An Overview of Organic Reactions

Why this chapter?

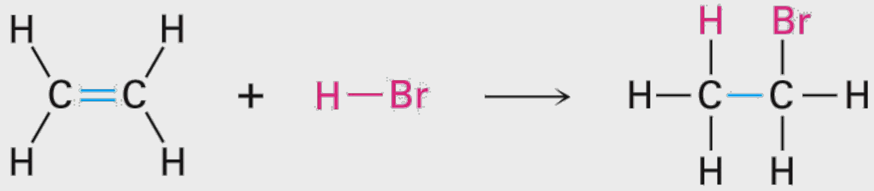
- To understand organic and/or biochemistry, it is necessary to know:
- -What occurs
- -Why and how chemical reactions take place

We will see how a reaction can be described

6.1 Kinds of Organic Reactions

- In general, we look at what occurs and try to learn how it happens
- Common patterns describe the changes
  - Addition reactions – two molecules combine

These two reactants . . .



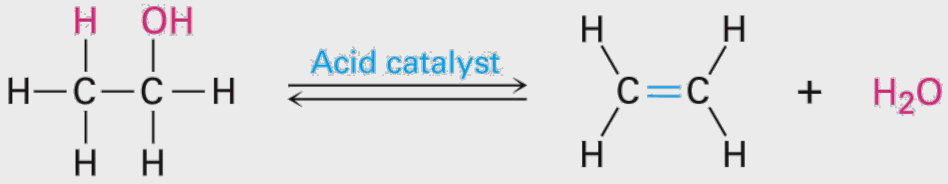
. . . add to give this product.

Ethylene
(an alkene)

Bromoethane
(an alkyl halide)

  - Elimination reactions – one molecule splits into two

This one reactant . . .



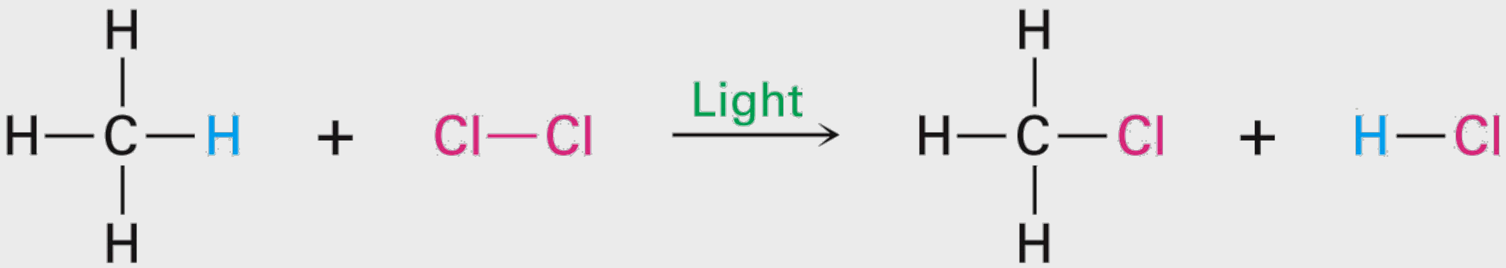
. . . gives these two products.

Ethanol
(an alcohol)

Ethylene
(an alkene)

Kinds of Organic Reactions (Continued)

- Substitution – parts from two molecules exchange



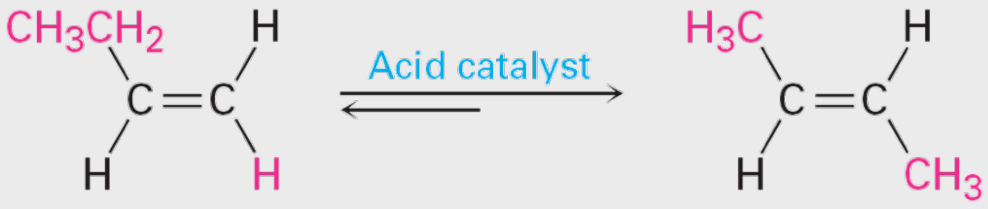
$$\mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}H} + \mathrm{Cl{-}Cl} \xrightarrow{\text{Light}} \mathrm{H{-}\overset{\displaystyle H}{\underset{\displaystyle H}{C}}{-}Cl} + \mathrm{H{-}Cl}$$

Methane **Chlorine** **Chloromethane**

Kinds of Organic Reactions (Continued)

- Rearrangement reactions – a molecule undergoes changes in the way its atoms are connected

This reactant . . .



. . . gives this isomeric product.

1-Butene

2-Butene

6.2 How Organic Reactions Occur: Mechanisms

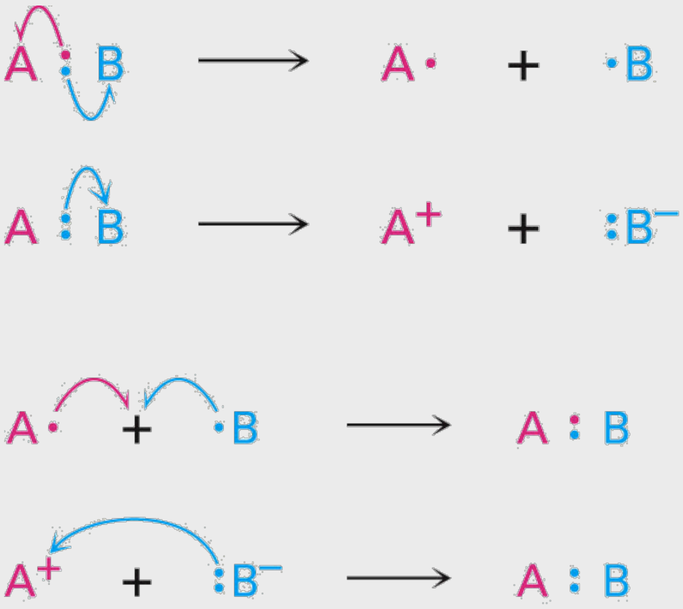
- In a clock the hands move but the *mechanism* behind the face is what causes the movement
- In an organic reaction, we see the transformation that has occurred. The mechanism describes the steps behind the changes that we can observe
- Reactions occur in defined steps that lead from reactant to product

Steps in Mechanisms

- We classify the types of steps in a sequence
- A step involves either the formation or breaking of a covalent bond
- Steps can occur individually or in combination with other steps
- When several steps occur at the same time, they are said to be **concerted**

Types of Steps in Reaction Mechanisms

- Bond formation or breakage can be symmetrical or unsymmetrical
- **Symmetrical-** homolytic
- **Unsymmetrical-** heterolytic



Symmetrical bond-breaking (radical):
one bonding electron stays with each product.

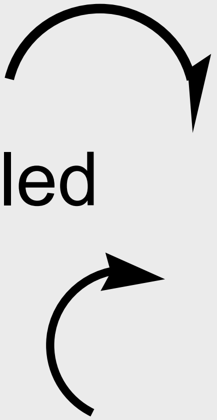
Unsymmetrical bond-breaking (polar):
two bonding electrons stay with one product.

Symmetrical bond-making (radical):
one bonding electron is donated by each reactant.

Unsymmetrical bond-making (polar):
two bonding electrons are donated by one reactant.

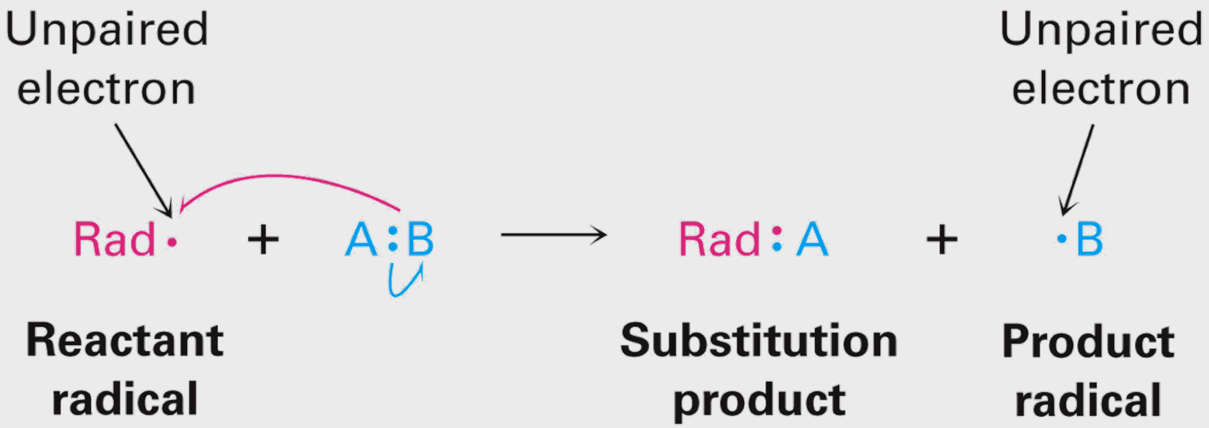
Indicating Steps in Mechanisms

- Curved arrows indicate breaking and forming of bonds
- Arrowheads with a "half" head ("fish-hook") indicate homolytic and homogenic steps (called 'radical processes')
- Arrowheads with a complete head indicate heterolytic and heterogenic steps (called 'polar processes')



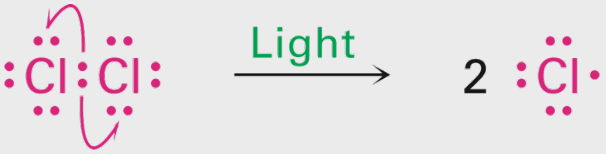
6.3 Radical Reactions

- Not as common as polar reactions
- **Radicals** react to complete electron octet of valence shell
  - A radical can break a bond in another molecule and abstract a partner with an electron, giving substitution in the original molecule
  - A radical can *add* to an alkene to give a new radical, causing an addition reaction

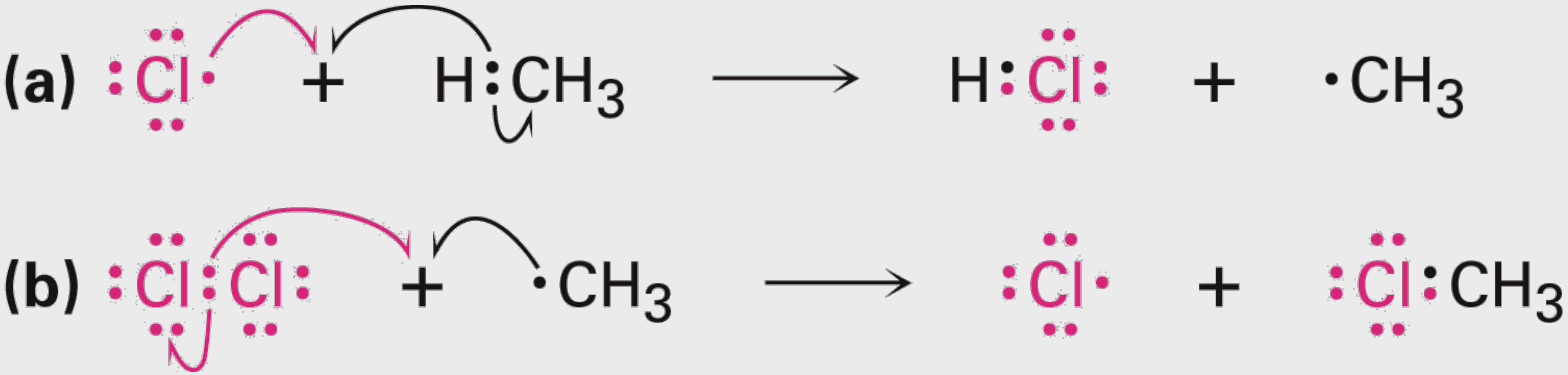


Steps in Radical Substitution

- Three types of steps
  - **Initiation** – homolytic formation of two reactive species with unpaired electrons

