Stereochemistry - Chirality

Chapter 5
Organic Chemistry, *8th Edition*
John E. McMurry

Isomerism

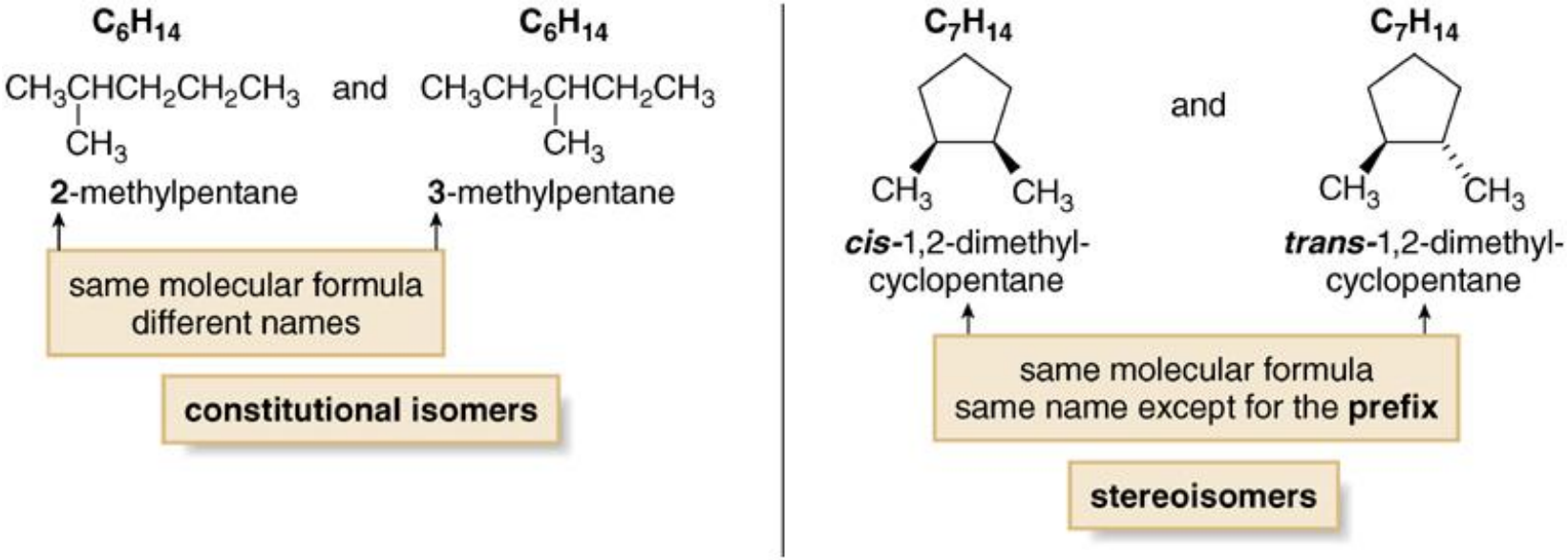
- The two major classes of isomers are constitutional isomers and stereoisomers.

  - Constitutional/structural isomers have different IUPAC names, different physical and chemical properties, and may have different functional groups.

  - Stereoisomers differ only in the way the atoms are oriented in space. They have identical IUPAC names (except for a prefix like *cis* or *trans*). They always have the same functional group(s).

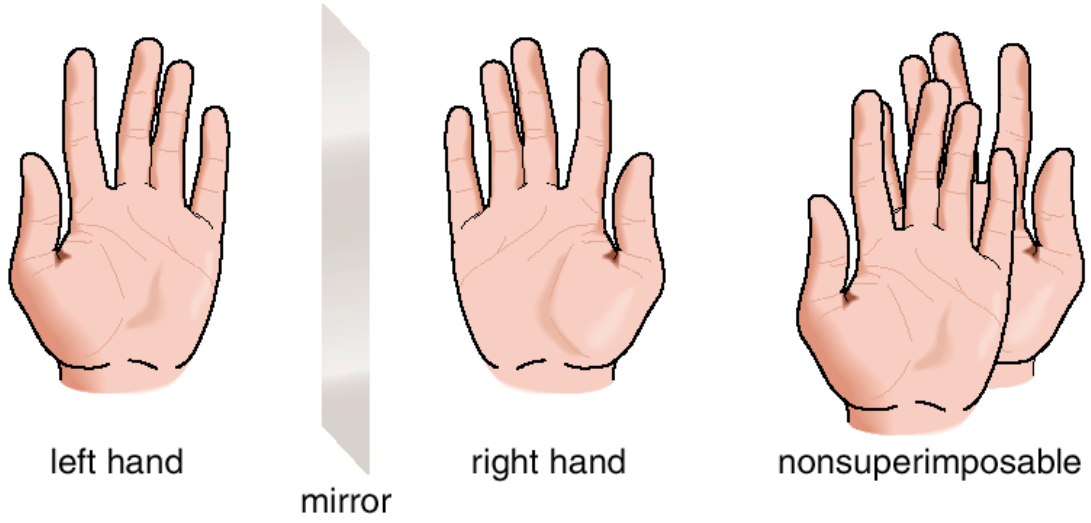
- A particular three-dimensional arrangement is called a configuration. Stereoisomers differ in configuration.

Stereoisomers



Chirality

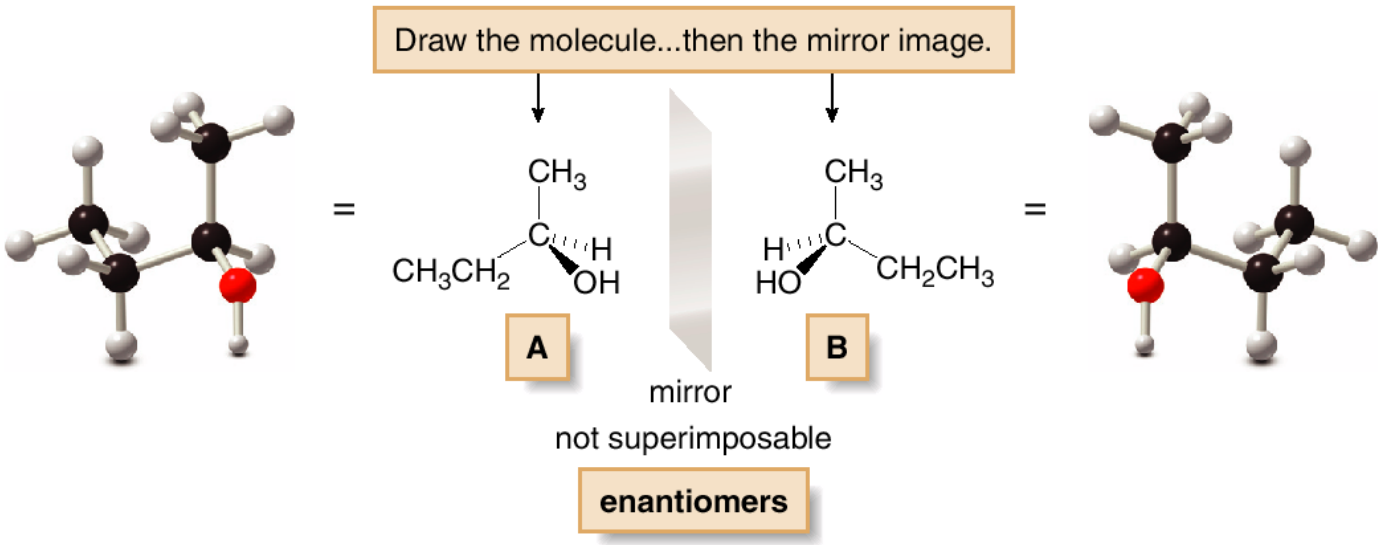
- Every object has a mirror image: mirror images may or may not be superimposable.
- Some molecules are like hands. Left and right hands are mirror images, but they are not identical, or superimposable.



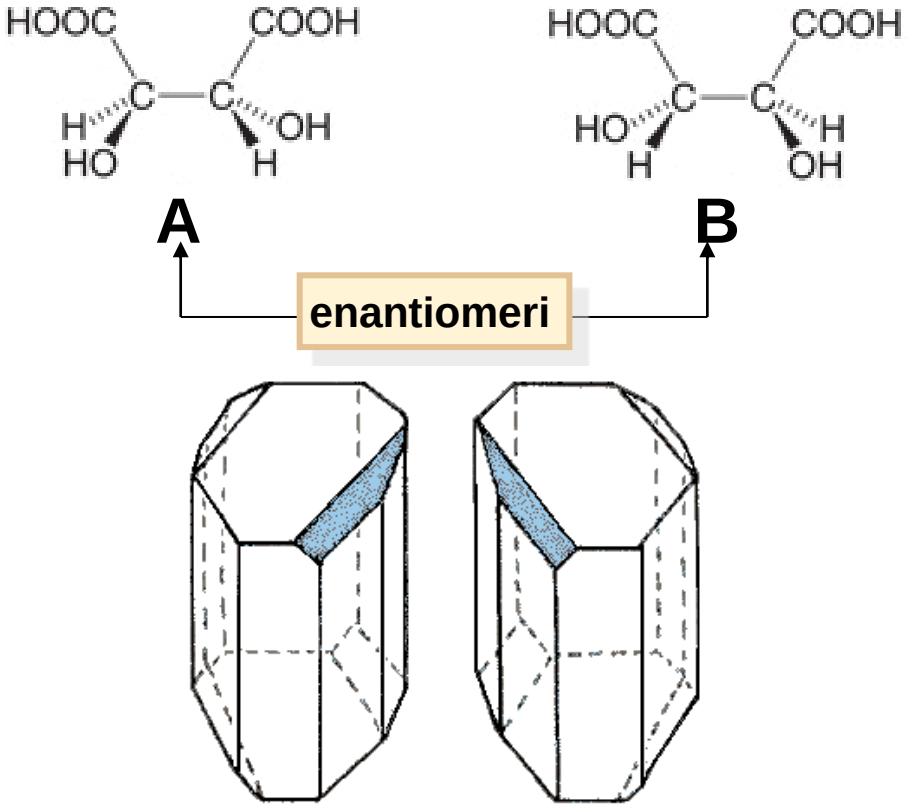
- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral.*

Chirality

- A and B are stereoisomers—specifically, they are enantiomers.
- A carbon atom with four different groups is a tetrahedral stereogenic center.

