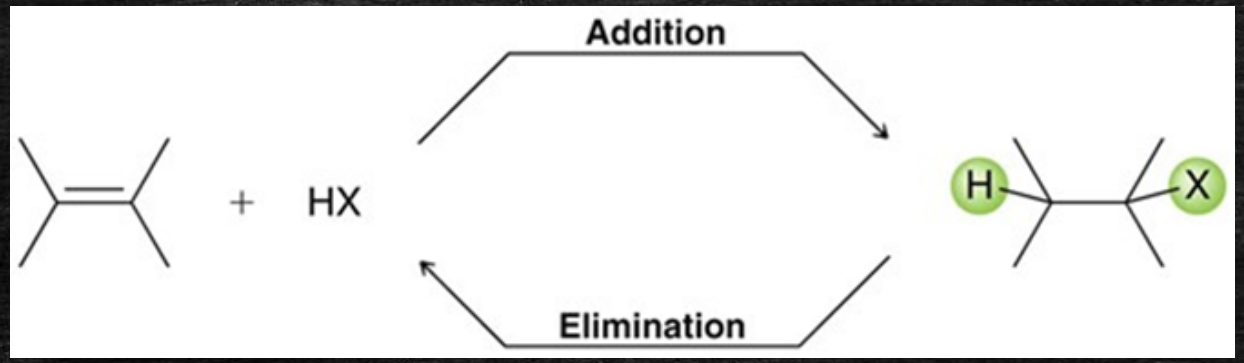
5. The C=C double bond locant is placed either just before the parent name or just before the -ene suffix.



Note: This alkene has the *E* configuration, which must be indicated in the name, in parentheses: **(*E*)-5,5,6-trimethylhept-2-ene.**

Addition vs. Elimination / Overview

- Addition and elimination are equilibrating reactions:
  - Which side is favored depends on temperature



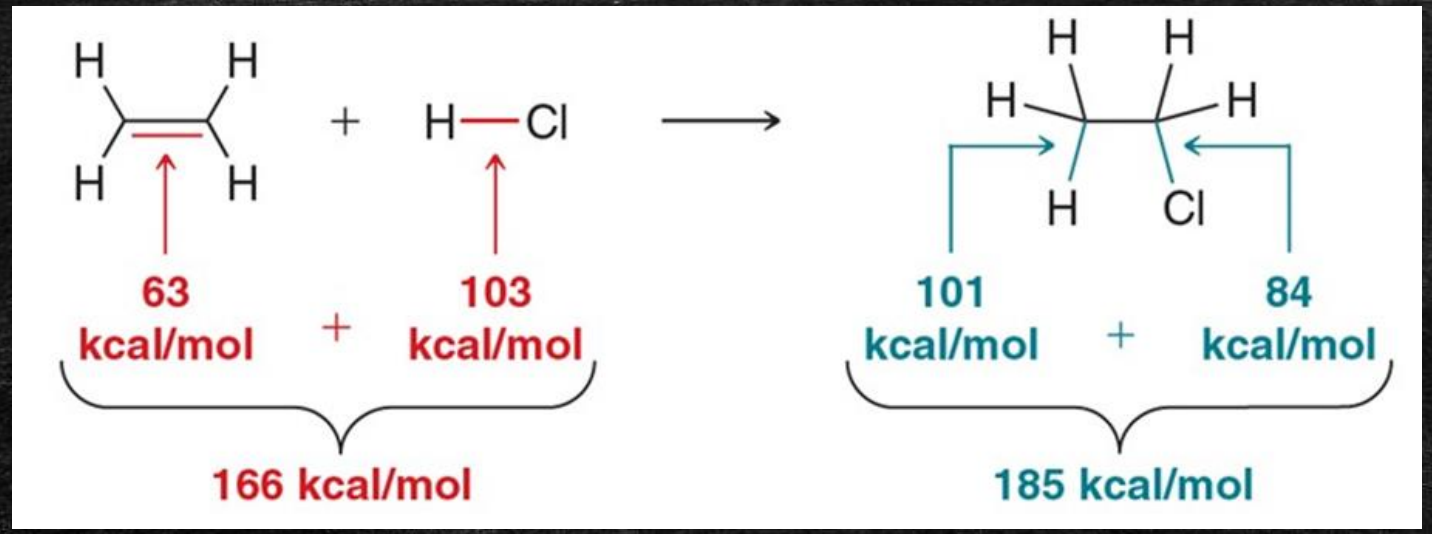
- The higher the temperature, the more important entropy becomes:

$$\Delta G = \underbrace{(\Delta H)}_{\text{Enthalpy term}} + \underbrace{(-T\Delta S)}_{\text{Entropy term}}$$

Higher temperature means a bigger entropy term

Addition vs. Elimination / Enthalpy

- Addition reactions are **favored by enthalpy.**
- Sigma (σ) bonds are stronger (more stable) than pi (π) bonds



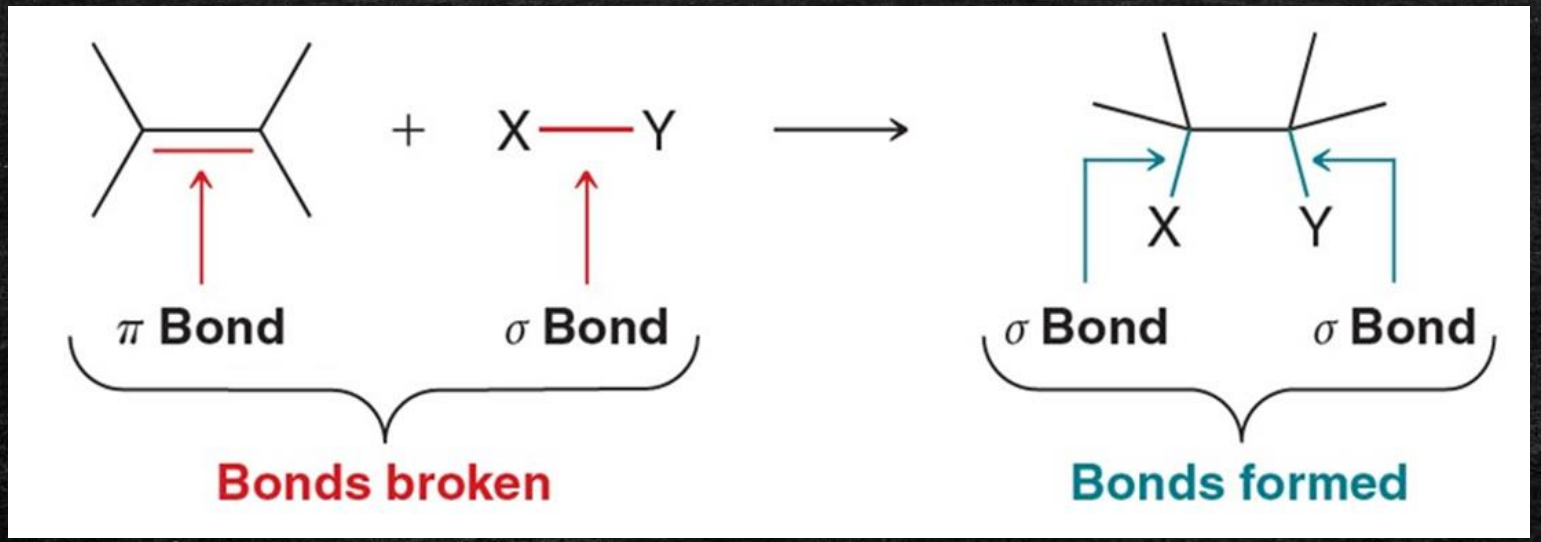
ΔH = Bond broken – bonds formed

ΔH = 166 kcal/mol – 185 kcal/mol

ΔH = –19 kcal/mol

Addition vs. Elimination / Entropy

- Addition reactions are **not favored by entropy.**
- Two molecules combine to form one product; entropy decreases

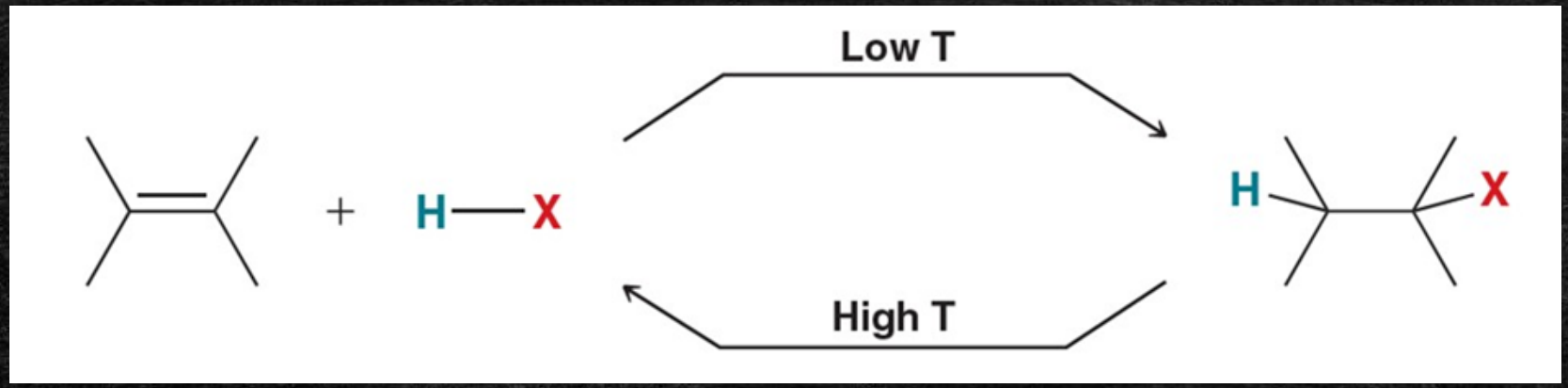


Two reactants

One product

Addition vs. Elimination / Enthalpy vs Entropy

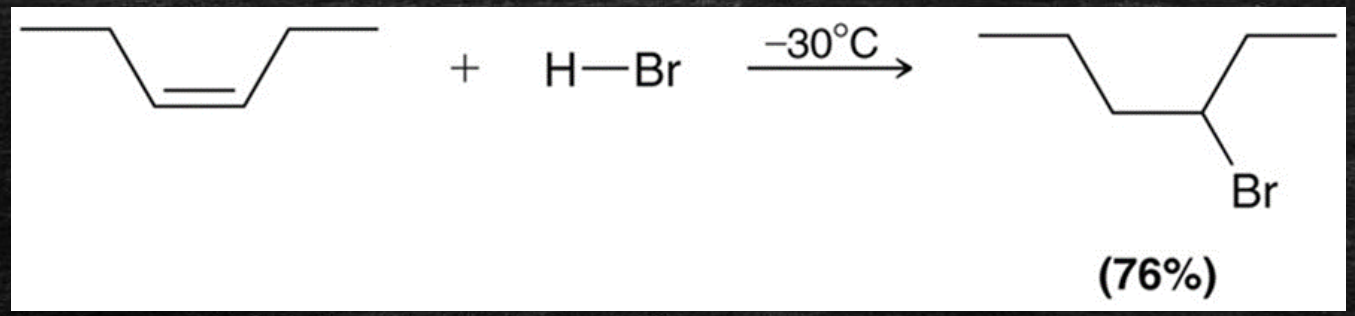
- At lower temperatures, **enthalpy dominates**, and addition reactions are favored
- At higher temperatures, **entropy dominates**, and elimination reactions are favored



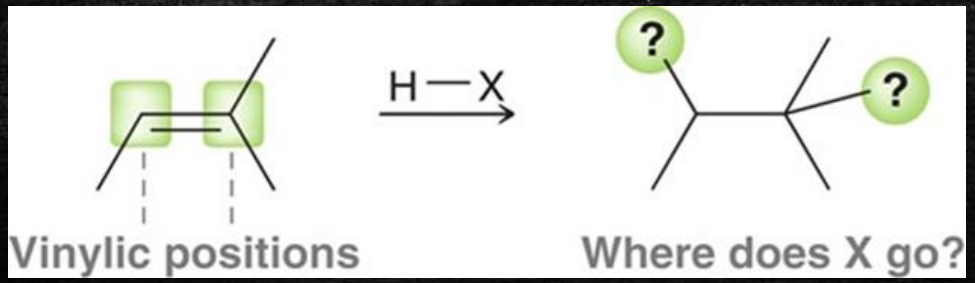
- **Therefore, lower temperatures are typically used when doing an addition reaction**

Hydrohalogenation

- **Hydrohalogenation**: addition of H-X to an alkene
- can use HCl, HBr, or HI

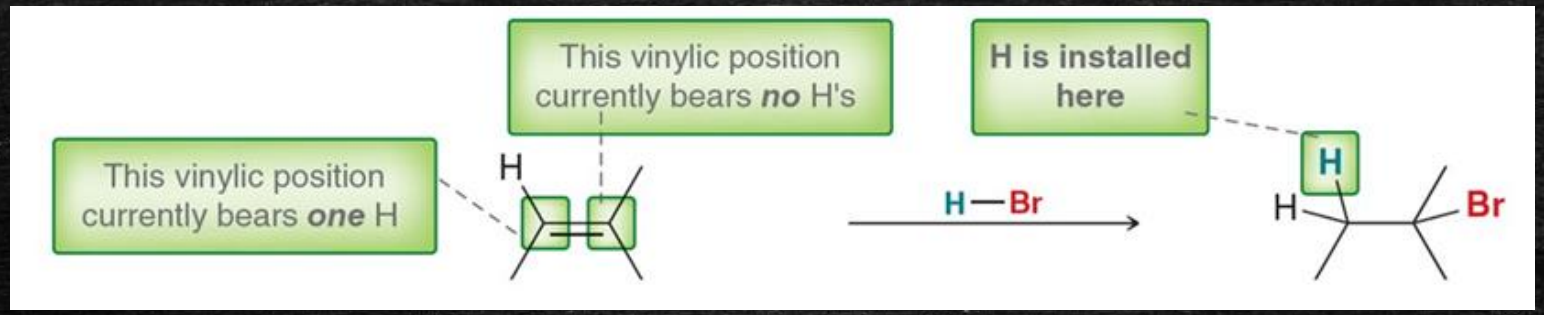


- If the alkene is not symmetrical, then two **regioisomers are possible**, depending on which carbon gets the "H" and the "X"

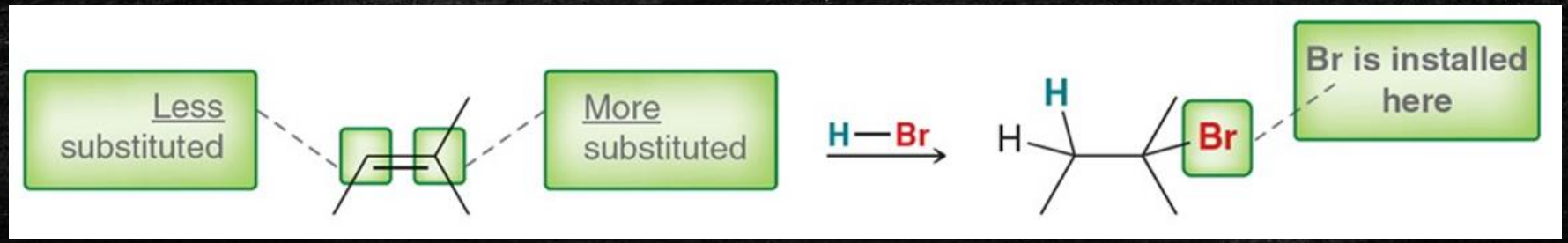


Hydrohalogenation – Regioselectivity / Adding HX

- Hydrohalogenation is **regioselective** for **Markovnikov addition**
- In 1869, Markovnikov observed the H atoms tend to add to the carbon already bearing more H atoms

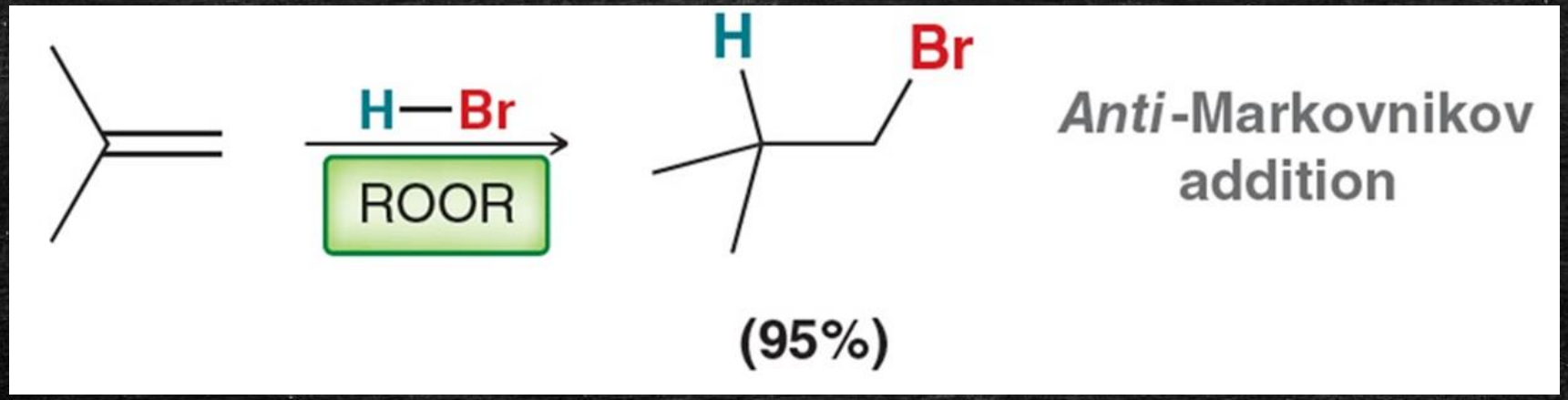


- **The halogen is generally installed at the more substituted carbon**



Hydrohalogenation – Regioselectivity / Adding HX in ROOR

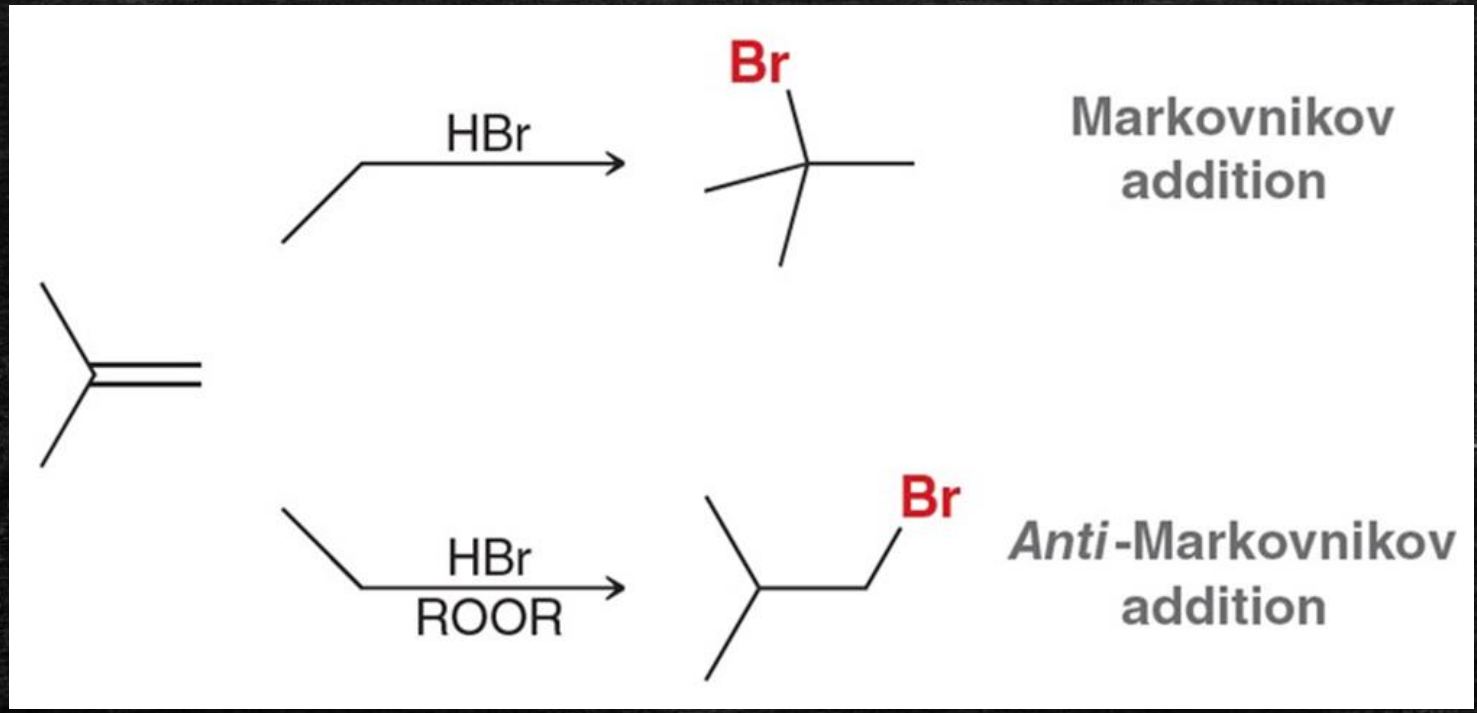
- When peroxides are used with HBr, **the opposite regioselectivity is observed.**



- The **reaction mechanism must be different**, when peroxides are present.

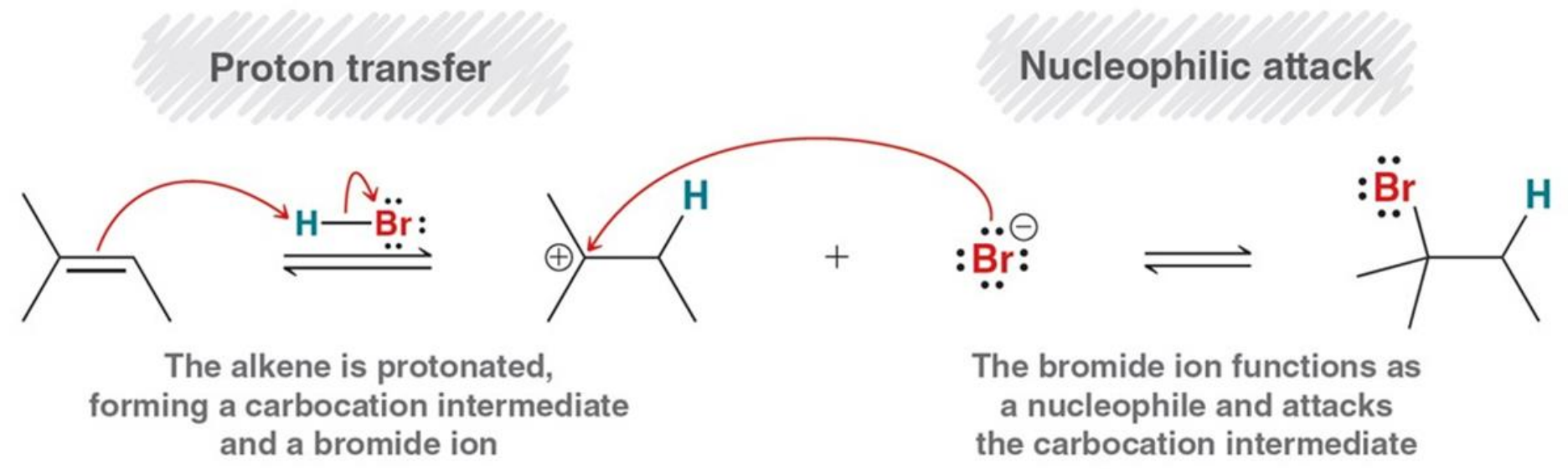
Hydrohalogenation – Regioselectivity / Modulating HX Addition

- The important lesson here is that the **regioselectivity of HBr addition can be controlled:**



