

Stereochemistry and chirality

Stereochemistry deals with the different ways the atoms in a molecules are **oriented in space**. **Stereoisomerism** affects **molecular recognition**:

- Structures of products from synthetic or biosynthetic reactions
- Ability of molecules to function as reactants in biochemical reactions and subsequent biochemical products
- Recognition of bioactive molecules by natural receptors
Simple example: (+) and (-) carvone

Variation in molecular structure that we've encountered so far:

-- **Structural/constitutional isomerism:** Molecules having the same formula but atoms connected in completely different patterns.

Nomenclature: Names are different

-- **Conformations:** Atoms are connected in a given pattern, but can rotate or move to give different arrangements in space. These can readily interconvert.

**Conformers are versions of a single molecule and therefore have the same name*

-- **Cis-trans and E/Z stereoisomerism (geometric isomerism):** Refers specifically to the spatial orientation of groups attached to a C = C bond or a ring, brought about by restricted rotation.

Nomenclature: Same name with a prefix to designate E or Z; cis or trans

NEW: Stereoisomerism at a chiral carbon, based on possible spatial arrangements that exist when four different groups or atoms are bonded to an sp^3 carbon called a **chirality center**.

Nomenclature: Stereoisomers with chirality have the same name with a letter designation prefix (R or S) to distinguish between isomers

Goals:

- Recognize chiral centers in a molecule
- Become familiar with 2-D representations of 3-D chiral molecules
- Identify molecules that are mirror images
- Assign configurations at the chiral center based on the R,S system
- Learn some properties of compounds that are affected by chirality
- Identify different types of stereoisomers
- Review the stereochemistry of some familiar reactions

Tools: Use your model kits as much as possible when working problems!

Recognizing and representing chirality

Origin of the term “chiral” : **Greek for “hand”** **Chirality =**
“handedness”

Chiral molecules like other **chiral objects** are objects which cannot be superimposed (matched up) on their mirror image. Chiral objects do not have a plane of symmetry

Some examples
of chiral objects?

Achiral objects have a plane of symmetry.
Some examples
of achiral objects?

Achiral molecules: CH_2Cl_2 , propanoic acid

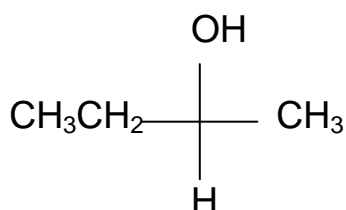
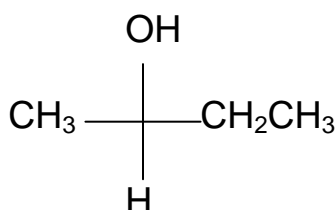
The existence of a chiral carbon center in a molecule can be recognized by the **general formula:** **CHXYZ**, where X, Y & Z are not equivalent

For example: CHBrCl has two possible spatial arrangements, which can be represented by tetrahedra using dash-wedge notation:

For chiral molecules, a mirror image can exist which is a different molecule.
Mirror-image molecules are called enantiomers.

Other examples: lactic acid, 2-butanol

Enantiomers and other stereoisomers are often represented by **Fischer projections:**



Distinguishing between enantiomers: The R, S system of nomenclature

Cahn, Ingold & Prelog invented a system to categorize enantiomers based on configuration around the chiral center using **priority groups**

Priority groups are determined by the same rules as used in E/Z system

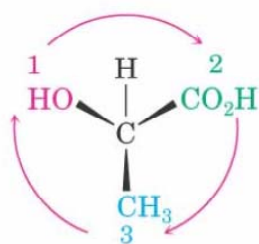
-- Examine the atomic weight of each atom directly bonded to the chiral C; if any are equal, consider the atoms bonded next in line, working out from the middle.

-- Assign each atom or group a priority number.

