

Stereochemistry - Chirality

Chapter 5

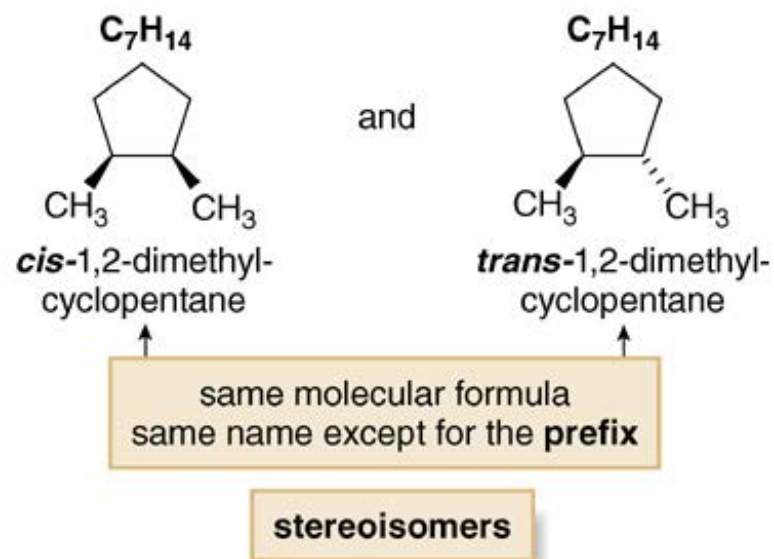
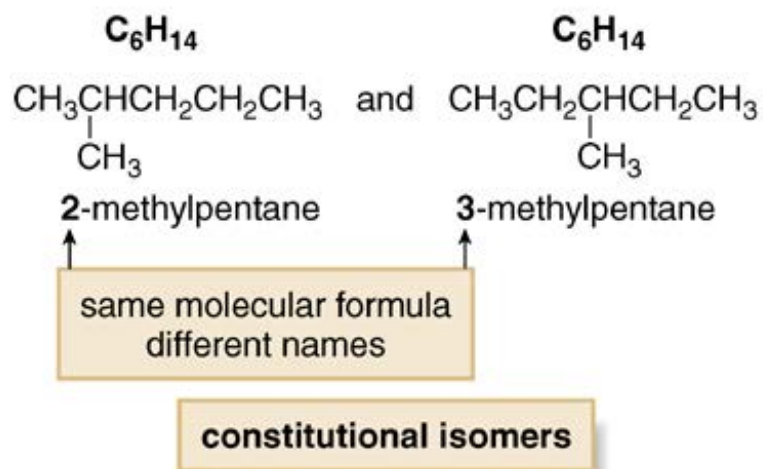
Organic Chemistry, *8th Edition*

John E. McMurry

Isomerism

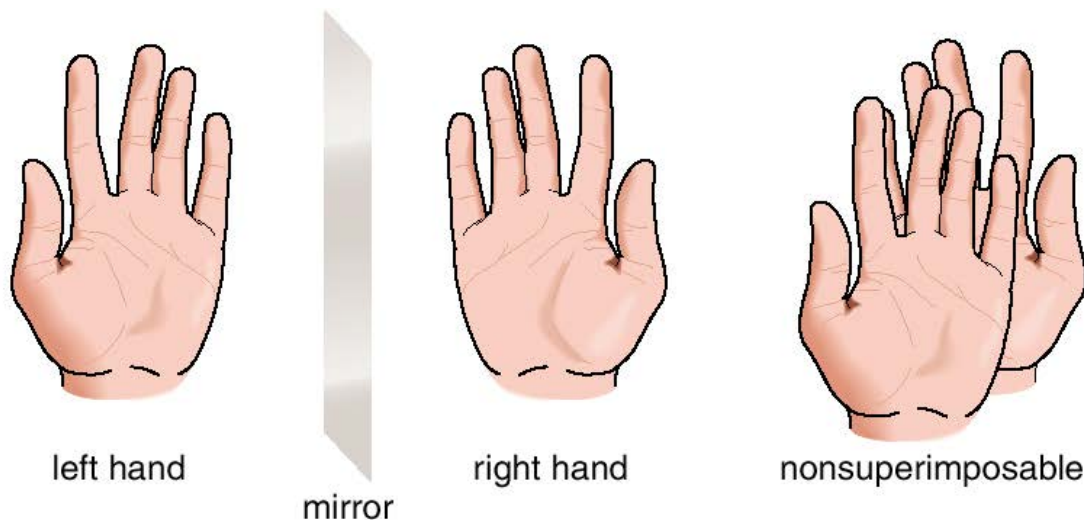
- The two major classes of isomers are **constitutional** isomers and **stereoisomers**.
 - ➡ **Constitutional/structural isomers** have different IUPAC names, different physical and chemical properties, and may have different functional groups.
 - ➡ **Stereoisomers** differ only in the way the atoms 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**.

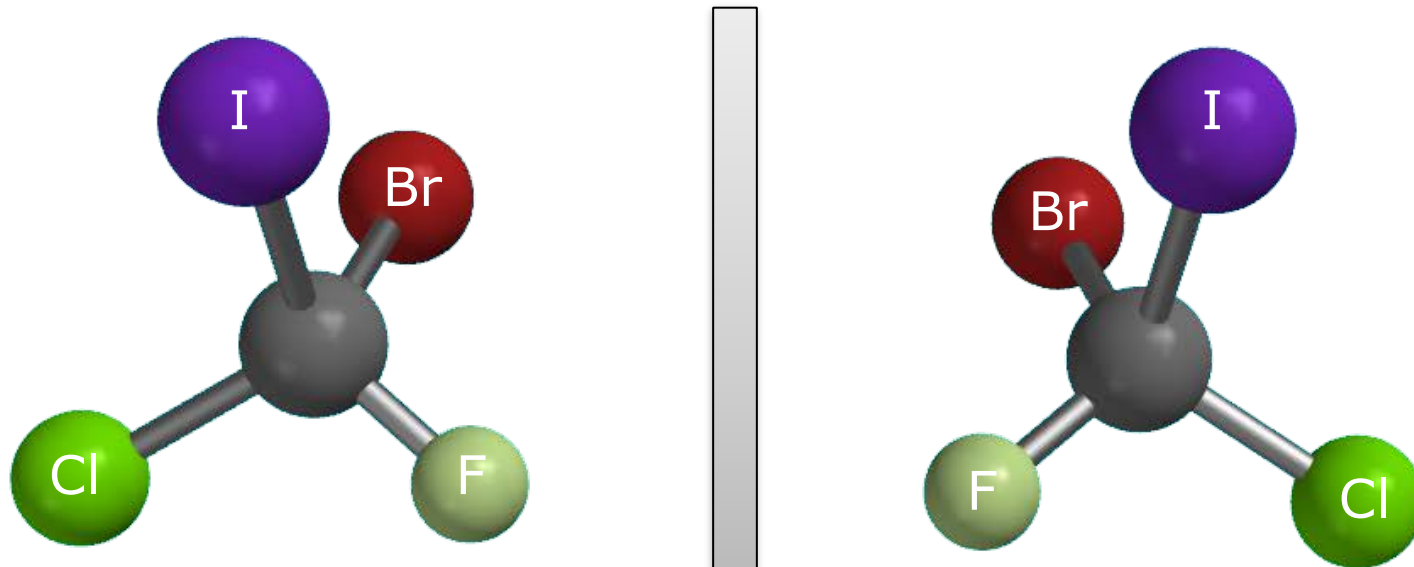


- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral*.

Chirality

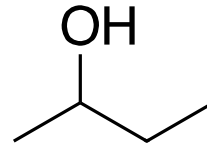


Enantiomers of bromo-chloro-fluoro-iodometahane

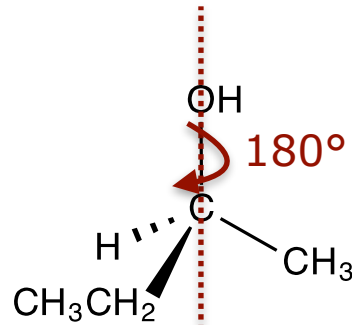
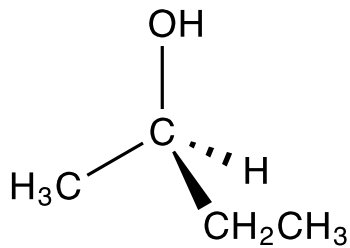


[modelli](#)