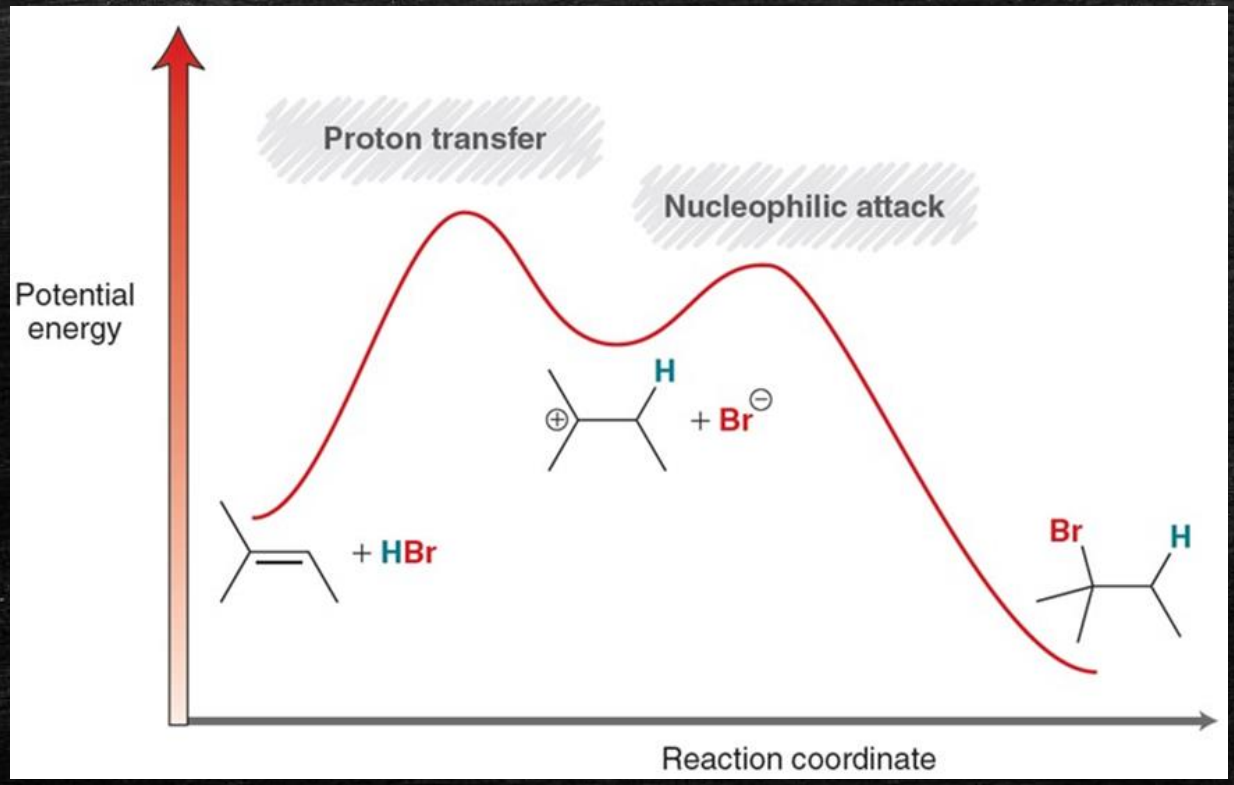
Hydrohalogenation – Mechanism / Overview

- The mechanism is a two-step process



Hydrohalogenation – Mechanism / Graphical Interpretation

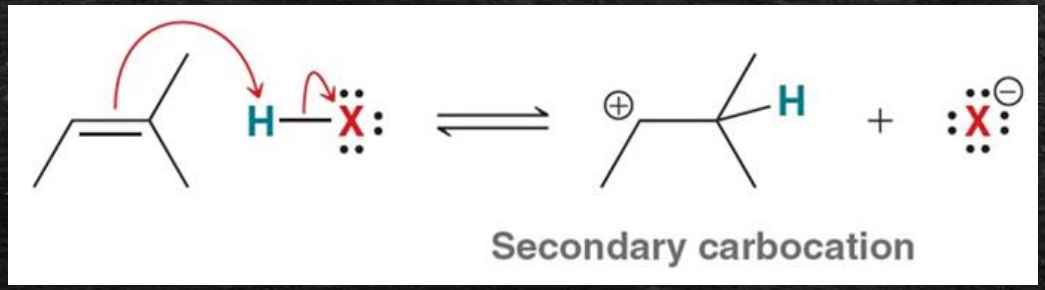
- The step with the highest E_a is the rate determining step, which is the formation of the carbocation intermediate (the first step)



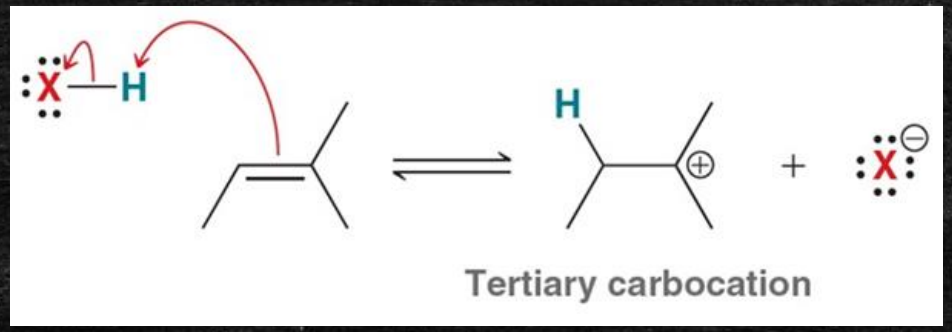
Hydrohalogenation – Mechanism / Two Pathways

- Recall that there are two possible products, Markovnikov and *anti*-Markovnikov

***Anti*-Markovnikov pathway**



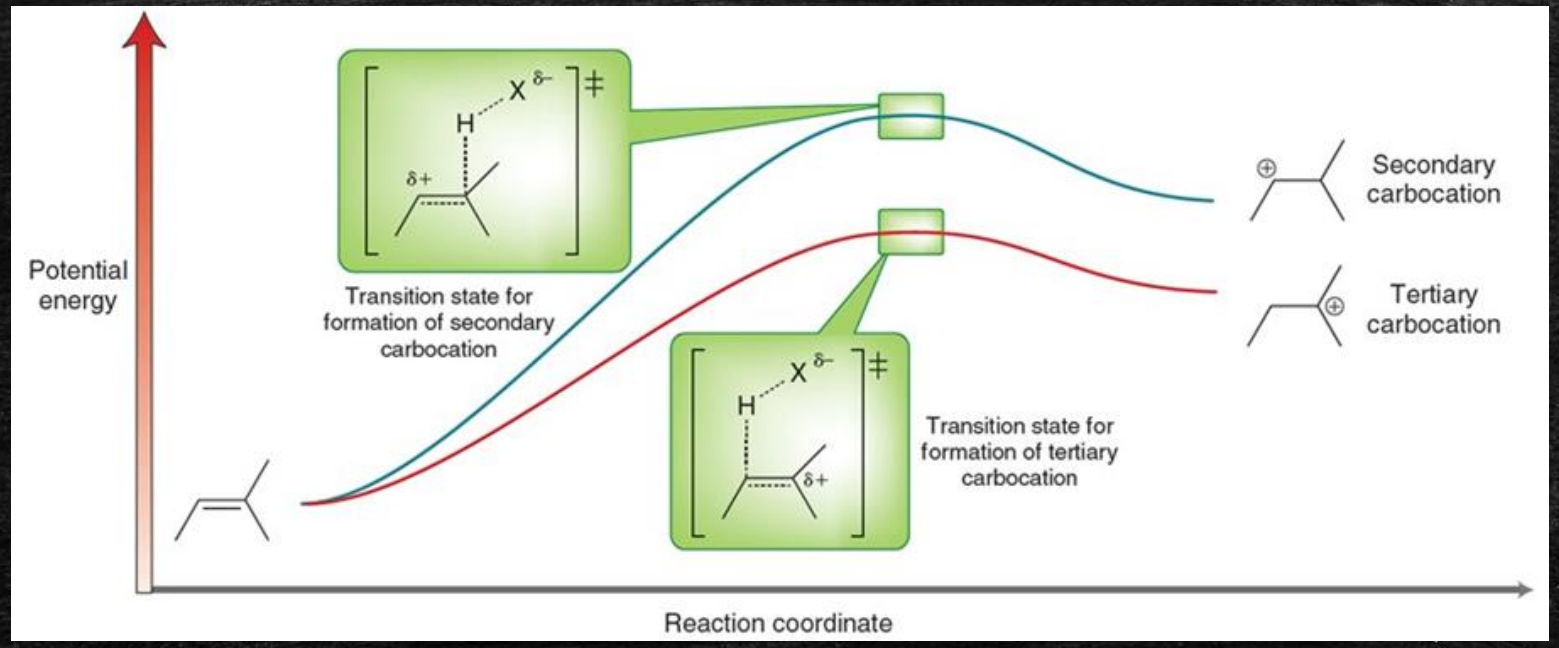
Markovnikov pathway



- Markovnikov product is formed because of carbocation stability

Hydrohalogenation – Mechanism / Forming the Markovnikov Product

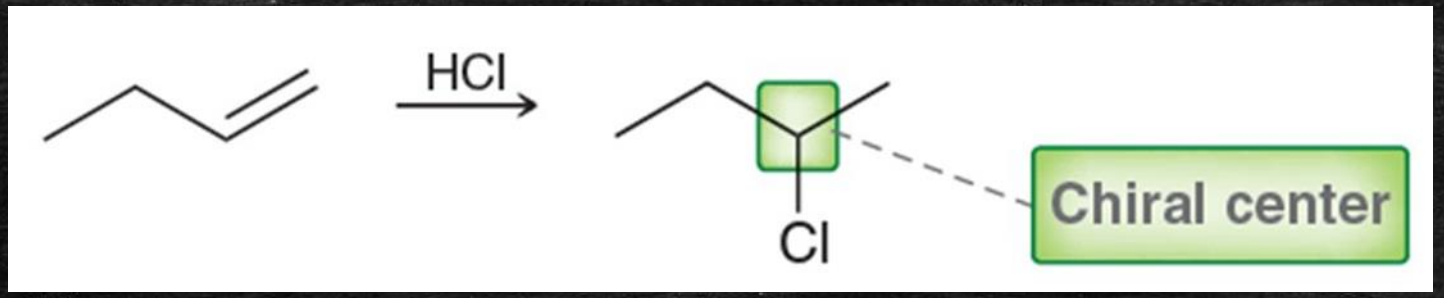
- The Markovnikov product is formed through a lower energy transition state (therefore, a faster reaction)



Practice with SkillBuilder 8.1 – Drawing a Mechanism (HX)

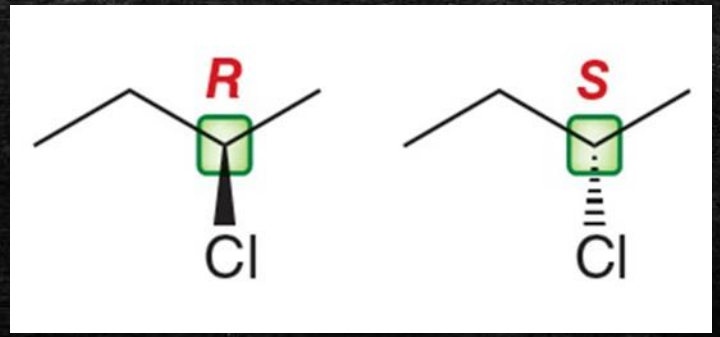
Hydrohalogenation – Stereochemistry / Overview

- Hydrohalogenation may result in the formation of a chiral center



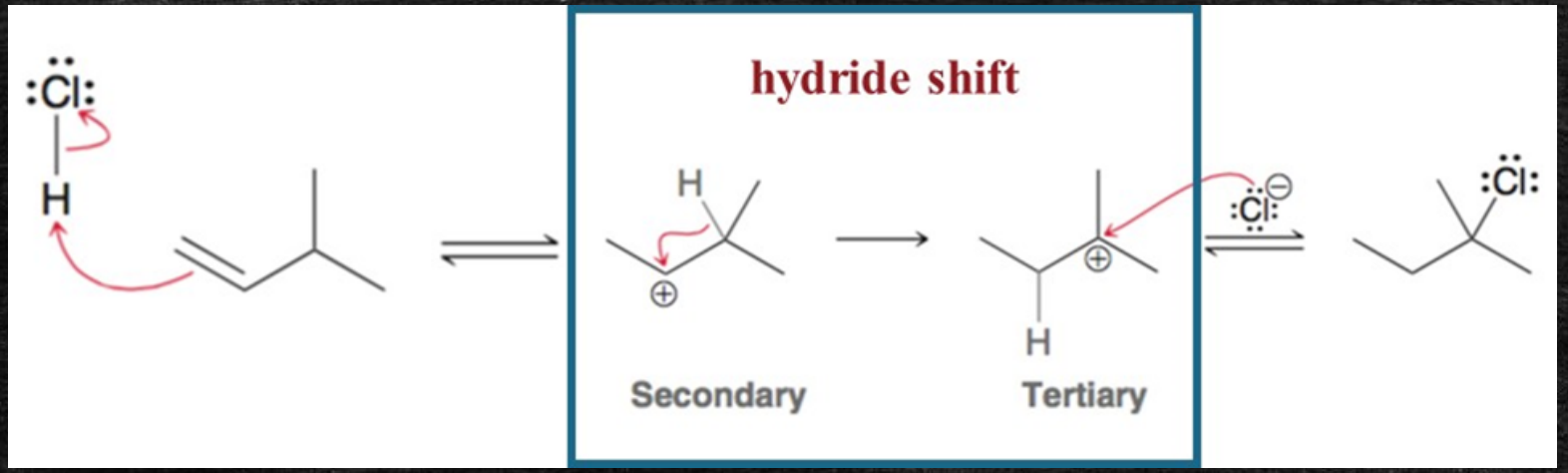
- There are actually two Markovnikov products formed in this rxn

Two enantiomers are formed in equal amounts



Hydrohalogenation – Rearrangements / Overview

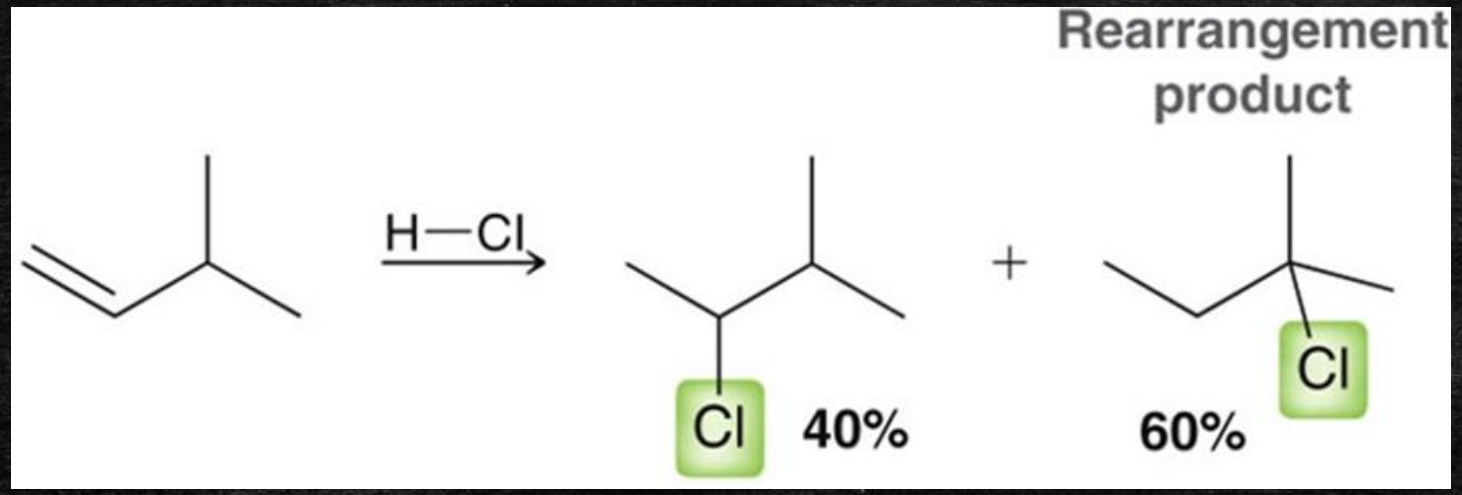
- Recall carbocations can rearrange (hydride or methyl shift) if they can become more stable.



- When this alkene undergoes hydrohalogenation, the 2° carbocation could rearrange to a more stable 3° carbocation.

Hydrohalogenation – Rearrangements / Common Outcome

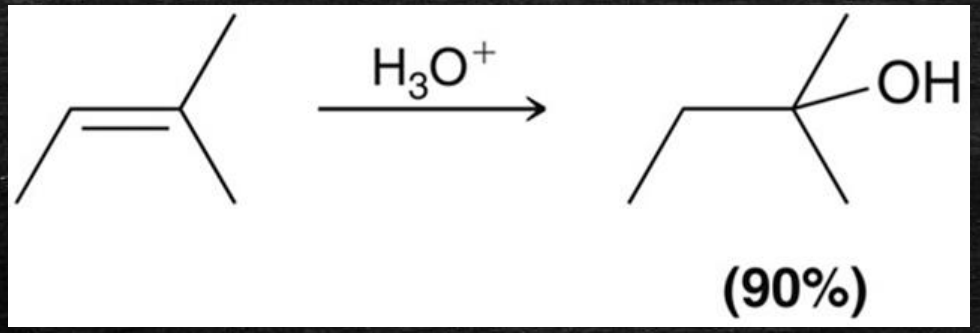
- Recall carbocations can rearrange (hydride or methyl shift) if they can become more stable.
- **When carbocation rearrangements can occur, they DO occur.**



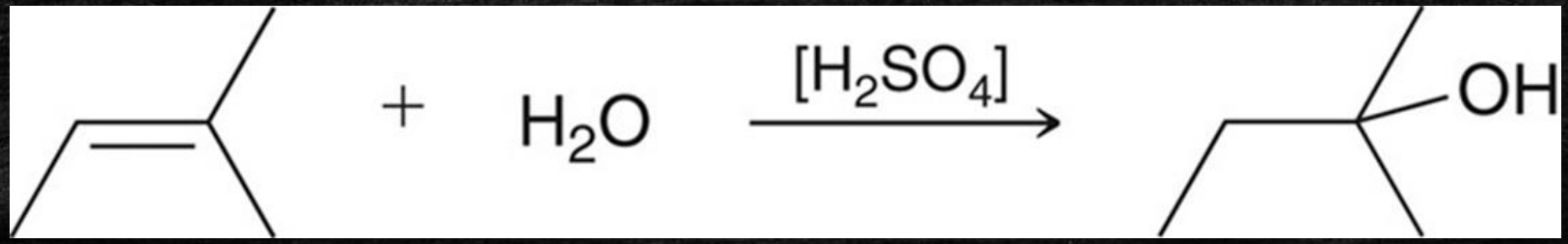
Practice with SkillBuilder 8.2 – Drawing a Mechanism

Acid-Catalyzed Hydration / Overview

- The components of **water** (**H** and **OH**) are added across the π bond
- **Acid-catalyzed hydration** follows **Markovnikov regioselectivity**



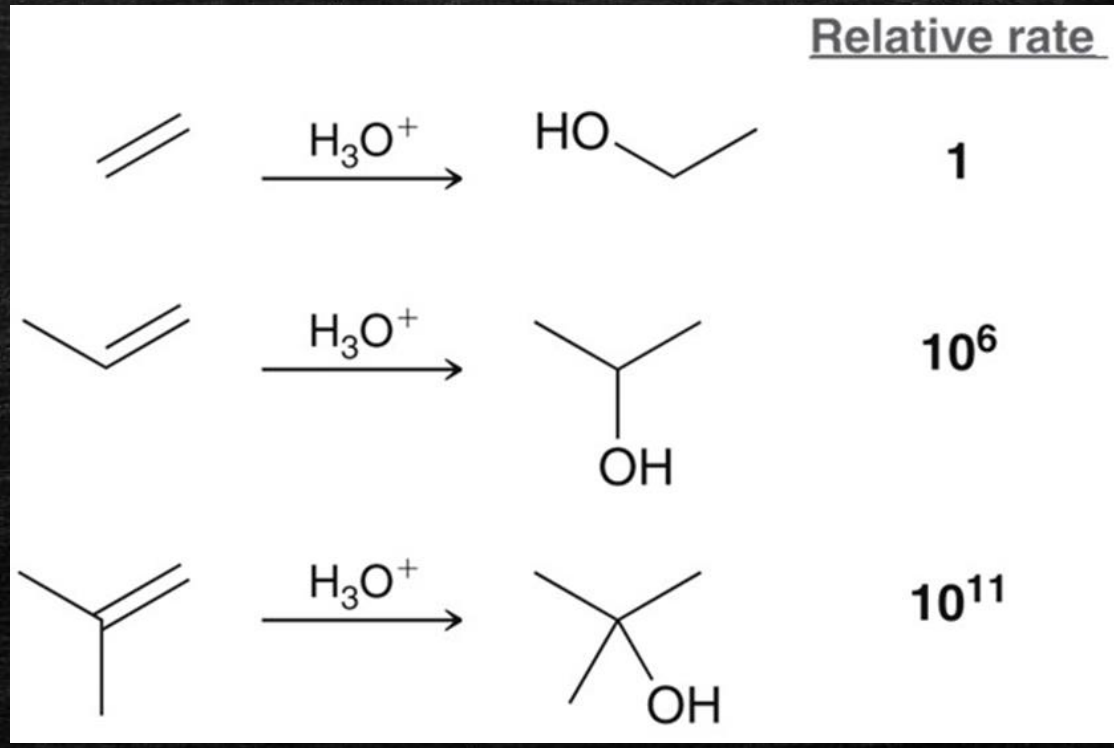
- Sulfuric acid is a commonly used acid catalyst



Acid-Catalyzed Hydration / More Substituted Carbon

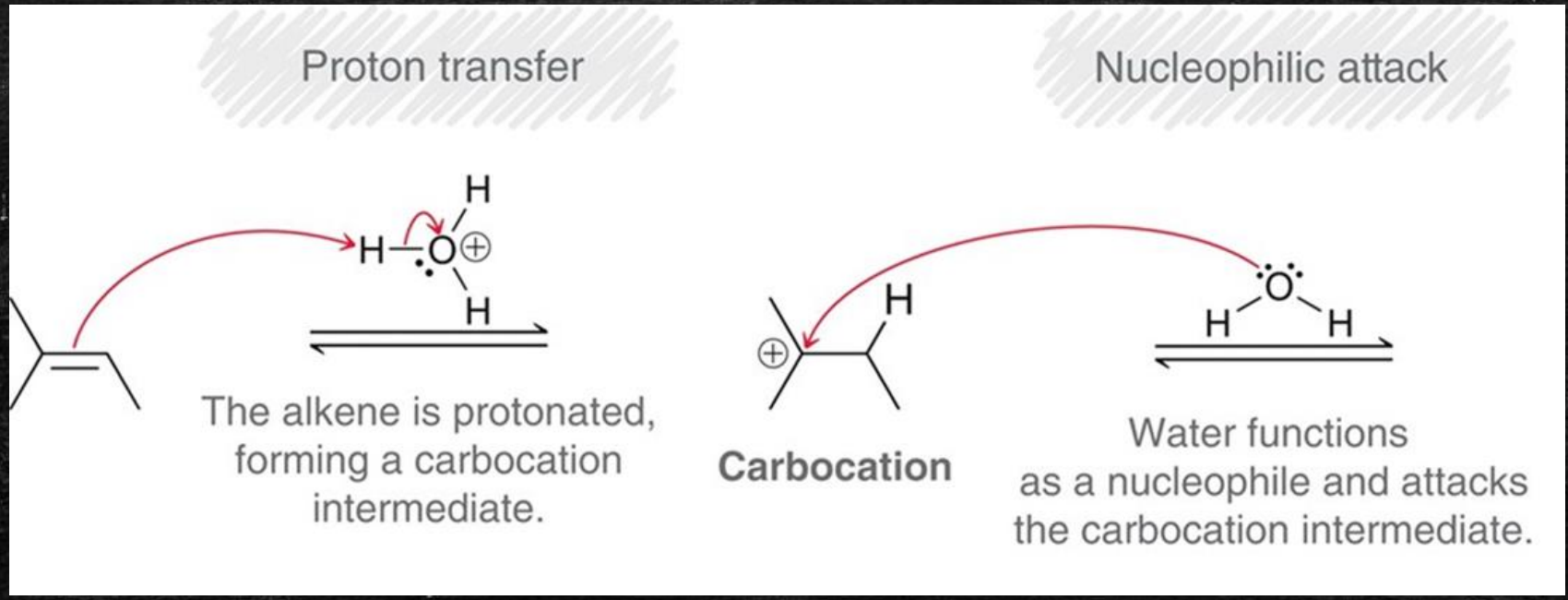
- The OH is added to the more substituted carbon of the alkene
- The more substituted the carbon atom is, the faster the reaction

This data is consistent with a mechanism that proceeds through a carbocation intermediate



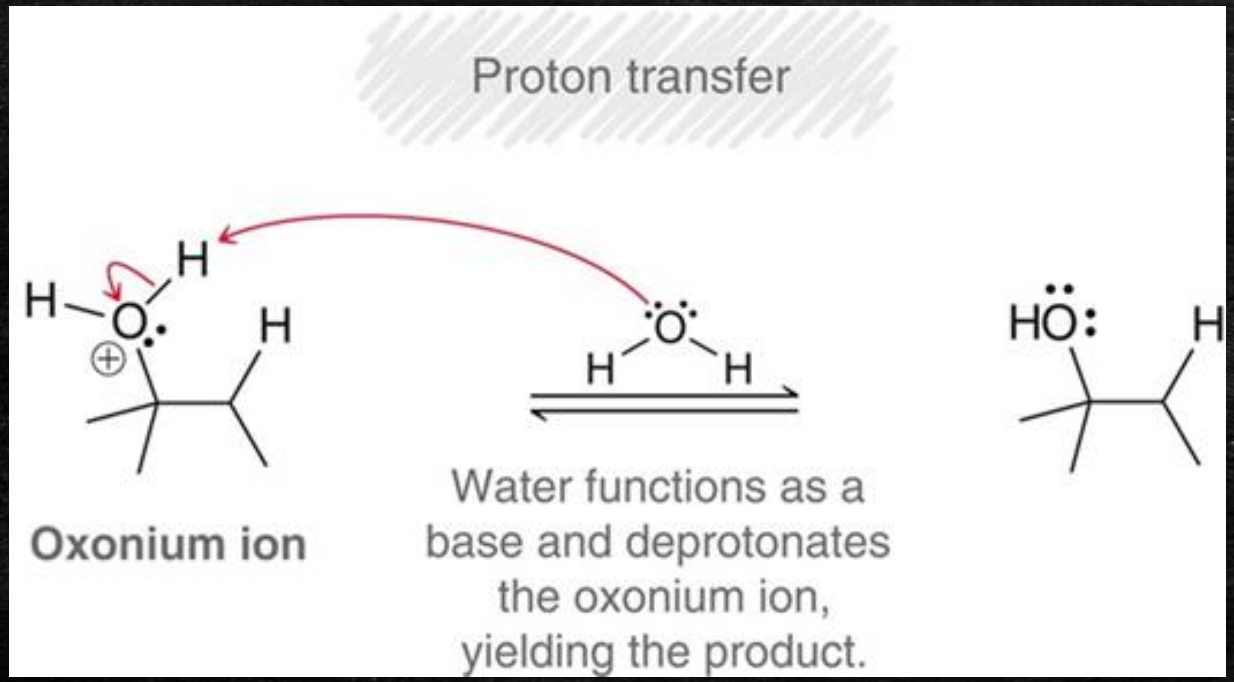
Hydration – Mechanism / Beginning is Familiar