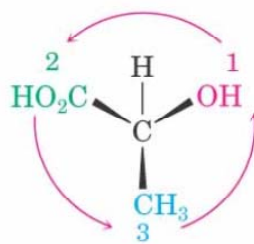
Determining R and S configurations using the wedge-dash notation:

Method #1 (preferred):

Draw the molecule so that the **lowest** priority group (usually H) is **in the back**. Then, draw a circular arrow around the 3 remaining groups from highest priority to next highest and so forth. The direction of the arrow determines R or S:



R configuration
(a) (-)-Lactic acid



S configuration
(b) (+)-Lactic acid

Direction
of arrow:

Clockwise (to right) = R

Counterclockwise (to left) = S

Determining R/S with a structure where the lowest priority group is **not** in back:

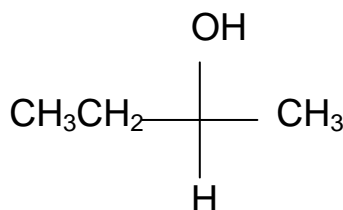
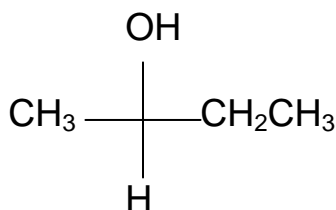
--Make a model of the molecule. Then orient the model so that the lowest priority group is in the back. Determine R or S using the rules above.

--If the lowest priority group is in the **front**, number the three groups in the rear and reverse the R/S conventions so that S = clockwise

Determining R/S configurations from Fischer projections:

Remember that top and bottom groups project back; side groups project forward:

When the lowest priority group is on the **top or bottom**, the same procedure is used as for dash-wedge notation:



When the lowest priority group is on **a side**, you reverse the R/S conventions:

Here, clockwise arrow = S

counterclockwise arrow = R

Don't reverse the structure! **Fischer projections cannot be flipped over**; it will not be the same molecule! **Nor can they be rotated by 90°**. (Rotation by 180° in the plane of the paper will still give the same molecule).

If you cannot easily determine R/S from Fischer projections, **make a model** and position it with the lowest priority group pointing to the back, and go from there.

Properties of chiral compounds:

Some physical properties of enantiomers are **identical**: boiling & melting points, solubilities, dipole moments, properties that depend on overall size & polarity

Other properties of enantiomers differ substantially:

Optical activity

Plane-polarized light consists of only waves that are oscillating in a single plane; all other light waves are blocked: a "slice" rather than a beam of light

Each enantiomer of a compound with a chiral center has the ability to rotate plane-polarized light.

- One enantiomer rotates the light clockwise = "right" = dextrorotatory = (+)
the other rotates light counterclockwise = "left" = levorotatory = (-)
- The magnitude of light rotation for both enantiomers is the same though the directions are opposite
- Achiral compounds do not rotate plane-polarized light
- A 50-50 mixture (racemic mixture) of the two enantiomers is also optically inactive
- (+) and (-) designations cannot be assigned based on structure (R, S), only on observed rotation of a solution measured by polarimeter

Optical rotation is measured in solution and is expressed as a specific rotation at a given temperature and wavelength of light (usually 589 nm from sodium lamp):

$$[\alpha]_{\lambda}^T = \frac{\alpha}{l \times c} \quad \text{where:} \quad \begin{array}{l} \alpha = \text{observed rotation in degrees} \\ l = \text{length of tube in dm} \\ c = \text{conc. in g/mL} \\ (\text{usually } l \text{ \& } c \text{ both} = 1.0) \end{array}$$

A **racemic mixture** (50:50), often the product of synthetic reactions, is labeled (\pm)

Enantiomers may be named with both designations: R/S and +/- (if known)

Enantiomerically pure samples are often encountered in nature.

The relative **enantiomeric purity** of a sample can be expressed as follows:

$$\begin{array}{l} \text{optical purity} \\ \text{or} \\ \text{enantiomeric excess (e.e.)} \end{array} = \frac{\text{observed specific rotation of sample}}{\text{specific rotation of pure enantiomer}} \times 100\%$$

Physiological activity: production and recognition of stereoisomers

1. Biochemical reactions:

Enzymes that catalyze physiological reactions are made up of proteins that contain a very specific binding site for a molecule. The binding sites have chirality.

- they only recognize a specific stereoisomer
- they control reactions such that a single stereoisomer is produced (fumarase)

2. Nerve Receptors:

Receptors are also made up of proteins with chiral binding sites that only recognize a specific stereoisomer.