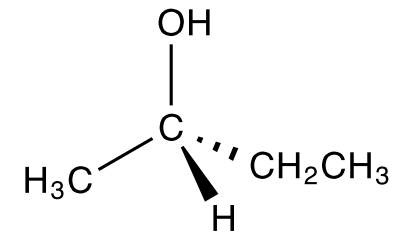
Enantiomers



specchio

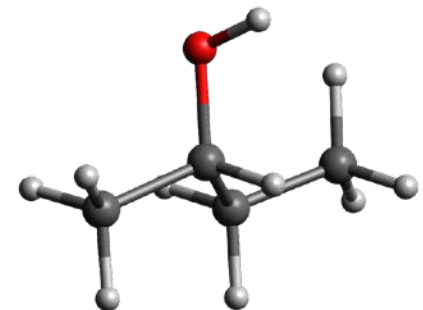
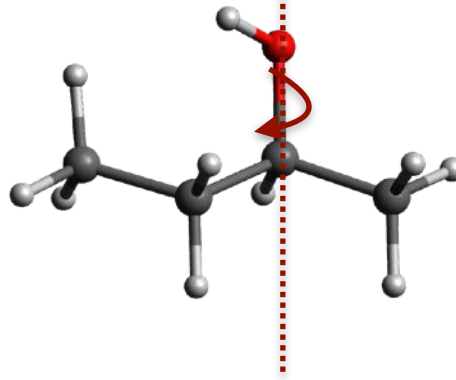
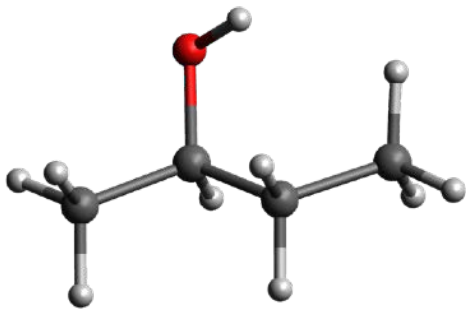


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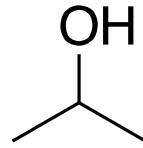
immagini speculari

non
sovrapponibili

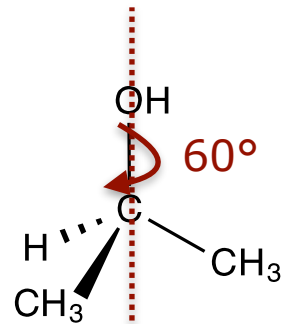
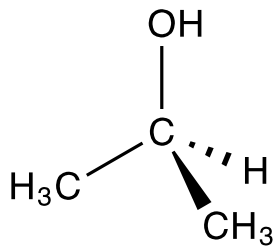


modelli

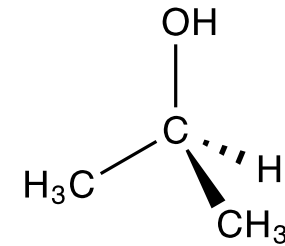
Chiral and Achiral Molecules



specchio

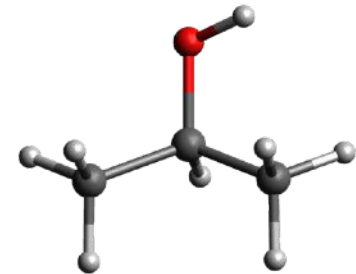
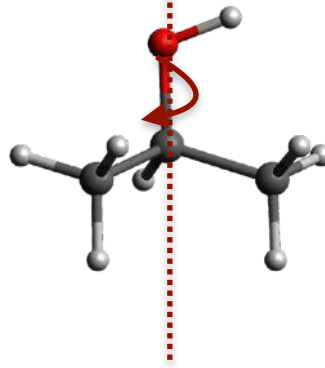
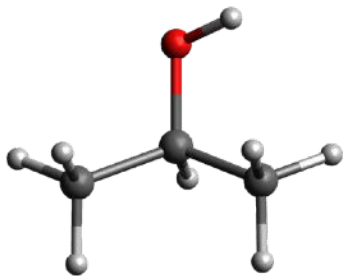


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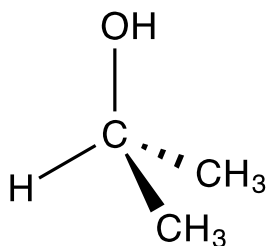


immagini speculari

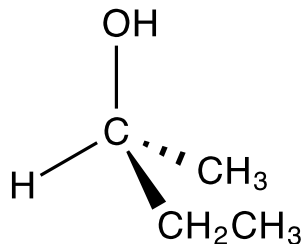
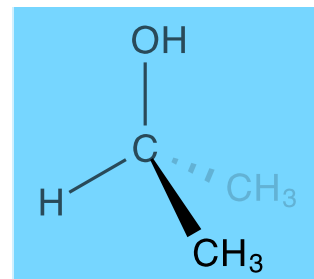
sovrapponibili