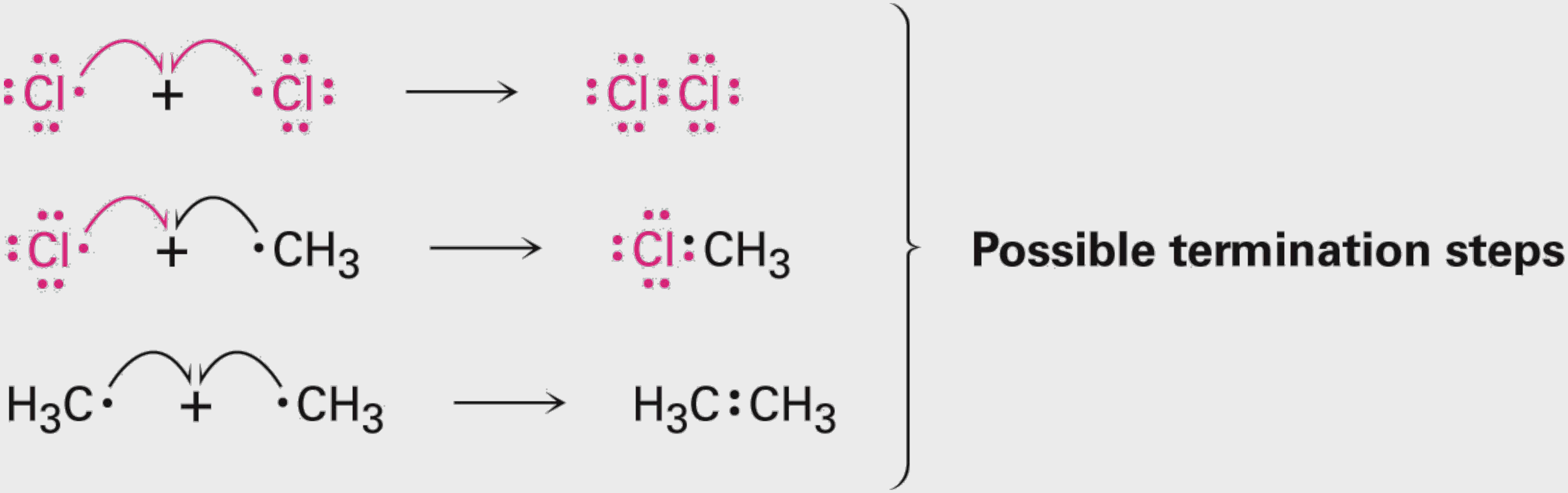


  - **Propagation** – reaction with molecule to generate radical
    - Example - reaction of chlorine atom with methane to give HCl and CH_3·



Steps in Radical Substitution

- **Termination** – combination of two radicals to form a stable product: $CH_3\cdot + CH_3\cdot \rightarrow CH_3CH_3$



6.4 Polar Reactions

- Molecules can contain local unsymmetrical electron distributions due to differences in electronegativities

- This causes a partial negative charge on an atom and a compensating partial positive charge on an adjacent atom

- The more electronegative atom has the greater electron density
- Elements such as O, F, N, Cl are more electronegative than carbon

Polarity Patterns in Some Common Functional Groups

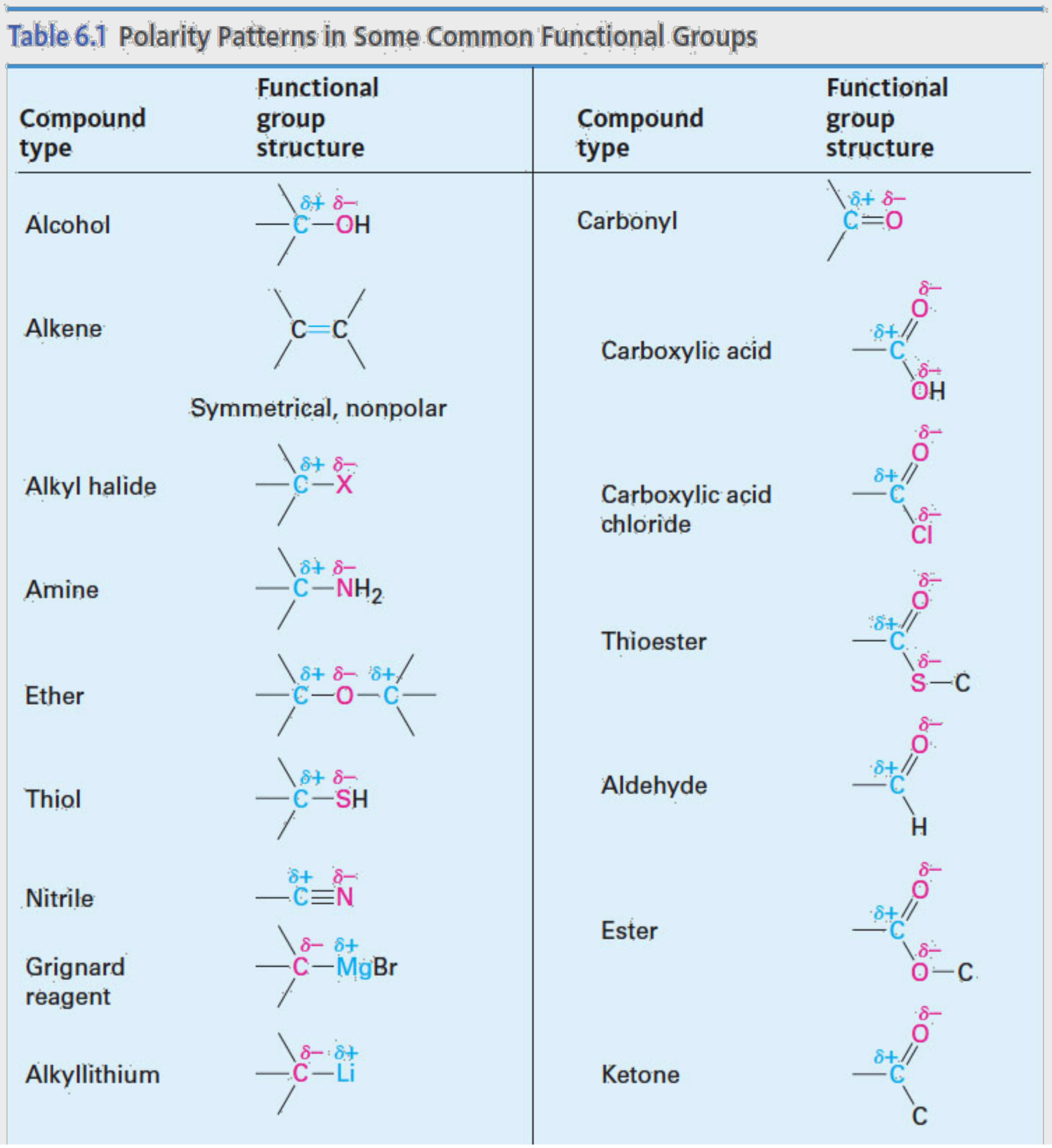
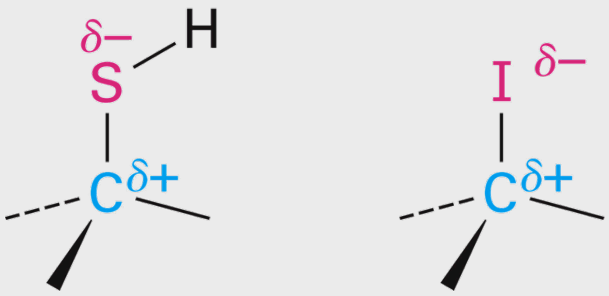


Table 6.1 Polarity Patterns in Some Common Functional Groups

Compound type	Functional group structure	Compound type	Functional group structure
Alcohol	$\overset{\delta+}{C}-\overset{\delta-}{O}H$	Carbonyl	$\overset{\delta+}{C}=\overset{\delta-}{O}$
Alkene	$C=C$ Symmetrical, nonpolar	Carboxylic acid	$-\overset{\delta+}{C}(=\overset{\delta-}{O})-\overset{\delta-}{O}H$
Alkyl halide	$\overset{\delta+}{C}-\overset{\delta-}{X}$	Carboxylic acid chloride	$-\overset{\delta+}{C}(=\overset{\delta-}{O})-\overset{\delta-}{Cl}$
Amine	$\overset{\delta+}{C}-\overset{\delta-}{N}H_2$	Thioester	$-\overset{\delta+}{C}(=\overset{\delta-}{O})-\overset{\delta-}{S}-C$
Ether	$\overset{\delta+}{C}-\overset{\delta-}{O}-\overset{\delta+}{C}$	Aldehyde	$-\overset{\delta+}{C}(=\overset{\delta-}{O})-H$
Thiol	$\overset{\delta+}{C}-\overset{\delta-}{S}H$	Ester	$-\overset{\delta+}{C}(=\overset{\delta-}{O})-\overset{\delta-}{O}-C$
Nitrile	$-\overset{\delta+}{C}\equiv\overset{\delta-}{N}$	Ketone	$-\overset{\delta+}{C}(=\overset{\delta-}{O})-C$
Grignard reagent	$\overset{\delta-}{C}-\overset{\delta+}{Mg}Br$		
Alkyllithium	$\overset{\delta-}{C}-\overset{\delta+}{Li}$		

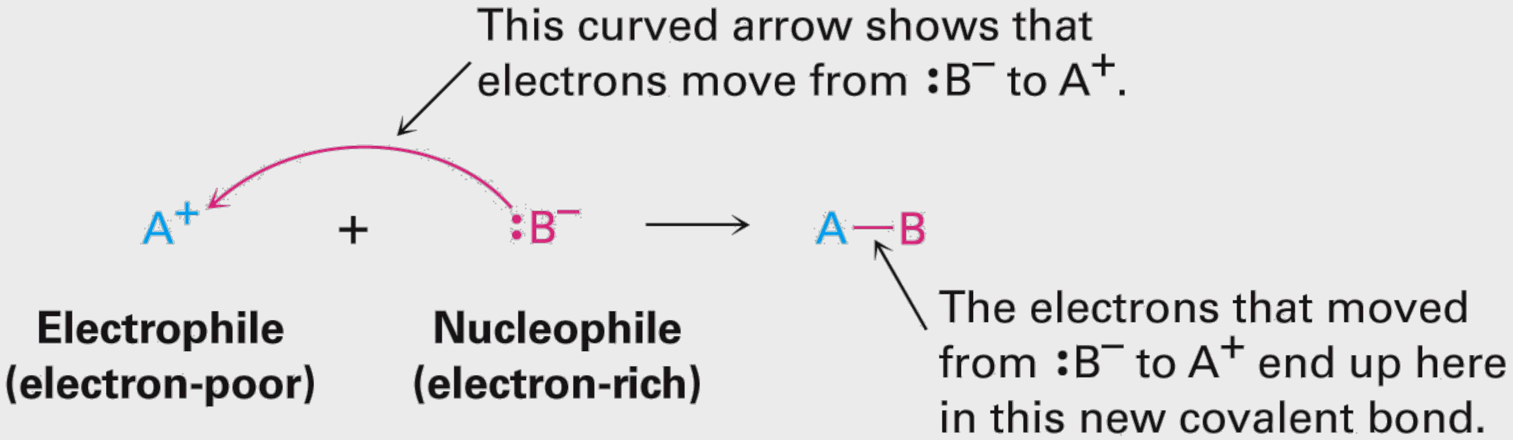
Polarizability

- **Polarization** is a change in electron distribution as a response to change in electronic nature of the surroundings
- Polarizability is the tendency to undergo polarization
- Polar reactions occur between regions of high electron density and regions of low electron density