Example: (R)-(-)-carvone is recognized as "spearmint" by a receptor in the nose
(S)-(+)-carvone is recognized as "caraway" by a separate receptor!

3. **Pharmacological activity** may differ between enantiomers:

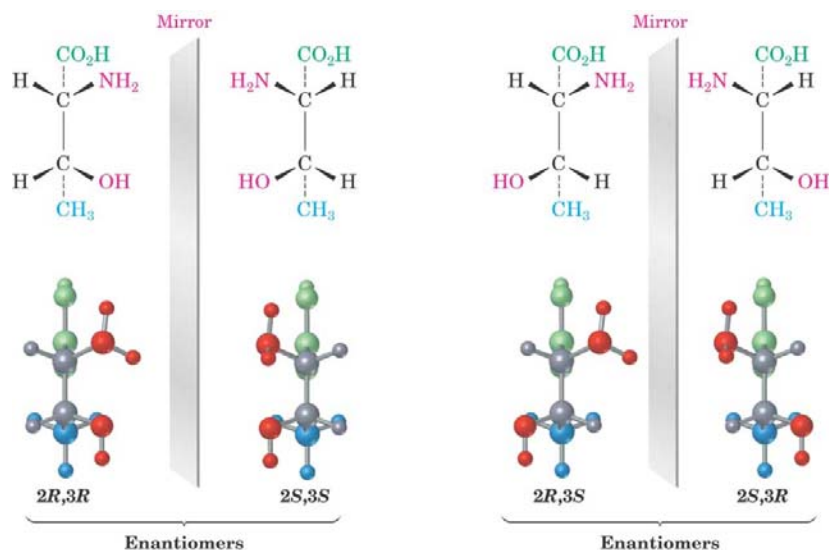
Chiral drugs: (S)-(+)-ketoprofen is an antiinflammatory
(R)-(-)-ketoprofen fights periodontal disease

Stereochemistry of compounds with more than one chirality center

As the number of chirality centers goes up, number of possible stereoisomers increases:

Maximum number of Stereoisomers = 2^n (where n = # of chirality centers)

These are best seen by drawing Fischer projections, orienting the C chain vertically:



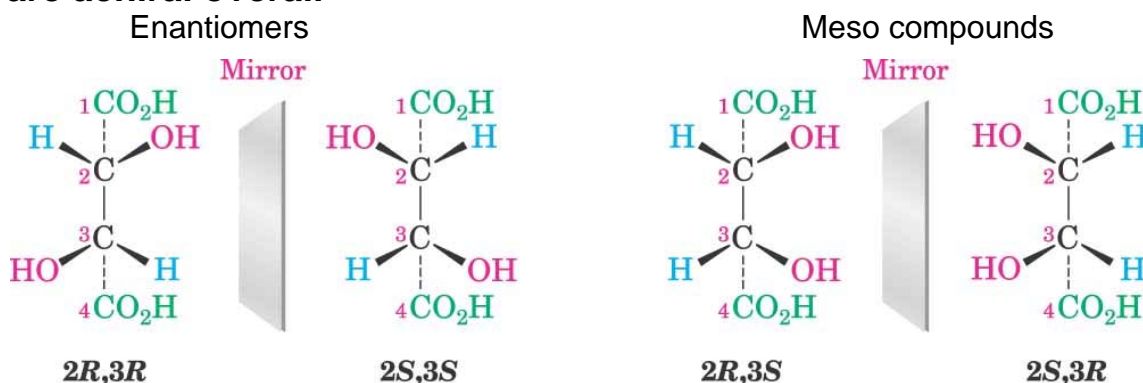
2 pairs of enantiomers are possible, or 4 different structures.

The relationship between a member of one set and the other: **diastereomers**

Diastereomers are stereoisomers that are NOT mirror images.

When examining a set of diastereomers, check for a **plane of symmetry** between the two chiral carbons: if you find one, that structure and its mirror image are actually the same!