Chirality and Symmetry

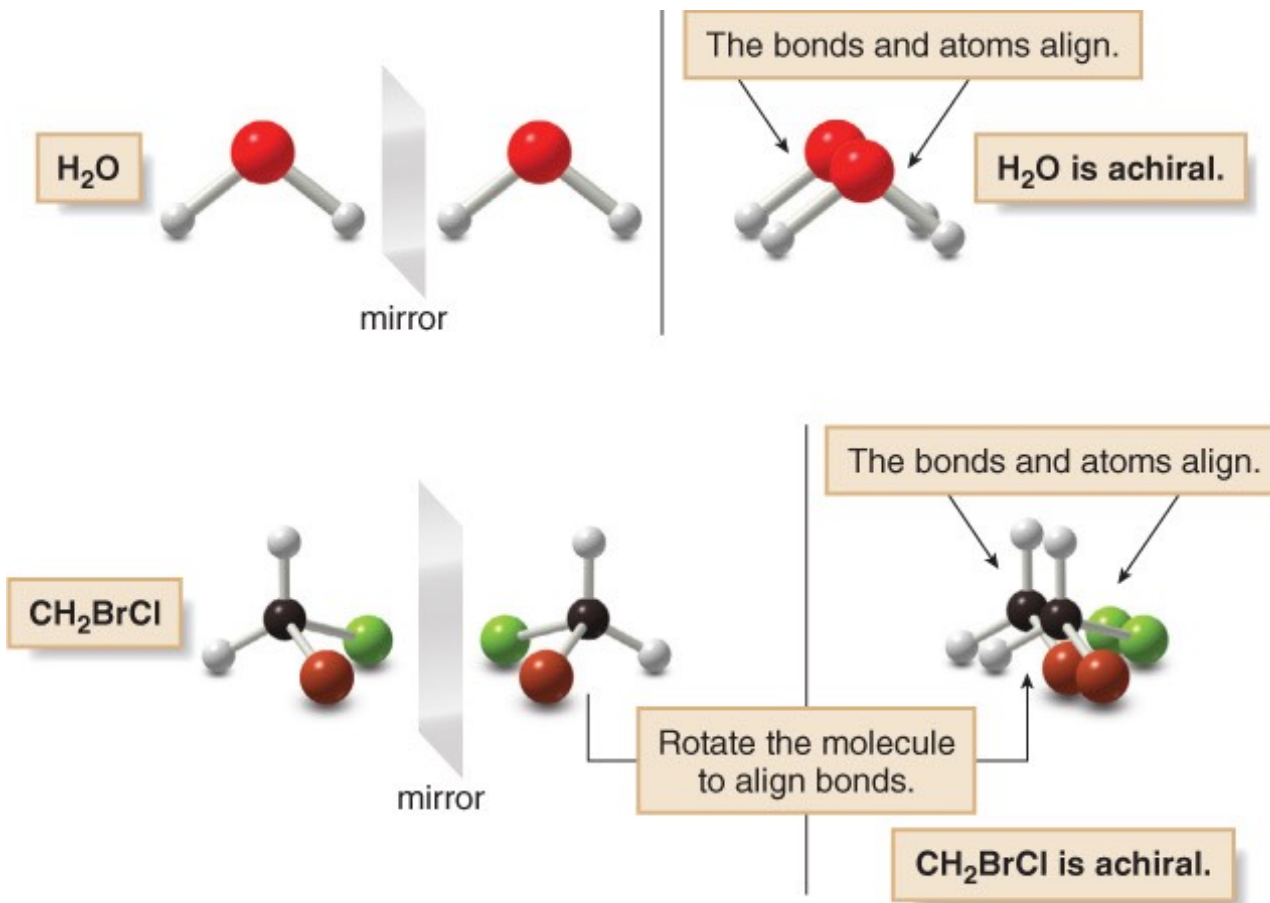


has a symmetry plane:
achiral

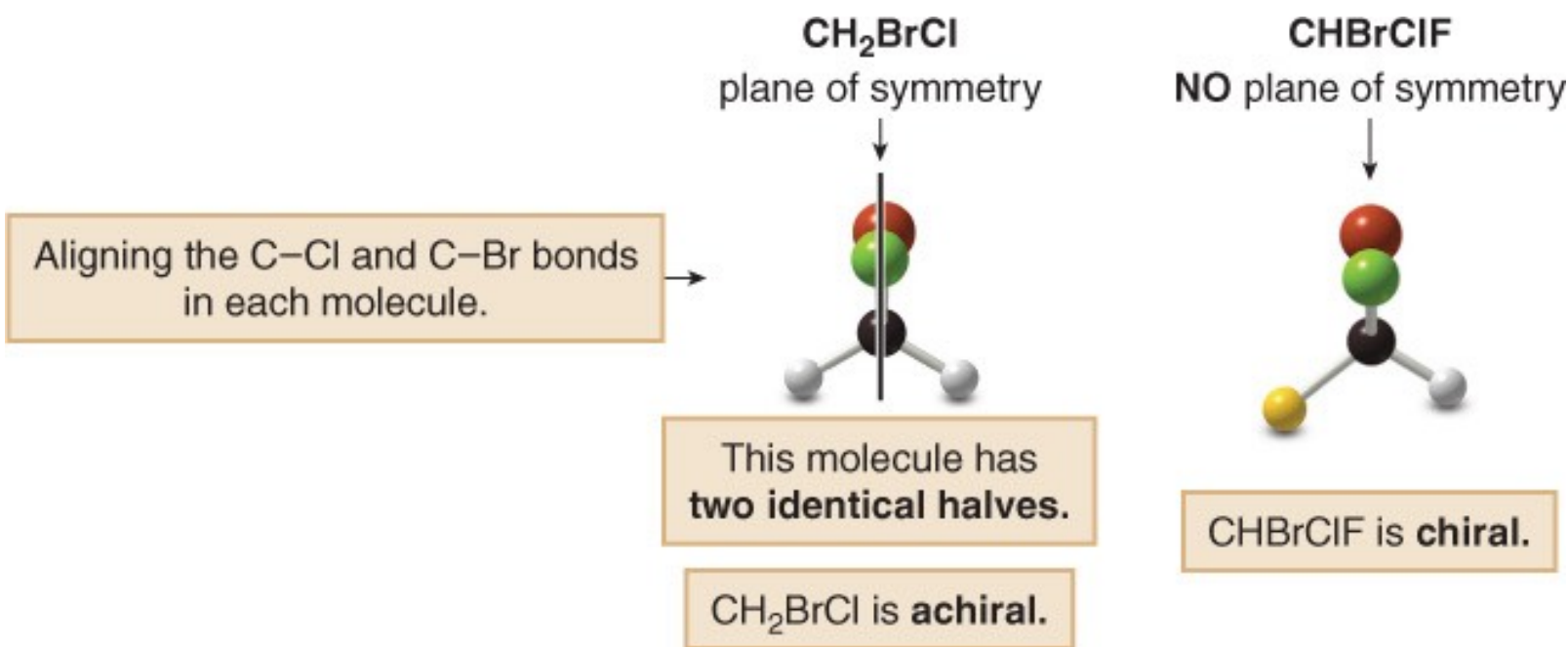


has no symmetry plane
chiral

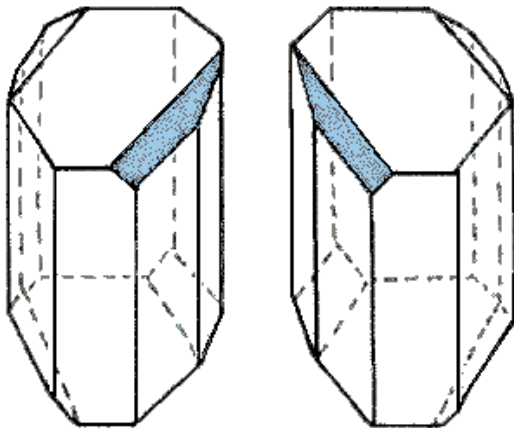
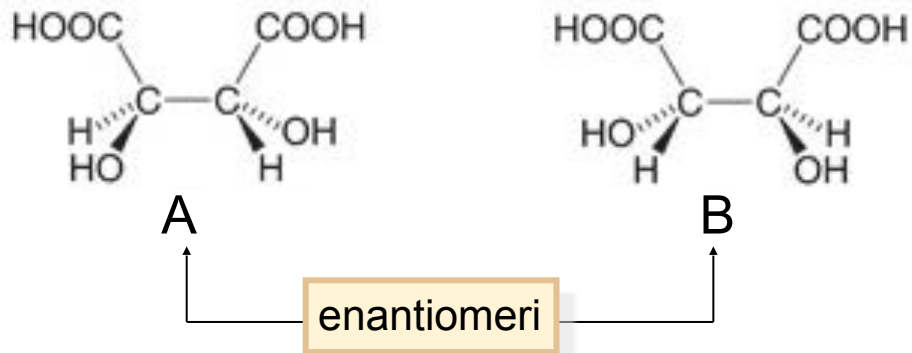
Chirality



Chirality and Symmetry



Tartaric acid

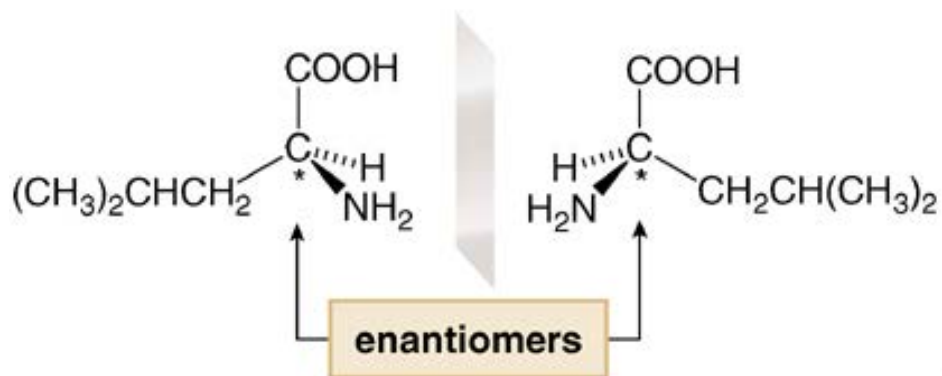


Louis Pasteur



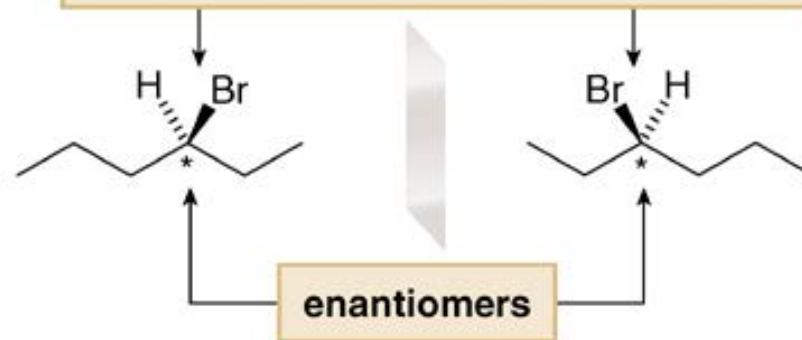
Stereogenic Centers

Leucine, an amino acid



3-Bromohexane

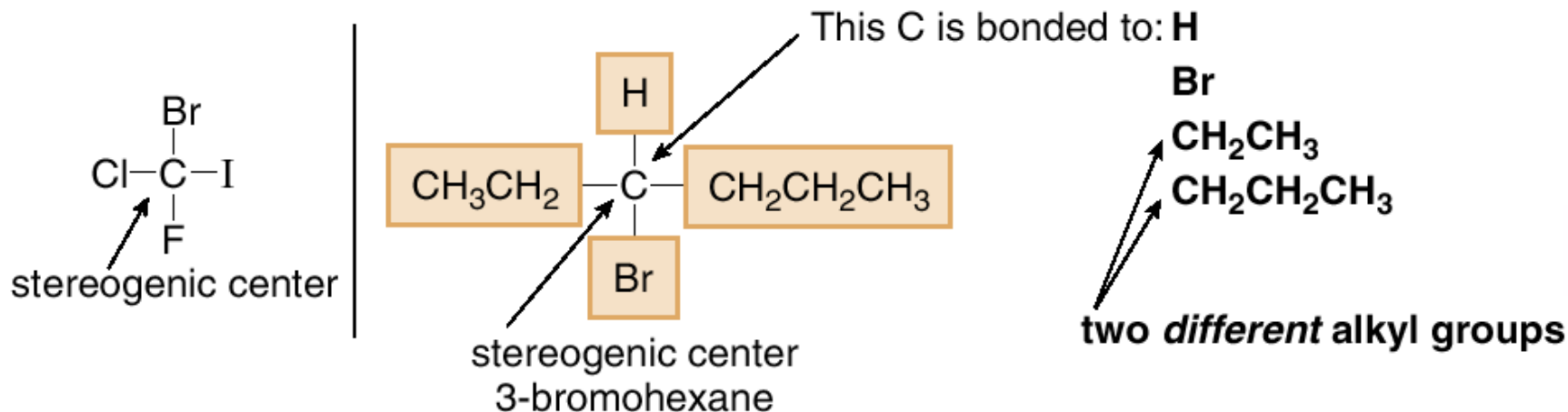
Remember: H and Br are directly aligned, one behind the other.