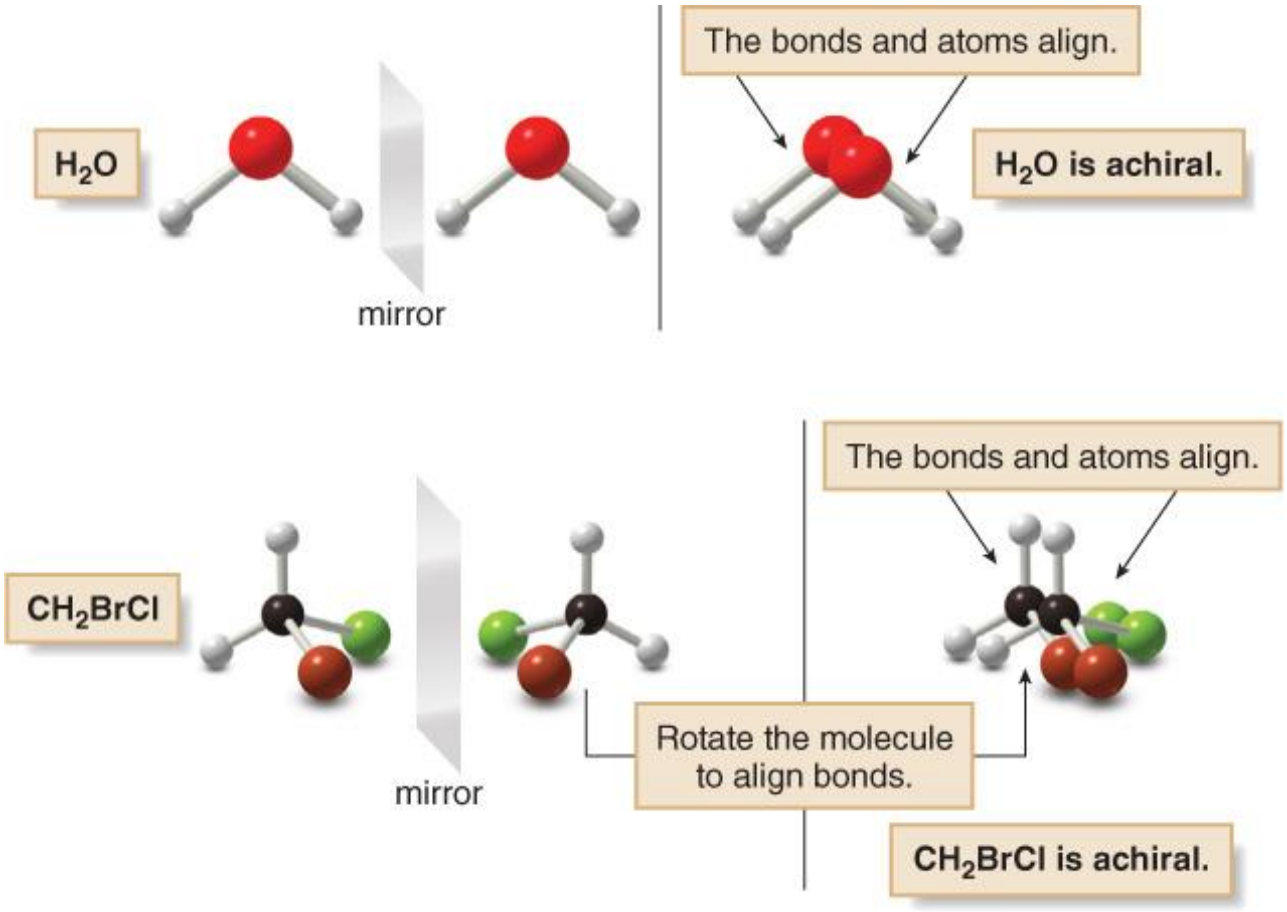


Tartaric acid



Louis Pasteur

Chirality

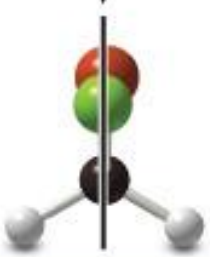

H_2O
mirror
The bonds and atoms align.
H_2O is achiral.
CH_2BrCl
mirror
The bonds and atoms align.
Rotate the molecule to align bonds.
CH_2BrCl is achiral.

Chirality and Symmetry

Aligning the C–Cl and C–Br bonds in each molecule.

CH_2BrCl

plane of symmetry



This molecule has **two identical halves.**

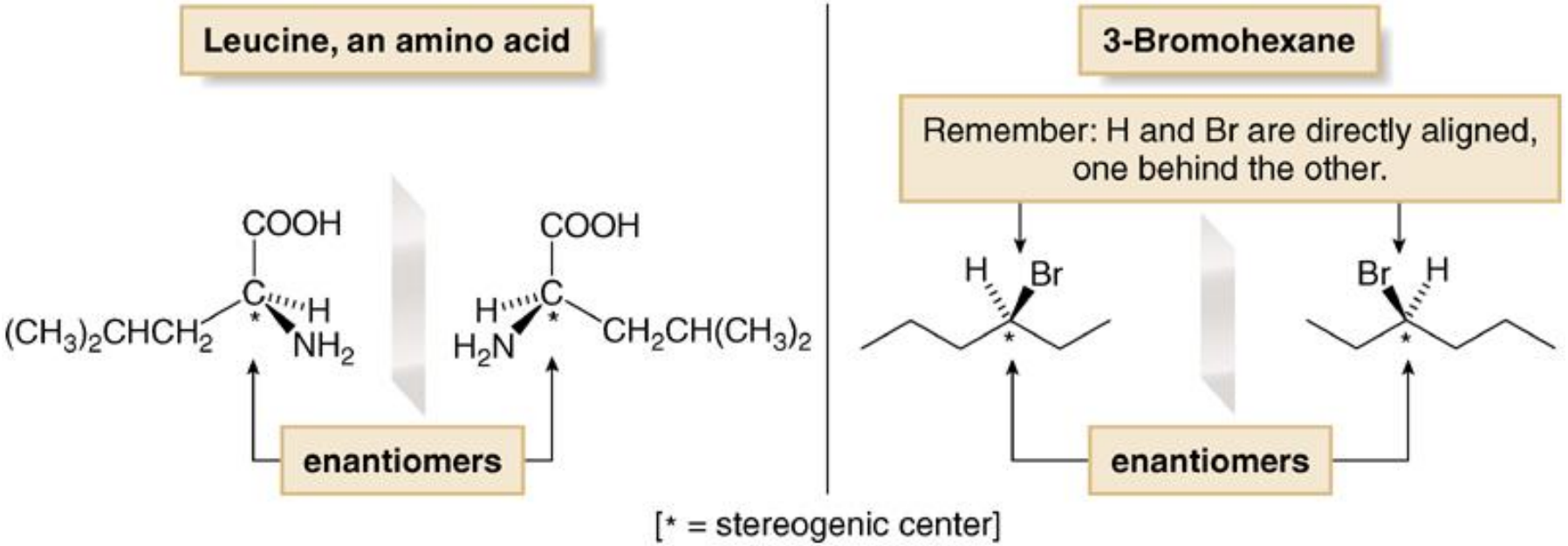
CH_2BrCl is **achiral.**

CHBrClF

NO plane of symmetry

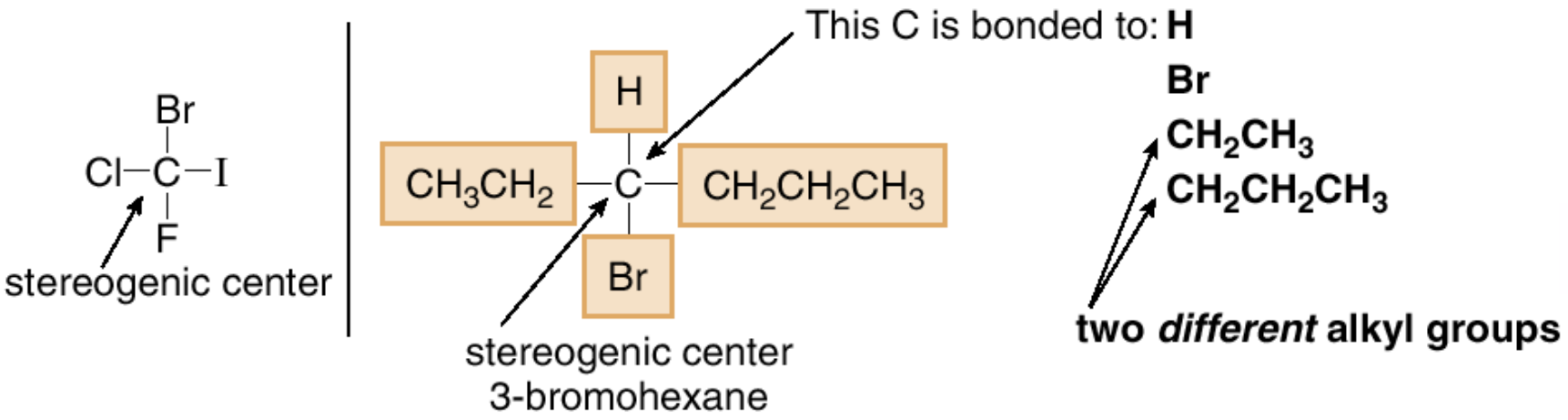
CHBrClF is **chiral.**

Stereogenic Centers



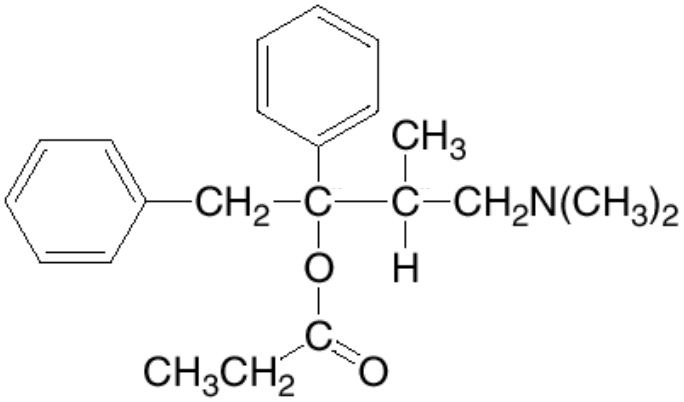
Stereogenic Centers

- To locate a stereogenic center, examine each tetrahedral carbon atom in a molecule, and look at the four groups—not the four atoms—bonded to it.
- Always omit from consideration all C atoms that cannot be tetrahedral stereogenic centers. These include
  - CH_2 and CH_3 groups
  - Any *sp* or sp^2 hybridized C

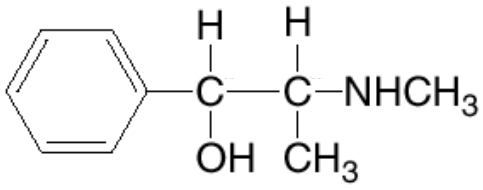


Stereogenic Centers

- Larger organic molecules can have two, three or even hundreds of stereogenic centers.

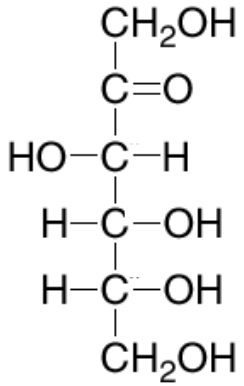


propoxyphene
Trade name: Darvon
(analgesic)



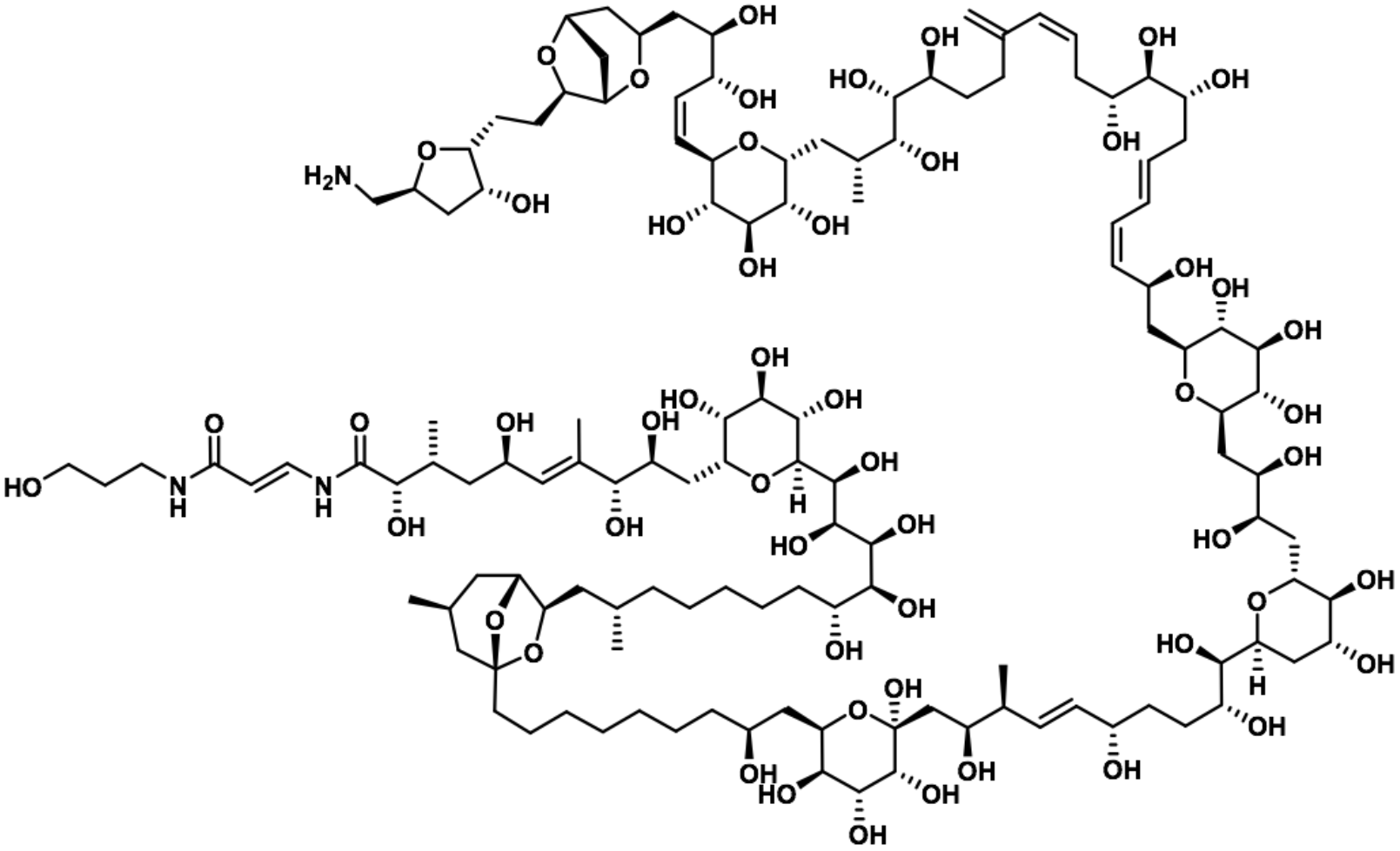
ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]



fructose
(a simple sugar)