- The mechanism for acid-catalyzed hydration begins the same as hydrohalogenation:



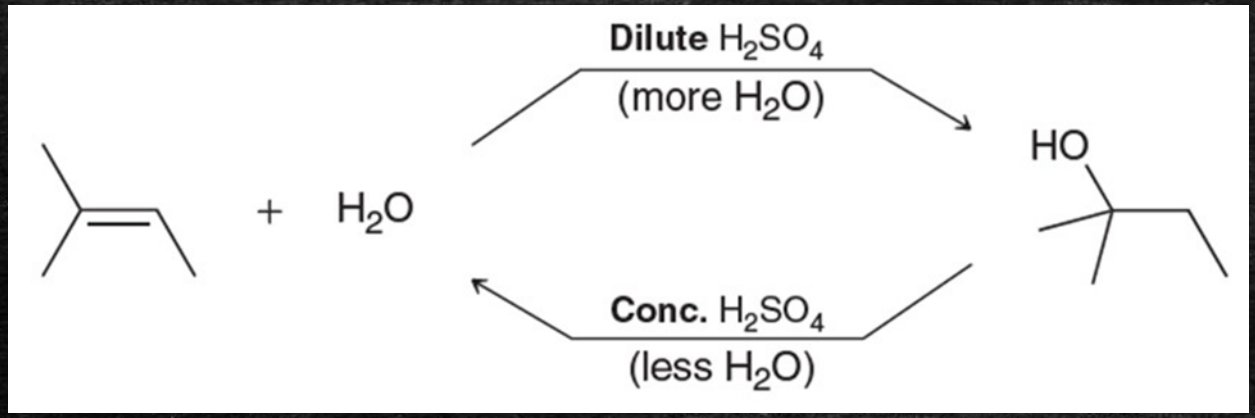
Hydration – Mechanism / Additional Final Step

- The mechanism for acid-catalyzed hydration begins the same as hydrohalogenation:
- But with hydration, **nucleophilic attack produces an oxonium ion, which is deprotonated** to afford the alcohol product:



Hydration – Thermodynamics

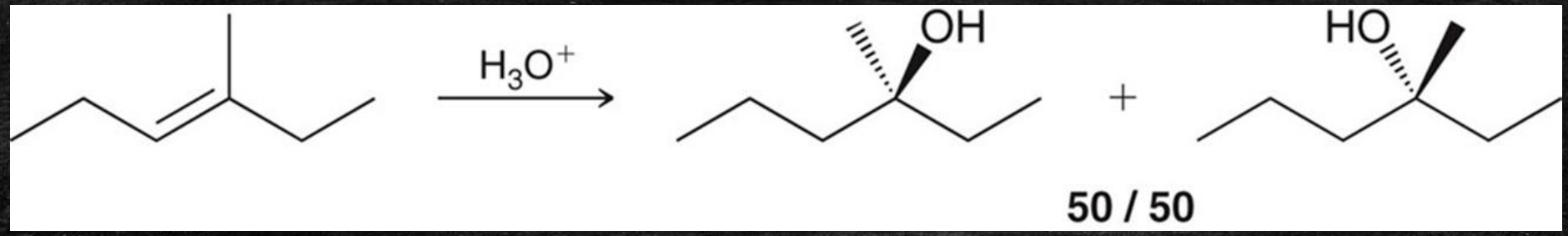
- The reactants and products of hydration are in equilibrium
- We exploit Le Chatelier's principle to control the equilibrium



- If we are **synthesizing an alcohol** from an alkene, we would **use excess water**
- If we are **synthesizing an alkene** from an alcohol, we would **use concentrated acid, and not add water** to the reaction

Hydration – Stereochemistry

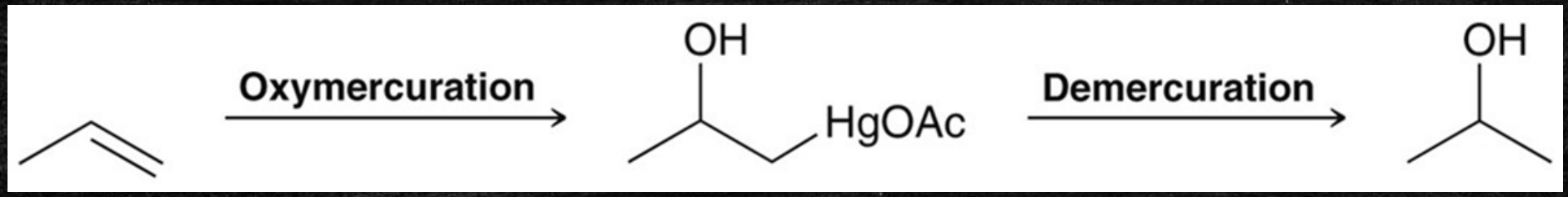
- The stereochemistry of hydration is analogous to hydrohalogenation, for the same reasons.
- If a new chiral center is formed, a mixture of *R* and *S* is obtained



- As always, if a chiral center is formed in a reaction, then a racemic mixture is obtained.
- **Practice with SkillBuilder 8.3 – Drawing a Mechanism**

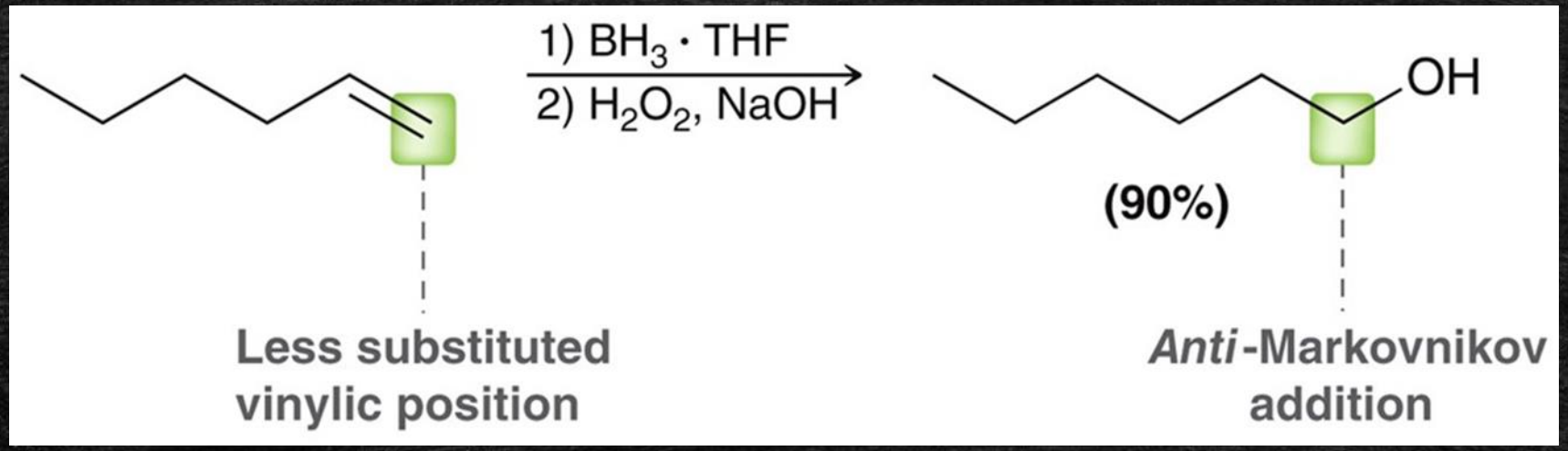
Oxymercuration-Demercuration / Overview

- Markovnikov hydration (H_2O, H_2SO_4) has limited application… rearrangements often occur, giving mixture of products
- **Oxymercuration-demercuration** is an alternative
  - Markovnikov addition of **H** and **OH**
  - **No rearrangements occur**



Hydroboration-Oxidation / Overview

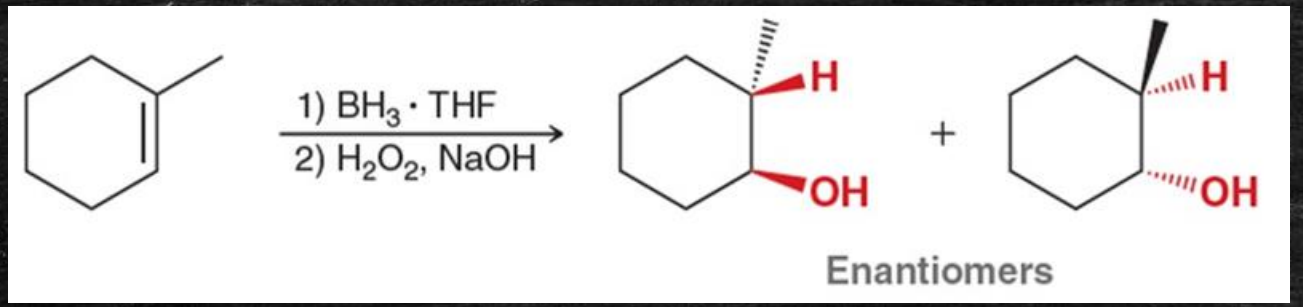
- **Hydroboration-Oxidation** adds **H** and **OH** with ***anti*-Markovnikov** regioselectivity



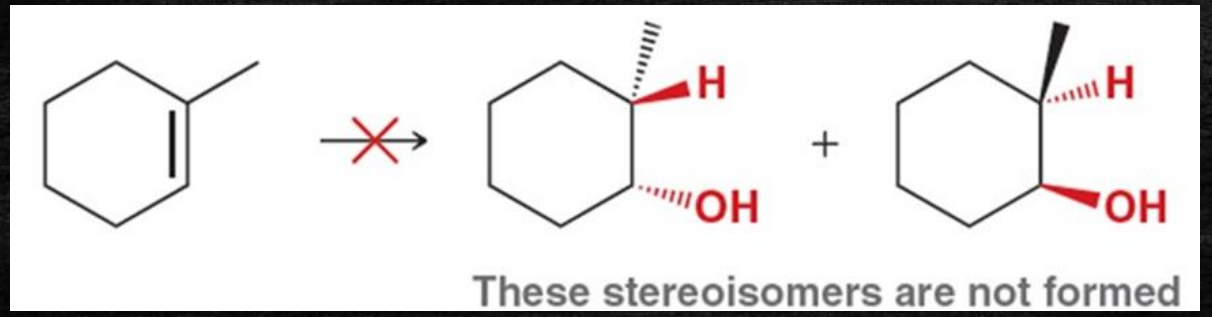
- Note that this is a two-reaction sequence

Hydroboration-Oxidation / Stereoselective

- Hydroboration-Oxidation is also **stereoselective**
  - **H** and **OH** are added in a ***syn*** fashion

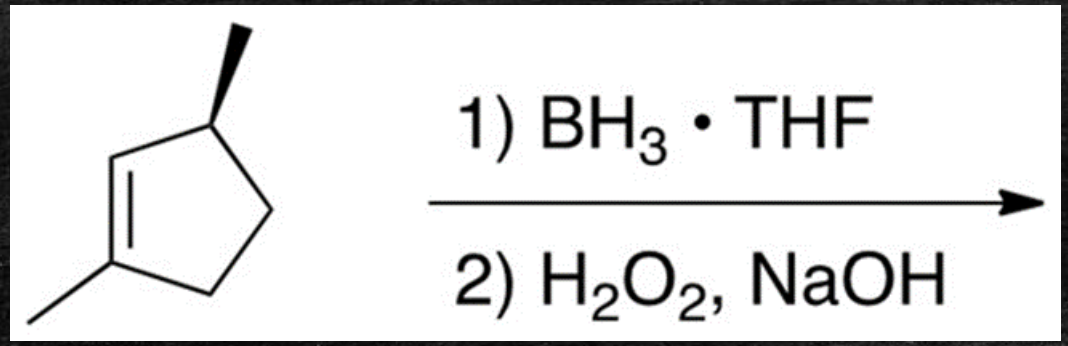


- ***Anti*** addition is NOT observed



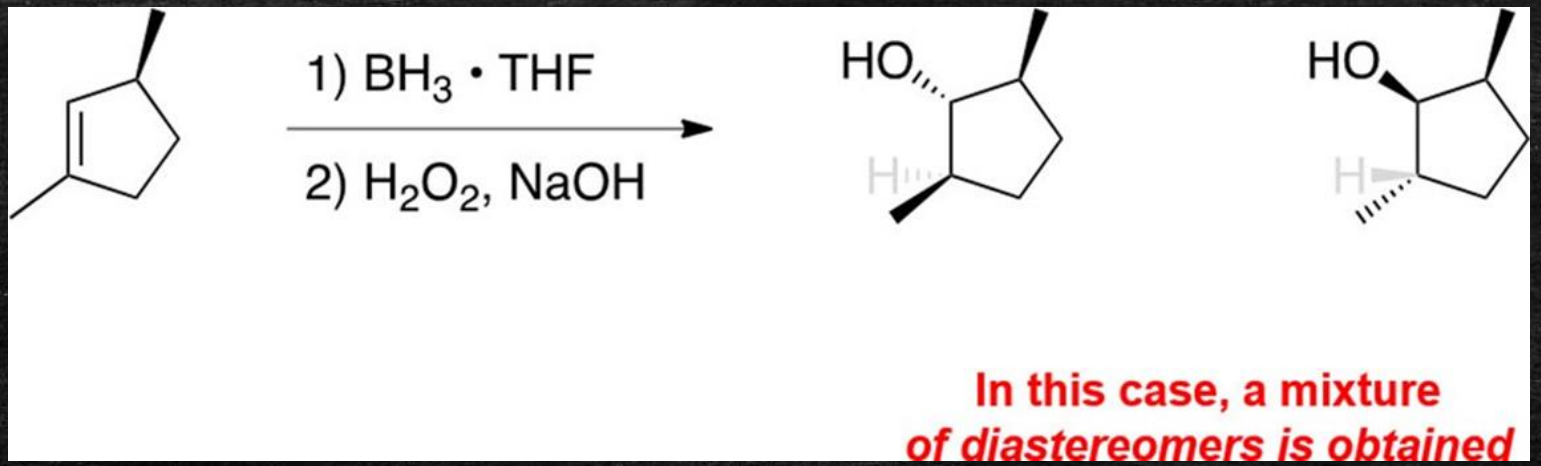
Hydroboration-Oxidation / Practice

- Predict the product(s) of the following reaction:



Hydroboration-Oxidation / Practice Answer

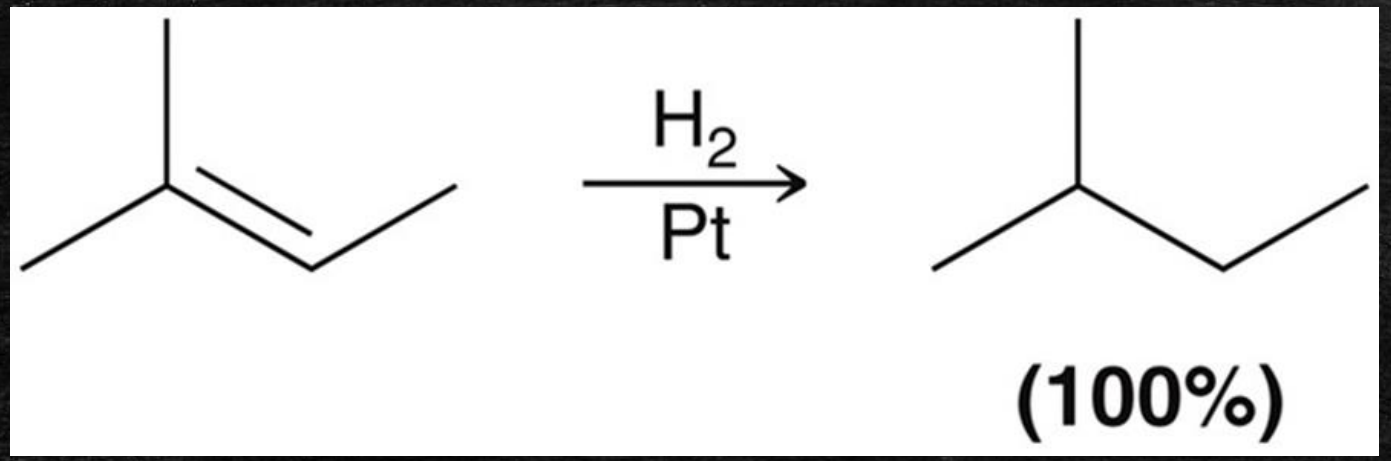
- Predict the product(s) of the following reaction:



- Two chiral centers are formed.
- **Practice with SkillBuilder 8.4 – Predict the Products**

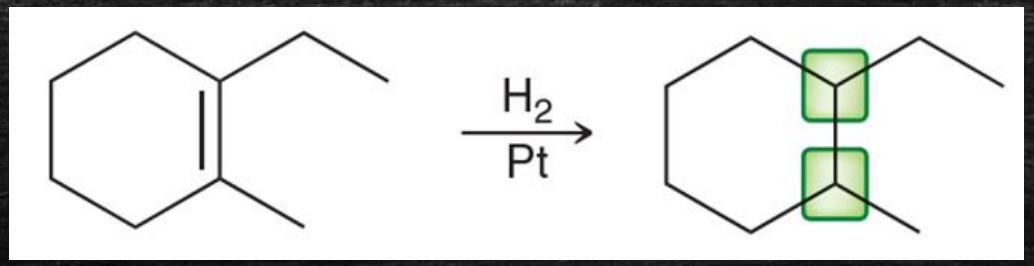
Catalytic Hydrogenation / Overview

- **Hydrogenation** – the addition of H_2 across a C=C double bond
- Requires a metal catalyst
- An **alkene** is reduced to the corresponding **alkane**

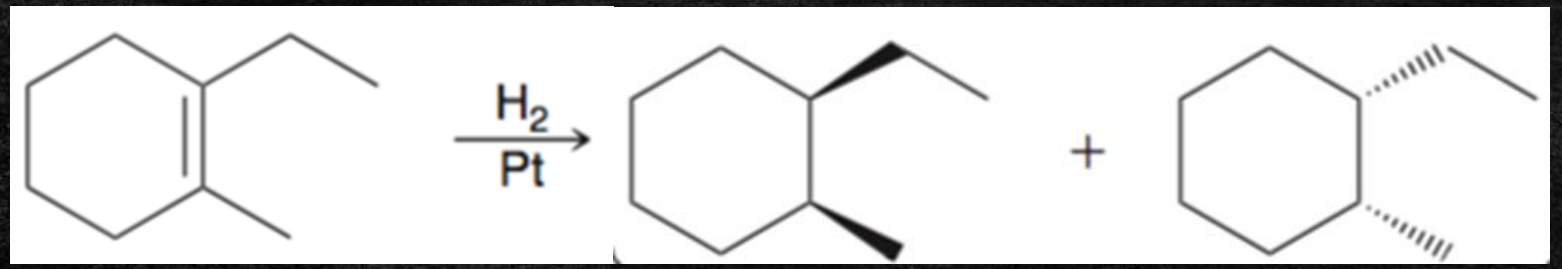


Catalytic Hydrogenation Stereoselectivity / Syn Addition

- **Hydrogenation** – the addition of H_2 across a C=C double bond
- **Stereospecific** – only ***syn* addition** is observed



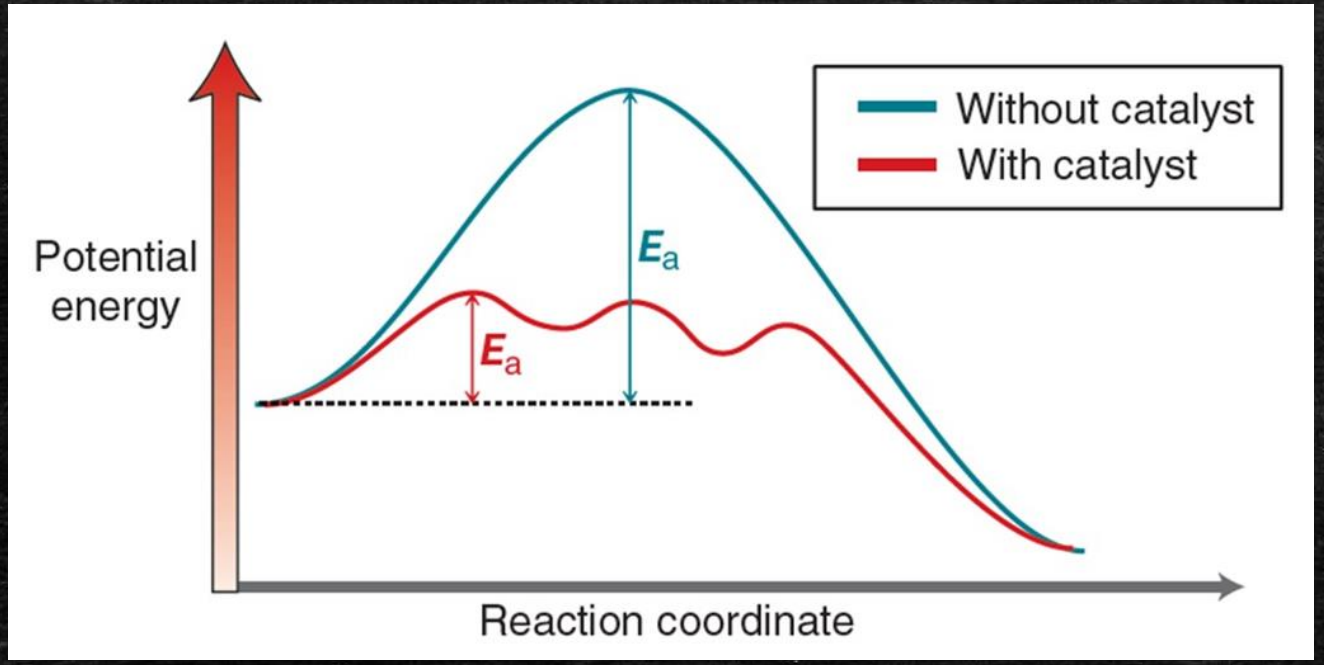
Two chiral centers are formed



only the stereoisomers resulting from *syn* addition are obtained

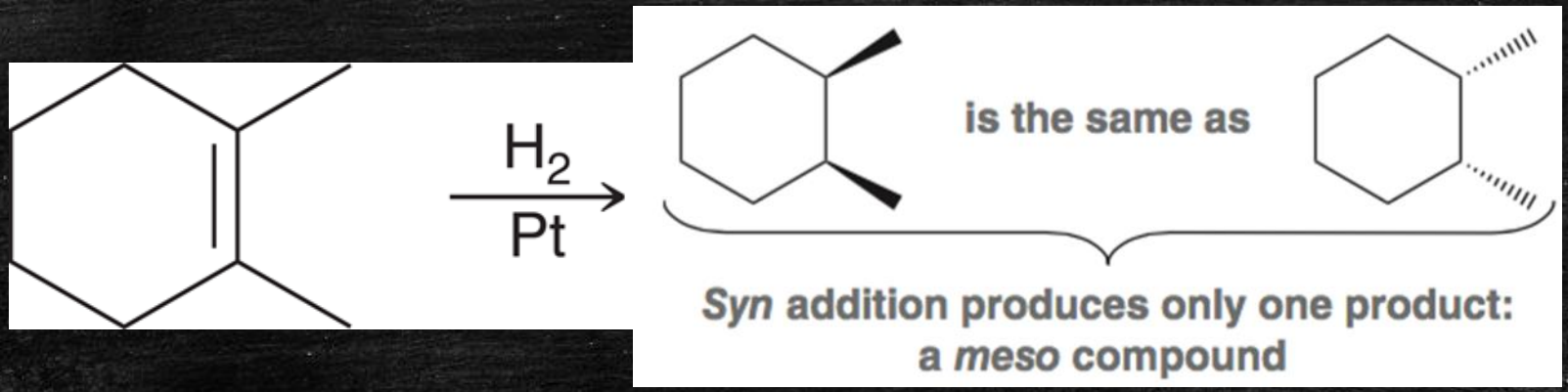
Catalytic Hydrogenation / Graphical Interpretation

- Without the metal catalyst, the addition of H_2 is too slow due to a very high activation energy (E_a)



Catalytic Hydrogenation / Symmetrical Alkenes

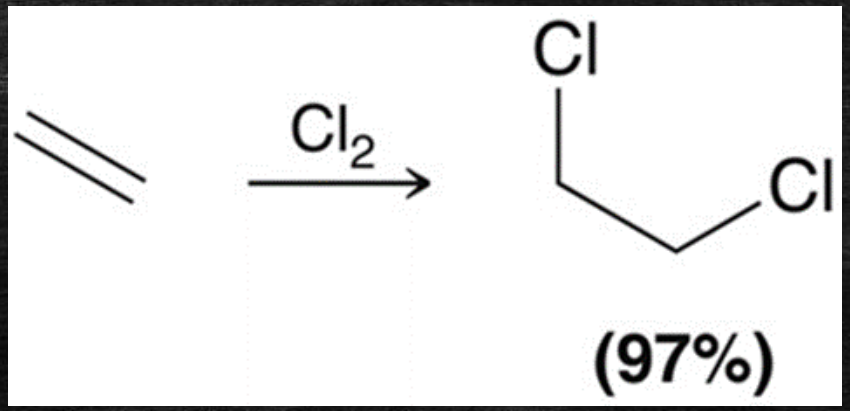
- *Syn* addition of H_2 to a symmetrical alkene will not produce a pair of enantiomers.
- A *meso* compound will be produced instead.