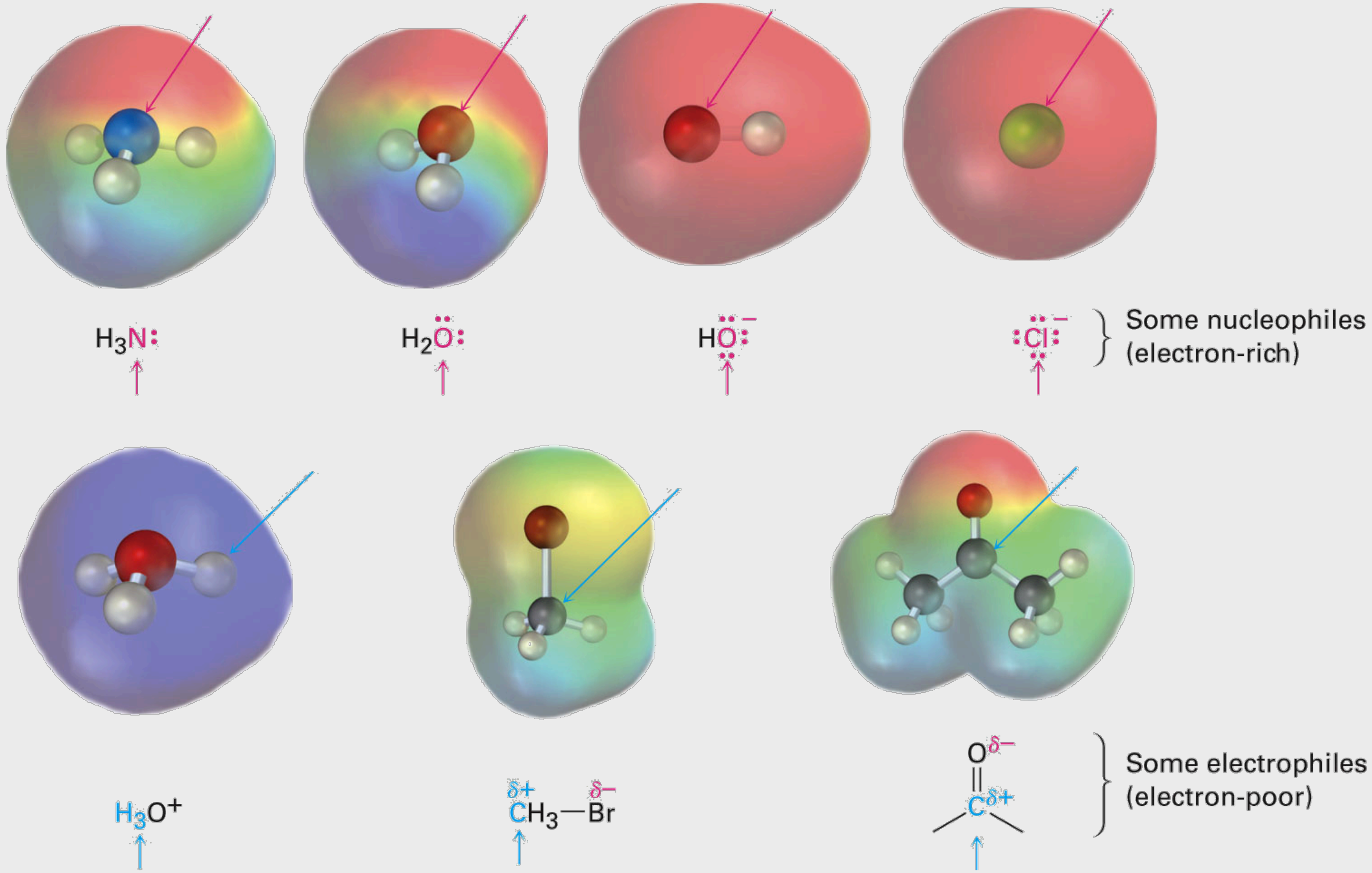


Generalized Polar Reactions

- An **electrophile**, an electron-poor species, combines with a **nucleophile**, an electron-rich species
- An electrophile is a Lewis acid
- A nucleophile is a Lewis base
- The combination is indicated with a curved arrow from nucleophile to electrophile

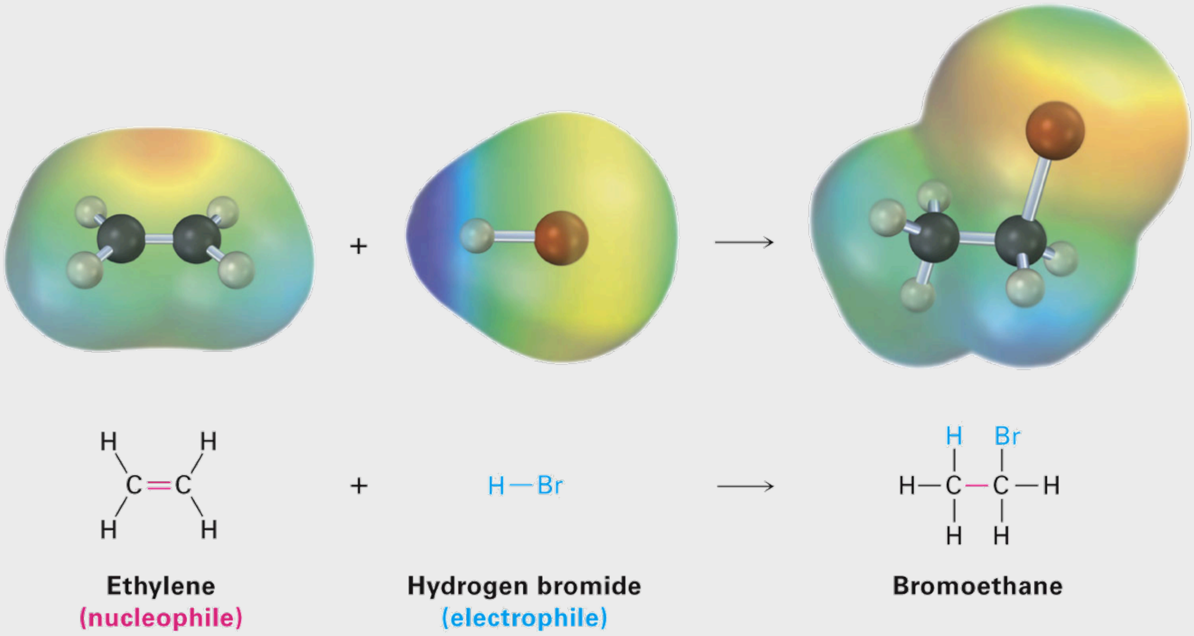


Some Nucleophiles and Electrophiles



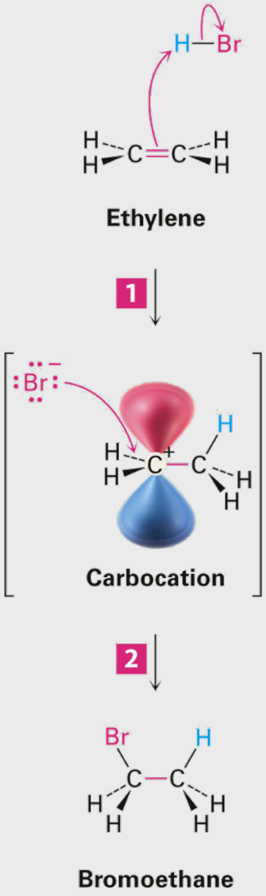
6.5 An Example of a Polar Reaction: Addition of HBr to Ethylene

- HBr adds to the π part of a C-C double bond
- The π bond is electron-rich, allowing it to function as a nucleophile
- H-Br is electron deficient at the H since Br is much more electronegative, making HBr an electrophile



Mechanism of Addition of HBr to Ethylene

- HBr electrophile is attacked by π electrons of ethylene (nucleophile) to form a carbocation intermediate and bromide ion
- Bromide adds to the positive center of the **carbocation**, which is an electrophile, forming a C-Br σ bond
- The result is that ethylene and HBr combine to form bromoethane
- All polar reactions occur by combination of an electron-rich site of a nucleophile and an electron-deficient site of an electrophile



1 A hydrogen atom on the electrophile HBr is attacked by *π* electrons from the nucleophilic double bond, forming a new C–H bond. This leaves the other carbon atom with a + charge and a vacant *p* orbital. Simultaneously, two electrons from the H–Br bond move onto bromine, giving bromide anion.

2 Bromide ion donates an electron pair to the positively charged carbon atom, forming a C–Br bond and yielding the neutral addition product.

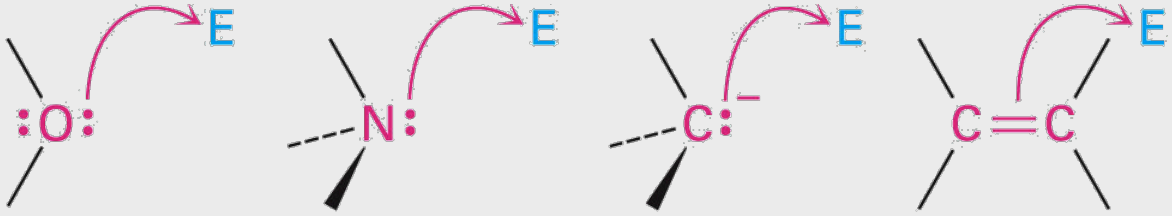
6.6 Using Curved Arrows in Polar Reaction Mechanisms

- Curved arrows are a way to keep track of changes in bonding in a polar reaction
- The arrows track “electron movement”
- Electrons always move in pairs
- Charges change during the reaction
- One curved arrow corresponds to one step in a reaction mechanism

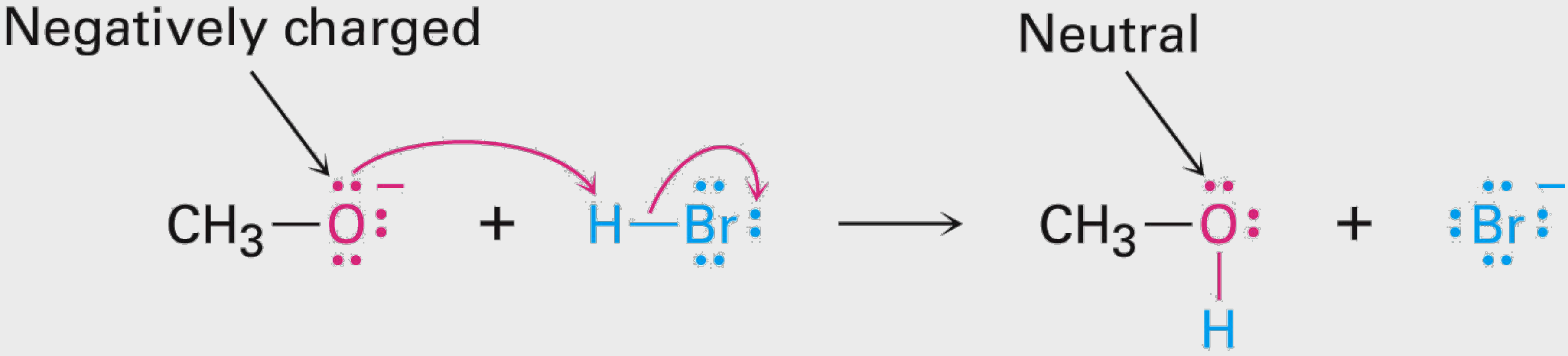
Rules for Using Curved Arrows

- The arrow goes from the nucleophilic reaction site to the electrophilic reaction site

Electrons usually flow *from* one of these nucleophiles.