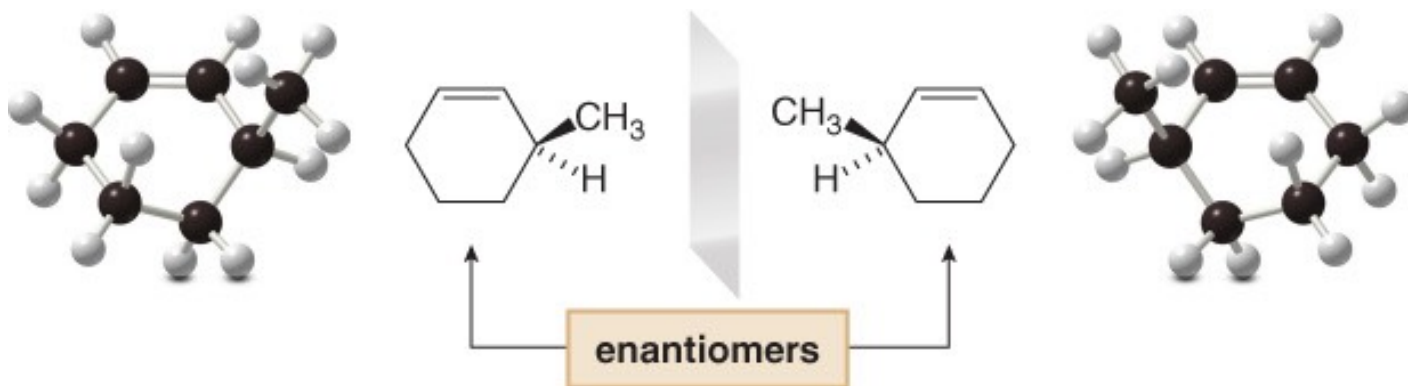
[* = stereogenic center]

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
 - ➡ CH₂ and CH₃ groups
 - ➡ Any *sp* or *sp*² hybridized C



Cyclic Compounds

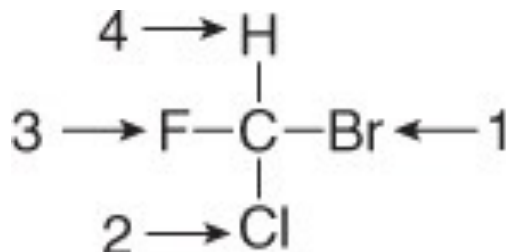


Chirality and Symmetry

- In general, a molecule with no stereogenic centers will not be chiral.
- 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

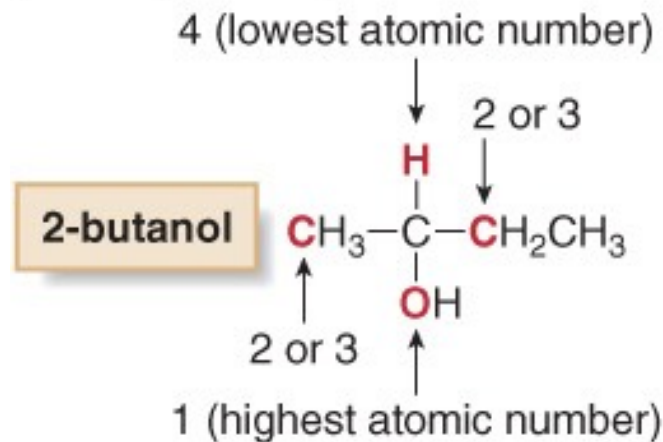
- Naming enantiomers with the prefixes *R* or *S* is called the **Cahn-Ingold-Prelog** system.
- **Priority rule 1.** The atom of highest atomic number gets the highest priority (1).



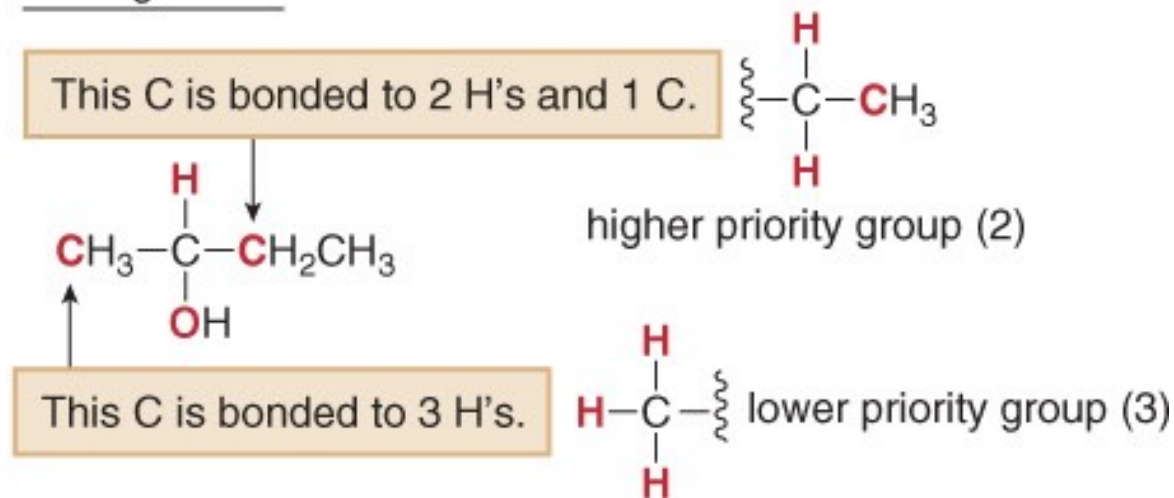
Cahn-Ingold-Prelog System

- **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.

Following rule 1:



Adding rule 2:



Cahn-Ingold-Prelog System

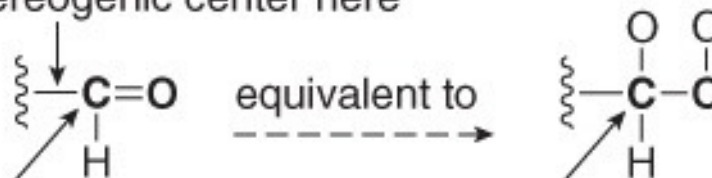
- **Priority rule 3.** If two isotopes are bonded to the stereogenic center, assign priorities in order of decreasing mass number. Thus, in comparing the three isotopes of hydrogen, the order of priorities is:

	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

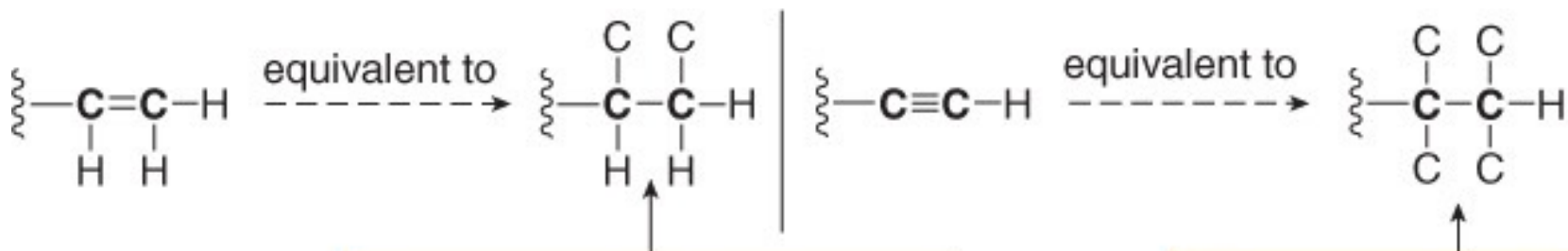
Cahn-Ingold-Prelog System

- **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.

bonded to a stereogenic center here



Consider this C bonded to 2 O's.



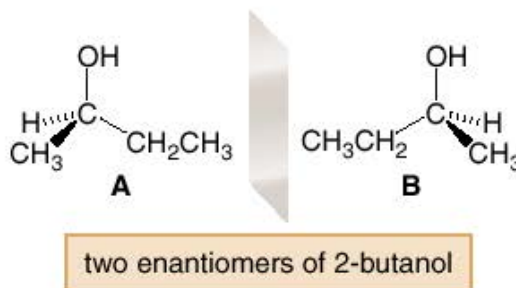
Each atom in the **double** bond is drawn **twice**.

Each atom in the **triple** bond is drawn **three** times.

Cahn-Ingold-Prelog System

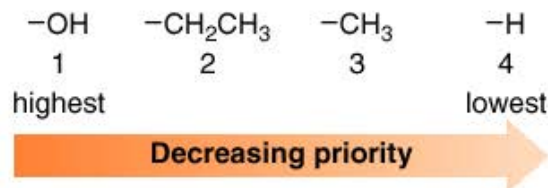
How To Assign *R* or *S* to a Stereogenic Center

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



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.