Stereogenic Centers

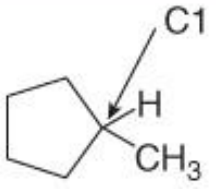


Palytoxin: 64 chiral centers

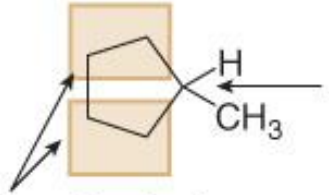
Cyclic Compounds

- Stereogenic centers may also occur at carbon atoms that are part of a ring.
- To find stereogenic centers on ring carbons, always draw the rings as flat polygons, and look for tetrahedral carbons that are bonded to four different groups.

Is C1 a stereogenic center?



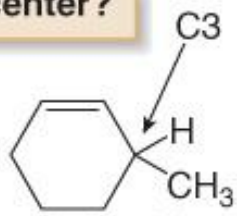
methylcyclopentane



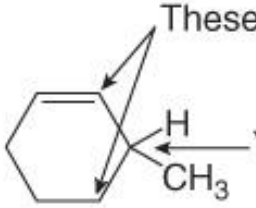
two identical groups, equidistant from C1

NO, C1 is **not** a stereogenic center.

Is C3 a stereogenic center?



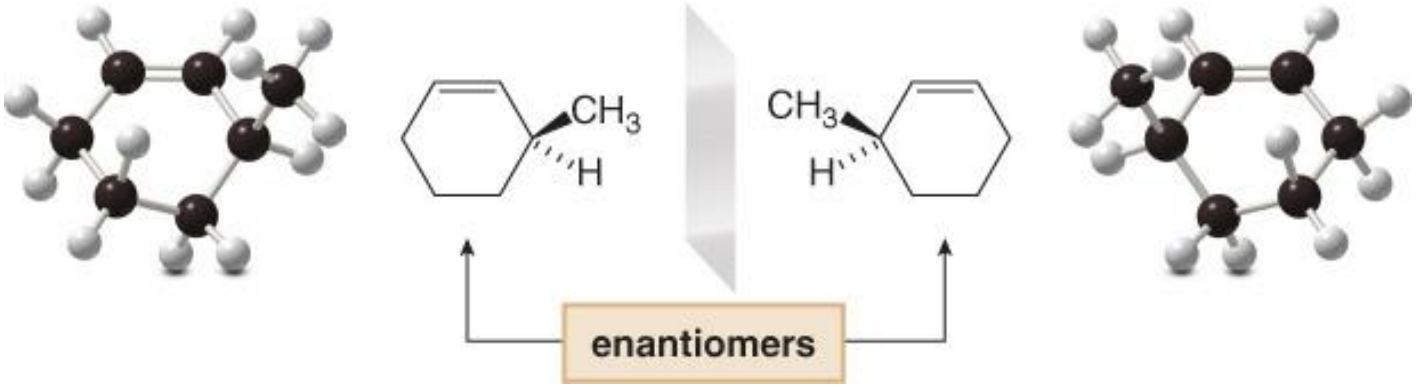
3-methylcyclohexene



These 2 C's are different.

YES, C3 is a stereogenic center.

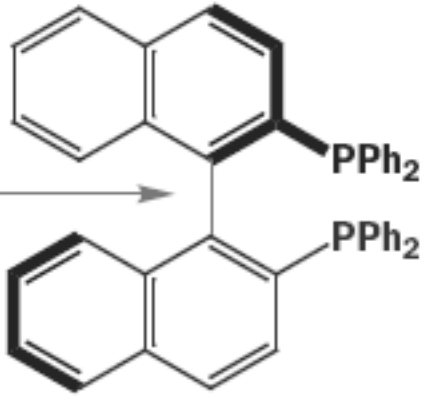
Cyclic Compounds



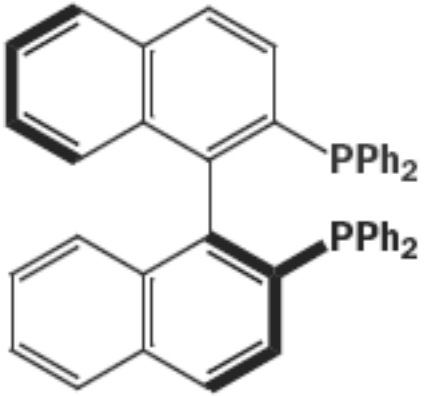
Stereoisomeris from Hindered Rotation

Binaphtalenes

steric hindrance means rotation about this bond is restricted

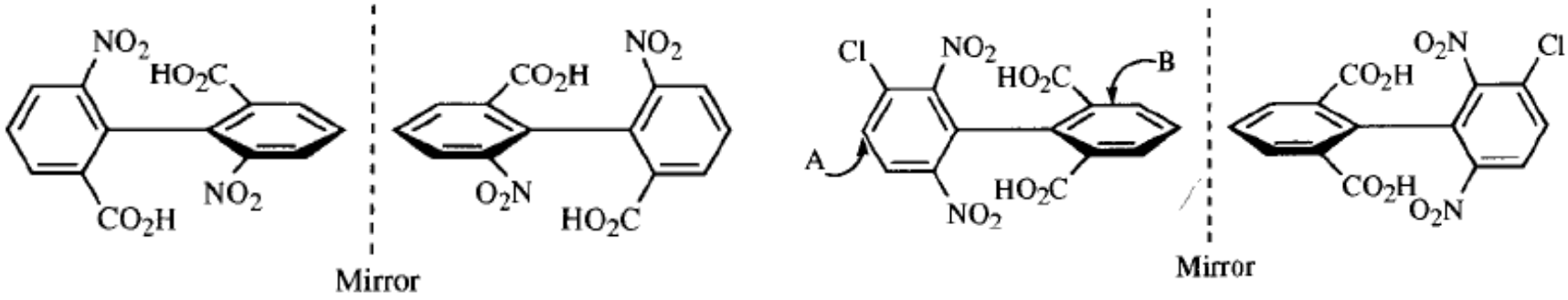


(*R*)-BINAP

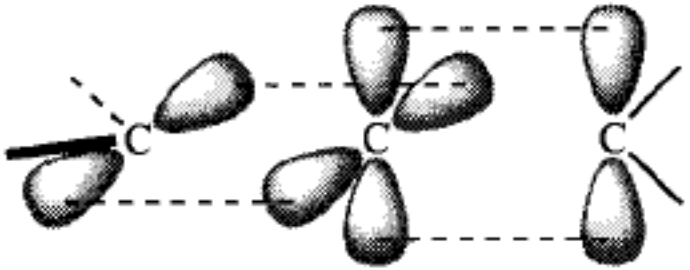


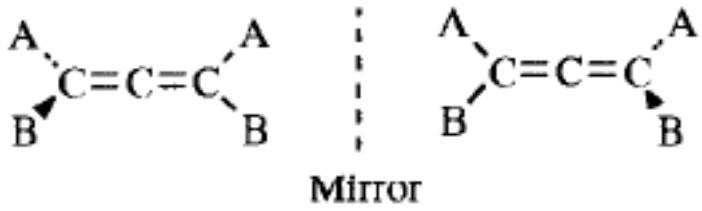
(*S*)-BINAP

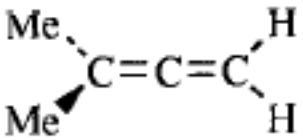
Biphenyl



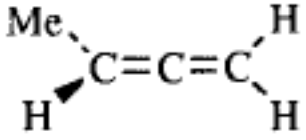
Allenes



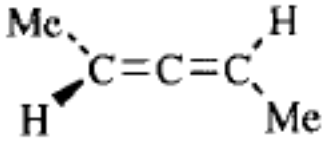




Inactive

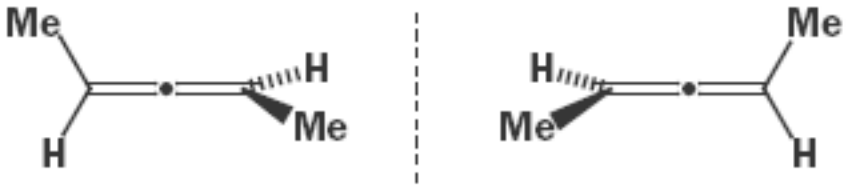


Inactive



Active

Enantiomers



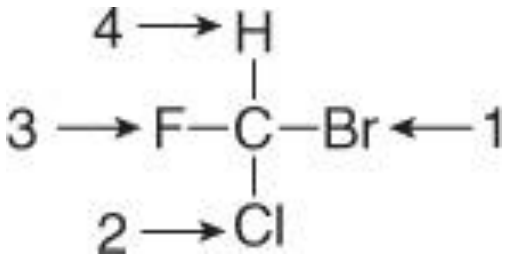
Chirality and Symmetry

- A sterogenic center is a sufficient but not necessary condition for chirality.
- With one stereogenic center, a molecule will always be chiral.
- With two or more stereogenic centers, a molecule may or may not be chiral.
- Achiral molecules usually contain a plane of symmetry but chiral molecules do not.
- A plane of symmetry is a mirror plane that cuts the molecule in half, so that one half of the molecule is a reflection of the other half.

Cahn-Ingold-Prelog System

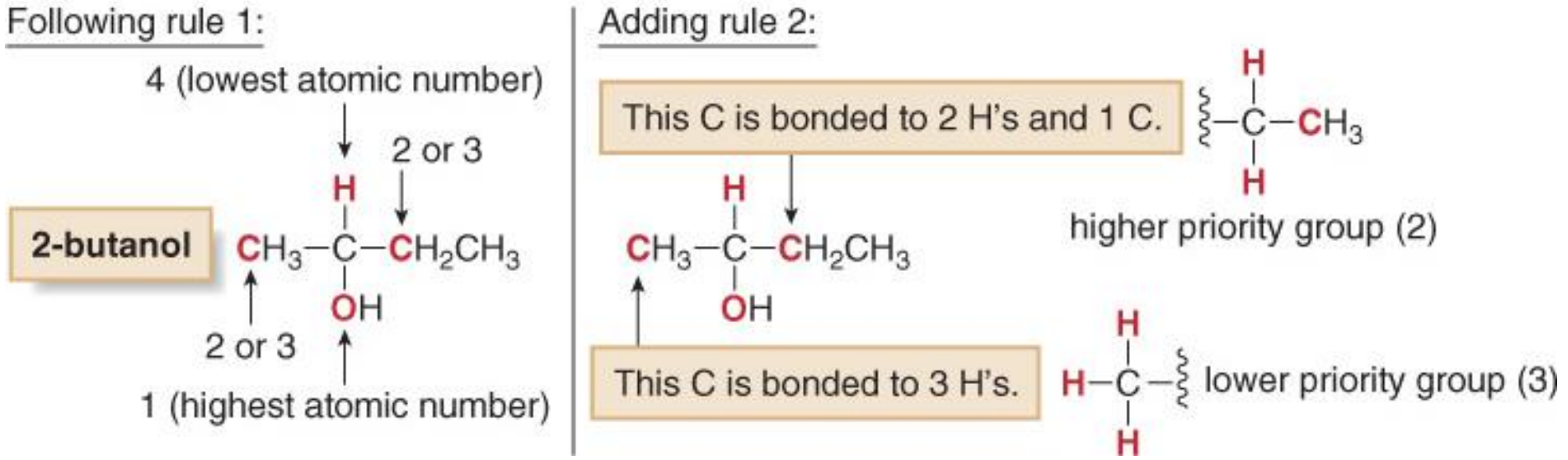
- Naming enantiomers with the prefixes *R* or *S* is called the Cahn-Ingold-Prelog system.