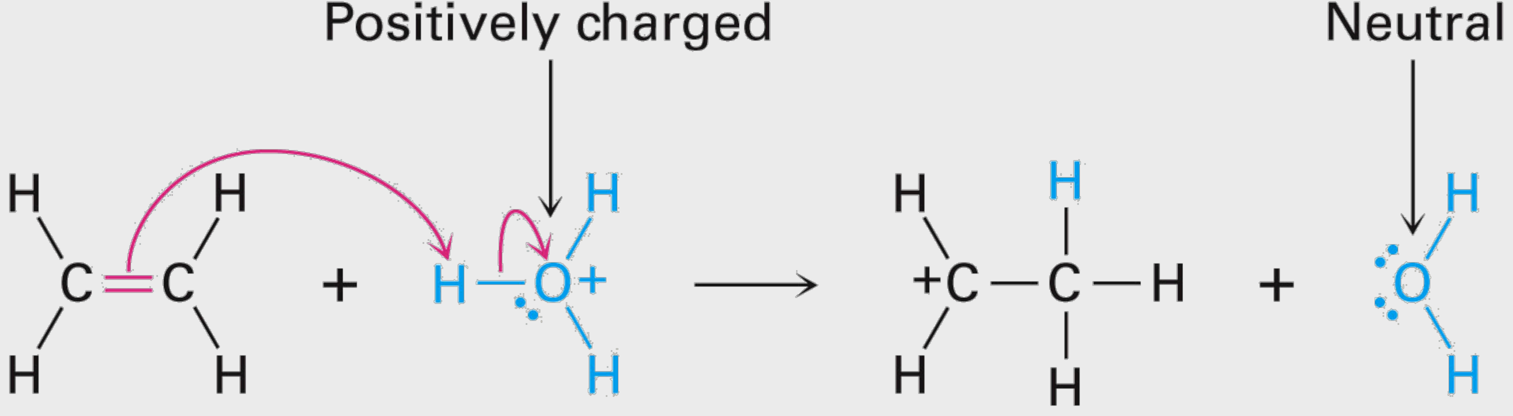


- The nucleophilic site can be neutral or negatively charged

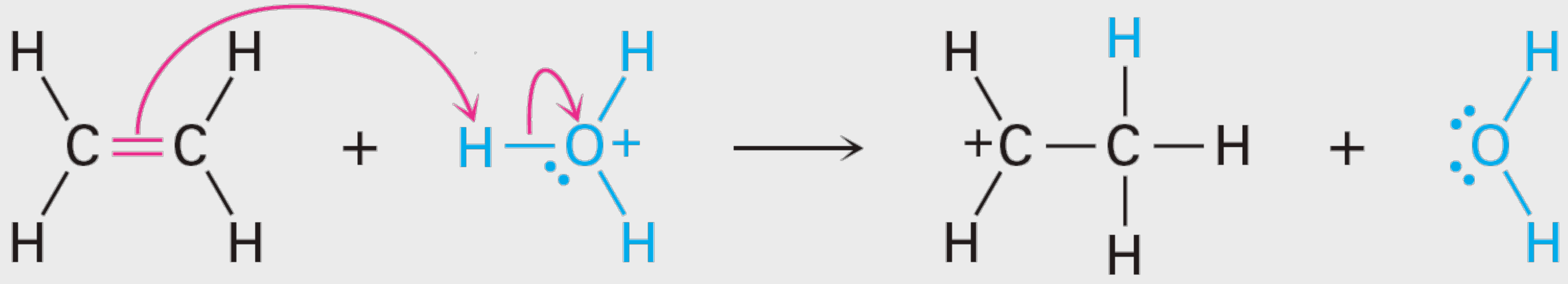


Rules for Using Curved Arrows (Continued)

- The electrophilic site can be neutral or positively charged



- The octet rule should be followed



6.7 Describing a Reaction: Equilibria, Rates, and Energy Changes

- Reactions may go either forward or backward to reach equilibrium
  - The multiplied concentrations of the products divided by the multiplied concentrations of the reactant is the **equilibrium constant, K_{eq}**
  - Each concentration is raised to the power of its coefficient in the balanced equation.

$$aA + bB \rightleftharpoons cC + dD$$

$$K_{\text{eq}} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

Magnitudes of Equilibrium Constants

- If the value of K_{eq} is greater than 1, this indicates that at equilibrium most of the material is present as products
  - If K_{eq} is 10, then the concentration of the product is ten times that of the reactant
- A value of K_{eq} less than one indicates that at equilibrium most of the material is present as the reactant
  - If K_{eq} is 0.10, then the concentration of the reactant is ten times that of the product

Free Energy and Equilibrium

- The ratio of products to reactants is controlled by their relative **Gibbs free energy**
- This energy is released on the favored side of an equilibrium reaction
- The change in Gibbs free energy between products and reacts is written as “ΔG”
- If $K_{eq} > 1$, energy is released to the surroundings (**exergonic** reaction)
- If $K_{eq} < 1$, energy is absorbed from the surroundings (**endergonic** reaction)

Numeric Relationship of Keq and Free Energy Change

- The standard free energy change at 1 atm pressure and 298 K is ΔG^o
- The relationship between free energy change and an equilibrium constant is:
  - $\Delta G^o = -RT \ln K_{eq}$ where
  - R = 1.987 cal/(K x mol)
  - T = temperature in Kelvin
  - $\ln K_{eq}$ = natural logarithm of K_{eq}

Thermodynamic Quantities

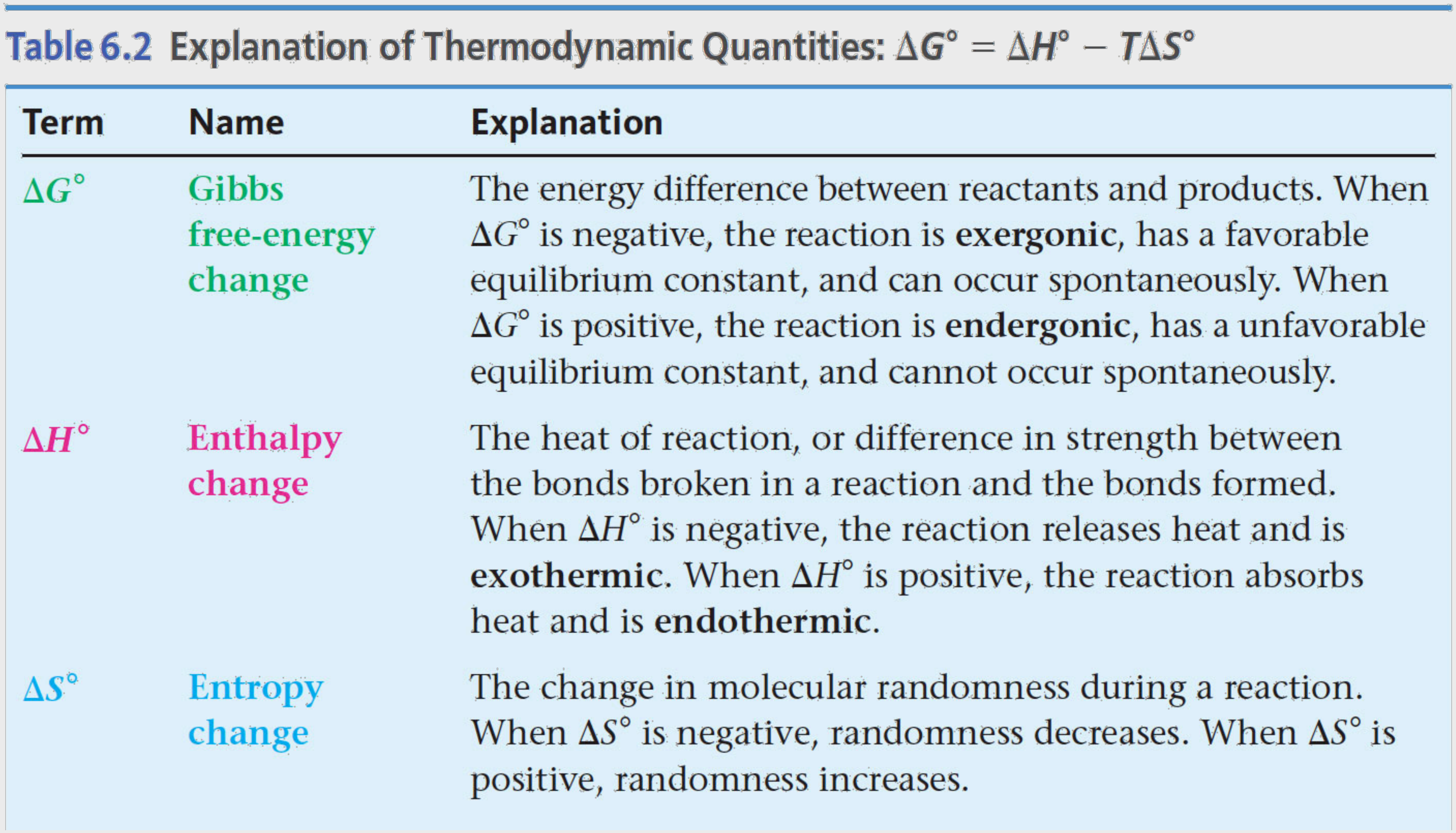
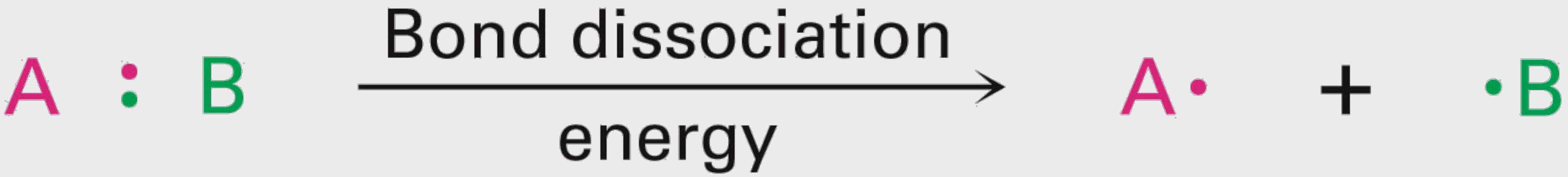


Table 6.2 Explanation of Thermodynamic Quantities: $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$

Term	Name	Explanation
ΔG°	Gibbs free-energy change	The energy difference between reactants and products. When ΔG° is negative, the reaction is **exergonic**, has a favorable equilibrium constant, and can occur spontaneously. When ΔG° is positive, the reaction is **endergonic**, has a unfavorable equilibrium constant, and cannot occur spontaneously.
ΔH°	Enthalpy change	The heat of reaction, or difference in strength between the bonds broken in a reaction and the bonds formed. When ΔH° is negative, the reaction releases heat and is **exothermic**. When ΔH° is positive, the reaction absorbs heat and is **endothermic**.
ΔS°	Entropy change	The change in molecular randomness during a reaction. When ΔS° is negative, randomness decreases. When ΔS° is positive, randomness increases.