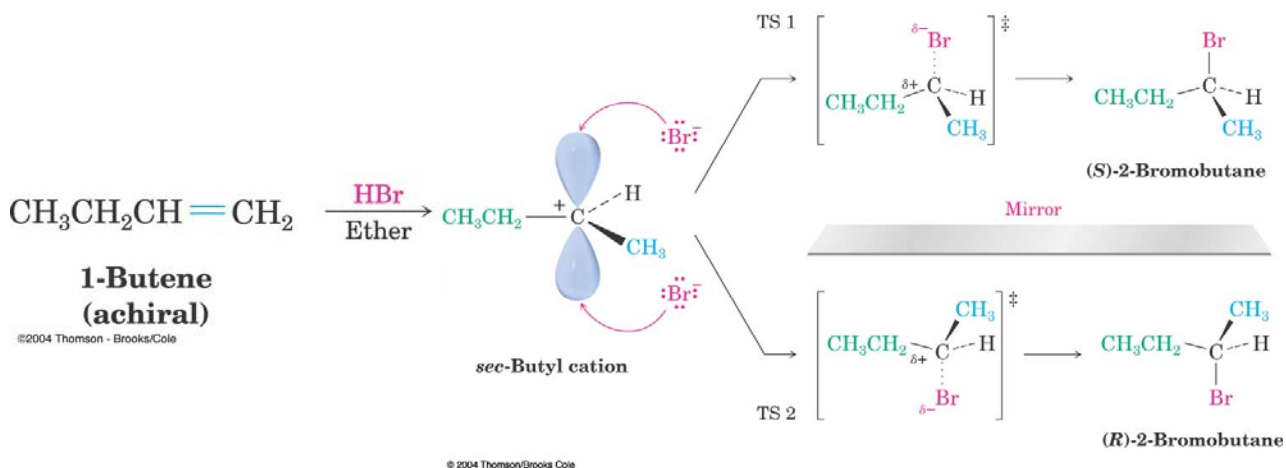
Meso compounds: Compounds which contain more than one chiral carbon but are achiral overall



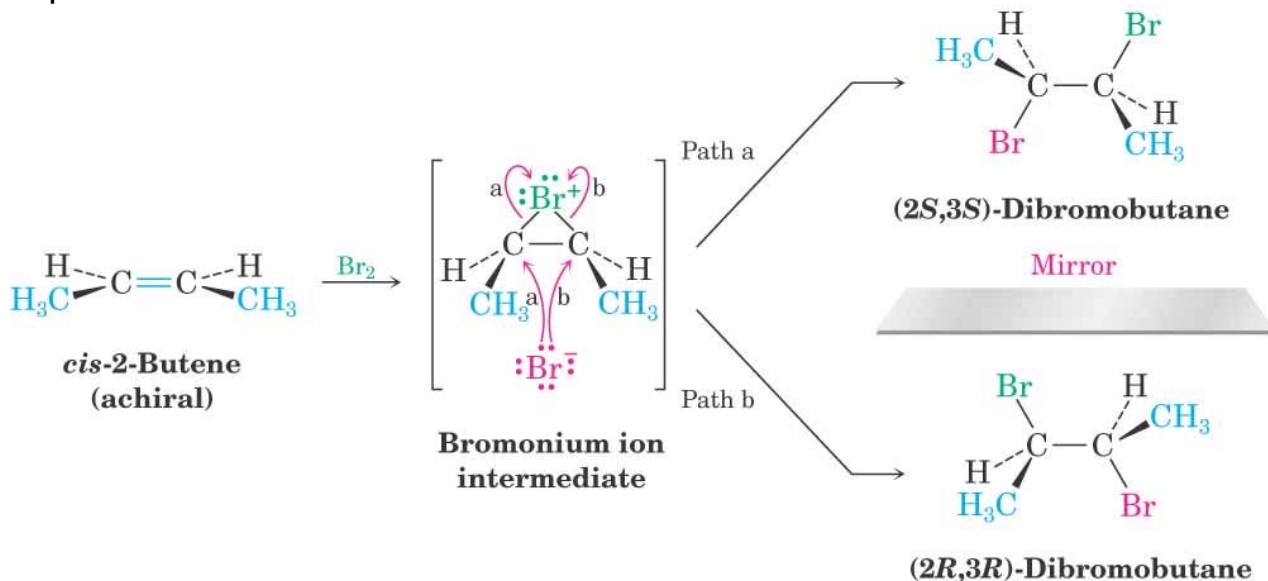
Stereochemistry of reaction products: Electrophilic addition

Reactions will either produce an optically active product (a single isomer predominates) or an optically inactive product (a racemic mix or a meso product).