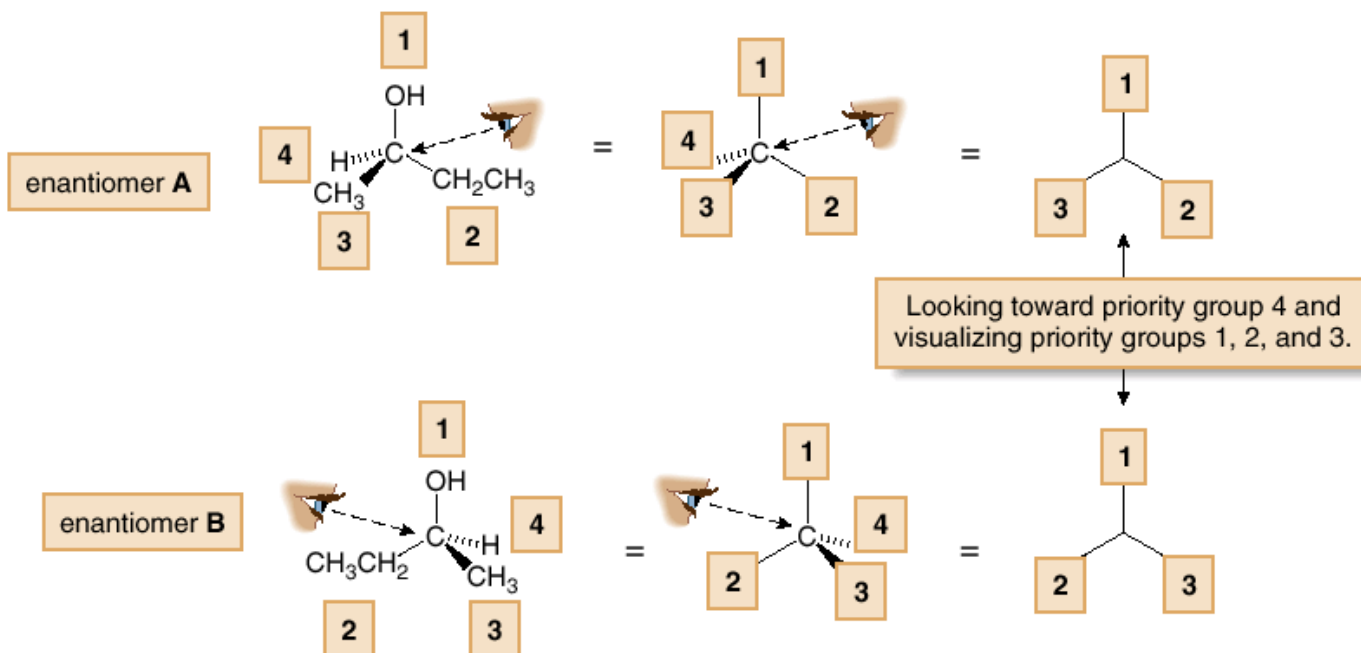


Cahn-Ingold-Prelog System

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).

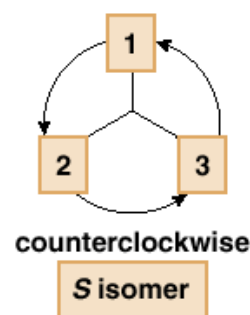
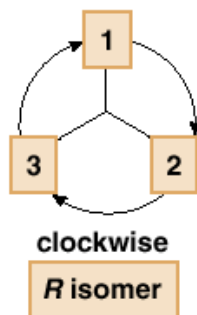
- For each enantiomer of 2-butanol, look toward the lowest priority group, drawn behind the plane, down the C–H bond.



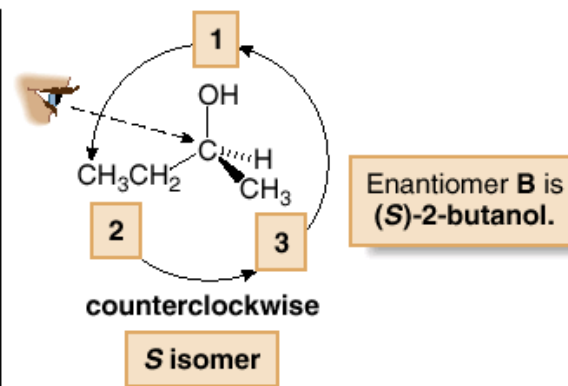
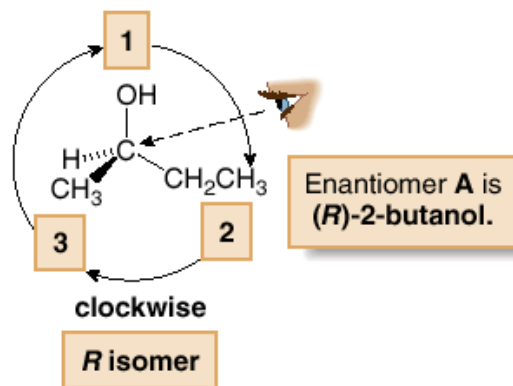
Cahn-Ingold-Prelog System

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**.

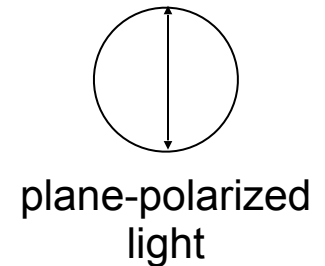
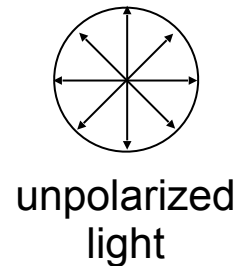
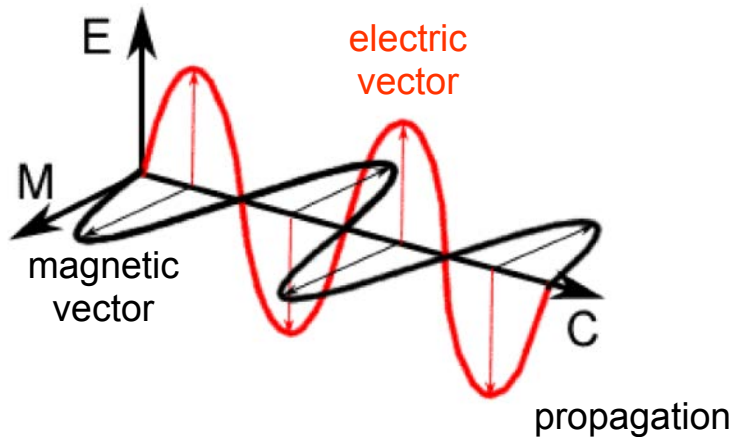


- The letters *R* or *S* precede the IUPAC name of the molecule. For the enantiomers of 2-butanol:



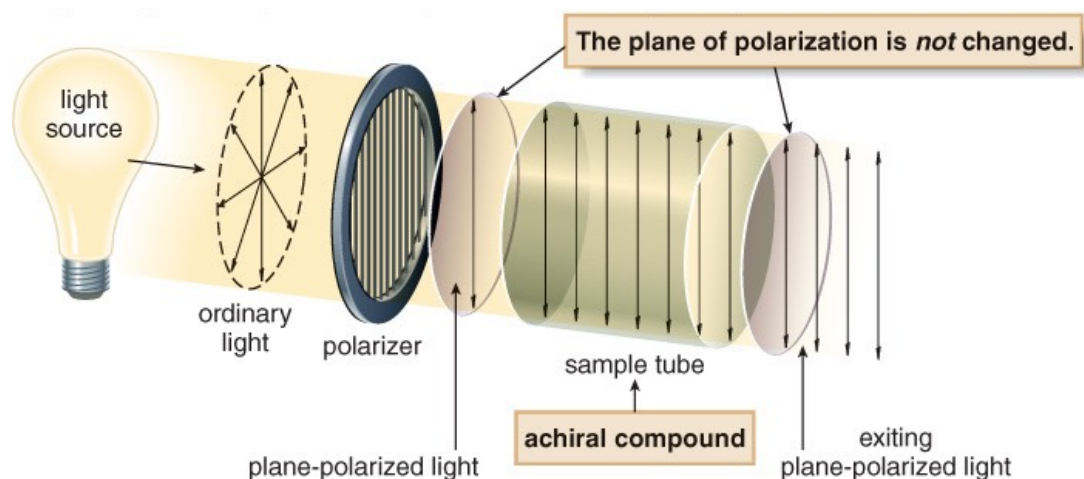
Optical Activity

- 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.



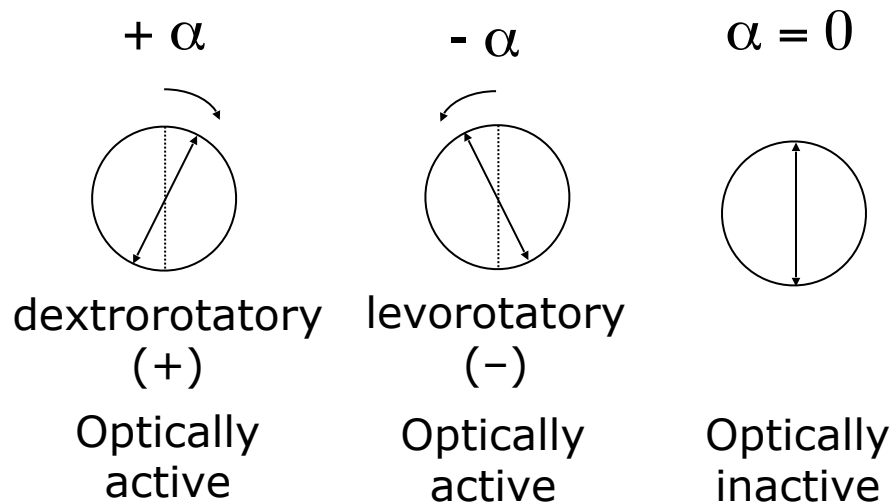
Optical Activity

- 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**.