6.8 Describing a Reaction: Bond Dissociation Energies

- Bond dissociation energy (***D***): amount of energy required to break a given bond to produce two radical fragments when the molecule is in the gas phase at 25˚ C

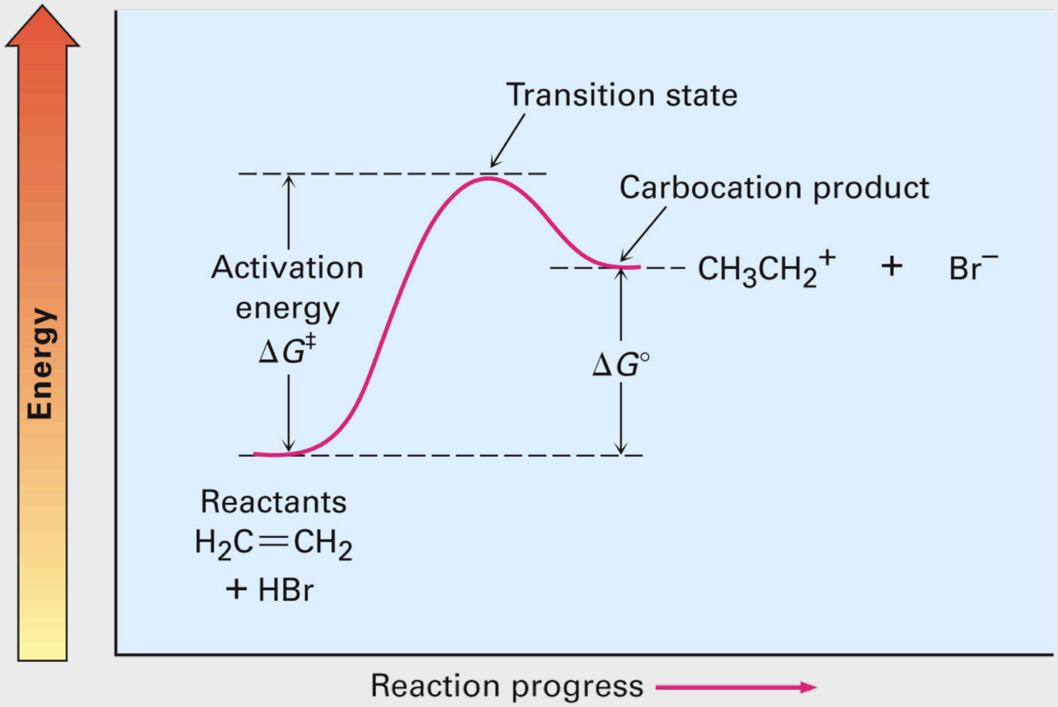


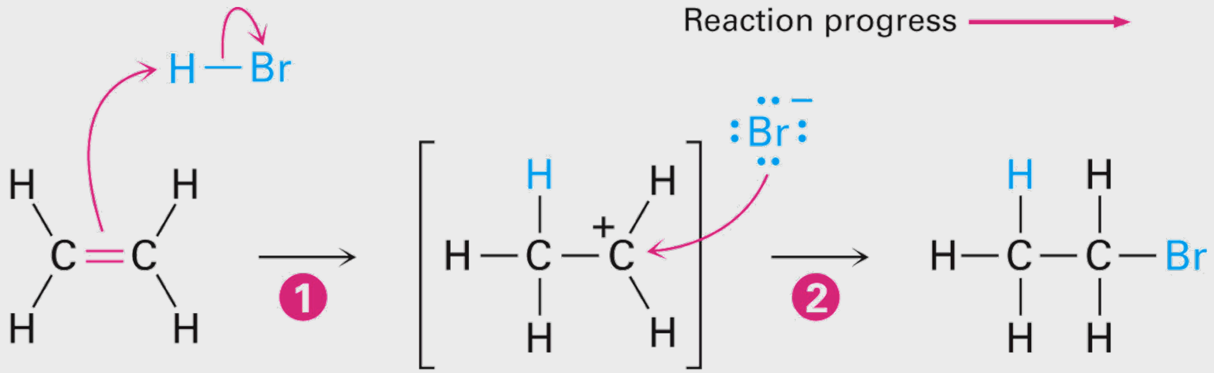
$$A : B \xrightarrow[\text{energy}]{\text{Bond dissociation}} A\cdot + \cdot B$$

- The energy is mostly determined by the type of bond, independent of the molecule
  - The C-H bond in methane requires a net energy input of 106 kcal/mol to be broken at 25 ºC.
  - Table 6.3 lists energies for many bond types
- Changes in bonds can be used to calculate net changes in heat

6.9 Describing a Reaction: Energy Diagrams and Transition States

- The highest energy point in a reaction step is called the **transition state**
- The energy needed to go from reactant to transition state is the **activation energy** ($\Delta G^\ddagger$)

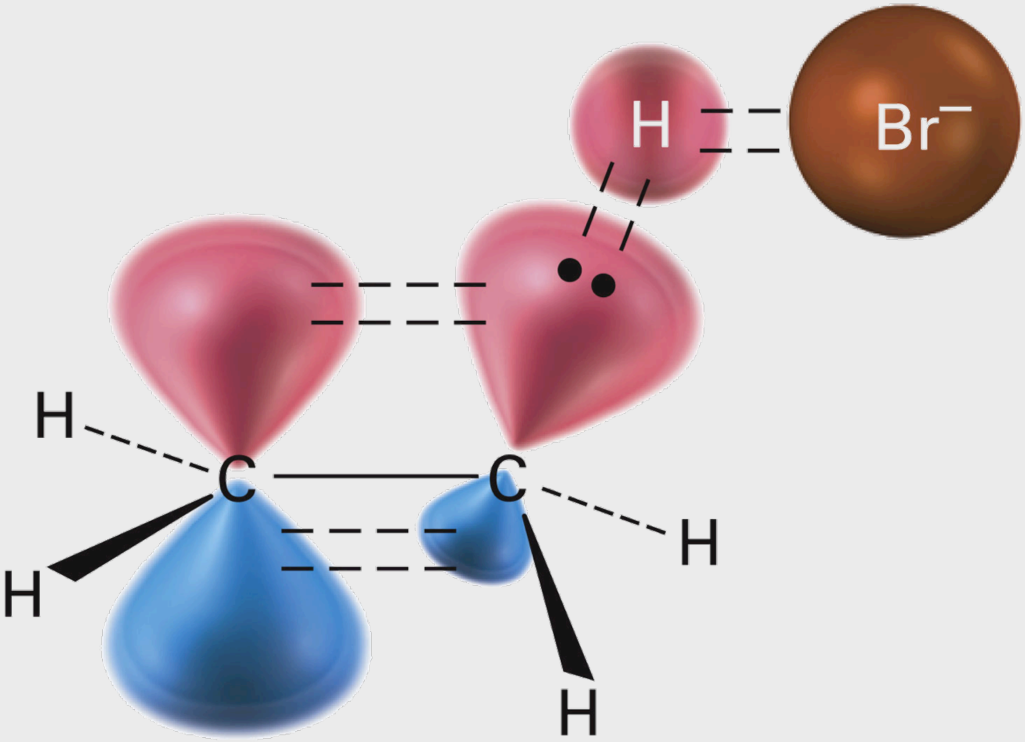




Carbocation

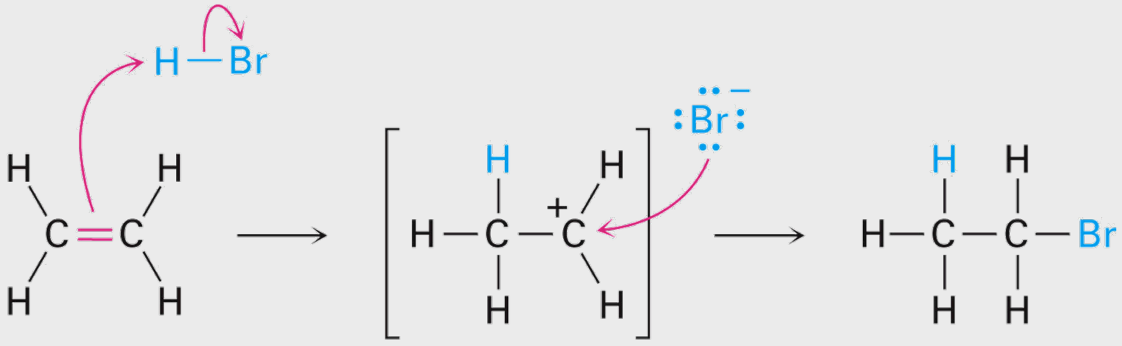
First Step in Addition

- In the addition of HBr the (conceptual) transition-state structure for the first step
- The π bond between carbons begins to break
  - The C–H bond begins to form
  - The H–Br bond begins to break

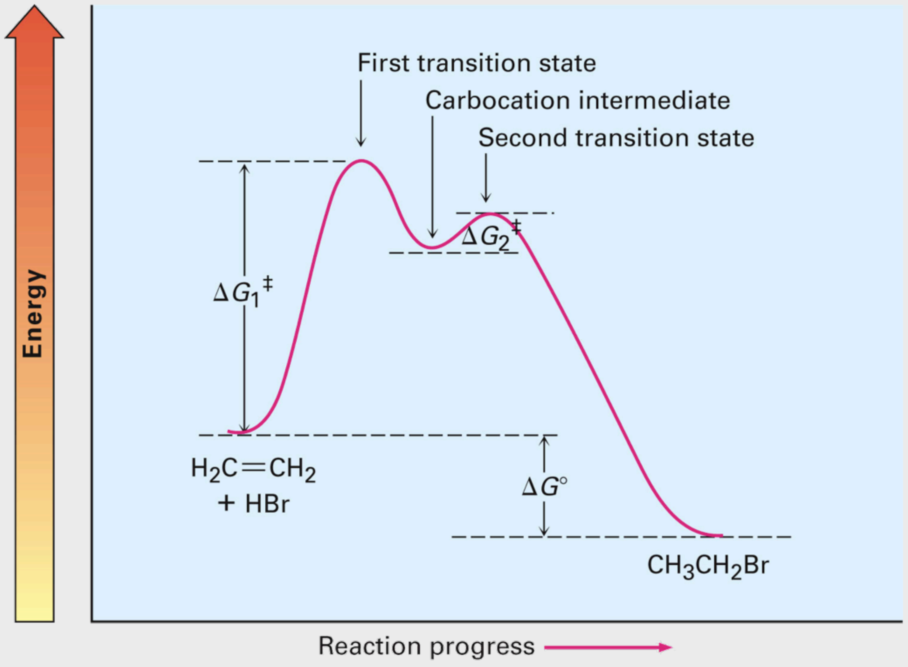


6.10 Describing a Reaction: Intermediates

- If a reaction occurs in more than one step, it must involve species that are neither the reactant nor the final product
- These are called **reaction intermediates** or simply “intermediates”
- Each step has its own free energy of activation
- The complete diagram for the reaction shows the free energy changes associated with an intermediate