- **Priority rule 1**. The atom of highest atomic number gets the highest priority (1).



Cahn-Ingold-Prelog System

- **Priority rule 2.** If two atoms on a stereogenic center are the same, assign priority based on the atomic number of the atoms bonded to these atoms. *One* atom of higher atomic number determines the higher priority.



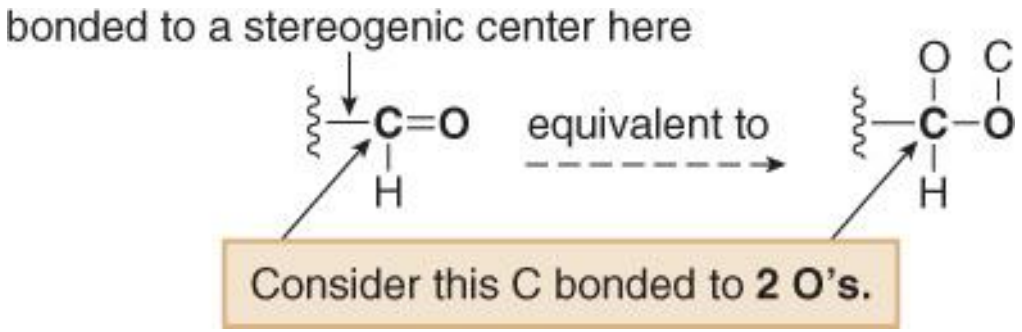
Cahn-Ingold-Prelog System

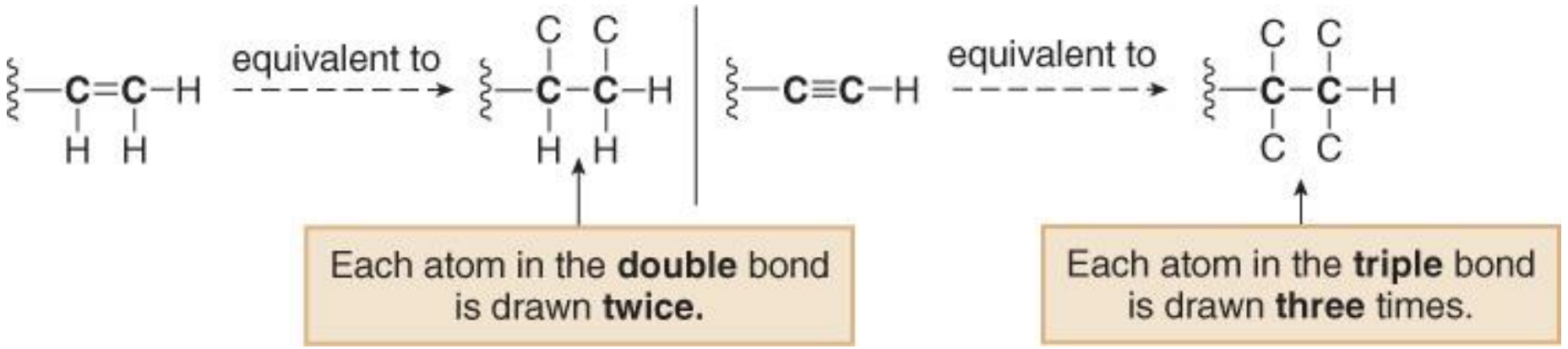
- **Priority rule 3.** If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number. Thus, in comparing the three isotopes of hydrogen, the order of priorities is:

	Mass number	Priority
T (tritium)	3 (1 proton + 2 neutrons)	1
D (deuterium)	2 (1 proton + 1 neutron)	2
H (hydrogen)	1 (1 proton)	3

Cahn-Ingold-Prelog System

- **Priority rule 4.** To assign a priority to an atom that is part of a multiple bond, treat a multiply bonded atom as an equivalent number of singly bonded atoms. For example, the C of a C=O is considered to be bonded to two O atoms.

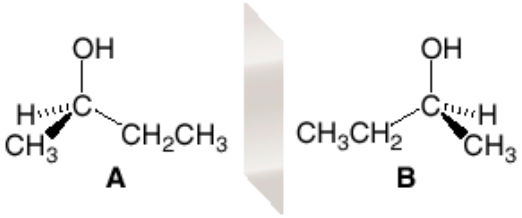




Cahn-Ingold-Prelog System

How To Assign *R* or *S* to a Stereogenic Center

Example Label each enantiomer as *R* or *S*.



two enantiomers of 2-butanol

Step [1] Assign priorities from 1 to 4 to each group bonded to the stereogenic center.

- The priorities for the four groups around the stereogenic center in 2-butanol were given in Rule 2, on page 172.

−OH	$-CH_2CH_3$	$-CH_3$	−H
1	2	3	4
highest			lowest

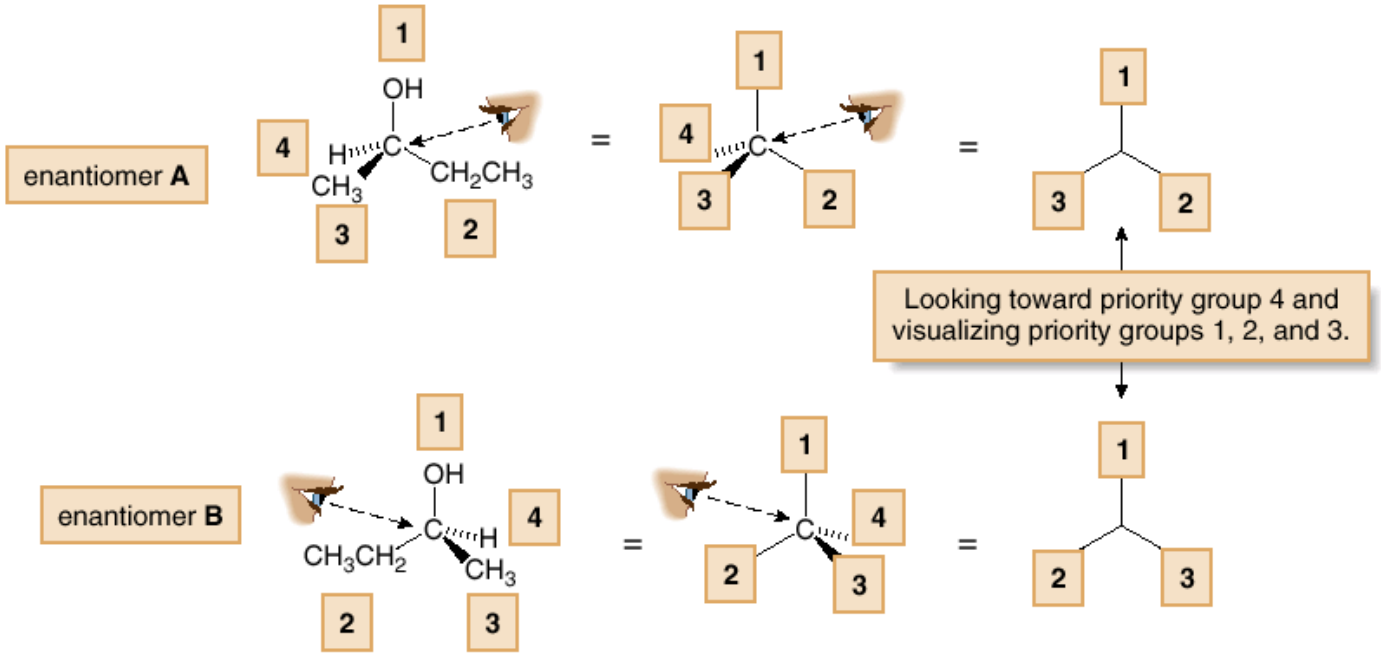
Decreasing priority

Cahn-Ingold-Prelog System

How To, continued . . .

Step [2] Orient the molecule with the lowest priority group (4) *back* (on a *dash*), and visualize the relative positions of the remaining three groups (priorities 1, 2, and 3).

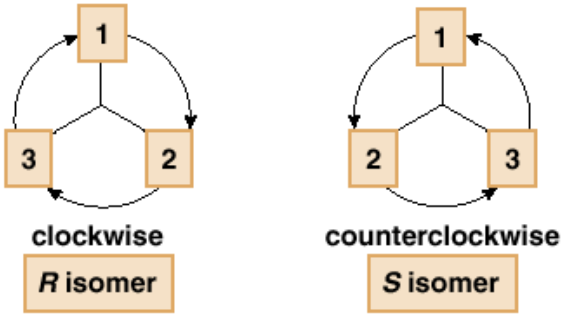
- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C–H bond.



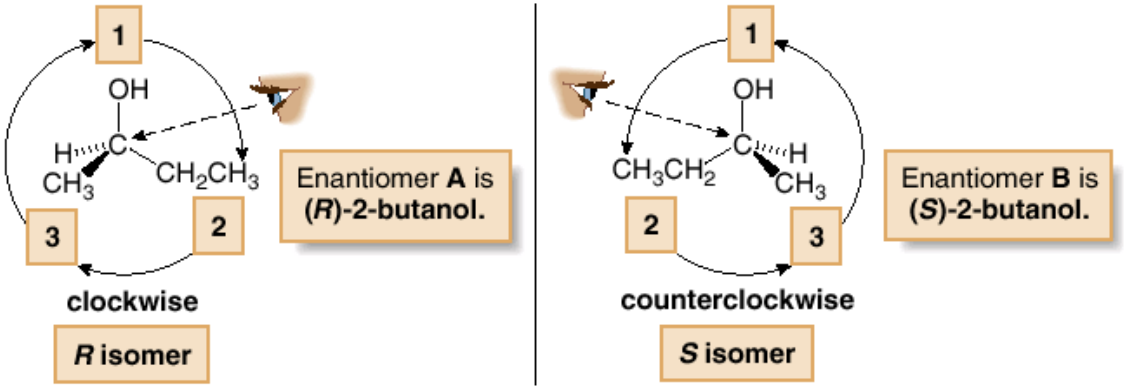
Cahn-Ingold-Prelog System

Step [3] Trace a circle from priority group 1 → 2 → 3.

- If tracing the circle goes in the **clockwise** direction—to the right from the noon position—the isomer is named ***R***.
- If tracing the circle goes in the **counterclockwise** direction—to the left from the noon position—the isomer is named ***S***.

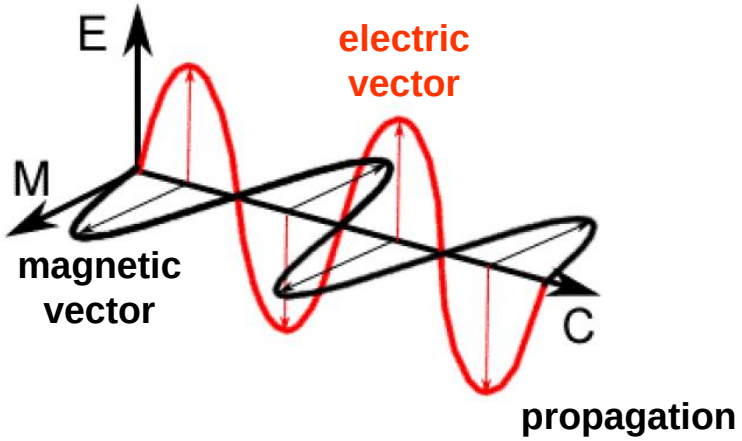


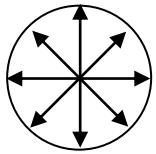
- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



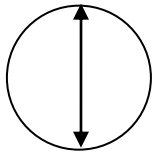
Optical Activity

- The physical properties of two enantiomers are identical except for how they interact with plane-polarized light.
- In ordinary light the electric vector oscillates in all planes perpendicular to the propagation direction.
- In plane polarized light the vector oscillates in a single plane. Polarized light is obtained with a polarizer.