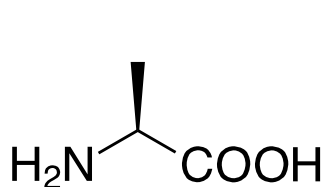


Optical Activity

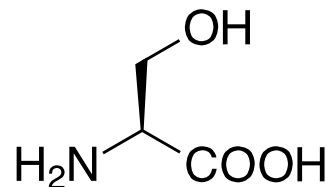
- Two enantiomers rotate plane-polarized light to an equal extent but in **opposite directions**.



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



(*S*)-(+)



(*S*)-(-)

Optical Activity

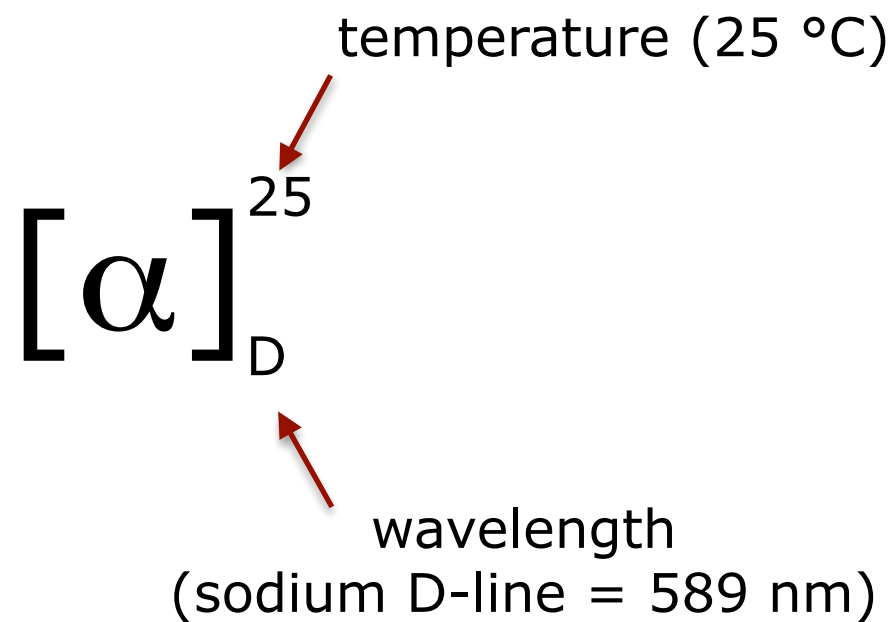
- **Specific rotation** is a standardized physical constant for the amount that a chiral compound rotates plane-polarized light.
- Specific rotation $[\alpha]$ is defined using a specific sample tube length (l , in dm), concentration (c in g/mL; for pure liquids $c = d$), temperature (generally 20 or 25 °C) 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)

$$\left[\begin{array}{l} \text{dm} = \text{decimeter} \\ 1 \text{ dm} = 10 \text{ cm} \end{array} \right]$$

Optical Activity



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 (slightly) 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.

$ee = \% \text{ of one enantiomer} - \% \text{ of the other enantiomer.}$

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

$$ee = ([\alpha] \text{ mixture} / [\alpha] \text{ pure enantiomer}) \times 100.$$

Enantiomeric Excess

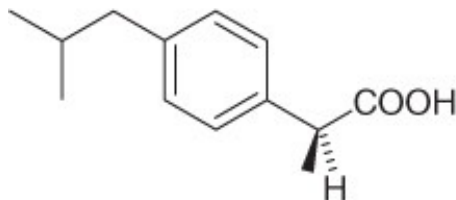
100% (+)	0% (-)	singolo enantiomero	$e.e. = 100\%$
50% (+)	50% (-)	miscela racemica	$e.e. = 0\%$
95% (+) (= 90% (+))	5% (-) 10% (\pm)	miscela	$e.e. = 90\%$ $[\alpha]_{mix} = 0.9[\alpha]_{(+)}$

1. Una soluzione di 400 mg di testosterone in 10,0 mL di etanolo è posta in una cella lunga 10,0 cm. La rotazione osservata per questo campione a 25°C usando la riga D del sodio è +4.36°. Calcolare la rotazione specifica del testosterone.

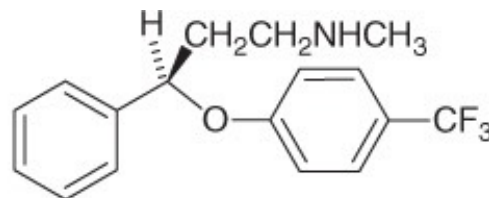
2. Una soluzione di un campione di canfora ottenuta sciogliendo 2.5 g del campione in 5 mL di metanolo ha una rotazione $\alpha = +10.5^\circ$, misurata in una cella di 5 cm. Sapendo che la rotazione specifica della (+) canfora è $[\alpha] = +44^\circ$, calcolare l'eccesso enantiomerico del campione.

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.

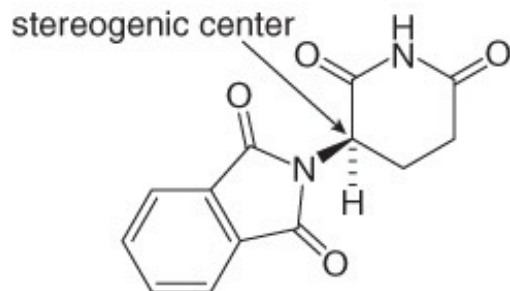


(S)-ibuprofen
anti-inflammatory agent

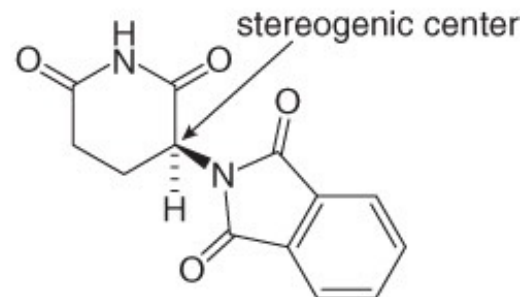


(R)-fluoxetine
antidepressant

Two enantiomers of thalidomide



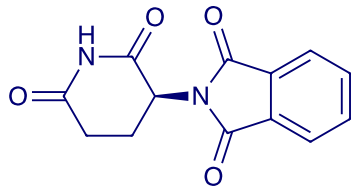
anti-nausea drug



teratogen

Thalidomide

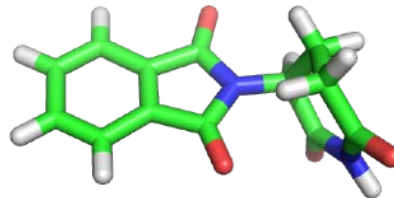
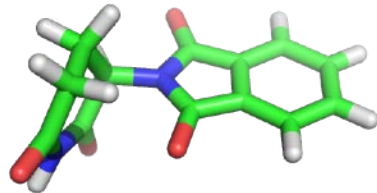
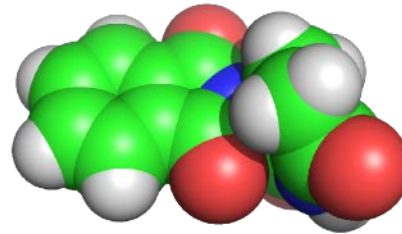
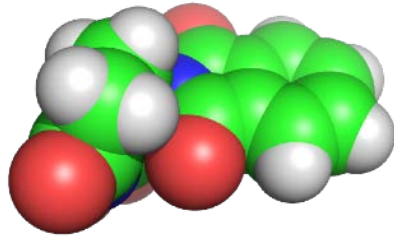
[modelli](#)



(-)



(+)



sedative

inhibits angiogenesis
teratogenic if taken
between 20-42 weeks
of pregnancy

1953: discovered in Germany

1957: commercialised as over-the-counter drug

1957-1961: widely used against morning sickness in pregnant women

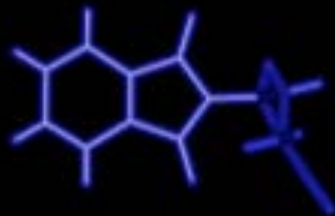
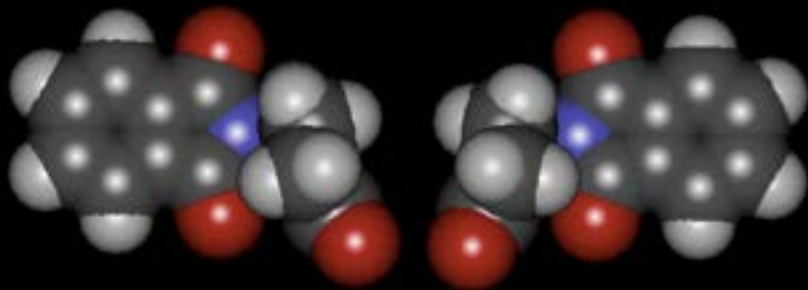
1957-1960: abnormal incidence of phocomelia.