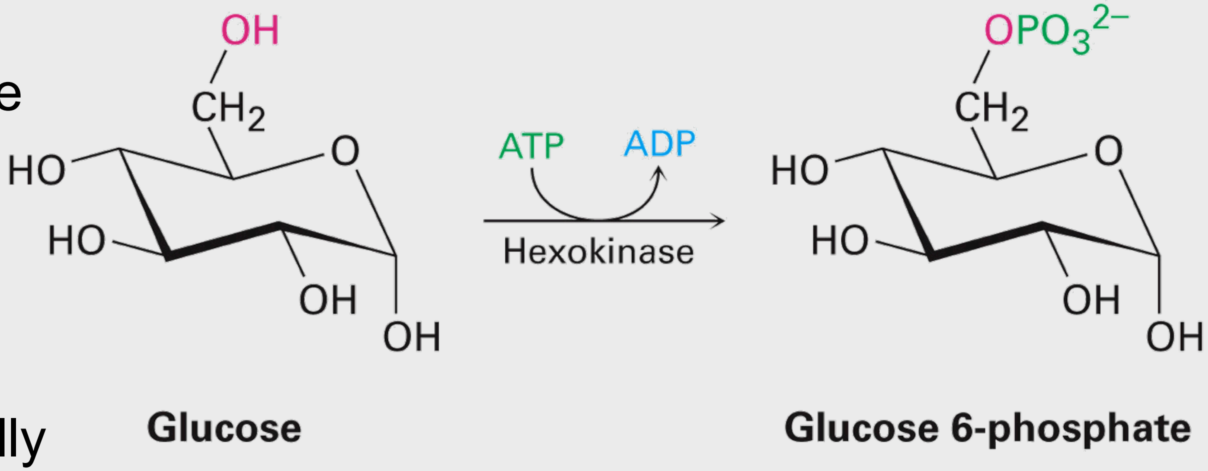


Reaction intermediate

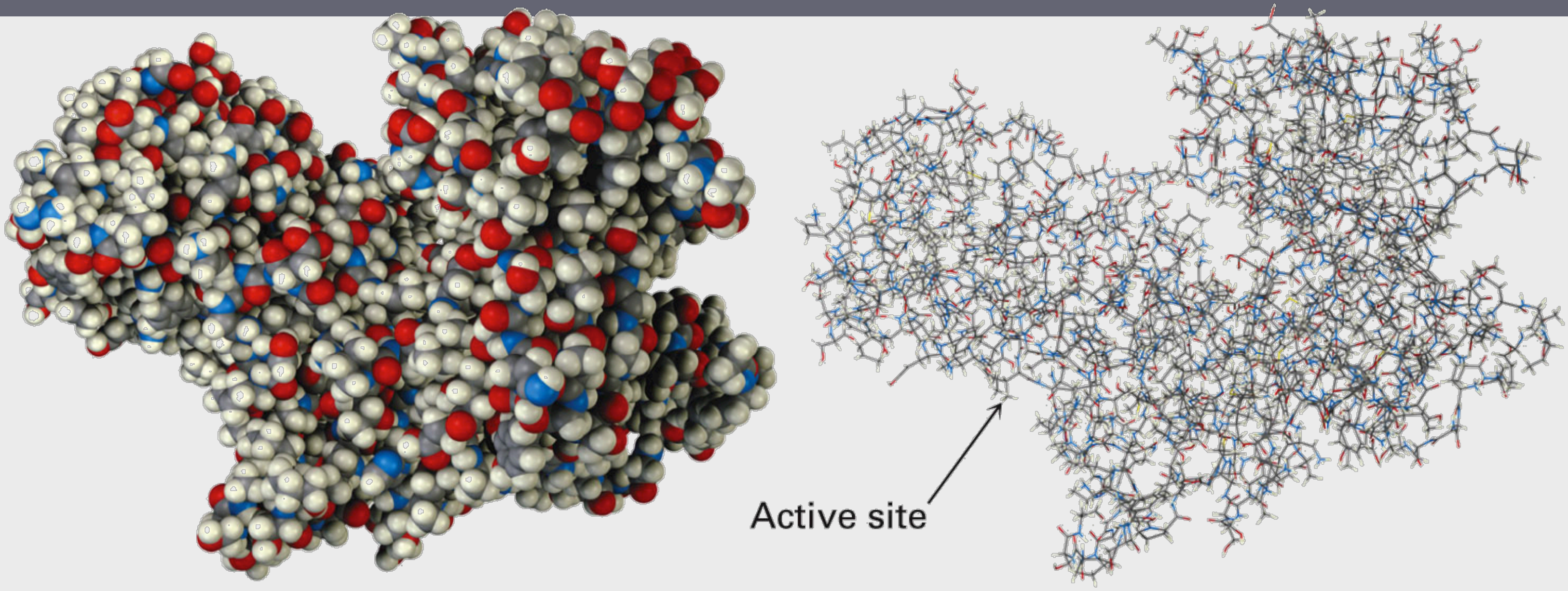


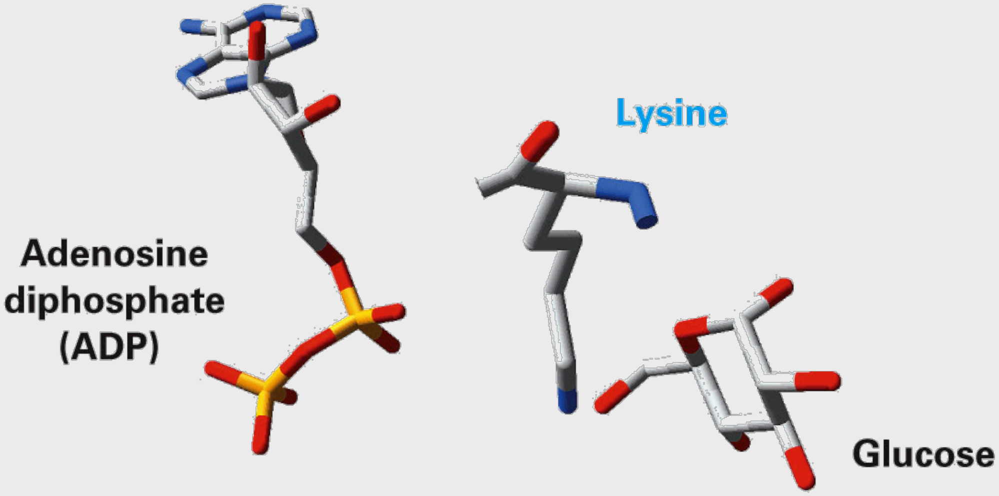
6.11 A Comparison between Biological Reactions and Laboratory Reactions

- Laboratory reactions are usually carried out in organic solvent
- Biological reactions in aqueous medium inside cells
- They are promoted by catalysts that lower the activation barrier
- The catalysts are usually proteins, called enzymes
- Enzymes provide an alternative mechanism that is compatible with the conditions of life



Molecular Models of Hexokinase





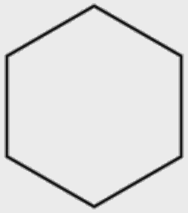
Let’s Work a Problem

Examine the following compounds and identify which of the compound(s) will radical chlorination give a SINGLE monochloro- product?

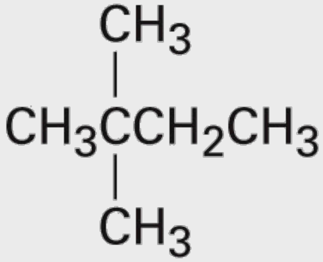
(a) CH_3CH_3

(b) $CH_3CH_2CH_3$

(c)



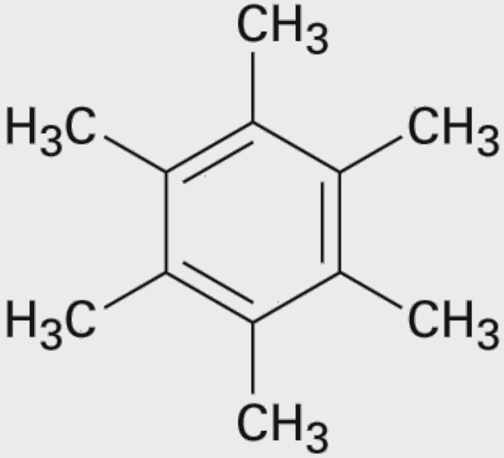
(d)



$$\begin{array}{c} CH_3 \\ | \\ CH_3CCH_2CH_3 \\ | \\ CH_3 \end{array}$$

(e) $CH_3C{\equiv}CCH_3$

(f)



Answer

To properly identify the compounds that will give monochloro- products, we must examine the compounds to identify those with only 1 kind of hydrogen atom. Of the compounds shown, compound b has 2 types of H's (1° and 2°), and compound d has 3 different types of H's.

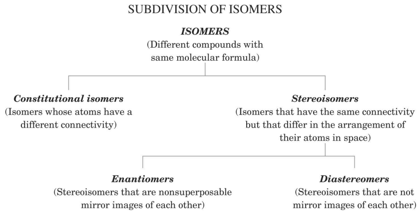
Therefore, the compounds identified by a,c,e, and f will give monohalogenated products because they all have only 1 type of hydrogen.

Stereochemistry: Chiral Molecules

Isomerism: Constitutional Isomers and Stereoisomers

Constitutional Isomers = same molecular formula, different connectedness

Stereoisomers = same molecular formula, same connectivity of atoms but different arrangement of atoms in space


SUBDIVISION OF ISOMERS

ISOMERS
(Different compounds with same molecular formula)

Constitutional isomers
(Isomers whose atoms have a different connectivity)

Stereoisomers
(Isomers that have the same connectivity but that differ in the arrangement of their atoms in space)

Enantiomers
(Stereoisomers that are nonsuperposable mirror images of each other)

Diastereomers
(Stereoisomers that are not mirror images of each other)

Constitutional Isomers - Review

Same molecular formula – different bond connectivities

Examples of Constitutional Isomers

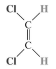
formula	constitutional isomers	
C_3H_8O	$CH_3CH_2CH_2OH$	$CH_3\overset{OH}{C}HCH_3$
C_4H_{10}	$CH_3CH_2CH_2CH_3$	$CH_3\underset{CH_3}{C}HCH_3$

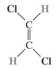
Always different properties

Very different properties if different functional groups

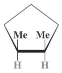
Two types of stereoisomers

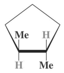
1. **Enantiomers: stereoisomers whose molecules are nonsuperposable mirror images**
2. **Diastereomers: stereoisomers whose molecules are not mirror images of each other**
   - **Example: cis and trans double bond isomers**


cis-1,2-Dichloroethene
($C_2H_2Cl_2$)


trans-1,2-Dichloroethene
($C_2H_2Cl_2$)

   - **Example: cis and trans cycloalkane isomers**

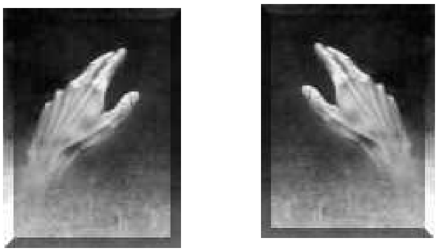

cis-1,2-Dimethylcyclopentane
(C_7H_{14})


trans-1,2-Dimethylcyclopentane
(C_7H_{14})

Enantiomers and Chiral Molecules

- **Chiral molecule - has the property of handedness**
  - **Not superposable on its mirror image**
  - **Can exist as a pair of enantiomers**
- **Pair of enantiomers**
  - **A chiral molecule and its mirror image**
- **Achiral molecule**
  - **Superposable on its mirror image**

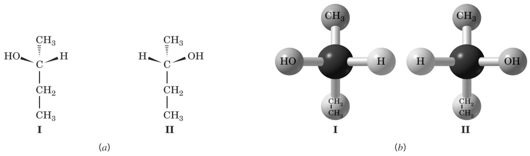
Mirror images = handedness



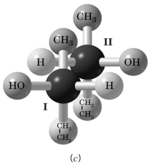
Left hand cannot be superimposed on the right hand

Mirror image = converts right hand into left

A chiral molecule: 2-butanol

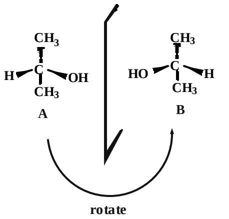


I and II are mirror images of each other
I and II are not superposable and so are enantiomers



2- propanol is not chiral

B is mirror image of A, but is superimposable by 180° rotation

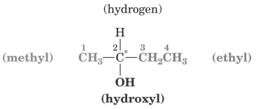


Everything has a mirror image, the question is whether it is superimposable

Chiral molecules and stereogenic centers

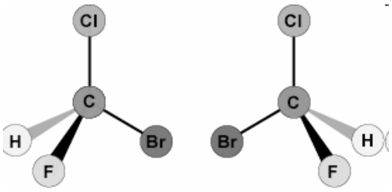
1. **A molecule with a single tetrahedral carbon bonded to four different groups will always be chiral**
2. **Switching two groups at the tetrahedral center leads to the enantiomeric molecule**
3. **A molecule with more than one tetrahedral carbon bonded to four different groups is not always chiral**

- **Stereogenic center (stereo center)**
  - **An atom bearing groups of such nature that an interchange of any two groups will produce a stereoisomer**
  - **Carbons at a tetrahedral stereogenic center are designated with an asterisk (*)**
- **Example: 2-butanol**



$$\overset{\text{(hydrogen)}}{} \quad \text{(methyl)}\ \overset{1}{C}H_3-\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{\overset{2}{C}^*}}-\overset{3}{C}H_2\overset{4}{C}H_3\ \text{(ethyl)} \quad \underset{\text{(hydroxyl)}}{}$$

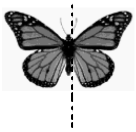
Mirror images not superimposable = enantiomers



Tests for achirality

1. Draw mirror image. Is it superimposable?

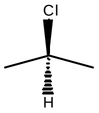
2. Does the species have a bisecting plane of symmetry?