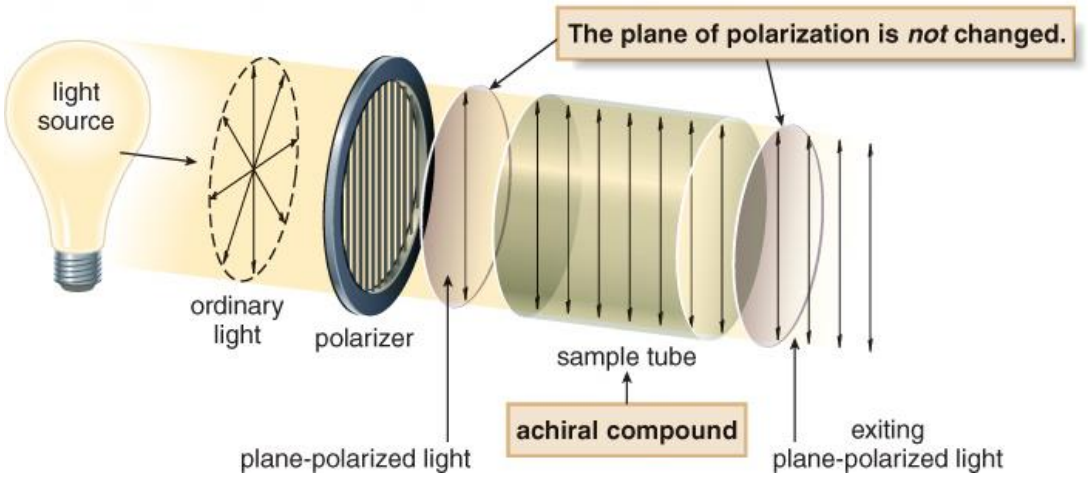
unpolarized light



plane-polarized light

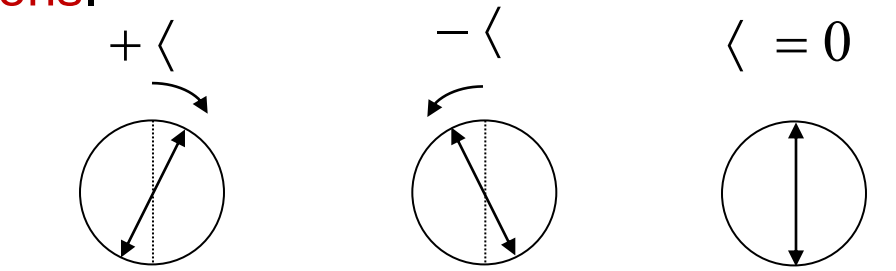
Optical Activity

- In a polarimeter polarized light travels through a sample tube containing an organic compound.
- With achiral compounds, the light that exits the sample tube remains unchanged. A compound that does not change the plane of polarized light is said to be optically inactive.



Optical Activity

- Two enantiomers rotate plane-polarized light to an equal extent but in opposite directions.



dextrorotatory (+) Optically active

levorotatory (–) Optically active

Optically inactive

- No relationship exists between *R* and *S* prefixes and the (+) and (-) designations that indicate optical rotation.

(*S*)-(+) **(*S*)-(-)**

Optical Activity

- Specific rotation is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light. Specific rotation [α] is defined using a specific sample tube length (*l*, in dm), concentration (*c* in g/mL for pure liquids [=d]; g/100mL for solutions), temperature (generally 25^0C) and wavelength (generally 589 nm).

$$\text{specific rotation} = [\alpha] = \frac{\alpha}{l \times c}$$

α = observed rotation (°)
l = length of sample tube (dm)
c = concentration (g/ml or g/100ml)

[dm = decimeter
1 dm = 10 cm]

Racemic Mixtures

- An equal amount of two enantiomers is called a racemic mixture or a racemate. A racemic mixture is optically inactive. Because two enantiomers rotate plane-polarized light to an equal extent but in opposite directions, the rotations cancel, and no rotation is observed.

Property	(+) Enantiomer	(-) Enantiomer	Racemic mixture
melting point	identical		may be different
boiling point	identical		may be different
optical rotation	+ α	- α	0

Optical Purity

- Enantiomeric excess (optical purity) is a measurement of how much one enantiomer is present in excess of the racemic mixture.

***ee* = % of one enantiomer - % of the other enantiomer.**

- The enantiomeric excess can also be calculated if the specific rotation [α] of a mixture and the specific rotation [α] of a pure enantiomer are known.

***ee* = ([α] mixture/[α] pure enantiomer) x 100.**

Enantiomeric excess

$$e.e. = \frac{[S] - [R]}{[S] + [R]} \times 100$$

[S] = centration of enantiomer S
[R] = concentration of enantiomer R

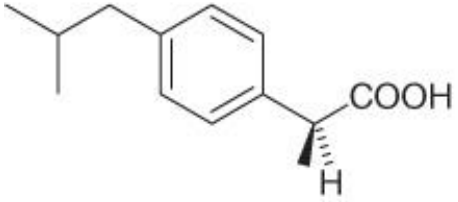
(e.e.) with respect to relative % of the two enantiomers :

[S]	e.e.
50	00
60	20
70	40
80	60
90	80
95	90
98	94
99	98

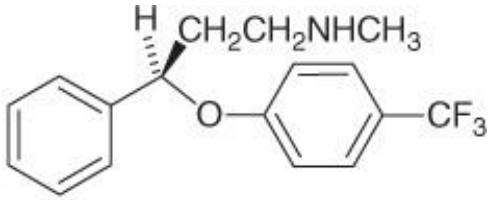
Chemical Properties of Enantiomers

- Two enantiomers have exactly the same chemical properties except for their reaction with chiral non-racemic reagents.

- Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.