In general, optically inactive reactants produce optically inactive products.

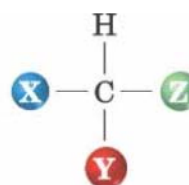
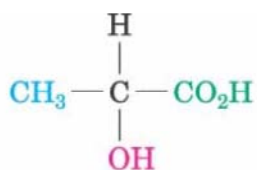


In this case, a chiral center is produced, but the reaction is not stereoselective, so the product distribution is 50:50

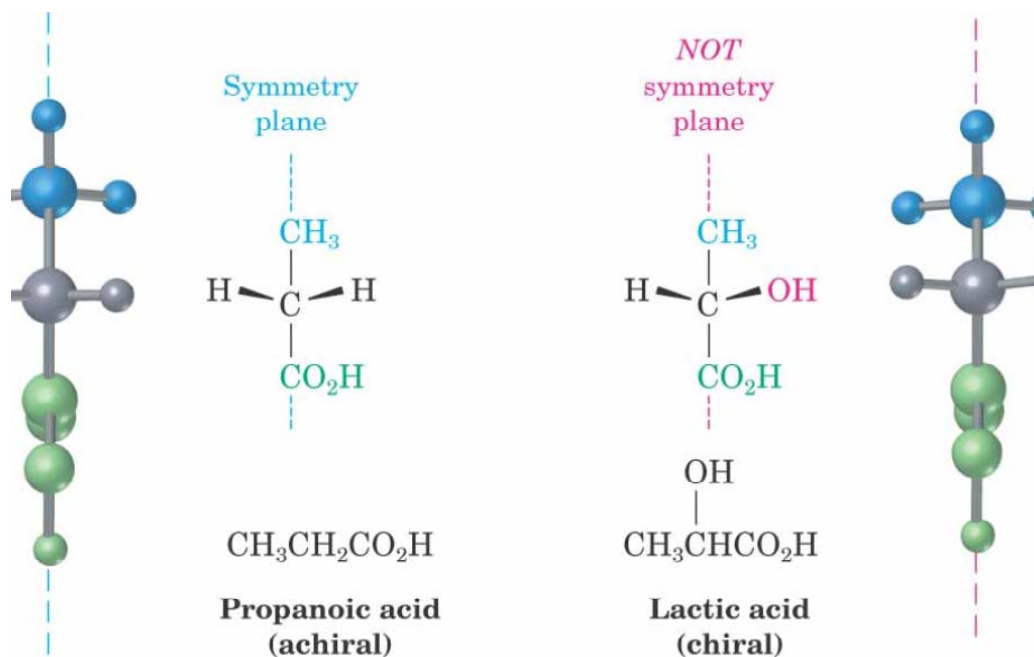
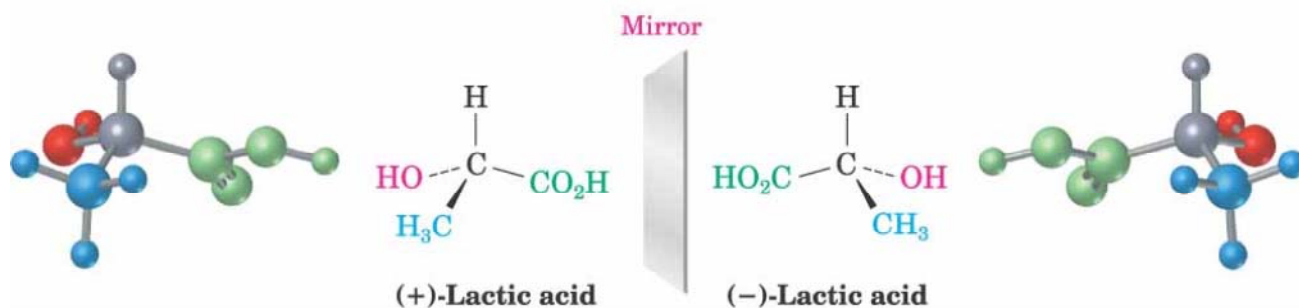


Here, there are two chiral centers generated, and the reaction IS stereoselective for anti addition, but a racemic mix of two stereoisomers is produced.