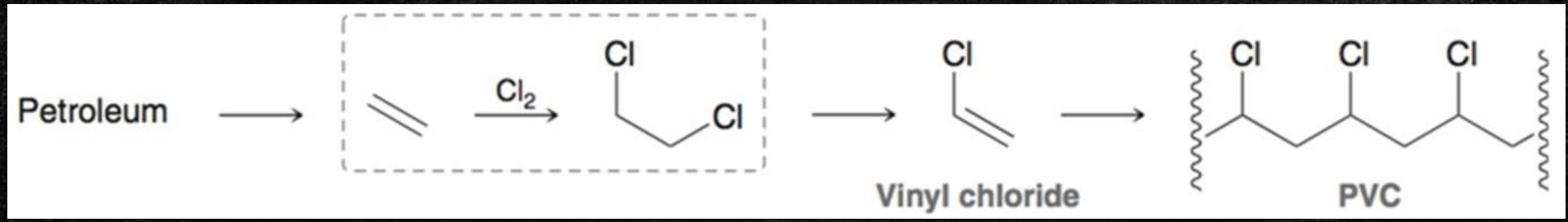
Practice with SkillBuilder 8.5 – Predict the Products (H_2)

Halogenation / Overview

- **Halogenation** – addition of two halogen atoms across a C=C double bond

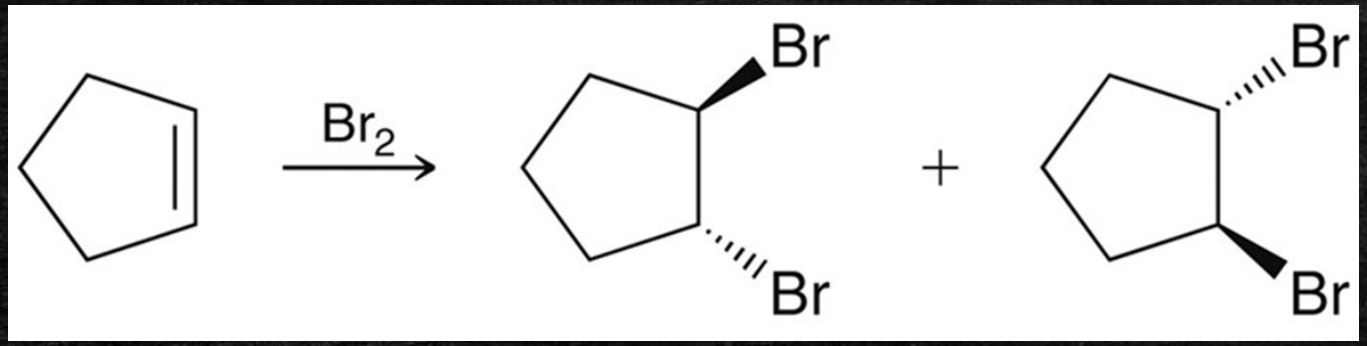


This is a key step in the production of polyvinylchloride (PVC)



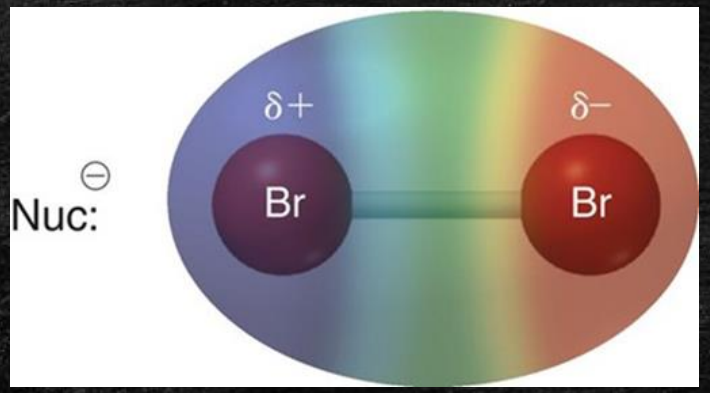
Halogenation / Anti Addition

- Halogenation only **practical with Cl_2 and Br_2**
- Halogenation with I_2 is poor; halogenation with F_2 is too violent
- **Stereoselectivity** – halogenation occurs with ***anti* addition**

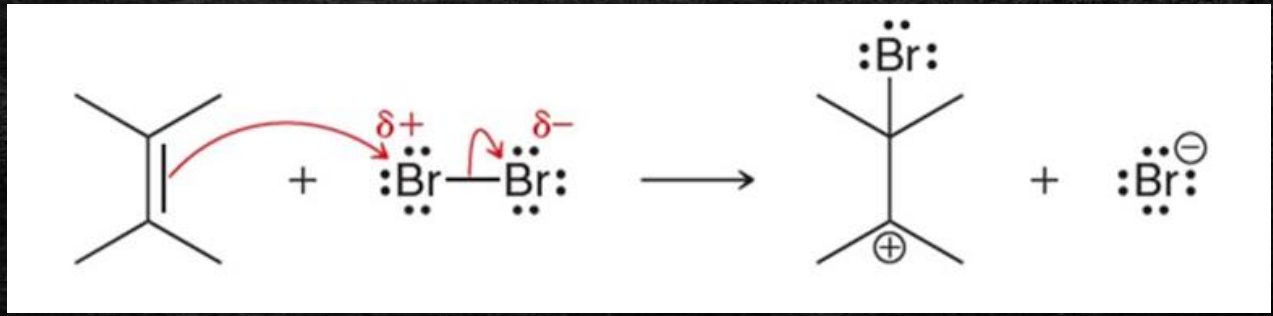


Halogenation / Bromine

- Br_2 is nonpolar, but polarizable. Approach of a nucleophile will induce a dipole
- Think of Br_2 as a bromine atom bonded to a good leaving group

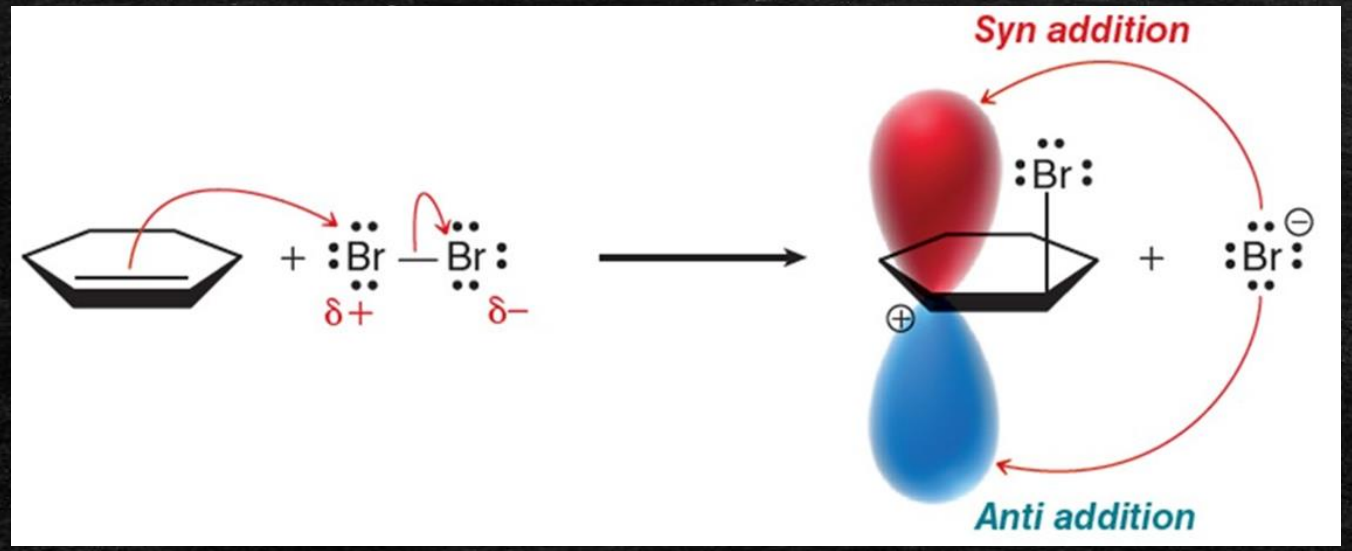


The alkene acts as the nucleophile



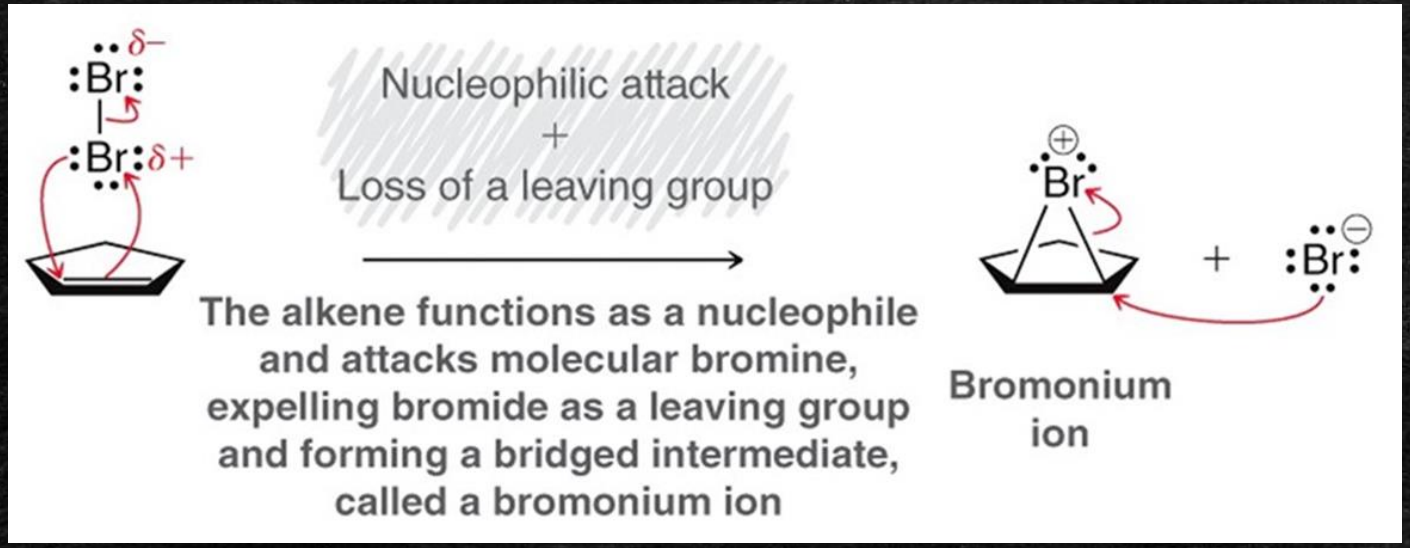
Halogenation – Mechanism / No Syn Addition

- Only ***anti addition*** is observed, so the mechanism is not consistent with a true carbocation intermediate
- *Syn* addition doesn't occur



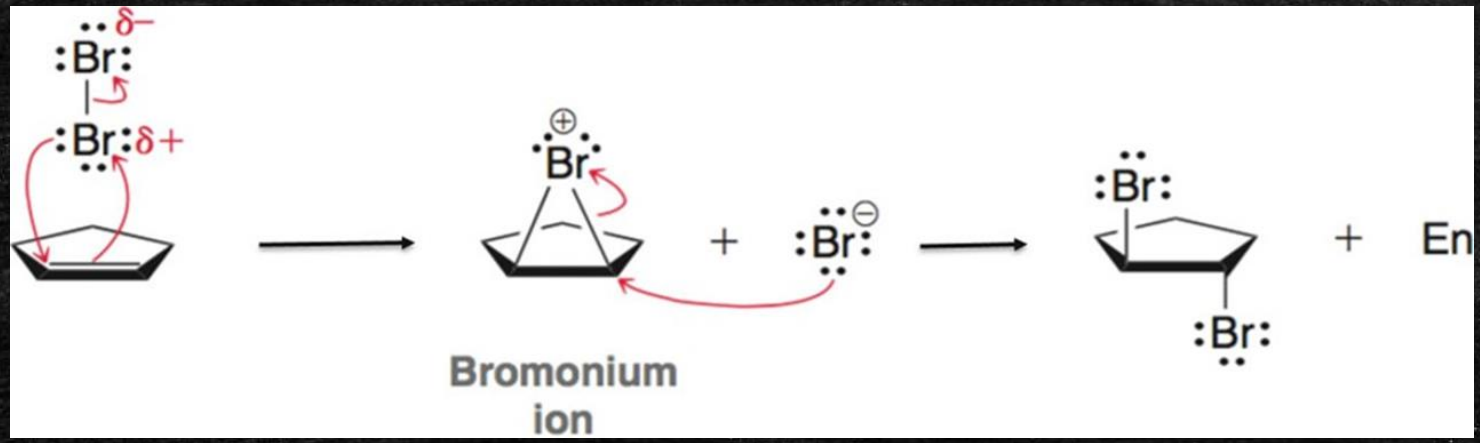
Halogenation – Mechanism / Anti Addition

- The formation of a **bromonium ion intermediate** is consistent with ***anti* addition**
- This intermediate is similar to the mercurinium ion



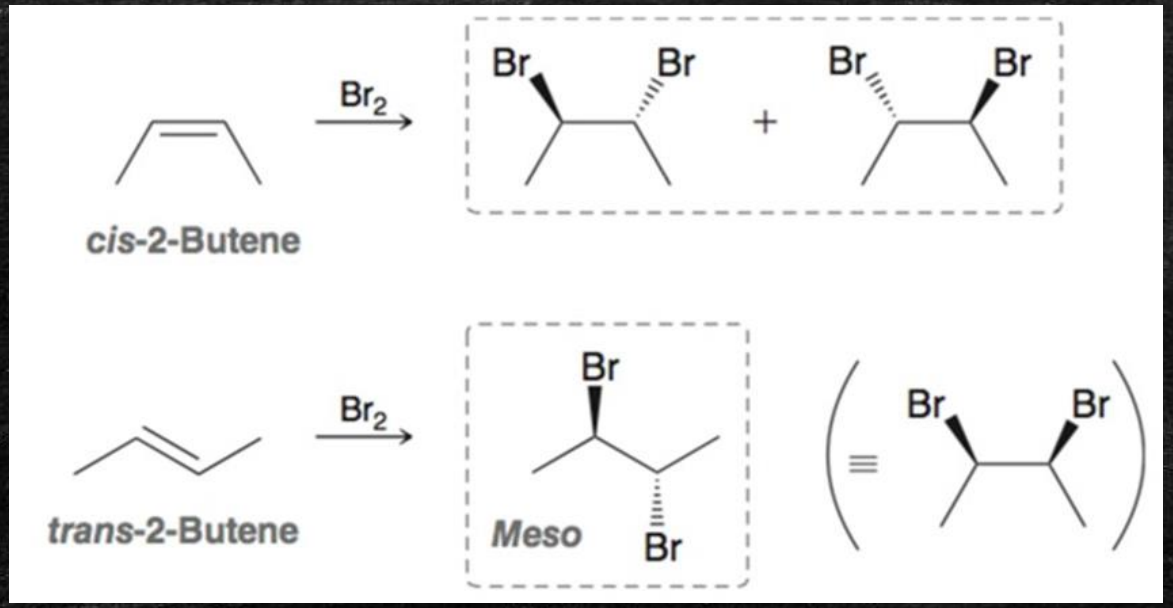
Halogenation – Mechanism / Final Step

- The formation of a **bromonium ion intermediate** is consistent with ***anti* addition**
- Br– attacks the bromonium ion in an S_N2 process (gives *anti* addition)



Halogenation – Stereoselectivity

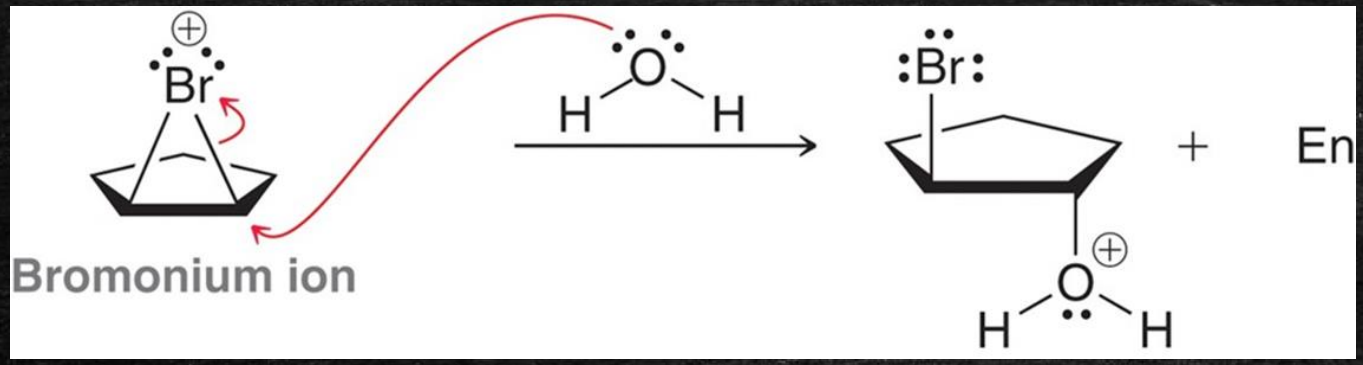
- Halogenation is **stereospecific**, the stereochemistry of the starting alkene determines the stereochemistry of the product(s)



Practice with CONCEPTUAL CHECKPOINT 8.24 – Predict the Product

Halohydrin Formation / Overview

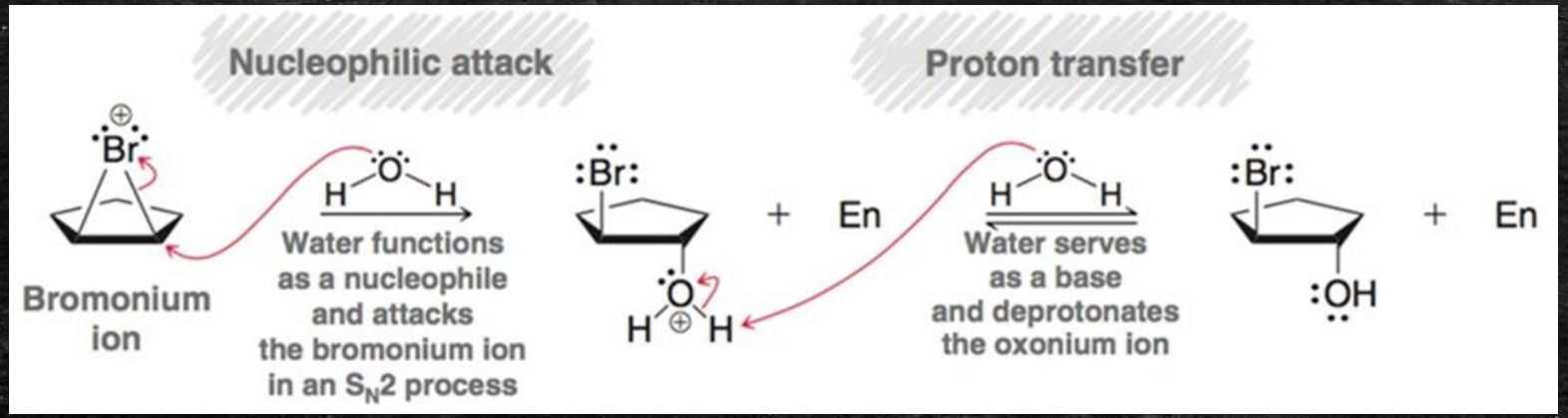
- **Halohydrins** – formed when halogenation is conducted in water
- **Water acts as the nucleophile** that attacks the bromonium ion

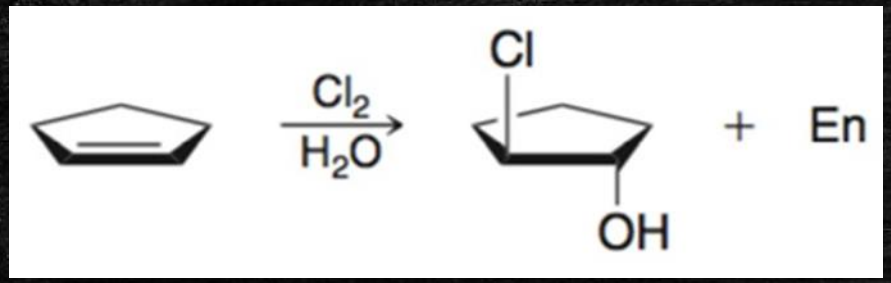


There are many more H_2O molecules compared to Br^- ions, so attack of the bromonium ion by H_2O is more likely than Br^-

Halohydrin Formation / Bromohydrin and Chlorohydrin

- After water attacks, it is deprotonated to yield the neutral **bromohydrin** product

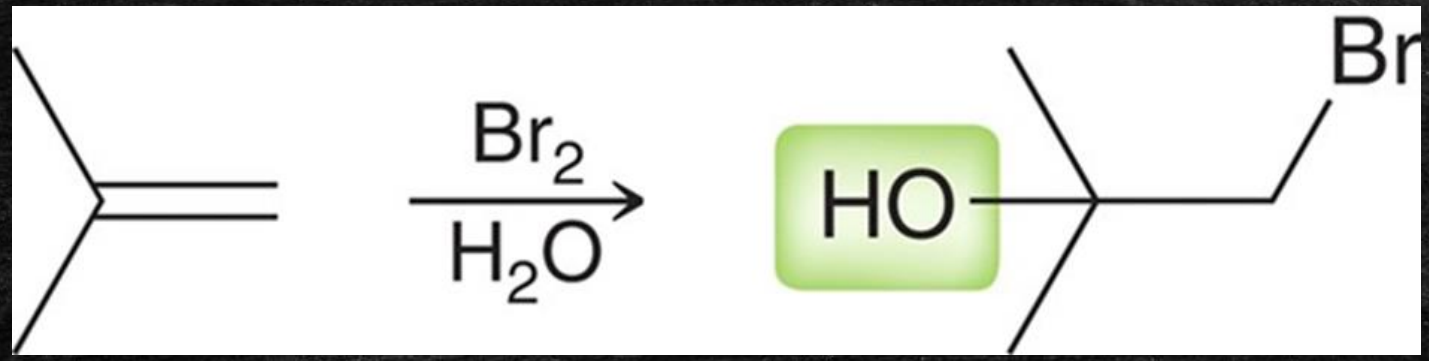




Here, the product is called a chlorohydrin

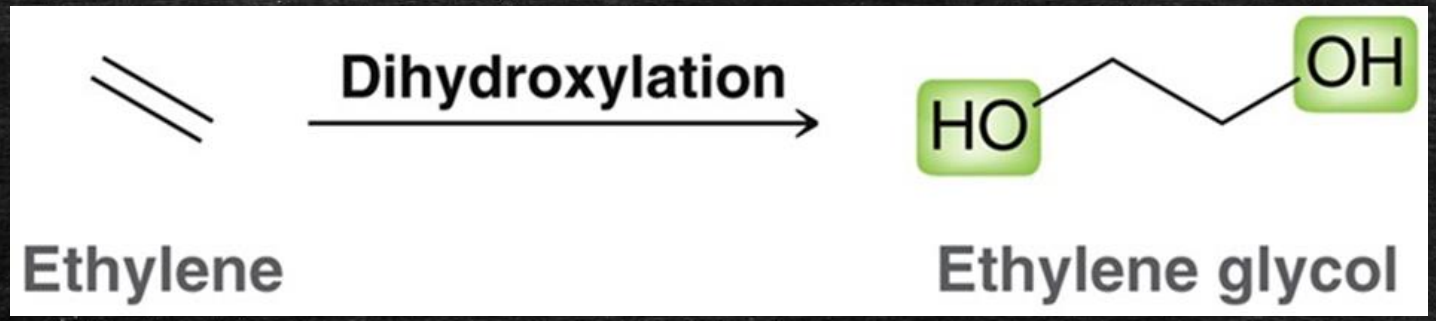
Halohydrin Formation – Regioselectivity / Halide vs OH addition

- Halohydrin Formation is **regioselective**
  - The **halide** adds to the **less-substituted carbon**
  - The **OH** adds to the **more-substituted carbon**