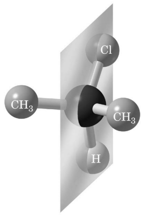
Plane of Symmetry = achiral

An imaginary plane that bisects a molecule in such a way that the two halves of the molecule are mirror images of each other

A molecule with a plane of symmetry cannot be chiral

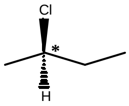


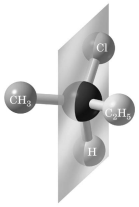
2-chloropropane



If any two groups on a C are identical, achiral

2 -chlorobutane: no plane of Symmetry

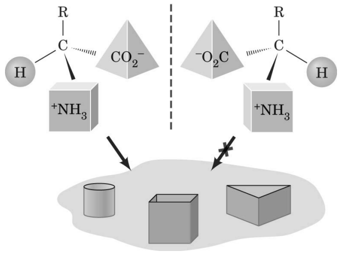




Compounds with 4 different groups attached to one Carbon must be chiral unless a meso compound (2 stereocenters)

Many biological processes depend on chirality

- **The binding specificity of a chiral receptor site for a chiral molecule is usually only favorable in one way**

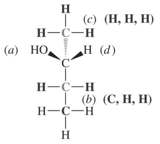


Nomenclature of Enantiomers: The *R,S* System

Developed as the Cahn-Ingold-Prelog system (1956)

1. **The four groups attached to the stereogenic carbon are assigned priorities from highest (a) to lowest (d)**
2. **Priorities are assigned as follows**
   - **Atoms directly attached to the stereogenic center are compared**
   - **Atoms with higher atomic number are given higher priority**
3. **If priority cannot be assigned based on directly attached atoms, the next layer of atoms is examined**

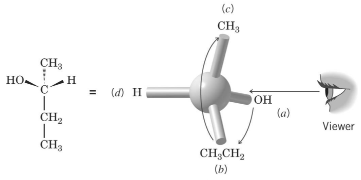
2-butanol



I

R,S nomenclature, cont.

4. **The molecule is rotated to put the lowest priority group back**
   - **If the groups descend in priority (a,b then c) in clockwise direction the enantiomer is *R* *(R=rectus, right)***
   - **If the groups descend in priority in counterclockwise direction the enantiomer is *S* *(S=sinister, left)***

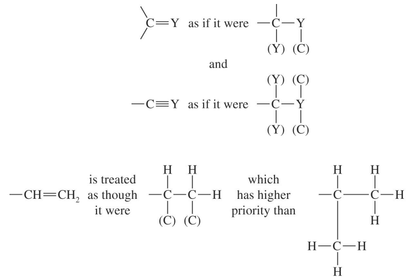


Arrows are clockwise

(*R*)-2-Butanol

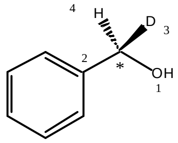
R,S nomenclature, cont.

5. **Groups with double or triple bonds are assigned priorities as if their atoms were duplicated or triplicated**



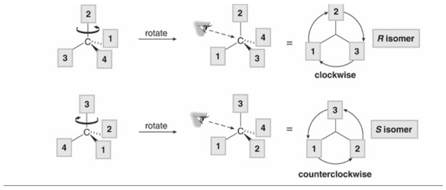
R,S nomenclature, cont.

6. **With isotopes, higher atomic weight gets priority**



If lowest priority group is not in back: 3 options

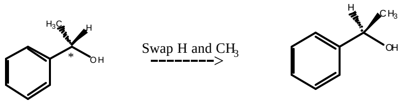
1. **Rotate molecule to put lowest priority in back**



2. **Move your eye to sight along bond toward group 4**

If lowest priority group is not in back: third option

1. **Swap any two groups and then assign the opposite of the new priority**
   - **This works because interchanging two groups automatically generates the enantiomer of the original**



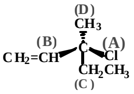
Swap H and CH_3 --------->

R

therefore: S

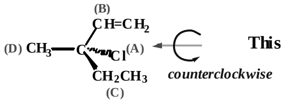
Name this enantiomer of 3-chloro-3-methyl-1-pentene

Assign an (R,S) label to this stereoisomer:



Step 1: Assign Priorities

Step 2: Visualize along the axis with the lowest priority group away from the viewer.

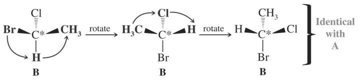


This stereoisomer is (S).

Step 3: Trace out the sequence A-->C.

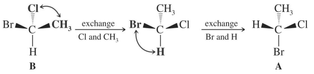
Comparing molecules: Are A and B identical or enantiomers?

Method 1:Rotate B to see if it will become superposable with A



Method 2: Exchange 2 groups to try to convert B into A

- **One exchange of groups leads to the enantiomer of B**
- **Two exchanges of groups leads back to B**



Properties of Enantiomers

◆ **Enantiomers have almost all identical physical properties (melting point, boiling point, density)**

Physical Properties of (R) and (S)-2-Butanol

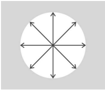
	(R)	(S)
boiling point	99.5°C	99.5°C
density (g/mL, 20°C)	0.808	0.808

◆ **However enantiomers rotate the plane of plane-polarized light in equal but opposite directions**

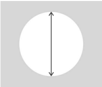
Properties of Enantiomers: Optical Activity

- ♦ **Enantiomers rotate the plane of plane-polarized light in equal but opposite directions**

Oscillation of the electric field of ordinary light occurs in all possible planes perpendicular to the direction of propagation



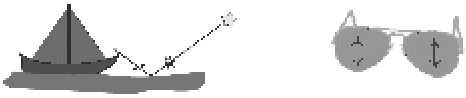
If the light is passed through a polarizer only one plane emerges



Plane polarized light

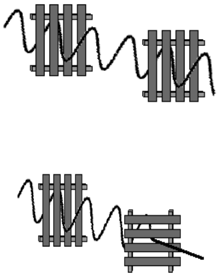
Plane polarized light

Reflected light is largely horizontally polarized

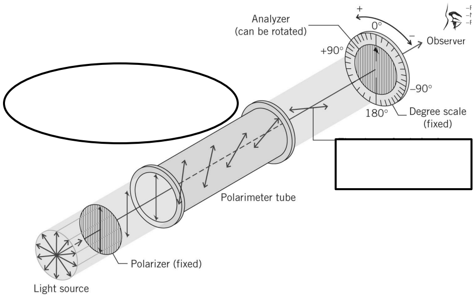


Plane polarized light oscillates in a single plane

Like a rope thru
a picket fence



Schematic of a Polarimeter



Specific Rotation – a property of an enantiomer

An optically active substance (*e.g.* one pure enantiomer) will rotate the plane-polarized light

- **The amount the analyzer needs to be turned to permit light through is called the observed rotation** a
- **We need to calculate a standard value specific rotation [**a **]**

$$[\alpha] = \frac{\alpha}{c \cdot l}$$

where $[\alpha]$ = the specific rotation

α = the observed rotation

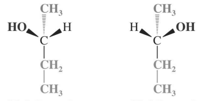
c = the concentration of the solution in grams per milliliter of solution (or density in g mL^{-1} for neat liquids)

l = the length of the tube in decimeters (1 dm = 10 cm)

- **If the analyzer is rotated clockwise the rotation is (+) and the molecule is dextrorotatory (D)**
- **If the analyzer is rotated counterclockwise the rotation is (-) and the molecule is levorotatory (L)**

Specific rotation of enantiomers

- **The specific rotation of the two pure enantiomers of 2-butanol are equal but opposite**



(*R*)-2-Butanol $[\alpha]_D^{25} = -13.52°$

(*S*)-2-Butanol $[\alpha]_D^{25} = +13.52°$

- **There is no straightforward correlation between the *R,S* designation of an enantiomer and the direction [(+) or (-)]in which it rotates plane polarized light**

An example of specific rotation

A sample of a compound A in chloroform (0.500 g/mL) at 25.0°C shows a rotation of +2.5° in a 1.0 decimeter cell. What is the specific rotation?

$$[a]_{l}^{temp} = \frac{\alpha}{L \times C} = \frac{+2.5^{\circ}}{1.0\ \text{dm} \times 0.5\ (\text{g/mL})} = +5.0^{\circ}\ \text{dm}^{-1}\ (\text{g/mL})^{-1}$$

What is the observed rotation of A in a 0.5 dm cell?

$$\alpha = [a] \times L \times C = 5.0^{\circ}\ \text{dm}^{-1}\ (\text{g/mL})^{-1} \times 0.5\ \text{dm} \times 0.5\ \text{g/mL} = +1.25^{\circ}$$

What is the observed rotation if C = 0.050 g/mL?

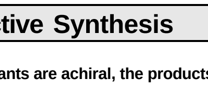
$$\alpha = [a] \times L \times C = 5.0^{\circ}\ \text{dm}^{-1}\ (\text{g/mL})^{-1} \times 1.0\ \text{dm} \times 0.050\ \text{g/mL} = +0.25^{\circ}$$

Racemic Mixture = A 1:1 mixture of enantiomers

- **No net optical rotation**
- **Often designated as (±)**
- **Racemic mixture = racemate**

(±)-2-butanol or as (±)-$CH_3CH_2CHOHCH_3$

Equal
amounts
of each



Enantiomeric Excess

A mixture of enantiomers may be enriched in one enantiomer
We can measure the enantiomeric excess (ee)

$$\%\ \text{Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

- **Example : The optical rotation of a sample of 2-butanol is +6.76°. What is the enantiomeric excess?**

$$\text{Enantiomeric excess} = \frac{+6.76^{\circ}}{+13.52^{\circ}} \times 100 = 50\%$$

Enantiomeric Excess

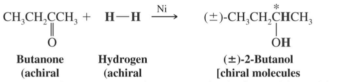
$$\text{Enantiomeric excess} = \frac{+6.76^{\circ}}{+13.52^{\circ}} \times 100 = 50\%$$

ee of 50% = 50% of one enantiomer (+)
50% of racemate (+/-)

Equivalently 75% of (+)-enantiomer
25% of (-)-enantiomer

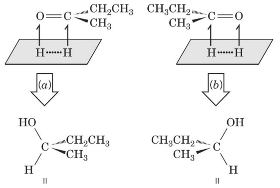
The Synthesis of Chiral Molecules

Most chemical reactions which produce chiral molecules generate the racemic mixture (50%R, 50% S)



$$CH_3CH_2\underset{\underset{O}{\|}}{C}CH_3 + H{-}H \xrightarrow{Ni} (\pm)\text{-}CH_3CH_2\overset{*}{\underset{\underset{OH}{|}}{C}}HCH_3$$

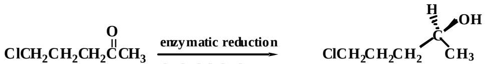
Butanone (achiral molecules) **Hydrogen (achiral molecules)** **(±)-2-Butanol [chiral molecules but 50 : 50 mixture (*R*) and (*S*)]**



Enantioselective Synthesis

If all starting materials and reactants are achiral, the products will be achiral or racemic
If one of the reagents is chiral, as is common in biological systems, then the products may be chiral

e.g.: picking out the left handed gloves from a racemic mixture of rights and lefts



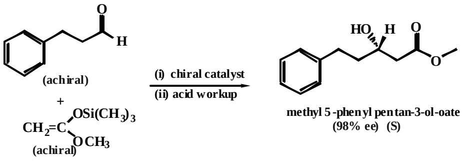
5-chloro-2-pentanone (achiral)

(S)-5-chloro-2-pentanol (98% ee)

Top and bottom faces of the ketone bond are different to handed reagents

Enantioselective Synthesis in the lab

Synthetic chemists are designing chiral catalysts that mimic the enantioselectivity of enzyme-catalyzed reactions.