10.000 - 20.000 cases worldwide.

50% mortality

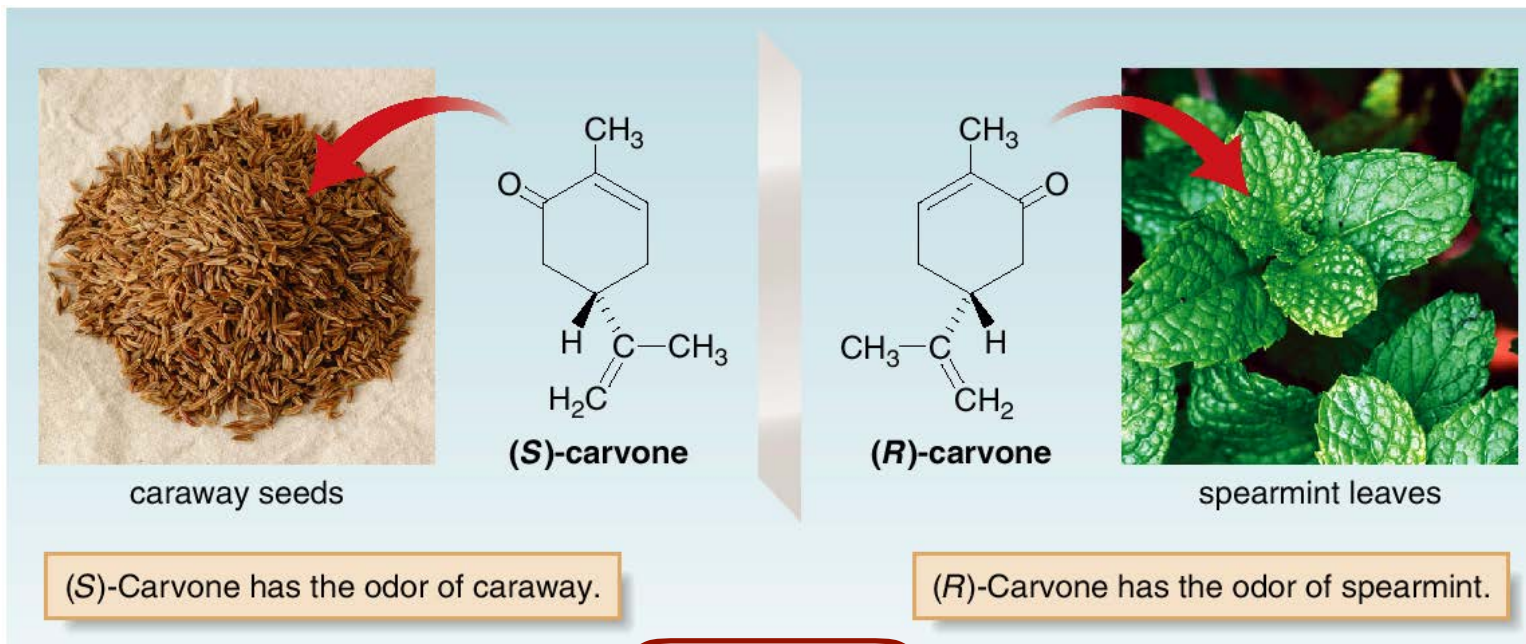
1961-1962: withdrawn from the market

Thalidomide

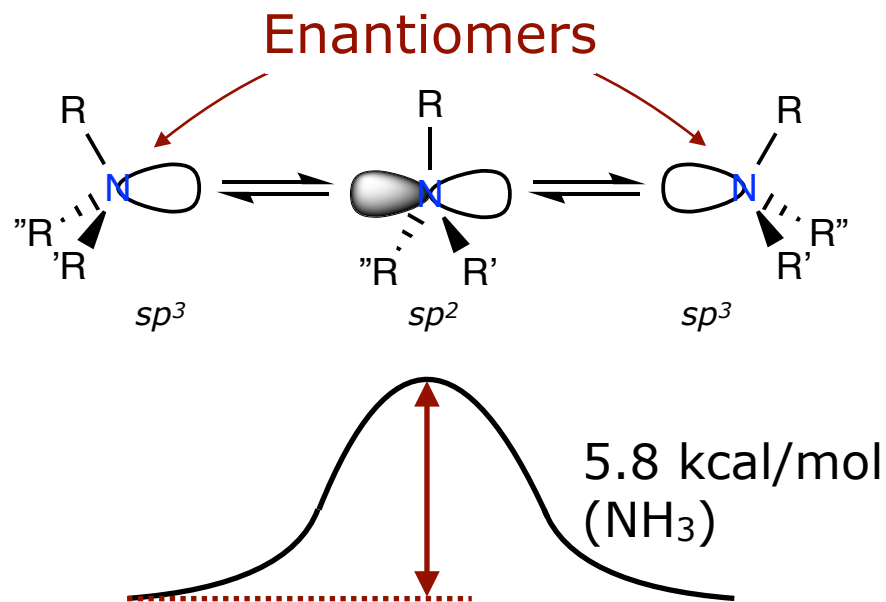


Chemical Properties of Enantiomers

- 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 odours.



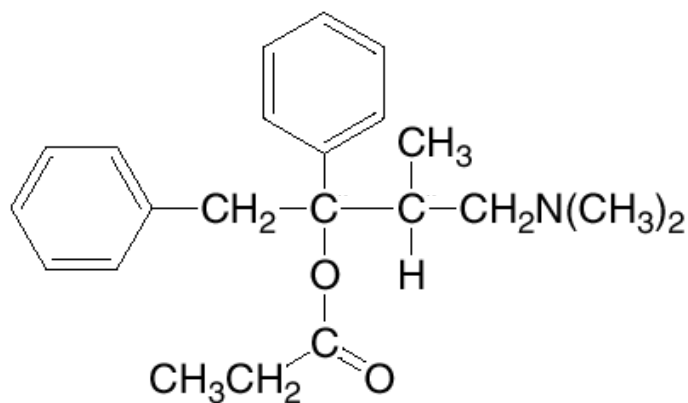
Pyramidal Inversion Amines



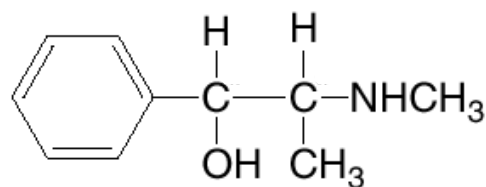
Amines are achiral because the barrier for interconversion of the enantiomers is low.

Stereogenic Centers

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

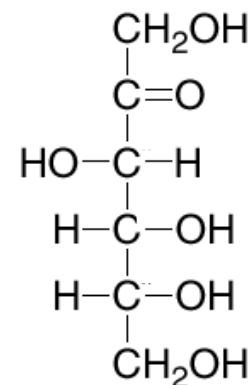


propoxyphene
Trade name: Darvon
(analgesic)