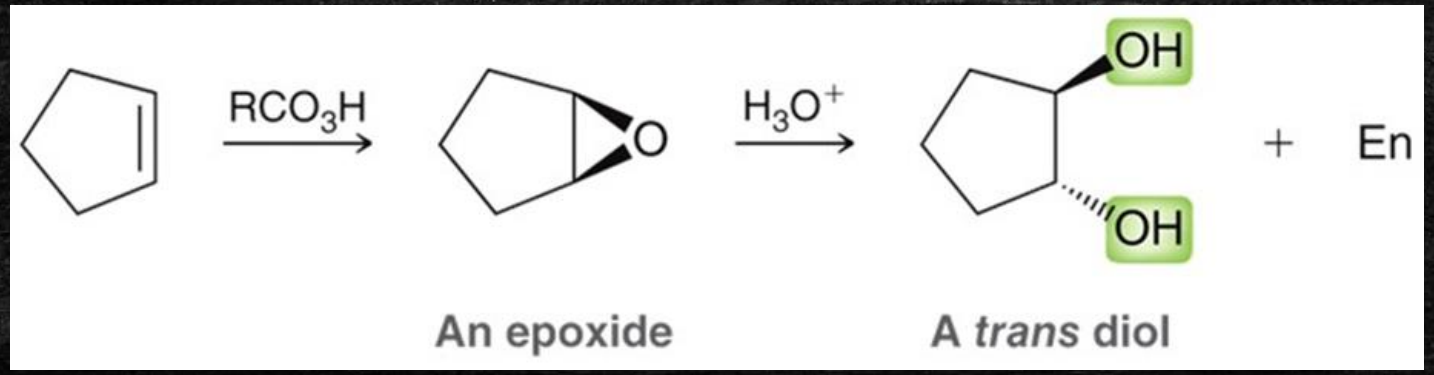


Anti Dihydroxylation / Overview

- **Dihydroxylation** – addition of **OH** and **OH** across the π bond

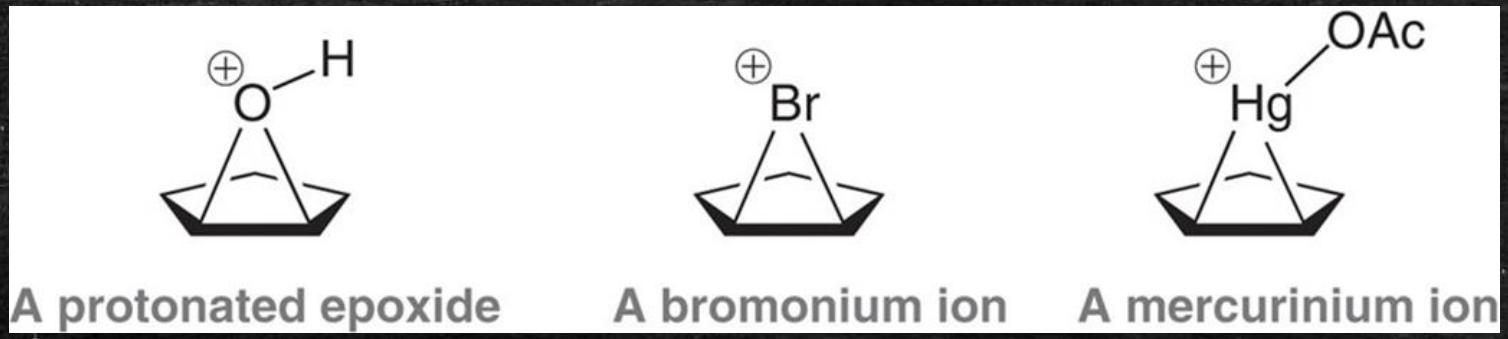


- ***Anti* dihydroxylation** of an alkene is a two-step procedure



Anti Dihydroxylation / Similar Intermediates

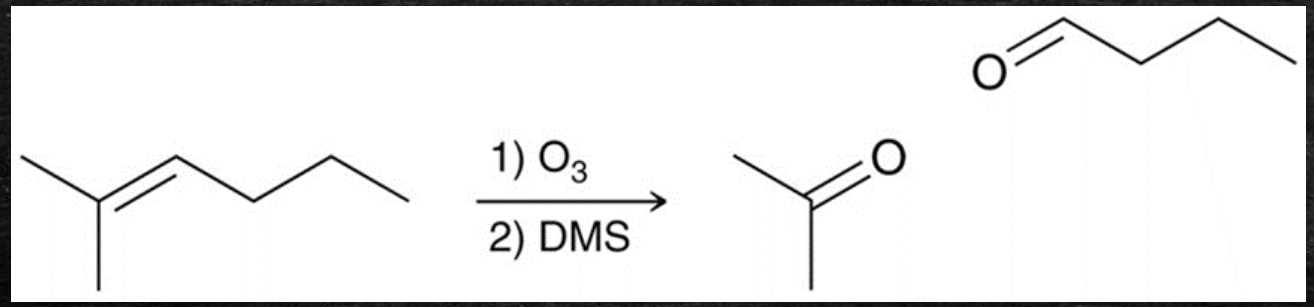
- Note the similarities between these three key intermediates



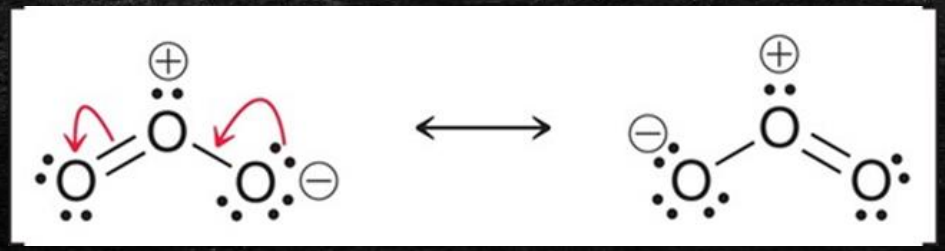
- Ring strain and a +1 formal charge makes these structures good electrophiles
- All three yield ***anti*** products, because the nucleophile must attack from the side opposite the leaving group (S_N2-like process)
- **Practice with SkillBuilder 8.7 – Predict the Products**

Oxidative Cleavage / Overview

- C=C double bonds are also reactive toward oxidative cleavage
- Ozonolysis is one such process



- Ozone exists as a resonance hybrid of two contributors



Predicting Products of Addition Rxns

1. Analyze the reagents used to determine what groups will be added across the C=C double bond
2. Determine the regioselectivity (Markovnikov or *anti*-Markovnikov)
3. Determine the stereospecificity (*syn* or *anti* addition)

- The more familiar you are with the **mechanisms** and the **Chapter 8 reagents**, the easier predicting products will be
- **Practice with SkillBuilder 8.9 – Predict the Products**

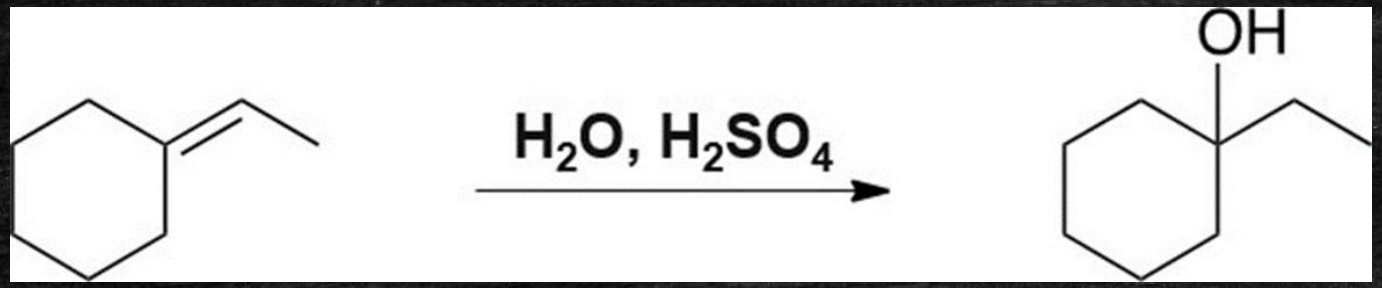
One-Step Syntheses / Practice

- To plan a synthesis, assess the reactants and products to see what changes need to be made
- Give reagents and conditions for the following:

- **Addition reaction**
- **Add H and OH**
- **Markovnikov regiochem.**

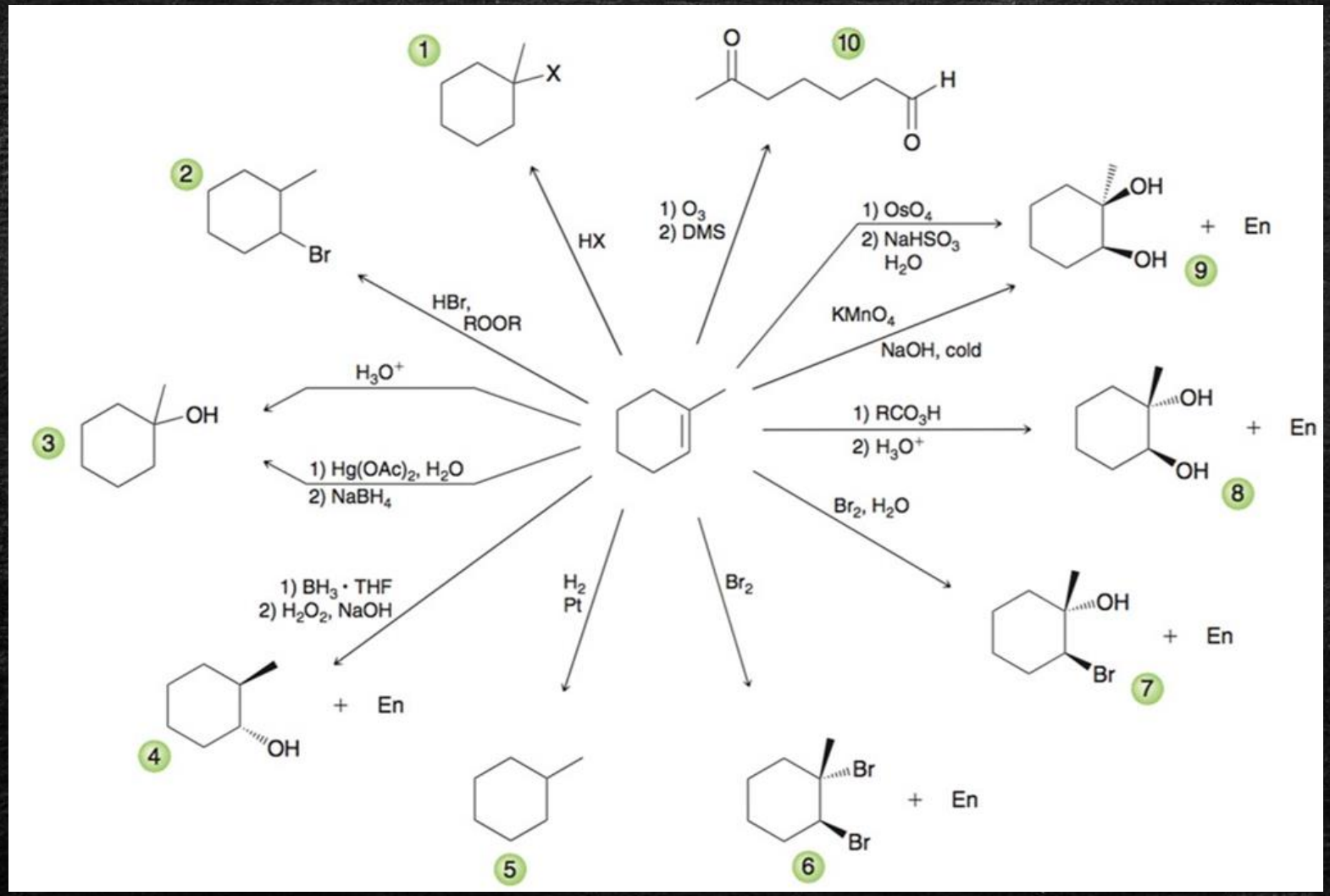
One-Step Syntheses / Practice Answer

- To plan a synthesis, assess the reactants and products to see what changes need to be made
- Give reagents and conditions for the following:



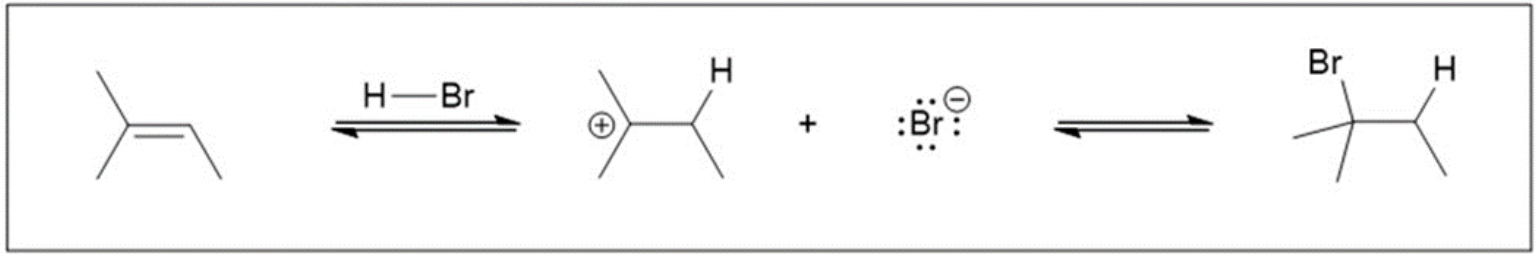
Practice with additional examples in SkillBuilder 8.10 – Propose a Synthesis

Review of Alkene Reactions (cont. 1)

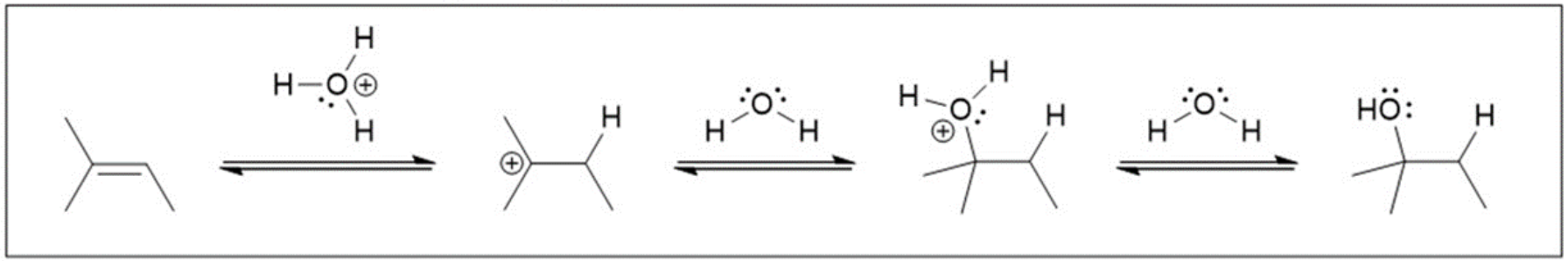


Mechanism 8.1 & 8.2 Review – Add Arrows

Mechanism 8.1 Hydrohalogenation

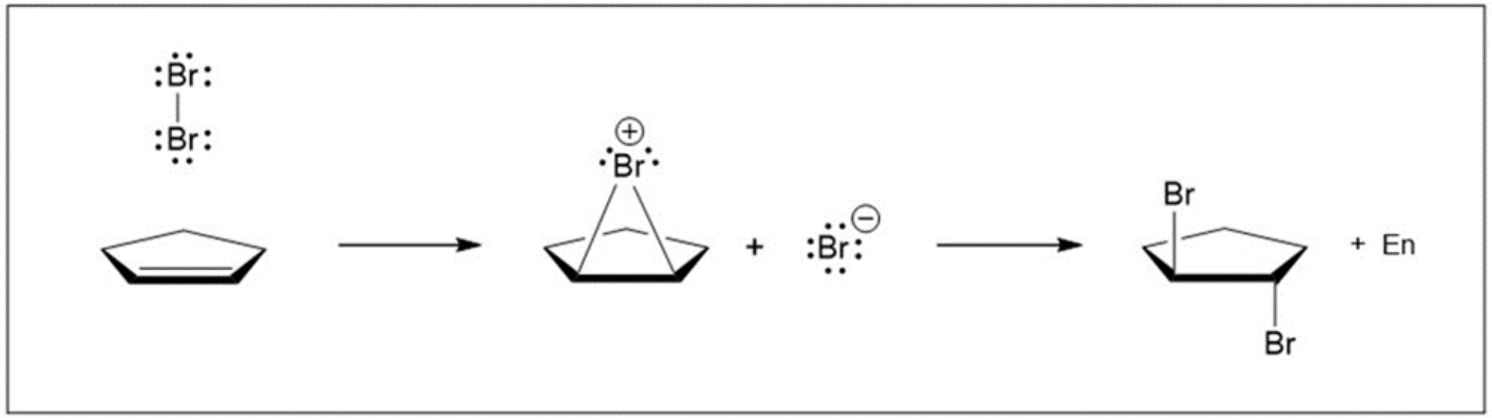


Mechanism 8.2 Acid-Catalyzed Hydration

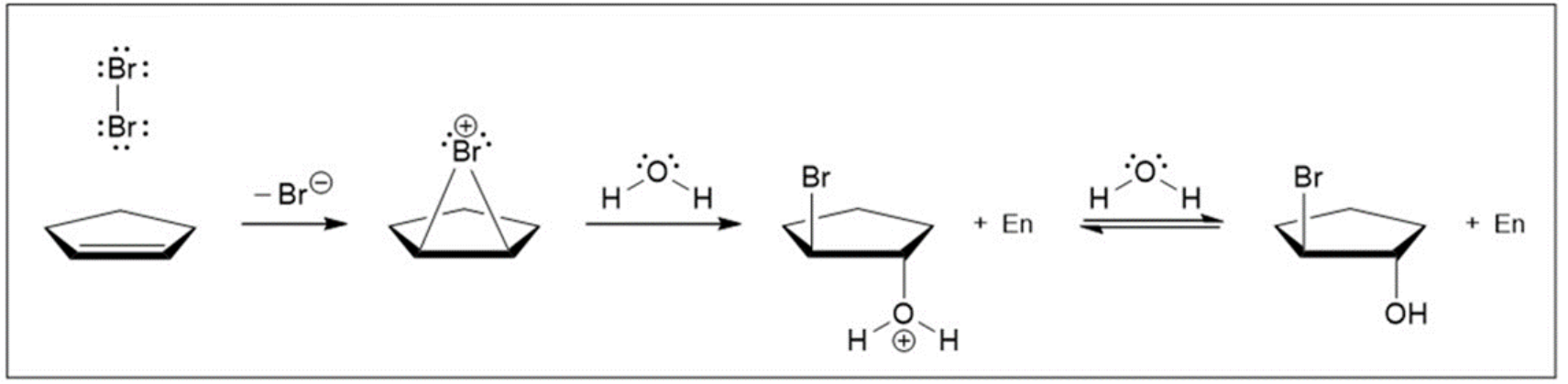


Mechanisms 8.4 & 8.5 Review – Add Arrows

Mechanism 8.4 Halogenation



Mechanism 8.5 Halohydrin Formation



CH-211 Organic Chemistry I

Chapter 5: Stereisomerism

By Ilari Filpponen

Textbook: Organic Chemistry, D.R. Klein. 4th ed. 2021 John Wiley & Sons, Inc.

Isomers – Overview / Two Types

- Isomers are different compounds that have the same formula
- There are two general types of isomers

Isomers

Constitutional isomers

Same molecular formula but different constitution (order of connectivity of atoms)

Stereoisomers

Same molecular formula and constitution but different spatial arrangement of atoms

Isomers – Overview / Stereoisomers

- Although the two molecules below have the same connectivity, they are not identical. So they are **stereoisomers**

(Both groups on same side of ring)

(Both groups on opposite sides)

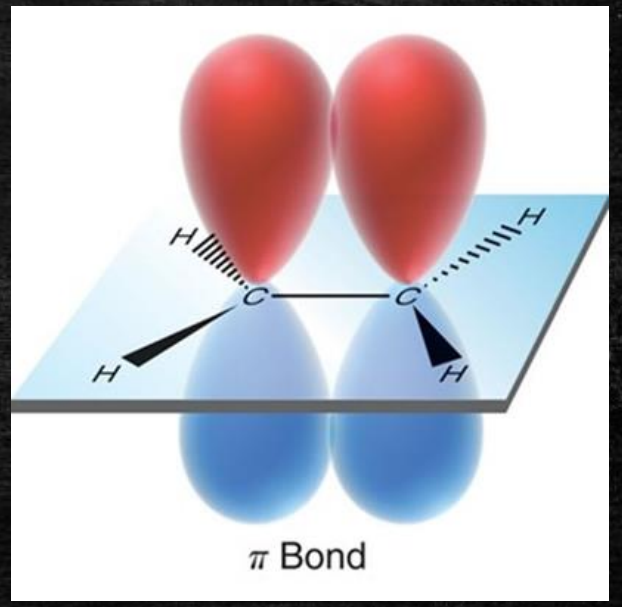
- In order to give these compounds unique IUPAC names, we use the *cis* and *trans* prefixes

Isomers – Overview / Examples

- To maintain orbital overlap in the pi bond, C=C double bonds cannot freely rotate.
- Although the two molecules below have the same connectivity, they are not identical… they are **stereoisomers**

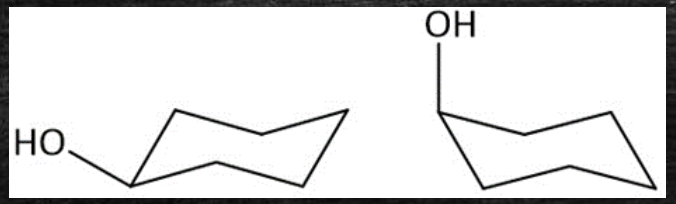
Groups on same side of pi bond

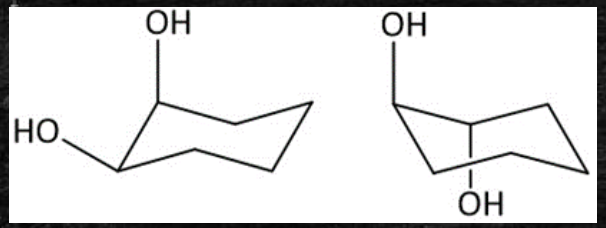
Groups on opposite sides

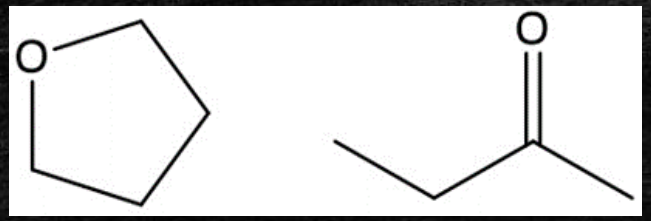


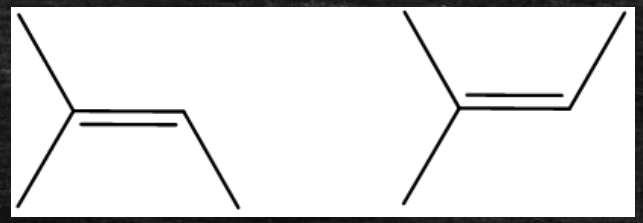
Isomers – Overview / Practice

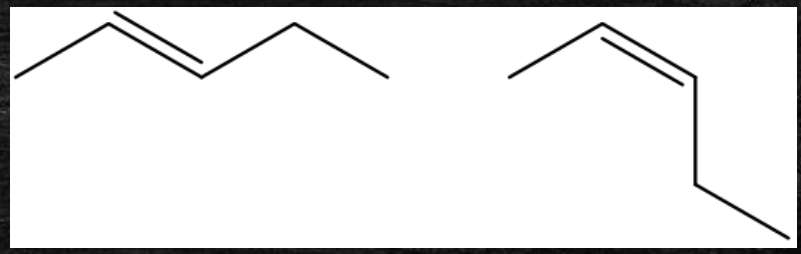
- Identify the following pairs as either constitutional isomers, stereoisomers, or identical structures







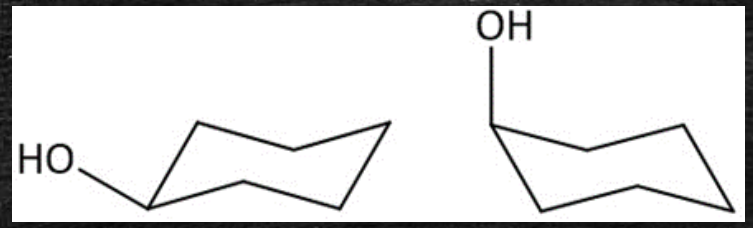




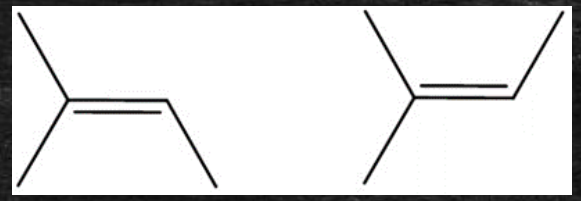
Answers on the next slide

Isomers – Overview / Practice Answers

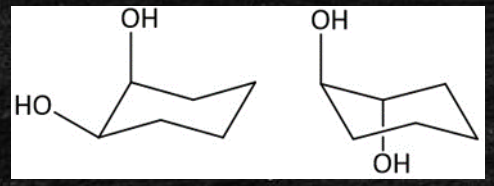
- Identify the following pairs as either constitutional isomers, stereoisomers, or identical structures



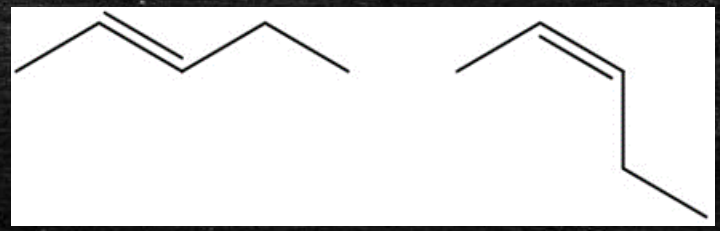
identical



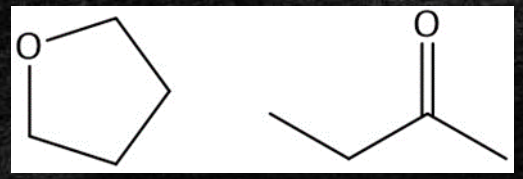
identical



stereoisomers



stereoisomers



constitutional isomers

Stereoisomers / Definition of a Chiral Molecule

- *cis-trans* isomerism is only one type… there are other important stereoisomeric relationships
- To identify such stereoisomers, we must be able to identify **chiral** molecules
- A **chiral** object is **asymmetric**, which means it is not the same as its mirror image (i.e. **not superimposable** on its mirror image)
- You can test whether two objects are identical by seeing if they are **superimposable**.