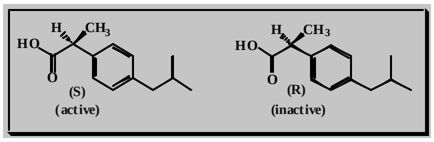


methyl 5-phenyl pentan-3-ol-oate
(98% ee) (S)

Chiral Drugs and Pharmaceutical Companies

Typically only one enantiomer of a drug is biologically active

Preparation of only the desiredenantiomer saves material, costs, and possible side effects

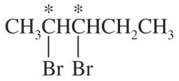


Ibuprofen

Molecules with More than One Stereogenic Center

Each new center may generate a potential pair of stereoisomers, so the theoretical number of possible stereoisomers is 2^n

(May have fewer if symmetry elements are present)

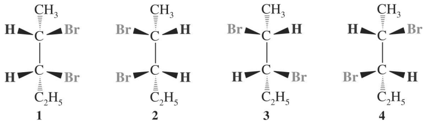


$$CH_3\overset{*}{C}H(Br)\overset{*}{C}H(Br)CH_2CH_3$$

2,3-Dibromopentane

How many stereoisomers?

Four stereoisomers of 2,3-dibromopentane



Relationship of 1 and 2 = enantiomers

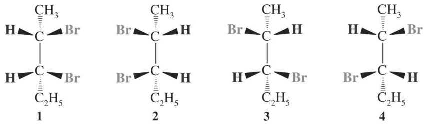
- **Enantiomers = same properties, cannot be separated**

Relationship of 3 and 4 = enantiomers

1 and 3 (or 1 and 4) = diastereomers

- **Diastereomers: stereoisomers not mirror images of each other**
- **Have different physical properties and can be separated**

Four stereoisomers of 2,3-dibromopentane



We cannot simply say that 1 is an enantiomer or a diasteromer

Stereoisomerism refers to the relationship between two isomers

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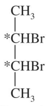
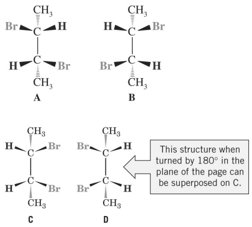
Meso compounds

Sometimes molecules with 2 or more stereogenic centers will have less than the maximum amount of stereoisomers



CH_3–*CHBr–*CHBr–CH_3

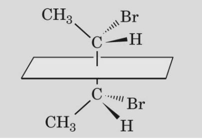
2,3-Dibromobutane



This structure when turned by 180° in the plane of the page can be superposed on C.

Meso compound are achiral

- ♦ Because superposable on its mirror image
- ♦ Despite the presence of stereogenic centers
- ♦ Not optically active
- ♦ Has a plane of symmetry



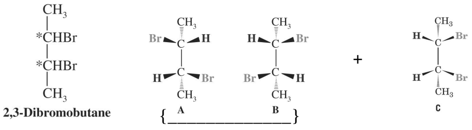
Definition: a meso compound is a compound that is achiral despite having stereogenic centers

---

Meso Compounds and Racemates

Under achiral conditions, a synthesis of 2,3-dibromobutane may create:

- ➡ **A and B in equal amounts (the racemate)**
- ➡ **C (the meso product)**
- ➡ **Some mixture of racemate (A/B) and meso compound C**



2,3-Dibromobutane

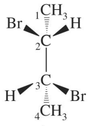
racemate

meso

Naming Compounds with More than One Stereogenic Center

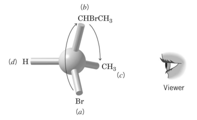
Using same rules, assign each stereogenic center separately

Example: (*2R*, *3R*)-2,3-dibromobutane

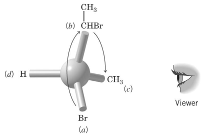


A

2,3-Dibromobutane



(*R*) Configuration

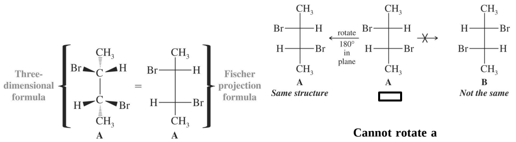


(*R*) Configuration

Fischer Projections

A 2-dimensional representation of chiral molecules

- **Vertical lines represent bonds projecting behind the plane of the paper**
- **Horizontal lines represent bonds projecting out of the plane of the paper**

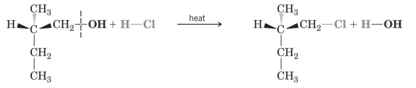


Cannot rotate a Fischer projection about either vertical or horizontal axis

Widely used in carbohydrate chemistry

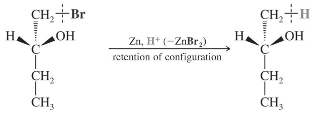
Relating Configurations of Stereogenic Centers

If no bonds to the stereogenic carbon are broken, the reaction proceeds with *retention of configuration*



(*S*)-(−)-2-Methyl-1-butanol
$[\alpha]_D^{25} = -5.756°$

(*S*)-(+)-1-Chloro-2-methylbutane
$[\alpha]_D^{25} = +1.64°$



(*R*)-1-Bromo-2-butanol

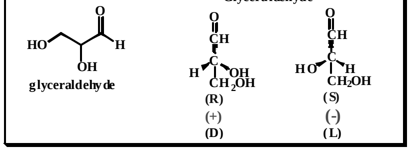
(*S*)-2-Butanol

Note change of R to S despite retention

Relative Configurations: (D)- and (L)-Glyceraldehyde

In the late 19th century, Emil Fischer developed a method for assigning configurations at stereocenters relative to the enantiomers of glyceraldehyde. For the next 50 or 60 years, configurations at stereocenters were labeled relative to the stereocenters in the stereoisomers of glyceraldehyde.

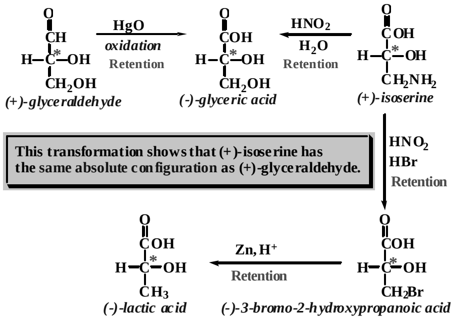
The Stereoisomers of Glyceraldehyde



Over 100 years ago, Fischer assigned the dextrorotatory (+) stereoisomer, the configuration we call (R), and the levorotatory (-) stereoisomer was assigned the (S) configuration.

The labels Fischer assigned were called (D) and (L). These assignments were a guess.

An Example: Relating (-)-Lactic Acid to (+)-Glyceraldehyde

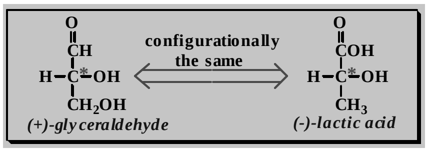


This transformation shows that (+)-isoserine has the same absolute configuration as (+)-glyceraldehyde.

This transformation shows that (+)-isoserine has the same absolute configuration as (-)-lactic acid.

Absolute Configurational Assignments

The series of chemical reactions involving retention of configuration at the stereocenters configurationally link (+)-glyceraldehyde and (-)-lactic acid.



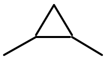
Before 1951 the absolute configurations were not known.
Only these relative configurations were known from carefully designed chemical transformations linking the assignments to the configurations of the glyceraldehydes assumed by Emil Fischer.

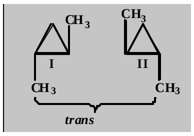
1951, X-ray crystal structure of (+) tartaric acid showed Fischer made the right guess!

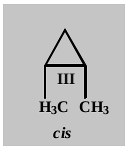
Stereoisomerism of Cyclic Compounds

Consider 1,2-dimethylcyclopropane

Two stereogenic centers







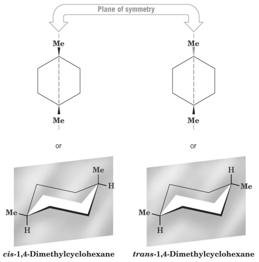
Trans isomer has two enantiomers

R,R and S,S

Cis isomer is a meso compound

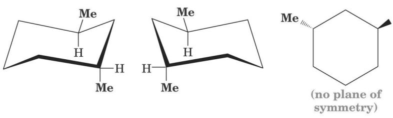
Stereoisomerism of Cyclic Compounds

- 1,4-dimethylcyclohexane
  - ➨ Neither the cis not trans isomers is optically active
  - ➨ Each has a plane of symmetry



cis-1,4-Dimethylcyclohexane *trans*-1,4-Dimethylcyclohexane

- ♦ 1,3-dimethylcyclohexane
  - The trans and cis compounds each have two stereogenic centers
  - The cis compound has a plane of symmetry and is meso
  - The trans compound exists as a pair of enantiomers



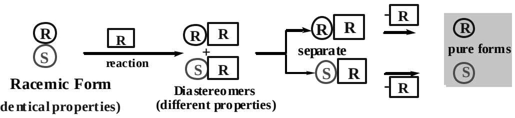
(*a*) (*b*) (*c*)

Ring flip of (*a*) produces another *(a)*, not the mirror image *(b)*

Separation of enantiomers = resolution

Cannot be separated directly Why not?

Can be separated by chiral reagent which creates diastereomeric relationship



Racemic Form
(identical properties)

Diastereomers
(different properties)

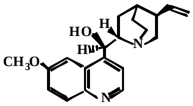
R is a resolving agent. It is a single enantiomer (such as R) of a chiral compound.

General Approach to Resolution

Often use organic acids or based which are found optically pure in nature

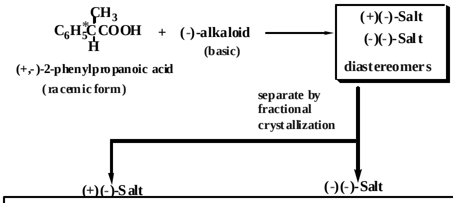
Can form acid-base salts which usually assures a high melting point and the potential to separate by selective crystallization

Easily regenerate starting acid or base



quinine
(primary alkaloid from various species of *Cinchona*)

Resolution of a Carboxylic Acid



$C_6H_5\overset{*}{C}(CH_3)(H)COOH$ + (-)-alkaloid (basic) → (+)(-)-Salt, (-)(-)-Salt — diastereomers

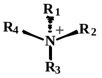
(+,-)-2-phenylpropanoic acid
(racemic form)

(+)(-)-Salt
(-)(-)-Salt
diastereomers

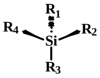
separate by fractional crystallization

(+)(-)-Salt **(-)(-)-Salt**

Chiral Molecules without a tetrahedral carbon



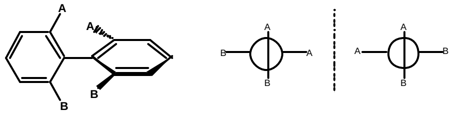
quaternary ammonium ion



silane

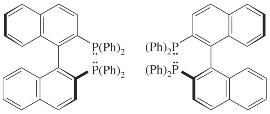
Chiral Molecules without a Stereocenter: Molecular Chirality

Some molecules begin a helical chirality by restricted rotation



Chirality without tetrahedral atoms

- **Atropoisomer: conformational isomers that are stable**



(S)-BINAP *(R)*-BINAP

- **Allenes: contain two consecutive double bonds**