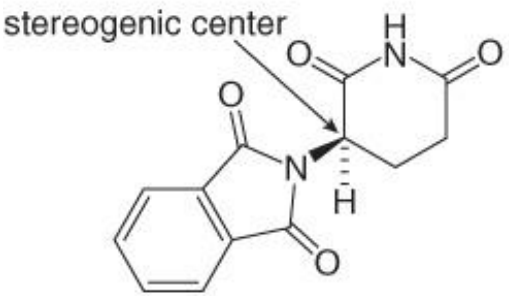


(*S*)-ibuprofen
anti-inflammatory agent

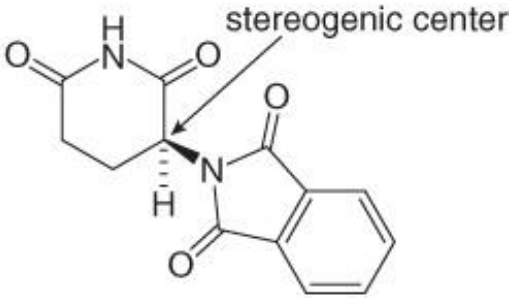


(*R*)-fluoxetine
antidepressant

Two enantiomers of thalidomide

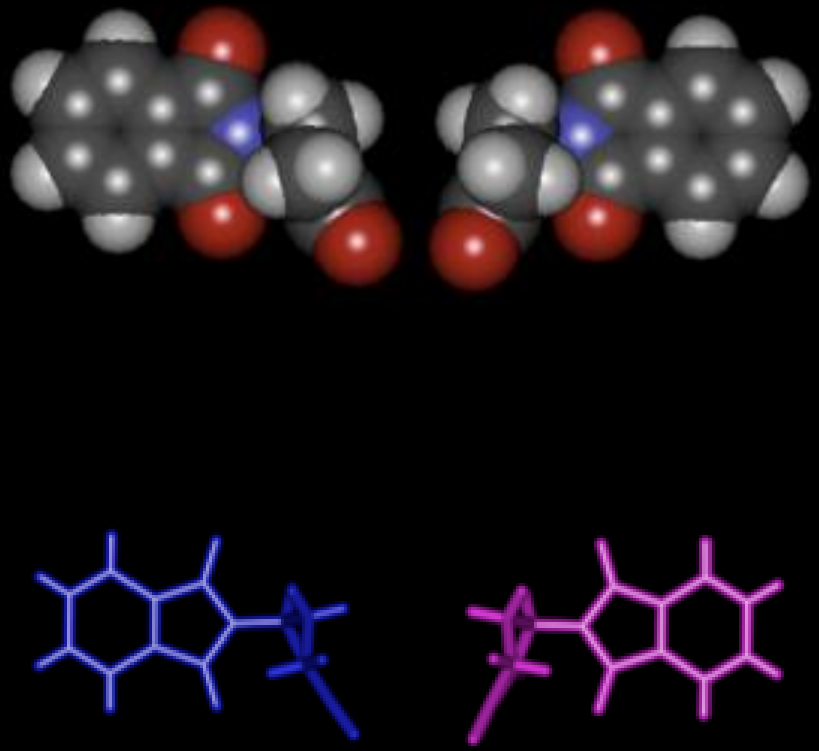


anti-nausea drug



teratogen

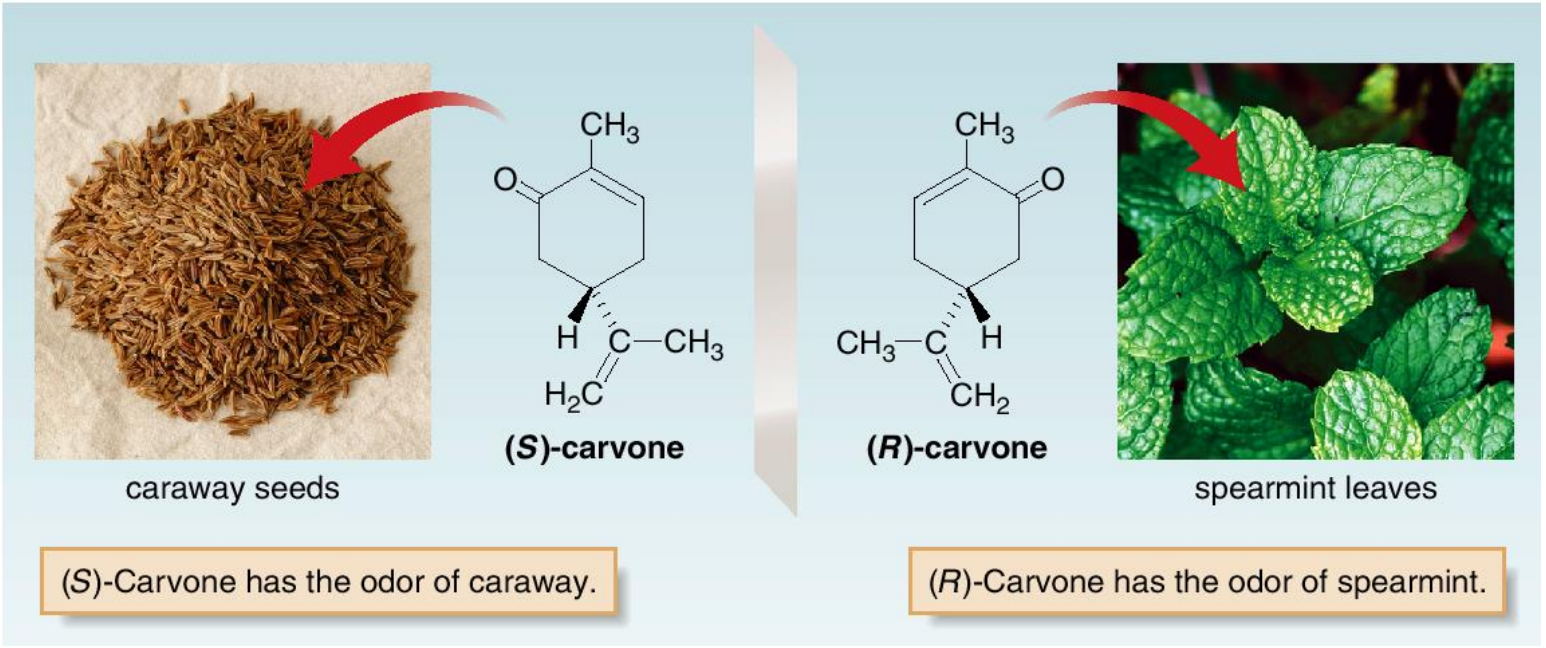
Thalidomide



Chemical Properties of Enantiomers

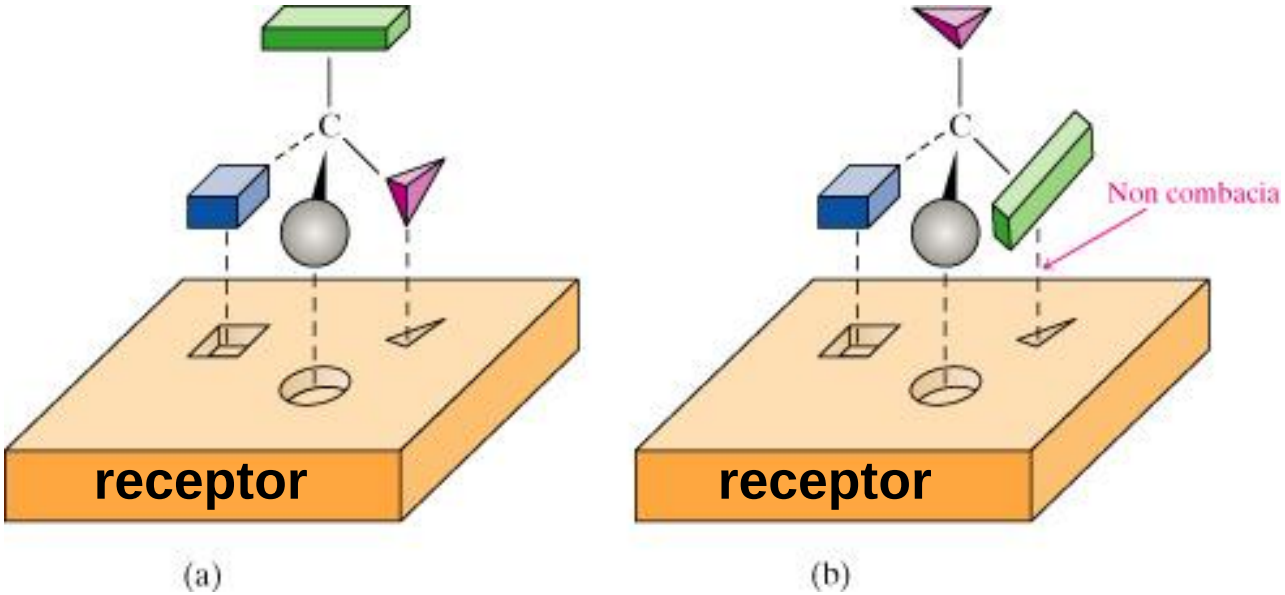
- Research suggests that the odor of a particular molecule is determined more by its shape than by the presence of a particular functional group.

- Because enantiomers interact with chiral smell receptors, some enantiomers have different odors.

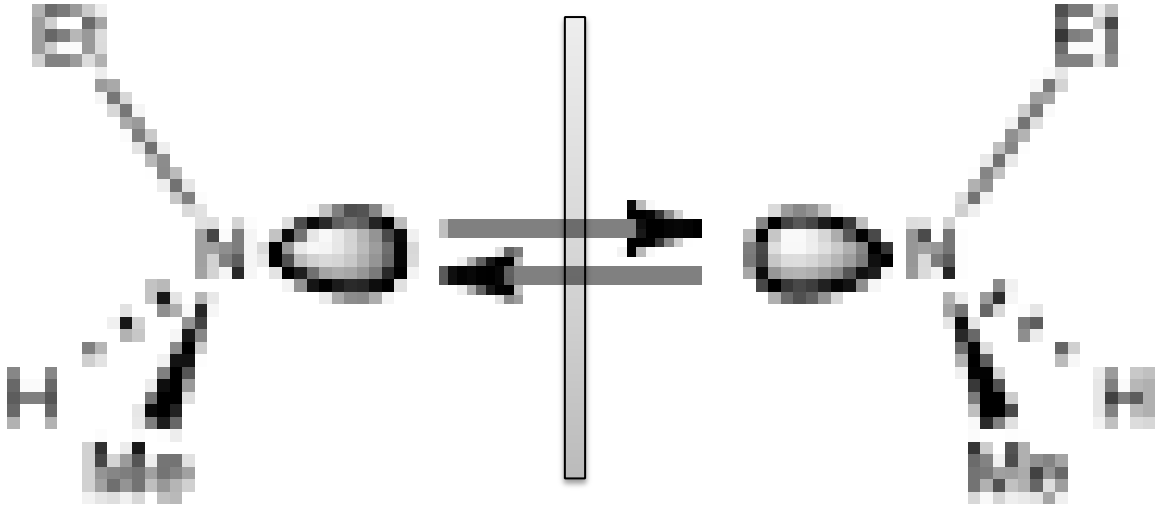


Chiral Recognition

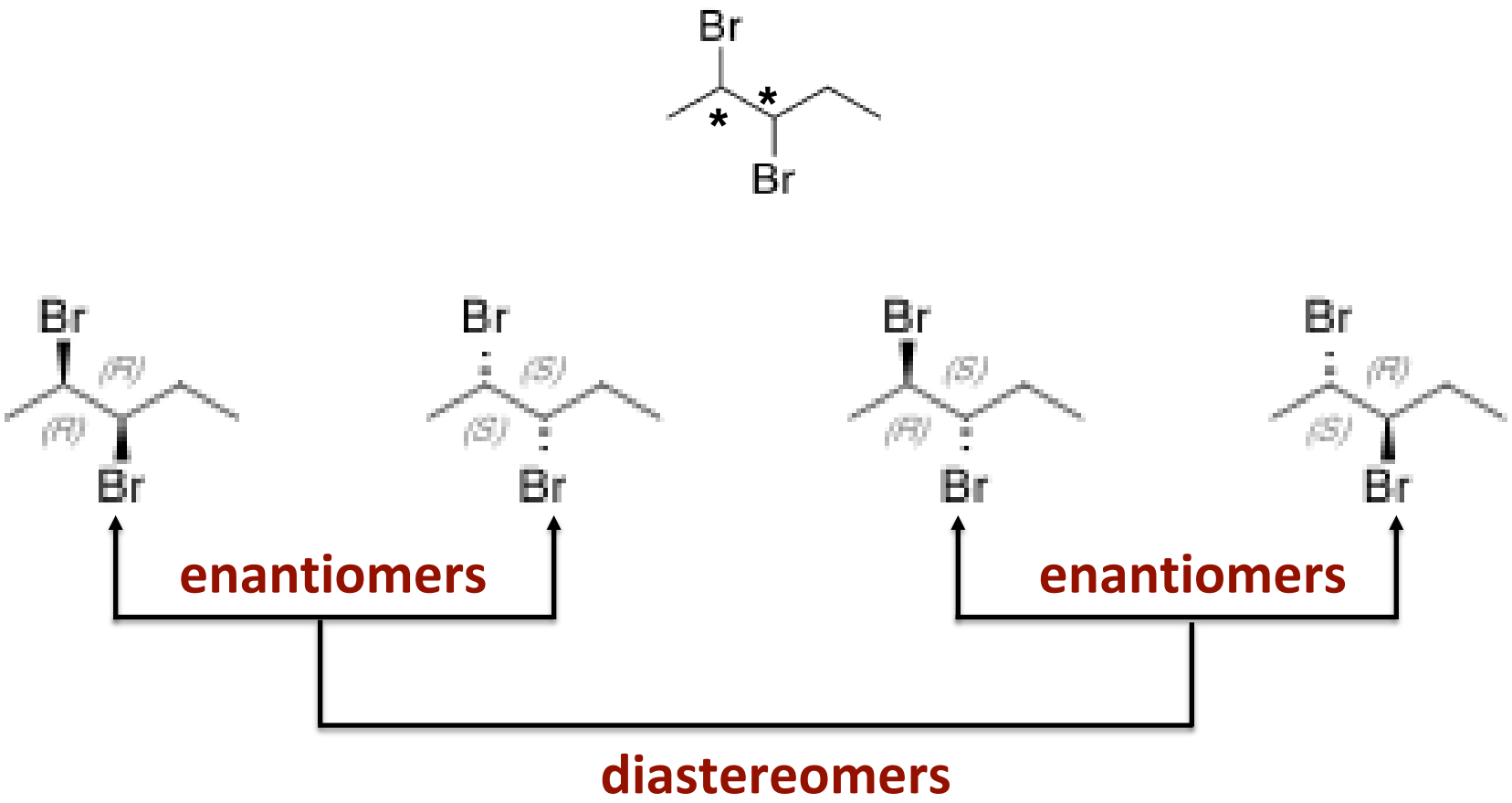
3 point theory:



Amines are Achiral

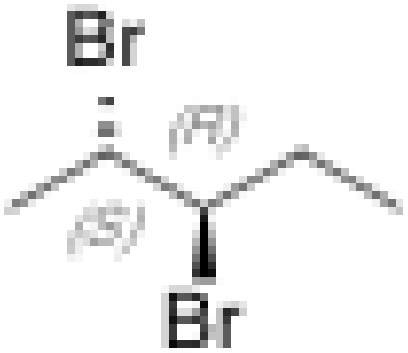


Diastereomers



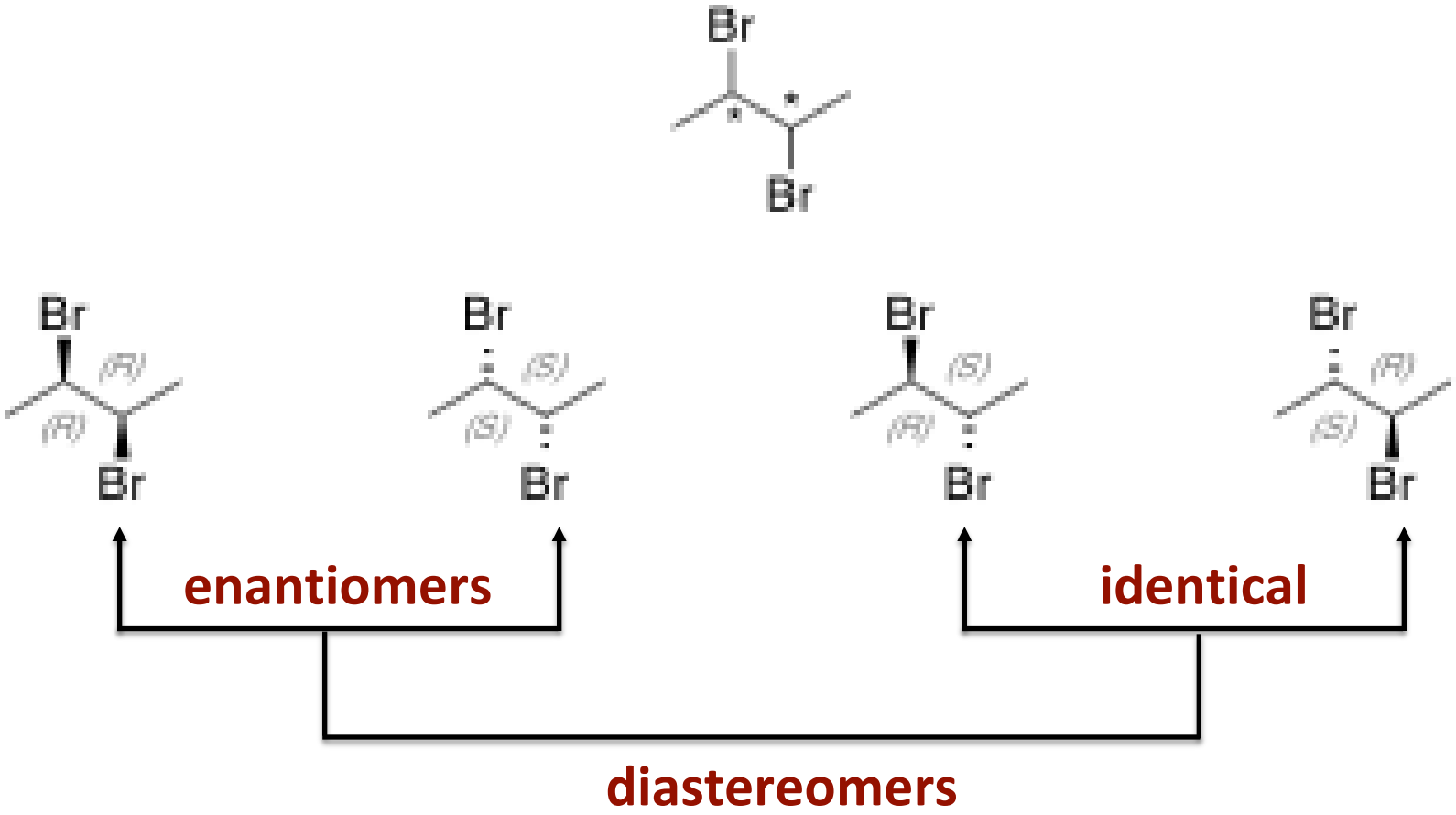
Diastereomers

- When a compound has more than one stereogenic center, *R* and *S* configurations must be assigned to each of them.