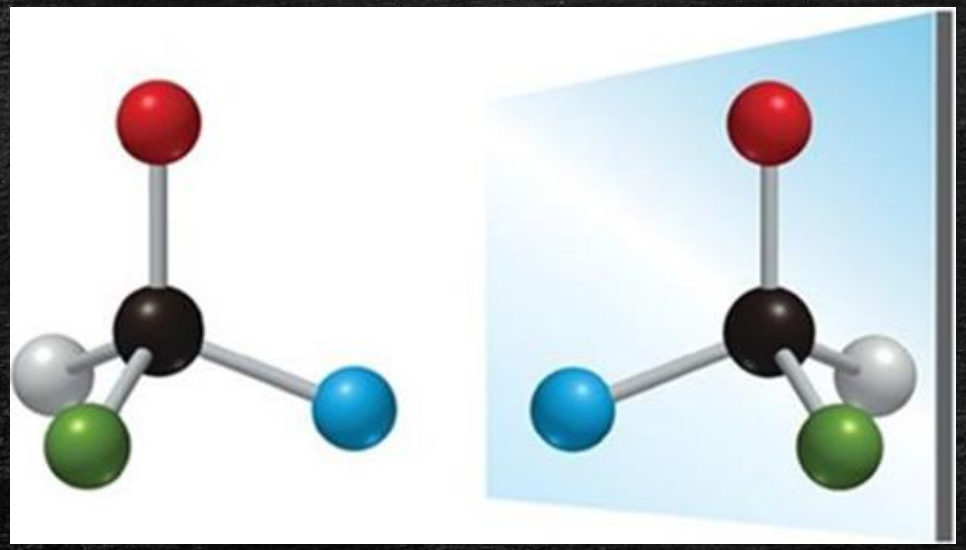
Molecular Chirality

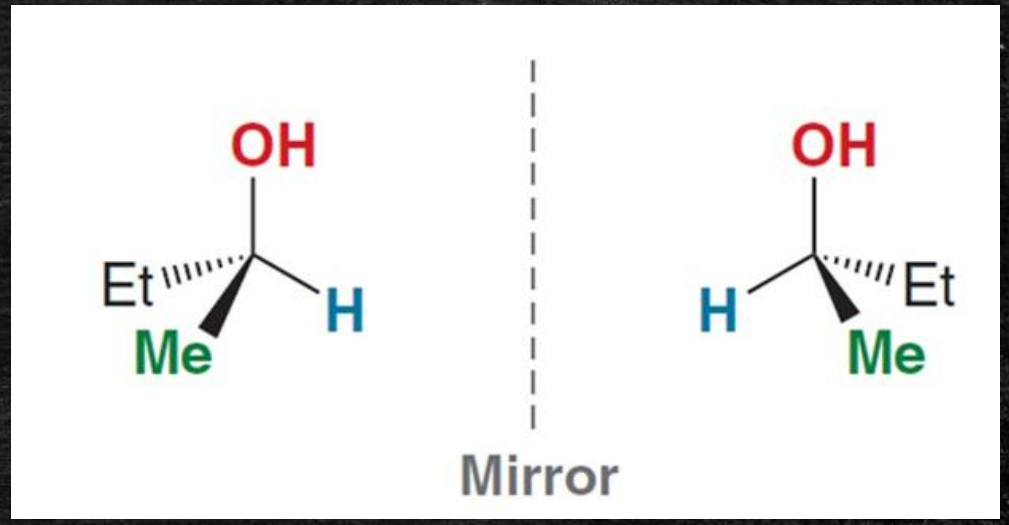
- Chirality is important in molecules
  - Because two chiral molecules are mirror images, they will have many identical properties, but because they are not identical, their **pharmacology** may be very different
- Visualizing mirror images of molecules and manipulating them in 3-D space to see if they are superimposable can be very challenging, so…

  …it is **absolutely critical** that you **use handheld models** as visual aids

Stereoisomers / Mirror Images

- Chirality most often results when a carbon atom is bonded to four unique groups of atoms.

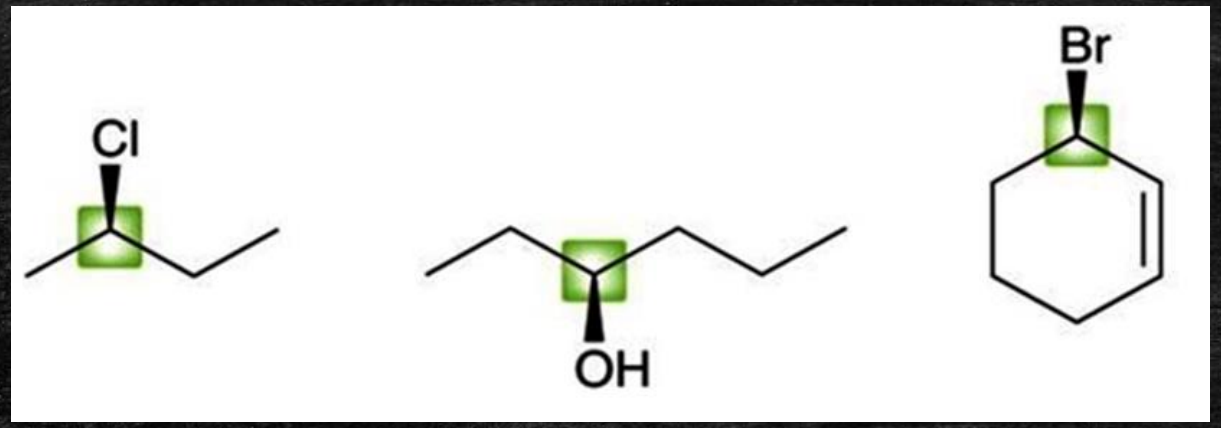




- Make a handheld model to prove to yourself that they are not superimposable

Stereoisomers / Practice One

- When an atom (like carbon) forms a tetrahedral center with four different groups attached to it, it is called a chiral center
- Analyze the attachments for each chiral center below

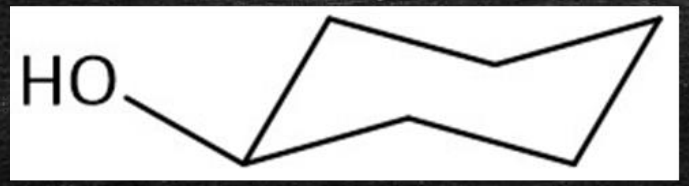


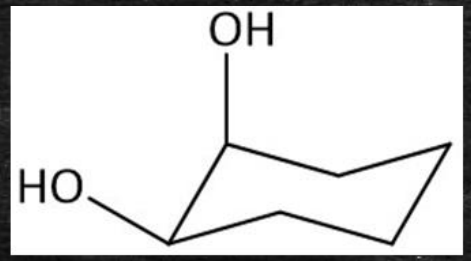
Each highlighted carbon is bonded to 4 different groups and is a chiral center

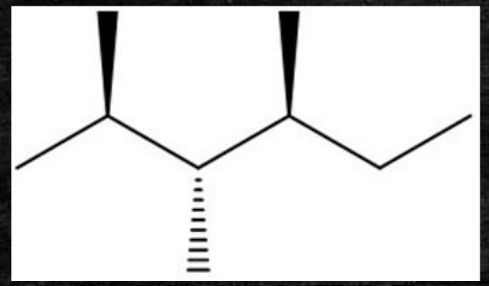
Practice with SkillBuilder 5.1 – Locating Chiral Centers.

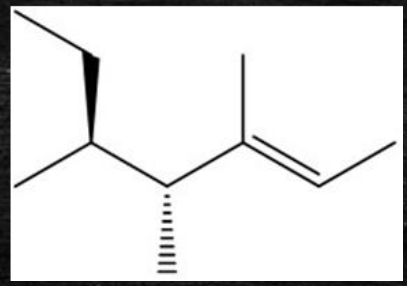
Stereoisomers / Practice Two

- How many chiral centers are in each of the following compounds?







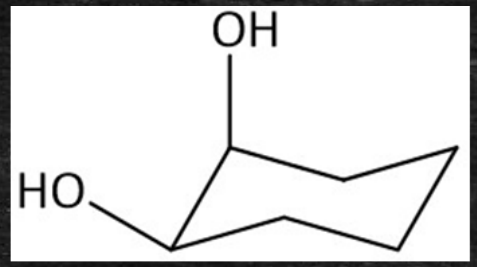


Answers on the next slide

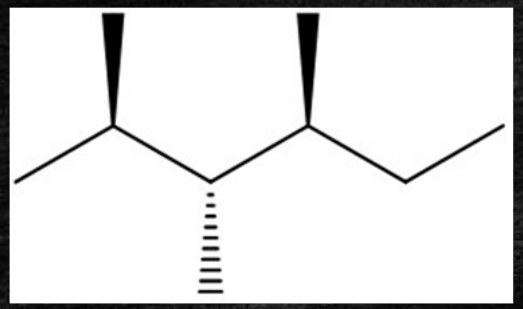
Stereoisomers / Practice Two Answers

- How many chiral centers are in each of the following compounds?

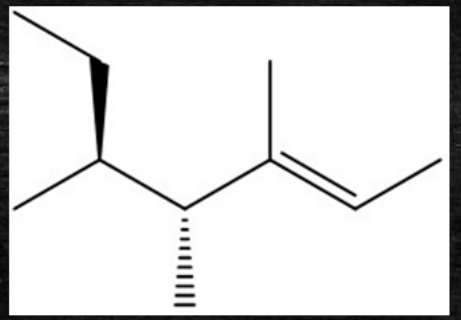
no chiral centers



two chiral centers



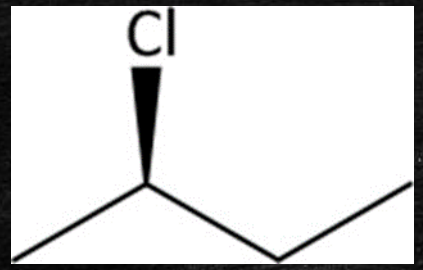
two chiral centers



two chiral centers

Enantiomers / Definition of Enantiomers

- Some stereoisomers can also be classified as enantiomers
- **Enantiomers** are two molecules that are mirror images but are **not superimposable**, therefore **not identical**
- Only a chiral compound can have an enantiomer

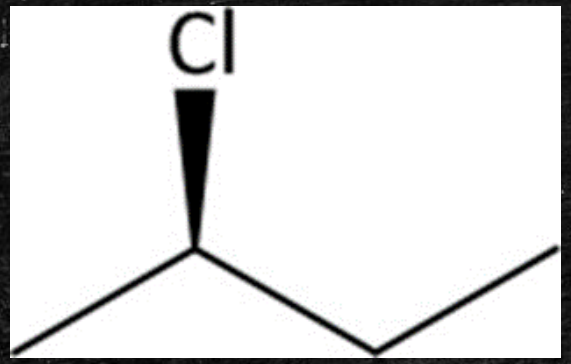


this is a **chiral compound…**

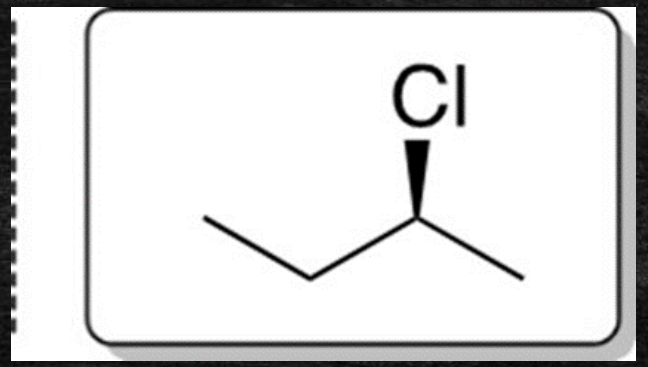
… the mirror image will be its enantiomer

Enantiomers / Example of Two Enantiomers

- Some stereoisomers can also be classified as enantiomers
- **Enantiomers** are two molecules that are mirror images but are **not superimposable**, therefore **not identical**
- Only a chiral compound can have an enantiomer



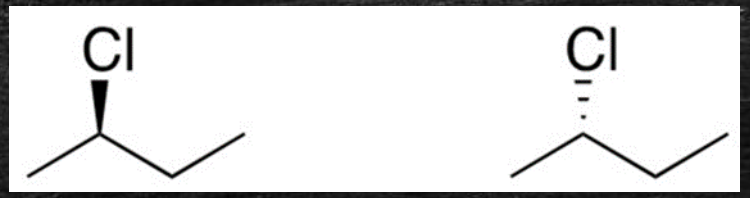
this is a chiral compound…



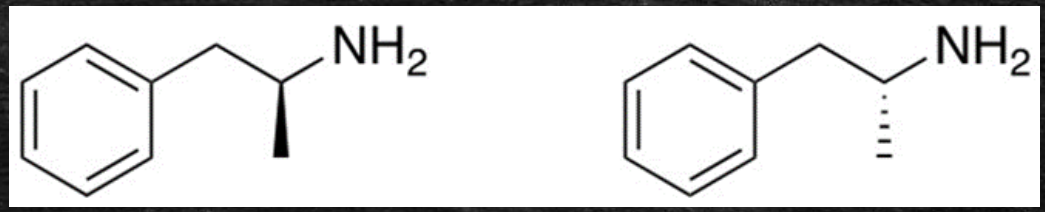
… the mirror image will be its enantiomer

Enantiomers / Drawing Enantiomers

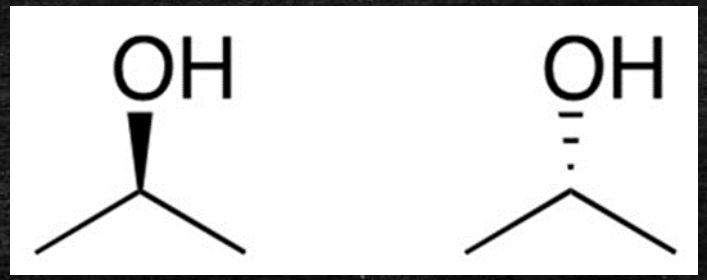
- Another, often easier way to draw the enantiomer of a chiral compound is to invert the dashes and wedges of a chiral center



enantiomers



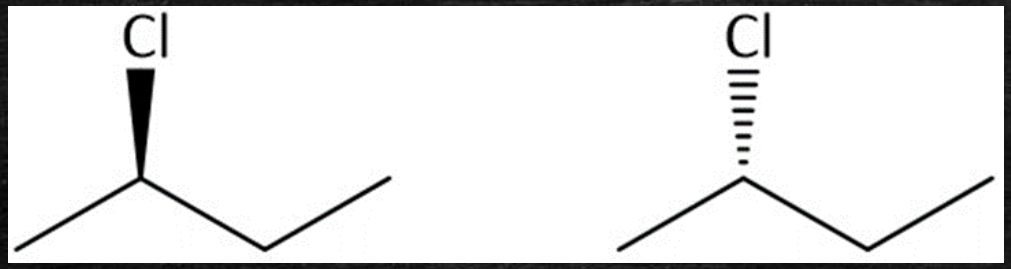
enantiomers



this is not a chiral compound, so inverting the dashes/wedges provides an identical structure!

Designating R vs. S Configuration / Introduction

- Enantiomers are different compounds, so they must not have identical names
- They have opposite configuration at their chiral center(s)



- We use the **Cahn-Ingold-Prelog system** to designate each chiral center as having either the "*R*" or "*S*" configuration.
- If a compound has the "*R*" configuration at a chiral center, then the enantiomer will have the "*S*" configuration

Designating R vs. S Configuration / Four Steps

- "R" or "S" is assigned to a chiral center using a stepwise procedure

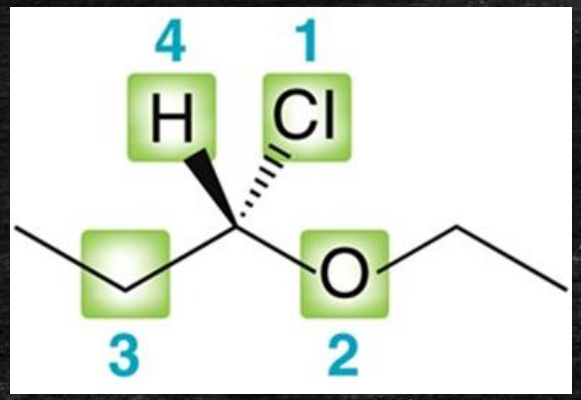
1. Using atomic numbers, prioritize the four groups attached to the chiral center (1, 2, 3 and 4)
2. Arrange the molecule in space so the lowest priority group faces away from you
3. Count the group priorities 1…2…3 to determine whether the order progresses in a clockwise or counterclockwise direction
4. Clockwise = *R* and Counterclockwise = *S*

- A handheld model can be very helpful visual aid for this process

Designating R vs. S Configuration / Step One

- The Cahn, Ingold and Prelog system

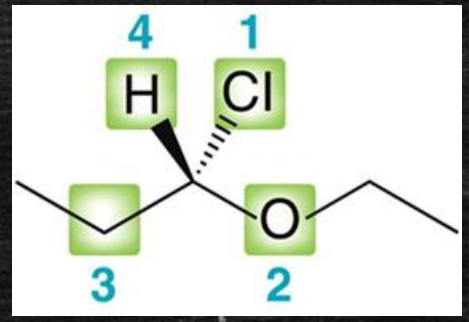
1. Using atomic numbers, prioritize the four groups attached to the chiral center. The higher the atomic number, the higher the priority

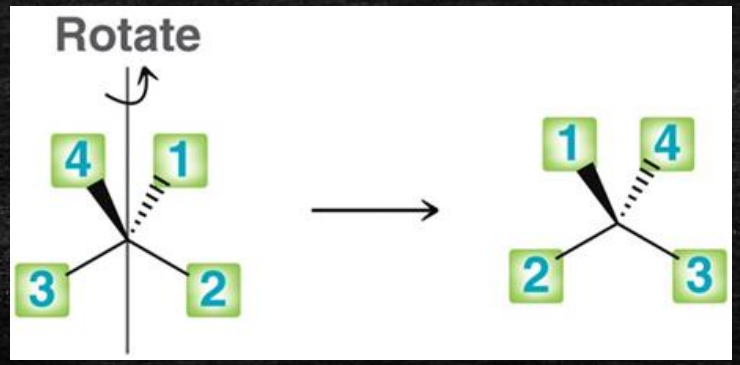


- The atom with the largest atomic number is assigned the highest priority (**1**), and so on…

Designating R vs. S Configuration / Step Two

- <u>The Cahn, Ingold and Prelog system end</u>
  2. Arrange the molecule in space so the lowest priority group faces away from you



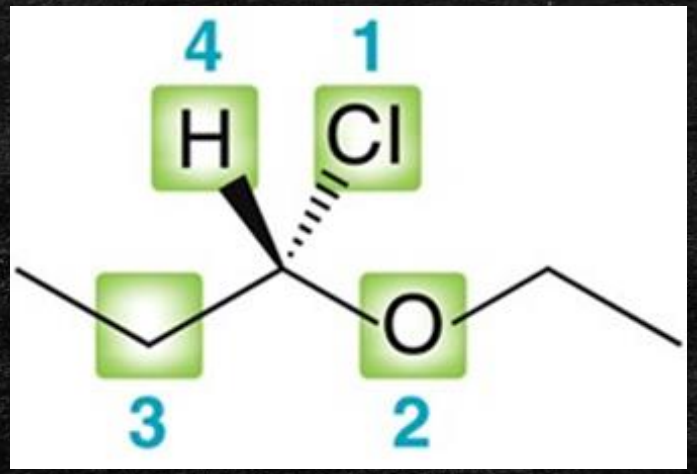


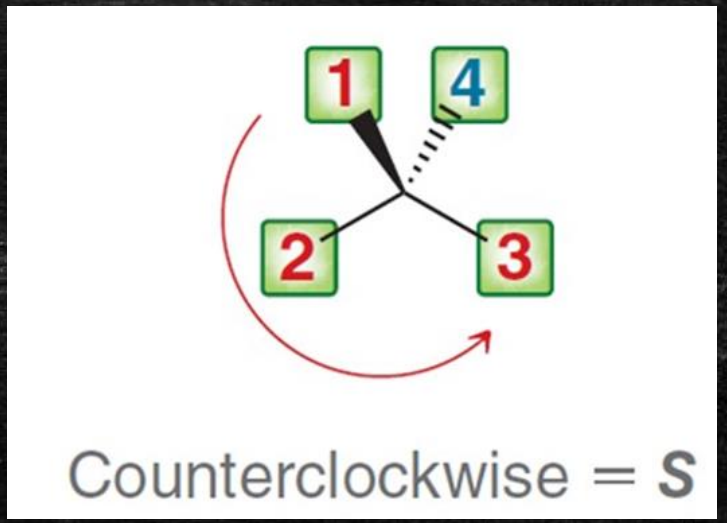
- **This is the step where it is most helpful to have a handheld model

Designating R vs. S Configuration / Step Three

- The Cahn, Ingold and Prelog system
  3. Counting the other group priorities, 1…2…3, determine whether the order progresses in a clockwise or counterclockwise direction

Clockwise = *R* and **Counterclockwise = *S***

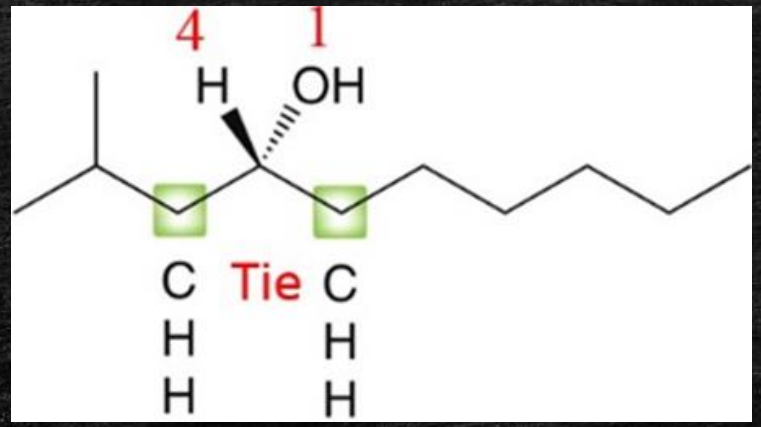




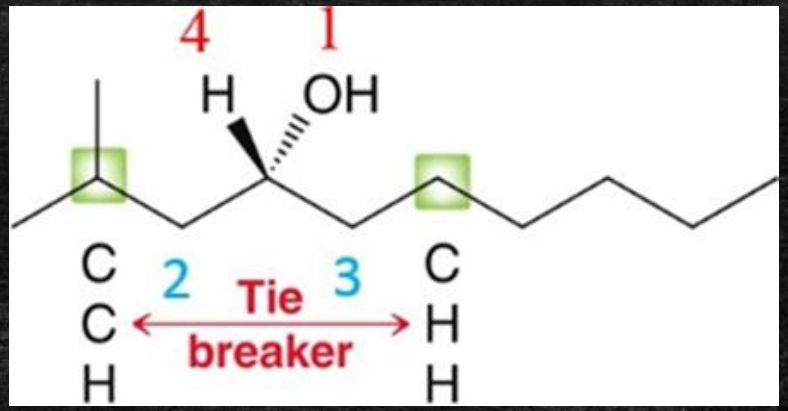
and so we just determined this chiral center has the (S) configuration

Designating R vs. S Configuration / Challenges

- When the groups attached to a chiral center are similar, it can be tricky to prioritize them
- Analyze the atomic numbers one layer of atoms at a time



The 1 and 4 groups are obvious, but there is a tie for priority 2 and 3

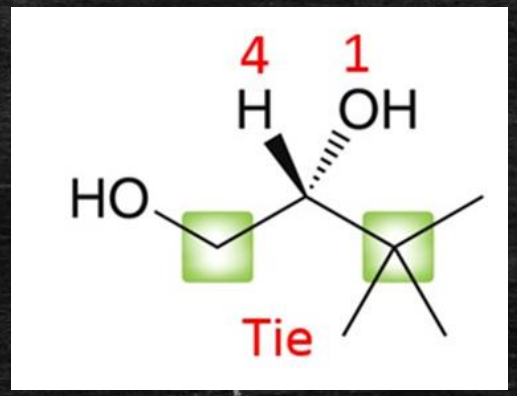


So we have to compare the atomic weights of the atoms bonded to each carbon to break the tie

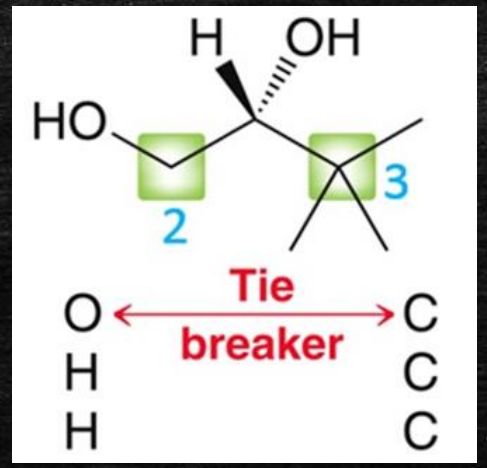
Designating R vs. S Configuration / First and Second Layers

- Analyze the atomic numbers one layer of atoms at a time

- **First layer**



- **Second layer**



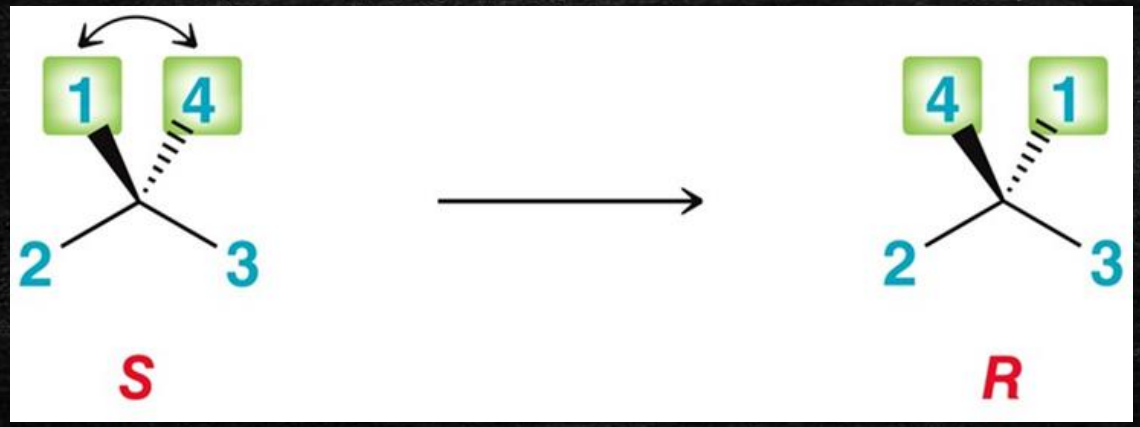
The priority is based on the first point of difference!