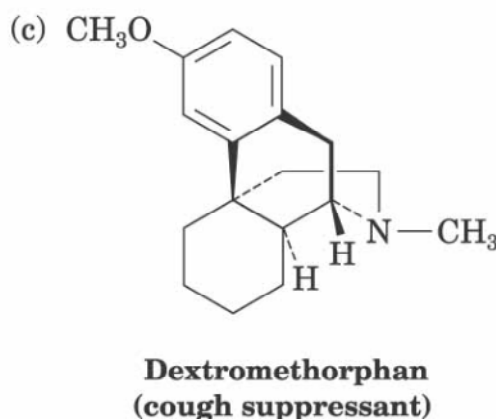
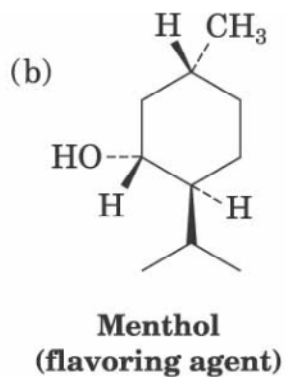
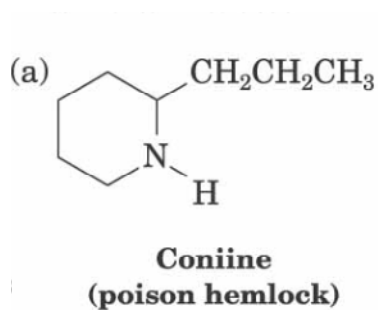
In Chapter 11 we'll learn about a substitution reaction of chiral molecules which does produce optically active products: the $\text{S}_{\text{N}}2$ reaction.



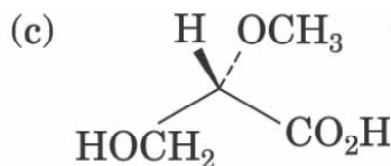
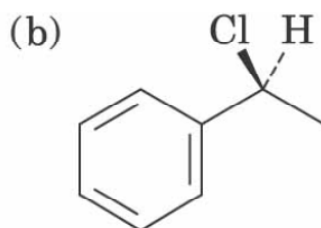
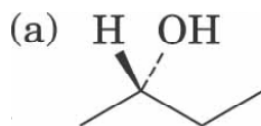
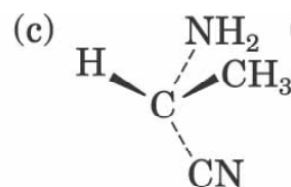
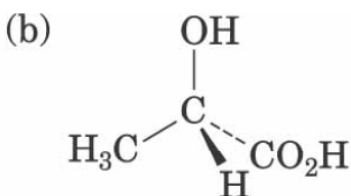
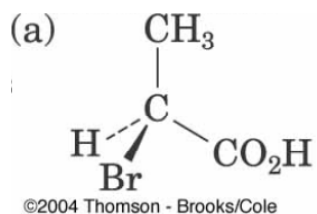
Lactic acid: a molecule of general formula CHXYZ



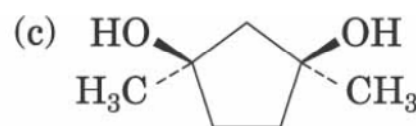
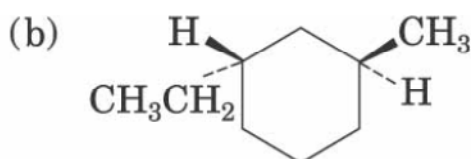
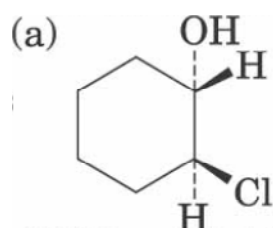
Identify the chiral centers with a *



Determine whether each is R or S configuration



More than one chiral center:



Which stereoisomers are produced in each reaction?