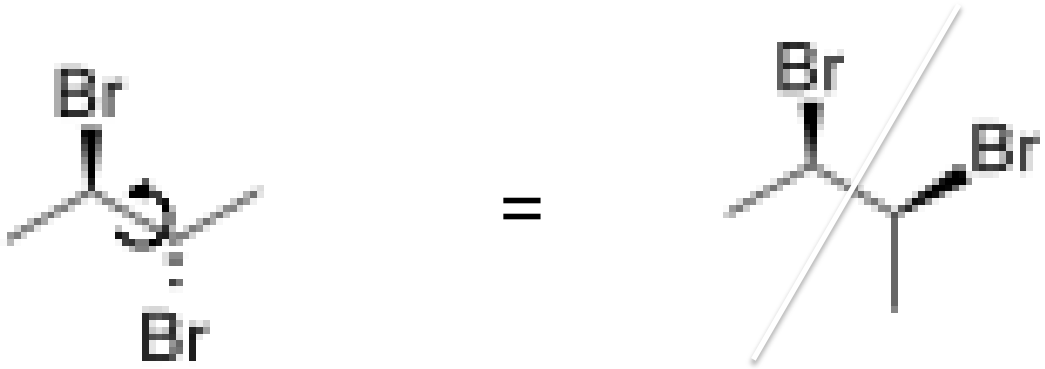


(*2S,3R*)-2,3-dibromopentane

Meso Compounds



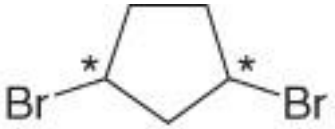
Meso Compounds



- Meso compounds contain a plane of symmetry, and are achiral.

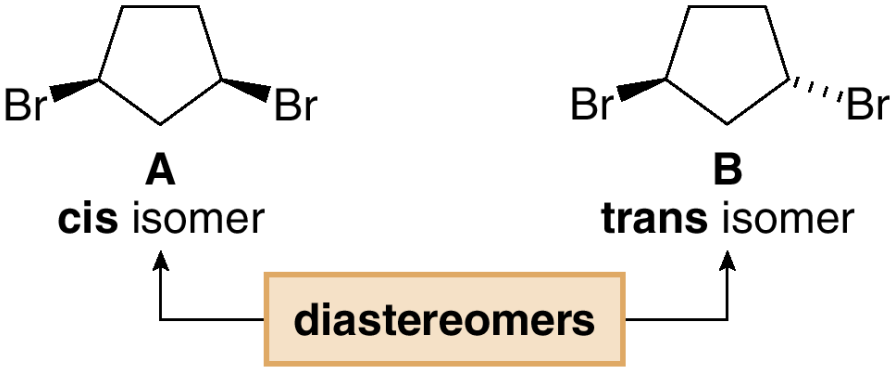
Diastereomers

- Consider 1,3-dibromocyclopentane. Since it has two stereogenic centers, it has a maximum of four stereoisomers.

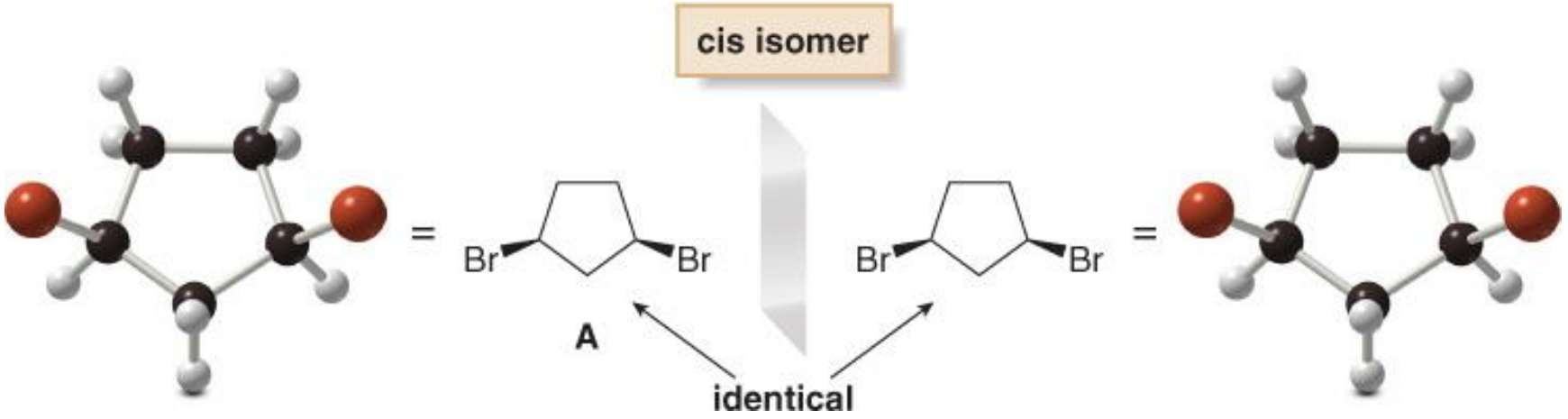


1,3-dibromocyclopentane
[* = stereogenic center]

- *cis* isomer (A) and *trans* isomer (B) are stereoisomers but not mirror images.

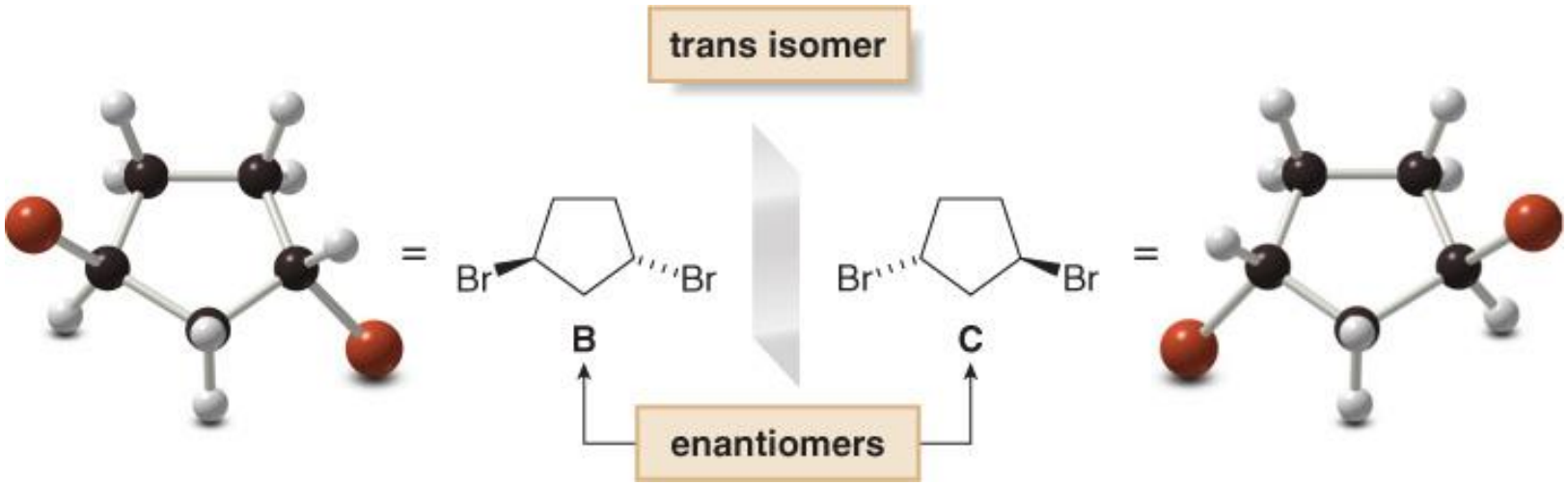


Diastereomers



- The *cis* isomer is superimposable on its mirror image, making the images identical. Thus, A is an achiral meso compound.

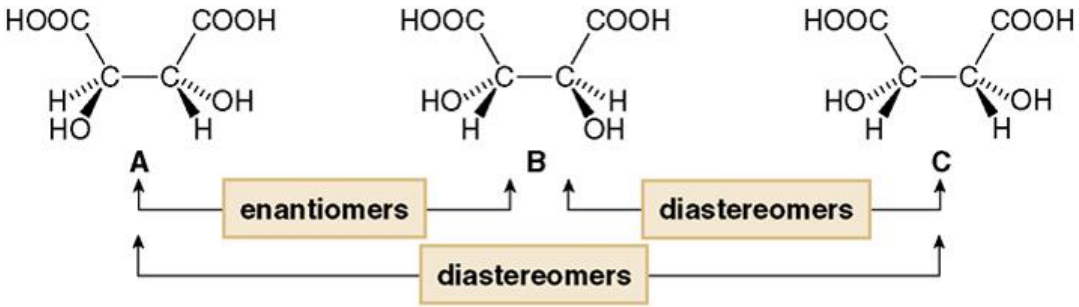
Diastereomers



- The trans isomer is not superimposable on its mirror image, labeled C, making B and C different compounds. B and C are enantiomers.

Diastereomers

- Diastereomers have different physical properties, and therefore can be separated by common physical techniques.



Property	A	B	C	A + B (1:1)
melting point (°C)	171	171	146	206
solubility (g/100 mL H_2O)	139	139	125	139
[α]	+13	−13	0	0
R,S designation	*R,R*	*S,S*	*R,S*	—
d,l designation	*d*	*l*	none	*d,l*