Designating R vs. S Configuration / Double Bonds

- When prioritizing for the Cahn, Ingold and Prelog system, double bonds count as two single bonds

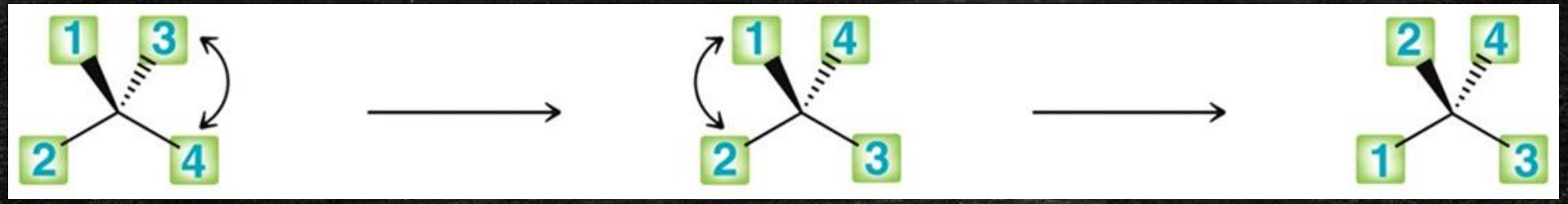
Rotating the Molecule / Useful Trick

- Handheld molecular models can be very helpful when arranging the molecule in space so the lowest priority group faces away from you
- Here are some other tricks that you can use
  - Switching two groups on a chiral center will produce its opposite configuration



Rotating the Molecule / More Useful Tricks

- Switching two groups on a chiral center will produce its opposite configuration
- You can use this trick to adjust a molecule so that the lowest priority group faces away from you.



- With the fourth priority group facing away, you can designate the configuration as *R*.
- Switching two of the groups, twice, returns the original configuration but allows us to put the priority 4 group pointing away.

CIP Rules Summary / Steps One - Three

- A review of Cahn-Ingold-Prelog rules: assigning the configuration of a chiral center

Step 1	Step 2	Step 3
Identify the four atoms directly attached to the chiral center.	Assign a priority to each atom based on its atomic number. The highest atomic number receives priority 1, and the lowest atomic number (often a hydrogen atom) receives priority 4.	If two atoms have the same atomic number, move away from the chiral center looking for the first point of difference. When constructing lists to compare, remember that a double bond is treated as two separate single bonds.

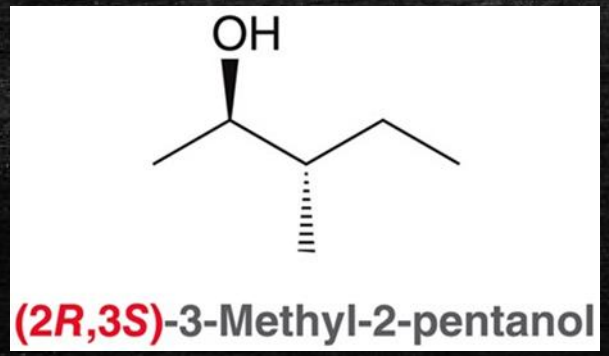
CIP Rules Summary / Steps Four and Five

- A review of Cahn-Ingold-Prelog rules: assigning the configuration of a chiral center

Step 4	Step 5
Rotate the molecule so that the fourth priority is on a dash (going behind the plane of the page).	Determine whether the sequence 1-2-3 follows a clockwise order (*R*) or a counter clockwise order (*S*).

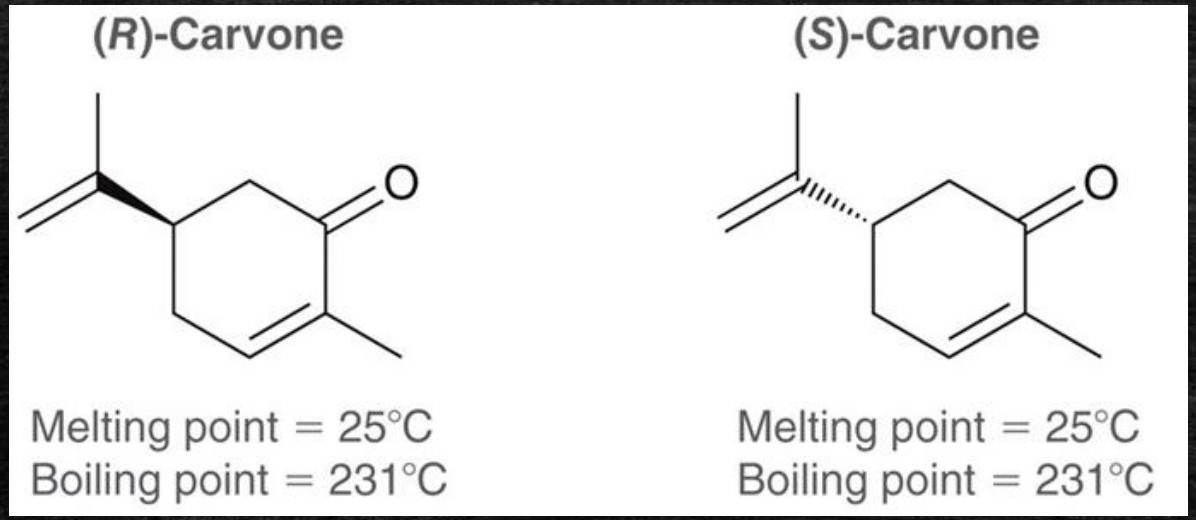
(R) and (S) in IUPAC Nomenclature

- The (*R*) or (*S*) configuration is used in the IUPAC name for a compound to distinguish it from its enantiomer



Optical Activity

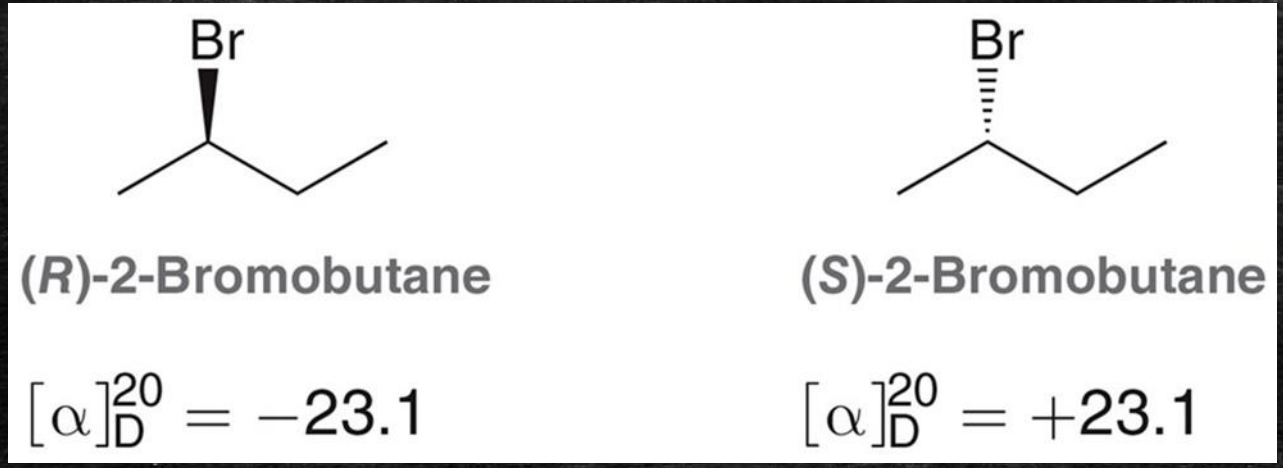
- Because the structures of enantiomers only differ in the same way your right hand differs from your left, they have the same physical properties.



- Enantiomers only differ in **(1)** **how they interact with other chiral compounds**, and **(2)** their **optical activity**

Optical Activity / Examples

- Consider the enantiomers of 2-bromobutane



- (*R*) and (*S*) refer to the configuration of the chiral center
- (+) and (–) signs refer to the direction that the plane of light is rotated

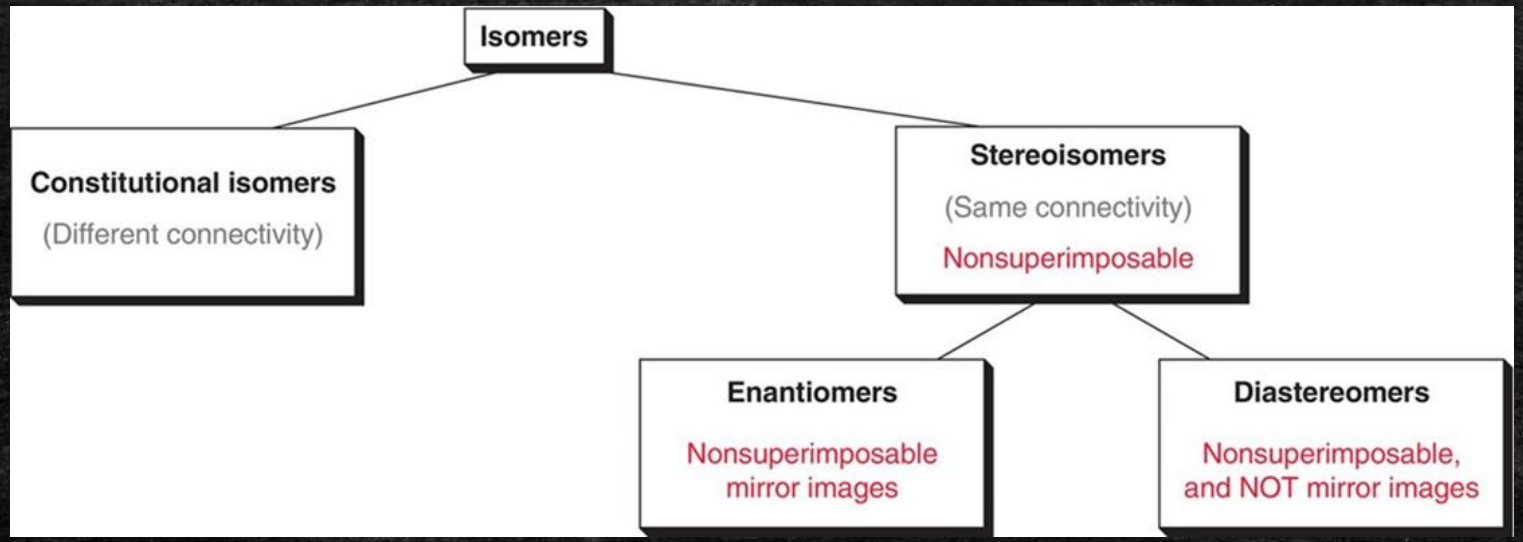
Optical Activity / Racemic Mixtures

- The magnitude and direction of optical rotation cannot be predicted, and has to be measured experimentally
- However, we can predict the rotation of a racemic mixture to be 0° (the optical rotation of each enantiomer cancels each other).
  - **Racemic mixture:** 50/50 mixture of two enantiomers
- If one enantiomer is present *in excess*, relative to the other, then the mixture will have an optical rotation, but it will be less than the pure enantiomer.

Enantiomers and Diastereomers / Definitions

Categories of isomers

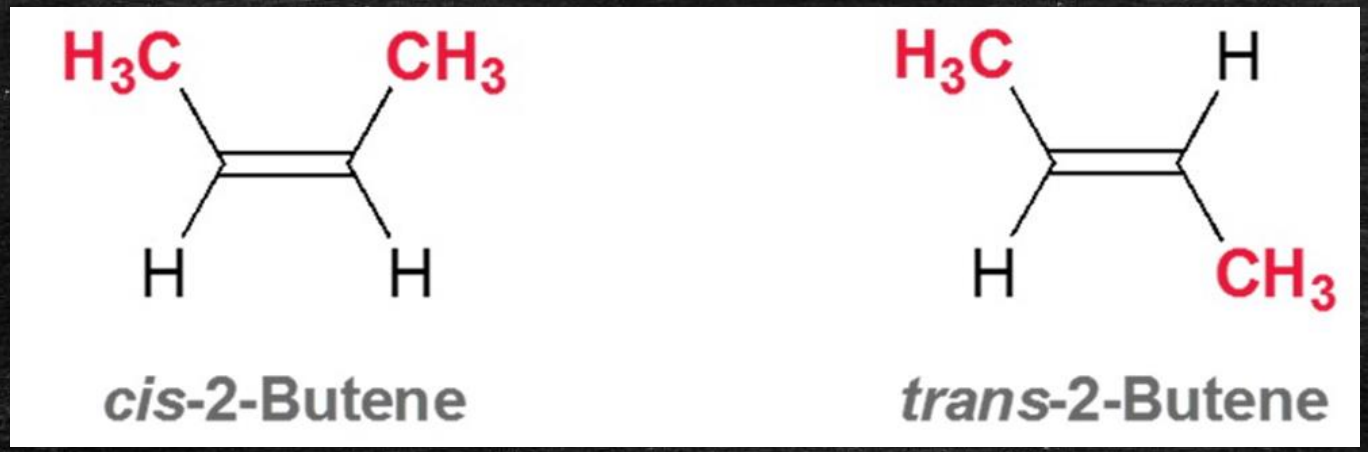
*** there are two sub-categories of stereoisomers**



- **Enantiomers:** stereoisomers that are mirror images
- **Diastereomers:** stereoisomers that are not mirror images

Enantiomers and Diastereomers / Examples

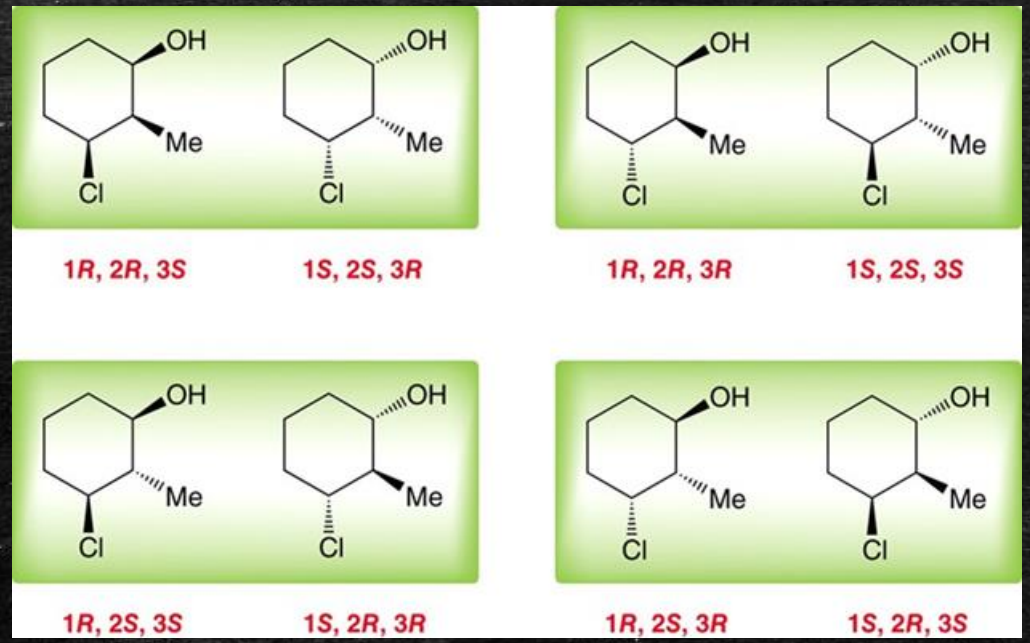
- Consider the structures of *cis*- and *trans*-2-butane.



- They are stereoisomers, but not mirror images of each other. So, they are **diastereomers**!
- Recall that enantiomers have identical physical properties.
- **Diastereomers have <u>different</u> physical properties.**

Stereoisomeric Relationships / Introduction

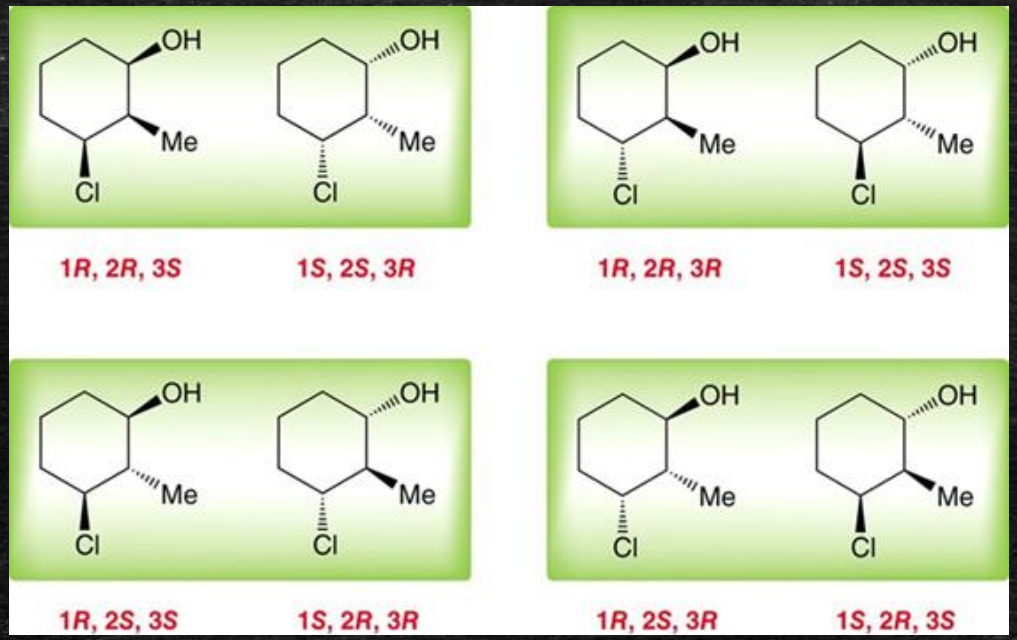
- Consider a cyclohexane with three substituents



- There are three stereocenters here, and so there are eight possible stereoisomers (all drawn above). Consider the relationship among them (enantiomers vs. diastereomers)

Stereoisomeric Relationships / Eight Stereoisomers

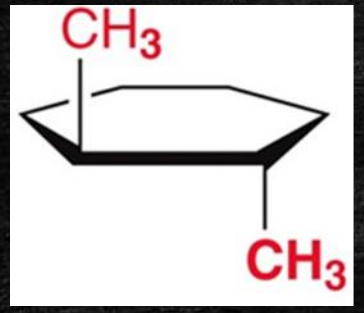
- Notice these eight stereoisomers are comprised of four pairs of enantiomers



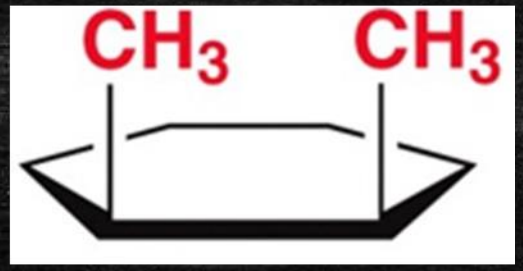
- You can think of this as a family where there are four pairs of twins, for a total of eight kids. Each kid has seven siblings, where one of them is their twin (i.e. enantiomer) and the other six are diastereomers

Symmetry and Chirality / Introduction

- Any compound with **only one chiral center will be a chiral compound**
- With more than one chiral center, a compound may not be chiral; it may have a plane of symmetry
- Consider the stereoisomers below, which possess TWO chiral centers:



***trans*-1,2-dimethylcyclohexane**



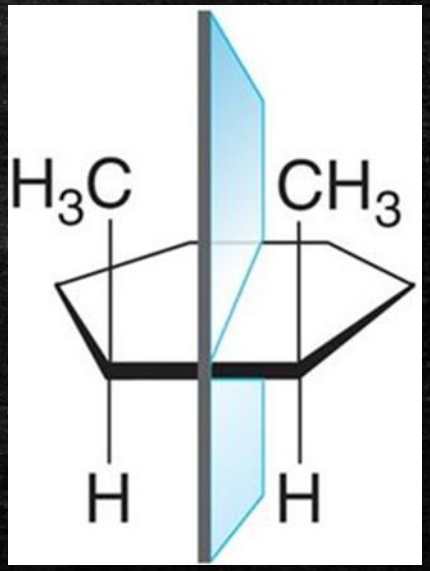
***cis*-1,2-dimethylcyclohexane**

Symmetry and Chirality / cis vs trans

- The *trans* isomer is chiral, but the *cis* isomer is not (it is achiral)

If a molecule has a plane of symmetry, it will be achiral

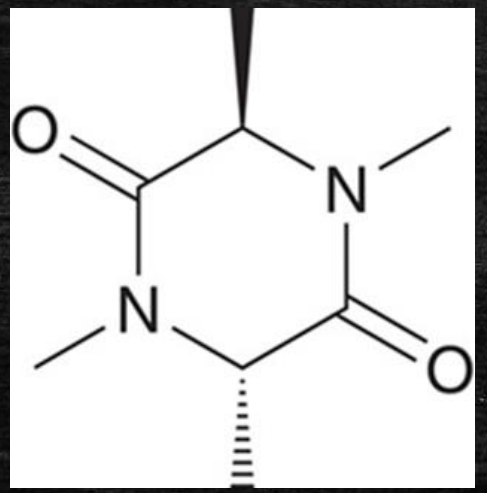
The *cis* isomer has a plane of symmetry, which means it will be superimposable on its mirror image, and is not a chiral compound



Symmetry and Chirality / Achiral Compounds

- If a compound has a **plane of symmetry**, it is **achiral**
- But… a compound that lacks a plane of symmetry may still be an achiral compound… if it has reflectional symmetry through **inversion** about a central point in the molecule

- The molecule to the right has two chiral centers, and no plane of symmetry, but it is still achiral because of inversion

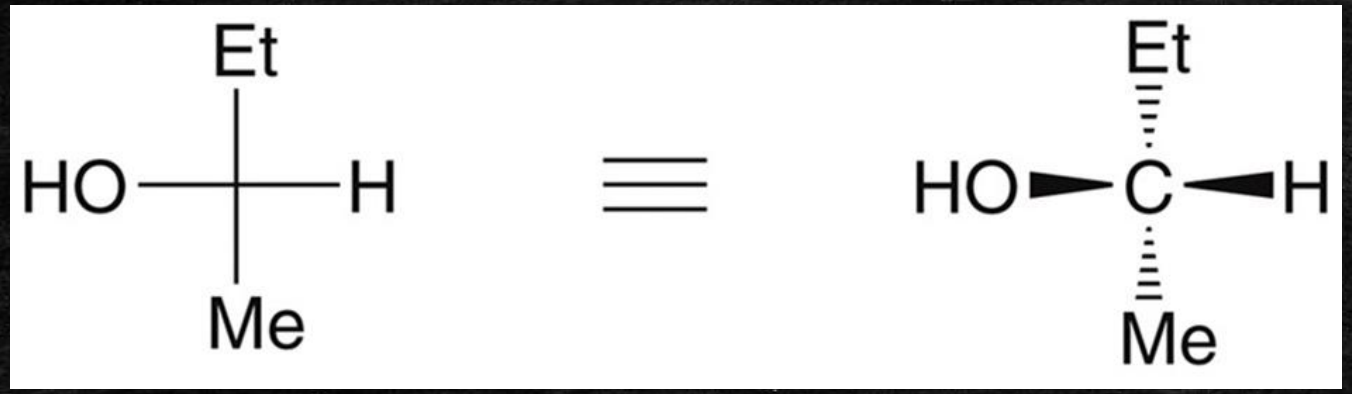


Symmetry and Chirality / Summary

- Overall:
  - The presence or absence of rotational symmetry is irrelevant to chirality.
  - **A compound that has a plane of symmetry is achiral.**
  - **A compound without a plane of symmetry will *usually be chiral*,** but there are exceptions (such as a compound with an inversion center).