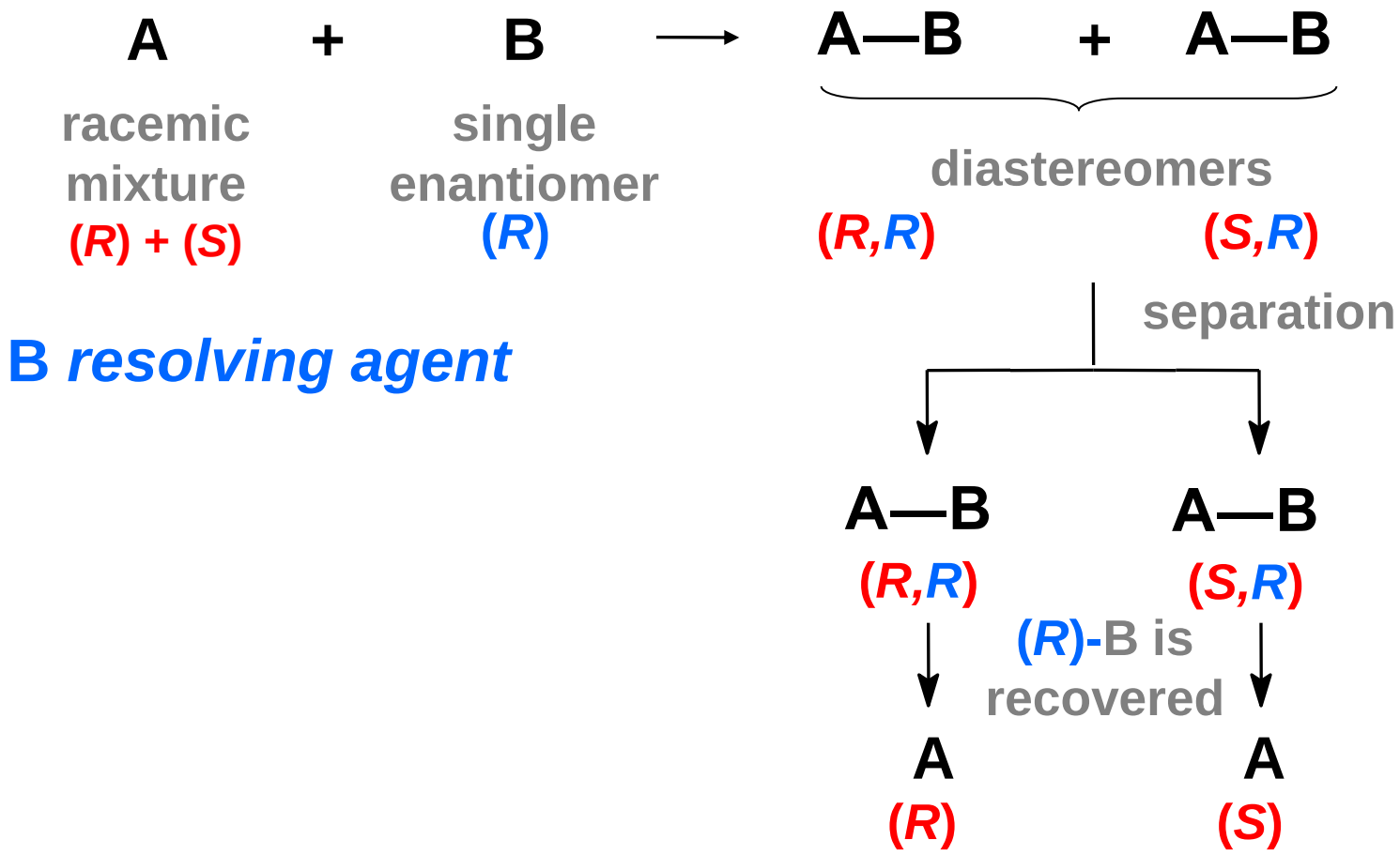
- The physical properties of **A** and **B** differ from their diastereomer **C.**
- The physical properties of a racemic mixture of **A** and **B** (last column) can also differ from either enantiomer and diastereomer **C.**
- **C** is an achiral meso compound, so it is optically inactive; [α] = 0.

Separation of Enantiomers

- Enantiomers have identical physical properties and can not be separated by conventional physical techniques (distillation, crystallization, etc).

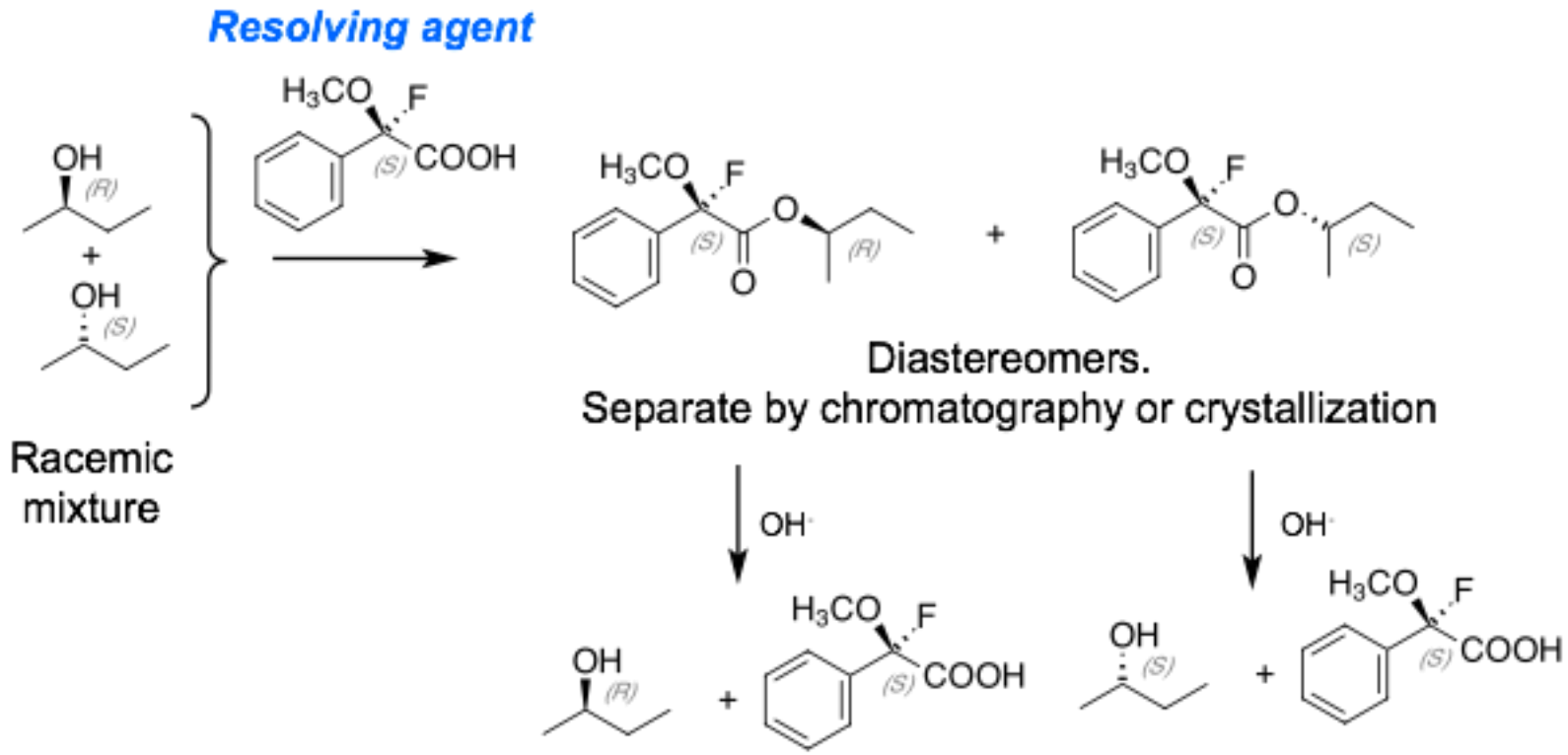
- The separation of enantiomers in a racemic mixture is called resolution.

Resolution of Enantiomers

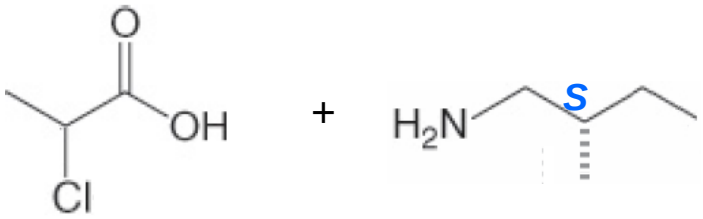


B *resolving agent*

Resolution of Enantiomers

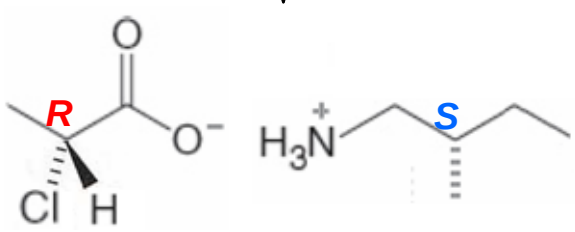


Resolution of Enantiomers



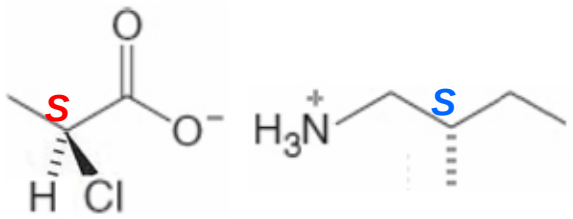
Racemic mixture
(*R*) + (*S*)

Resolving agent



(*R*,*S*)

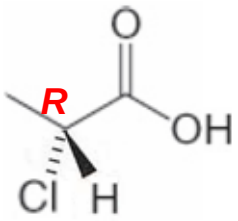
+

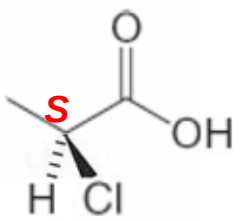


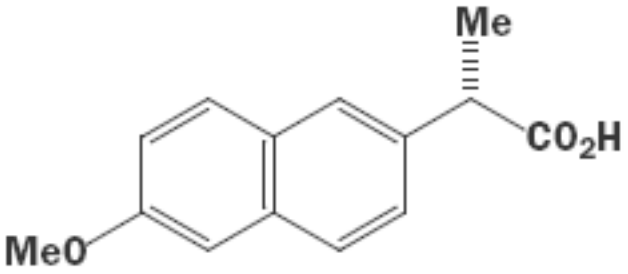
(*S*,*S*)

1) Separation of diastereoisomeric salts

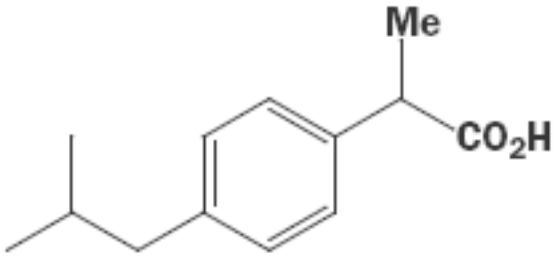
2) HCl



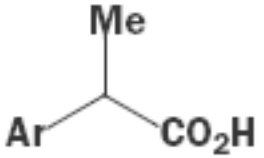




(*S*)-naproxen

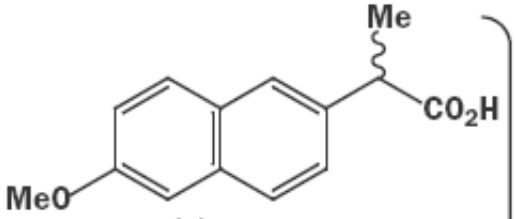


ibuprofen

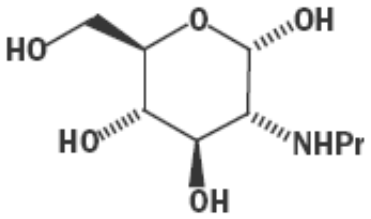


2-arylpropionic acids

resolution of naproxen via an amine salt

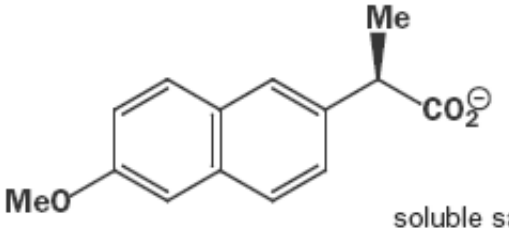


(±)-naproxen

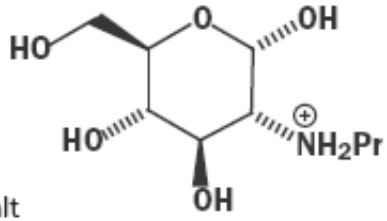


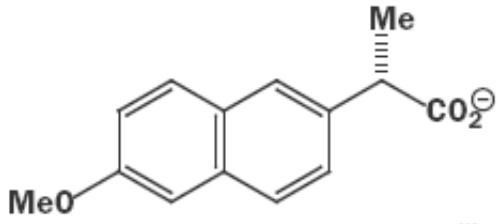
N-propylglucosamine

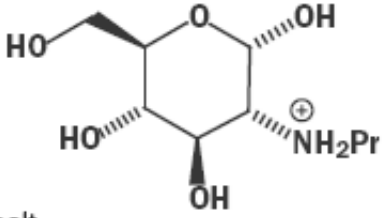
mixed to give



soluble salt

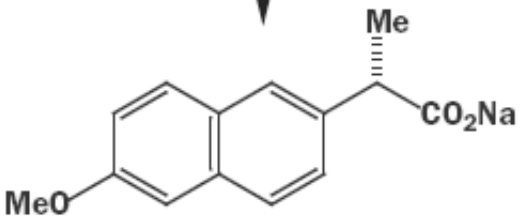






crystalline salt

filtered off and
basified with NaOH



sodium salt of (*S*)-naproxen

plus

N-propylglucosamine

reusable