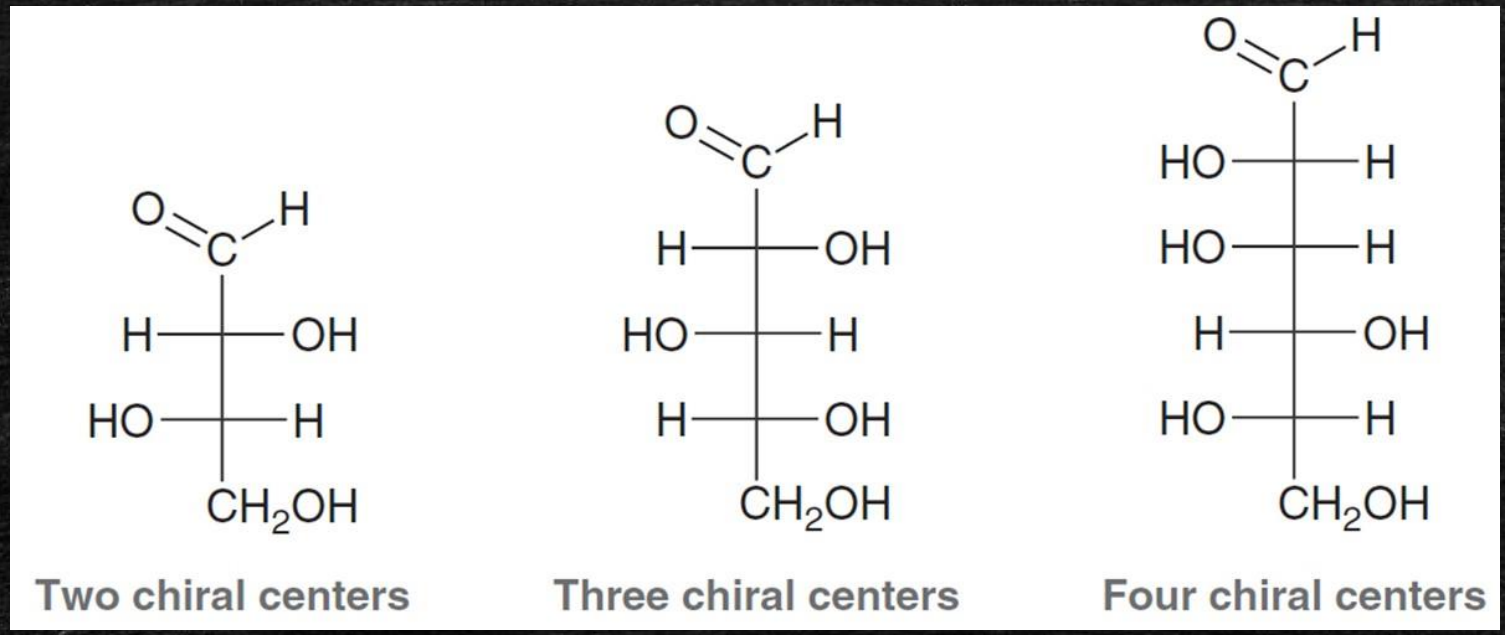
Fischer Projections / Introduction

- Fischer projections can also be used to represent molecules with chiral centers
- **Horizontal lines** represent attachments **coming out of the page**
- **Vertical lines** represent attachments going **back into the page**



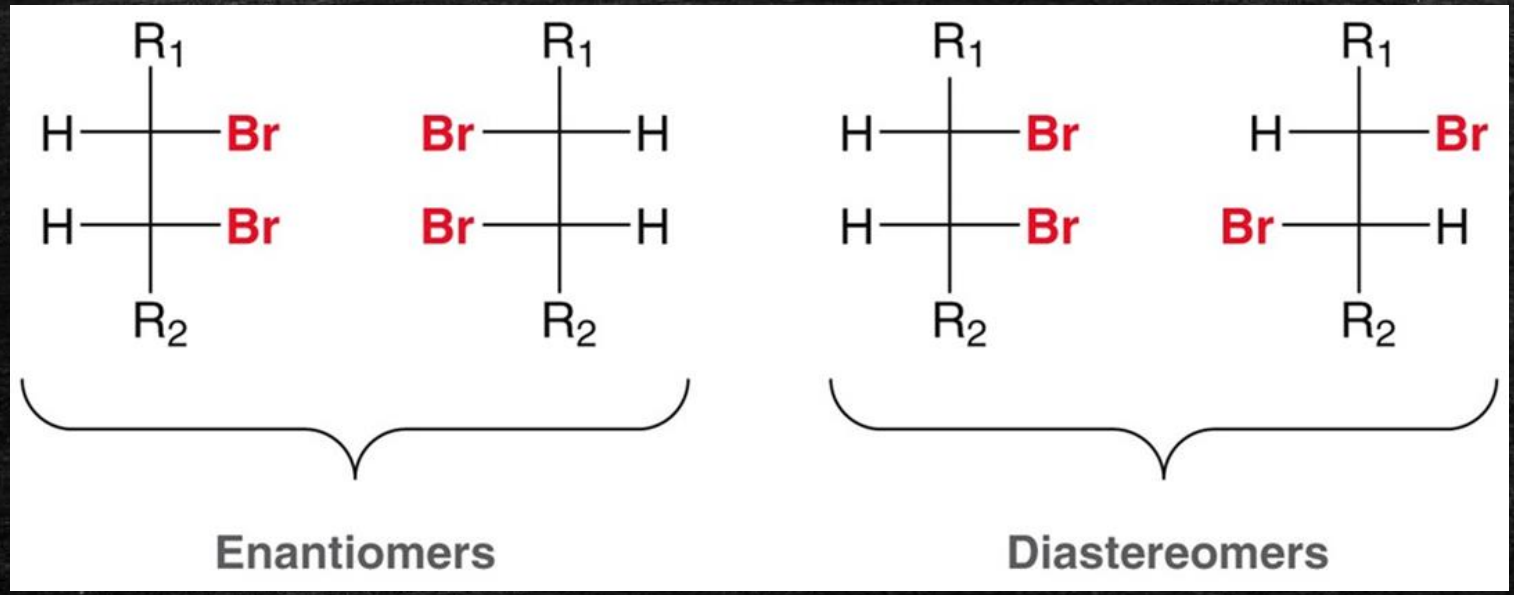
Fischer Projections / Examples

- Fischer projections are most useful when drawing molecules having multiple chiral centers (like sugars, shown below).



Fischer Projections / Enantiomers vs Diastereomers

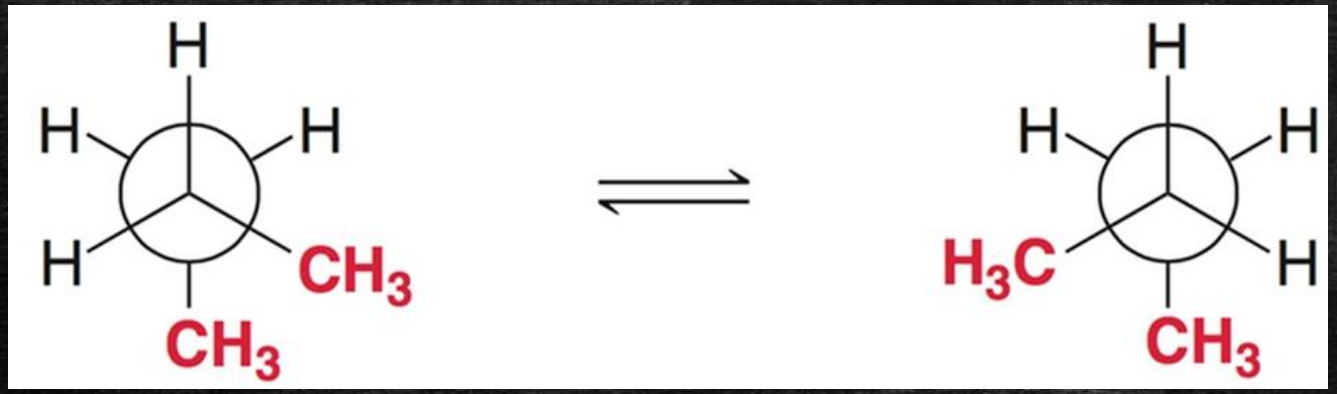
- Fischer projections are also useful to quickly assess stereoisomeric relationships



Practice with SkillBuilder 5.8 – Assigning Configuration.

Conformationally Mobile Compounds

- Molecules can rotate around single bonds.
- Recall the *gauche* rotational conformations of butane.



- Realize that these *conformations* are chiral and are actually enantiomeric.
- But, because these rotatomers are interchangeable via bond rotation, butane is not a chiral compound.

CH-211 Organic Chemistry I

Chapter 15: Nuclear Magnetic Resonance Spectroscopy

By Ilari Filpponen

Textbook: Organic Chemistry, D.R. Klein. 4th ed. 2021 John Wiley & Sons, Inc.

Intro to NMR Spectroscopy / Overview

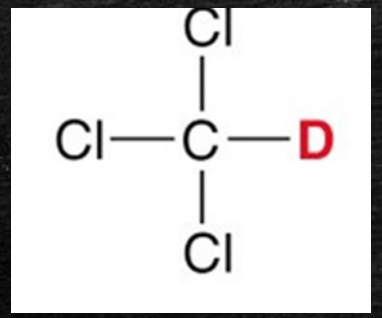
- **Nuclear Magnetic Resonance** (NMR) spectroscopy may be the most powerful method of gaining structural information about organic compounds
- **NMR** involves an interaction between electromagnetic radiation (light) and the **nucleus** of an atom
  - We will focus on C and H nuclei for analysis of organic compounds, for obvious reasons
  - The structure (connectivity) of a molecule affects how the radiation interacts with each nucleus in the molecule

Intro to NMR Spectroscopy / Magnetic Moment

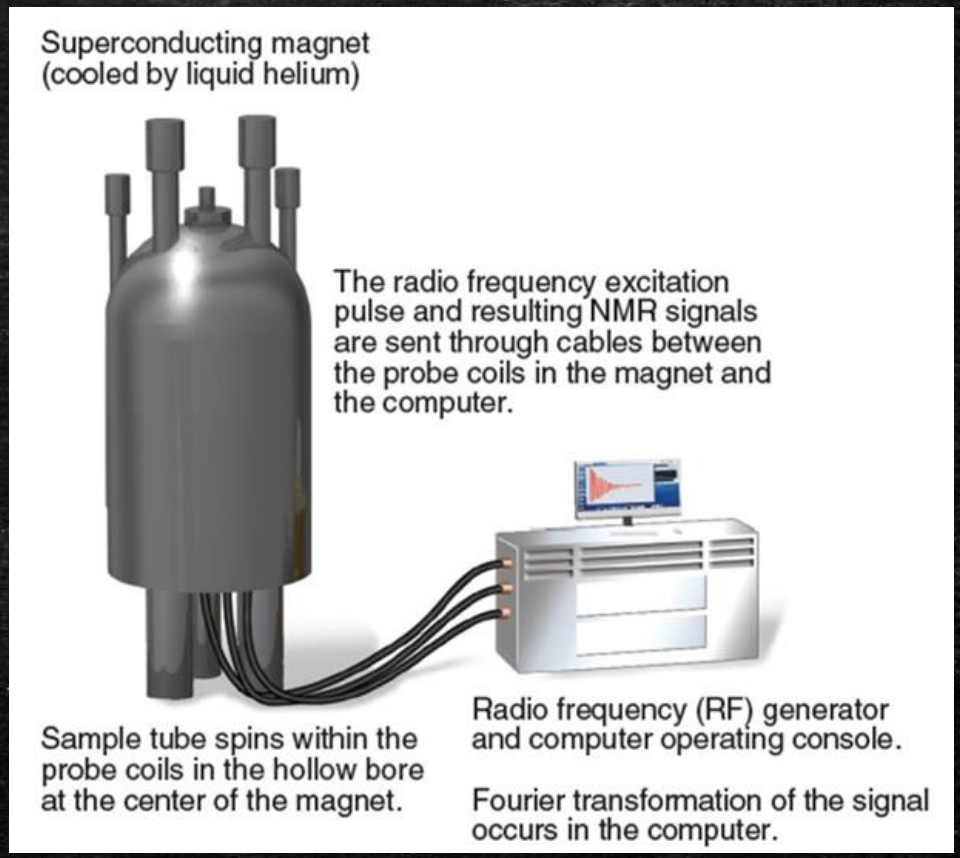
- Protons and neutrons in a nucleus behave as if they are spinning
- If an atom has an **odd number** of protons and/or odd number of neutrons, it will have net nuclear spin
- Examples: ^{1}H, ^{13}C, ^{15}N, ^{19}F, and ^{31}P.
- The spinning charge in the nucleus creates a **magnetic moment**
- Magnetic moment = magnetic field

Acquiring a 1H NM R Spectrum / Instrument

- Deuterated solvents must be used (no Hs)

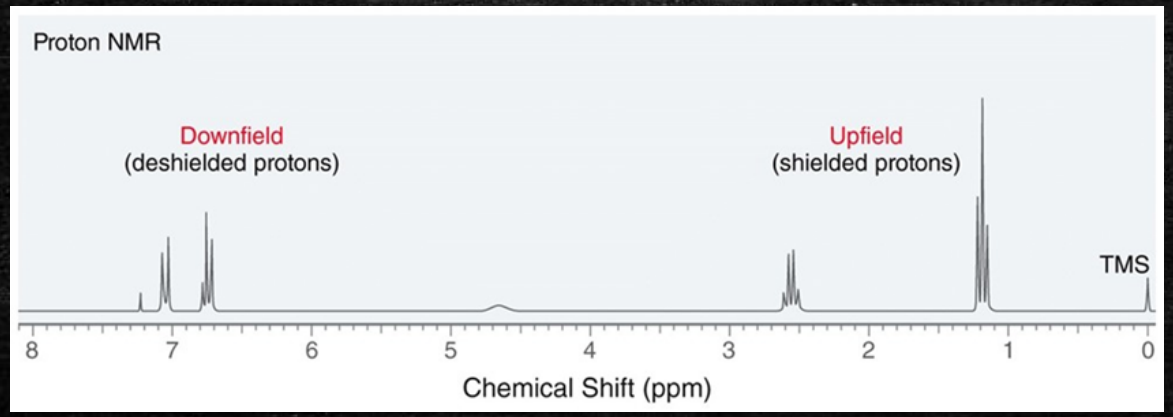


- The sample is generally at room temp when collecting the ^{1}H NMR spectrum



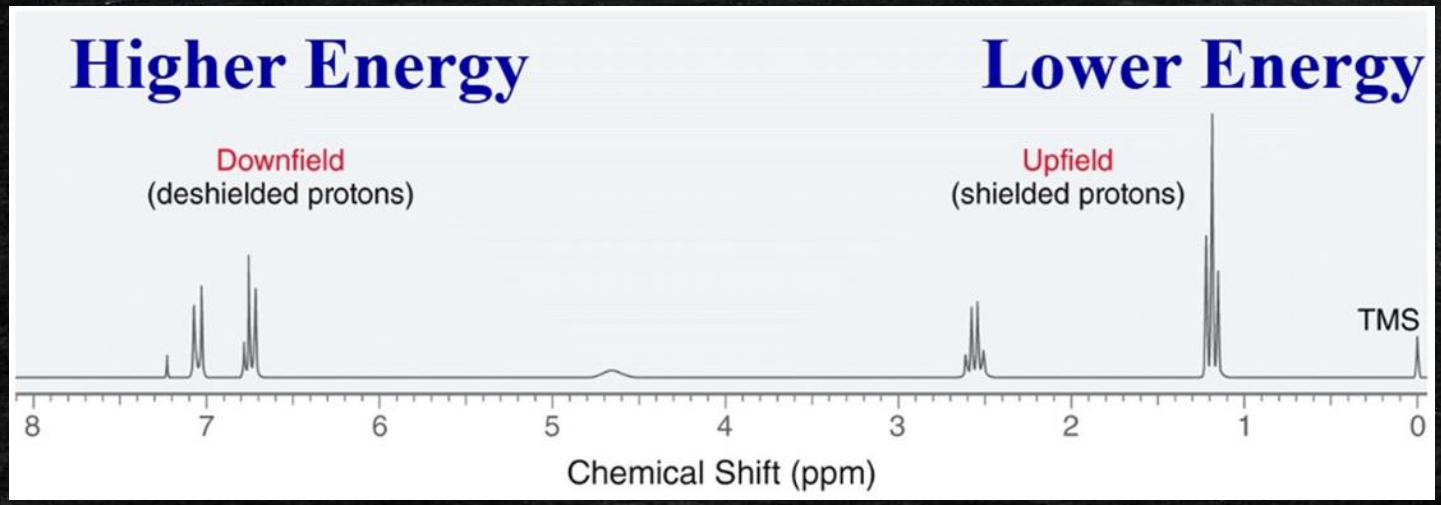
Chemical Shift / Downfield and Upfield

- Early NMRs analyzed samples at a constant energy over a range of magnetic field strengths
- low field strength = **downfield**
- high field strength = **upfield**
- Shielded protons required a stronger external magnetic field to be excited at the same energy as deshielded protons.



Chemical Shift / High and Low Energy

- Current NMRs analyze samples at a constant field strength over a range of energies
- Shielded protons have a smaller magnetic force acting on them, so they have smaller energy gaps and absorb lower energy radio waves

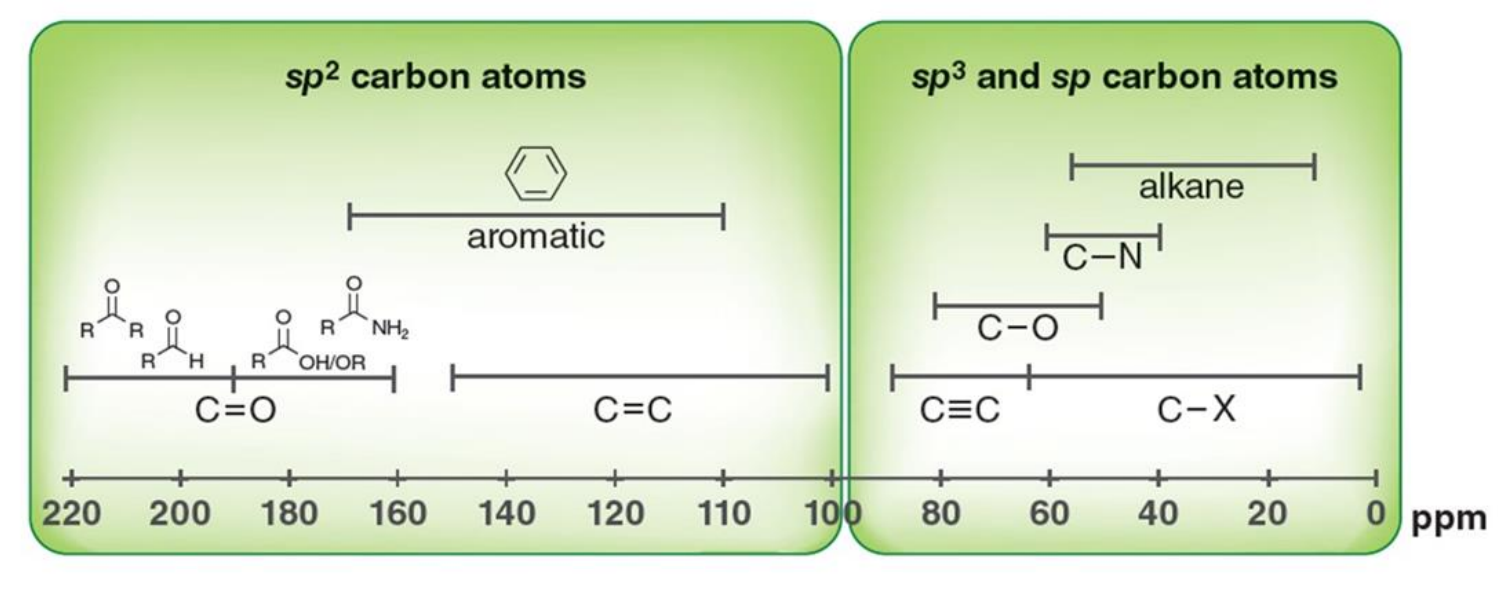


Acquiring a ^{13}C NMR Spectrum / Overview

- Because ^{1}H is by far the most abundant isotope of hydrogen, ^{1}H NMR signals are generally strong
- ^{13}C only accounts for about 1% of carbon atoms in nature, so a sensitive receiver coil and/or concentrated NMR sample is needed
- In ^{1}H NMR, shift, splitting, and integration are important
- **In ^{13}C NMR, only the number of signals and the chemical shift will be considered**

Chemical Shifts in ^{13}C NMR / Shielding and Deshielding

- Like ^{1}H signals, chemical shifts for ^{13}C signals are affected by shielding or deshielding



- **Practice with SkillBuilder 15.9 – Predicting the Number of Signals.**

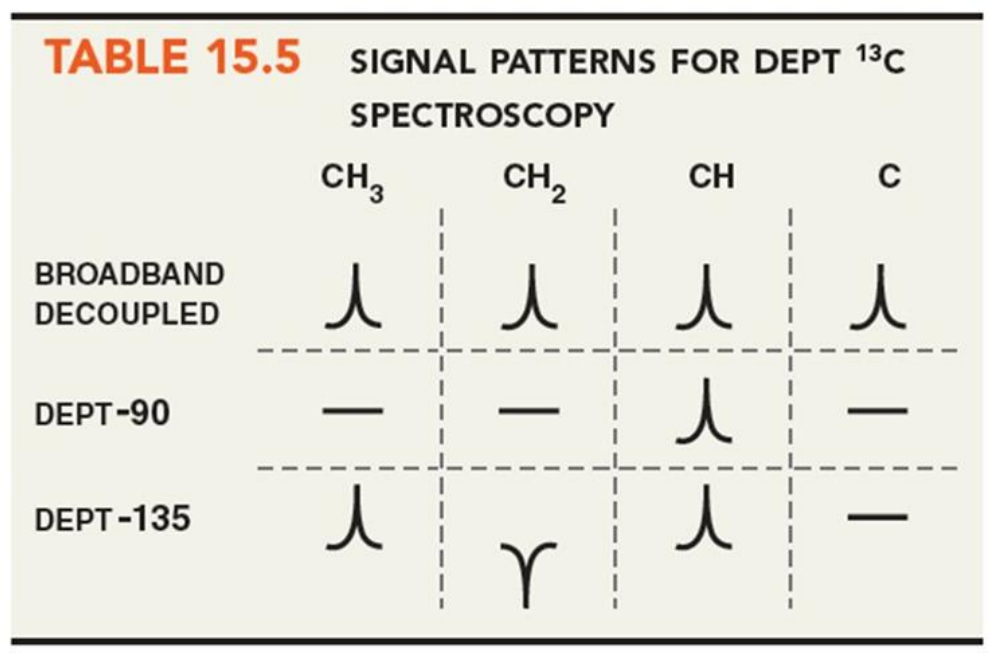
DEP T ^{13}C NMR Spectroscopy / Overview

- ^{13}C spectra generally give singlets that do not provide information about the number of hydrogen atoms attached to each carbon
- **Distortionless Enhancement by Polarization Transfer (DEPT)** ^{13}C NMR provides information the number of hydrogen atoms attached to each carbon
- DEPT-90: Only CH signals appear
- DEPT-135: CH_3 and CH give (+) signals, and CH_2 give (–) signals

DEPT ^{13}CNMR Spectroscopy / Examples

- DEPT-90: Only CH signals appear
- DEPT-135: CH_3 and CH = (+) signals, CH_2 = (–) signals

TABLE 15.5 SIGNAL PATTERNS FOR DEPT ^{13}C SPECTROSCOPY



- **Practice with SkillBuilder 15.10 – Determining Molecular Structure.**