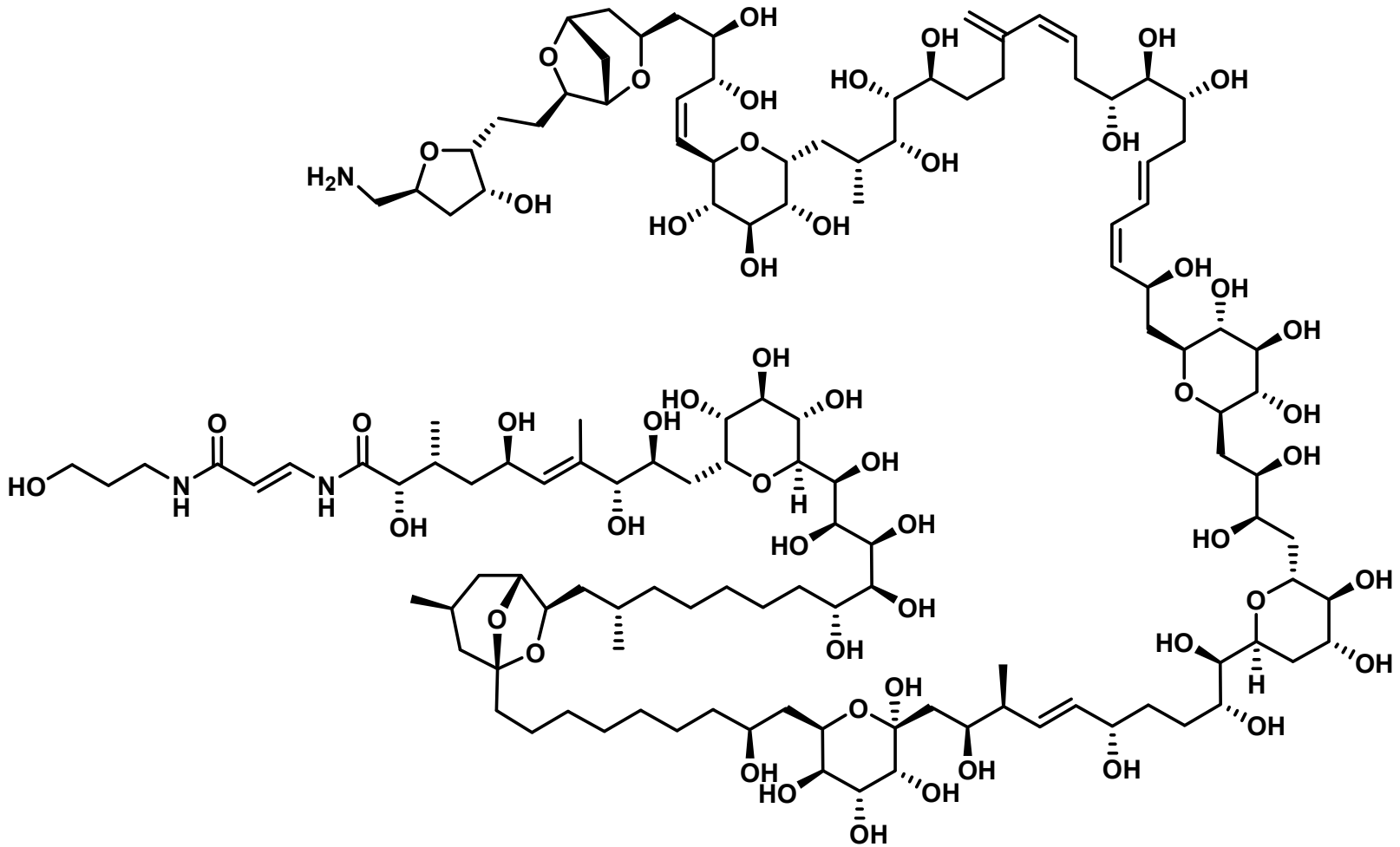
ephedrine
(bronchodilator, decongestant)

[* = stereogenic center]



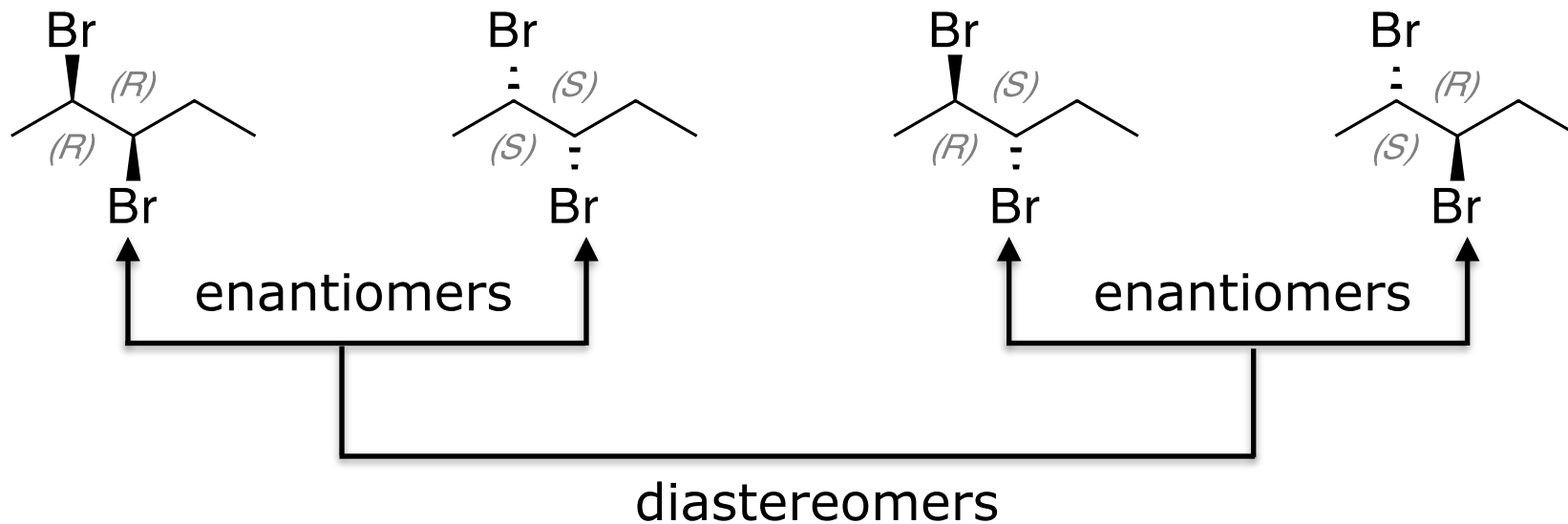
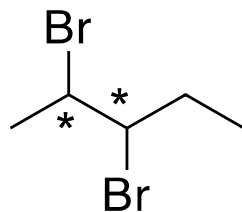
fructose
(a simple sugar)

Stereogenic Centers



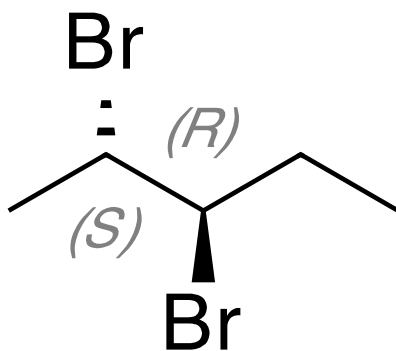
Palytoxin: 64 chiral centers

Diastereomers



Diastereomers

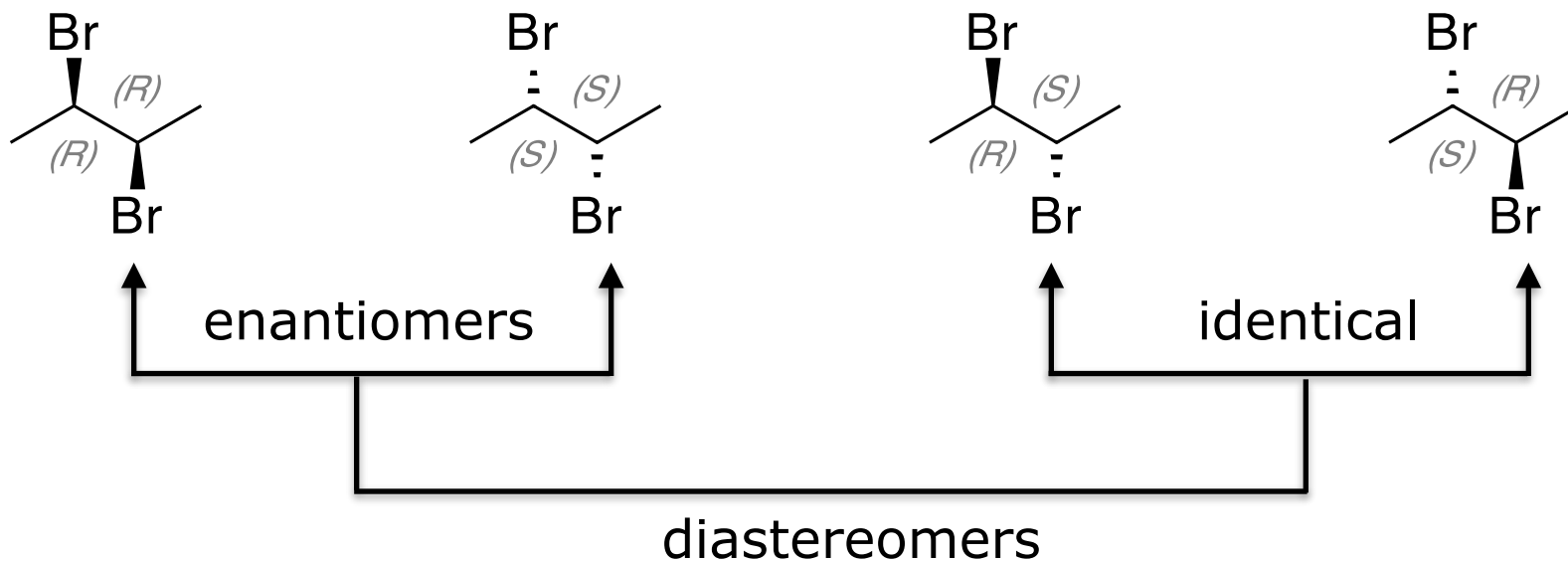
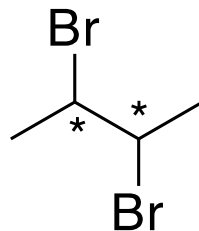
- When a compound has more than one stereogenic center, R and S configurations must be assigned to each of them.



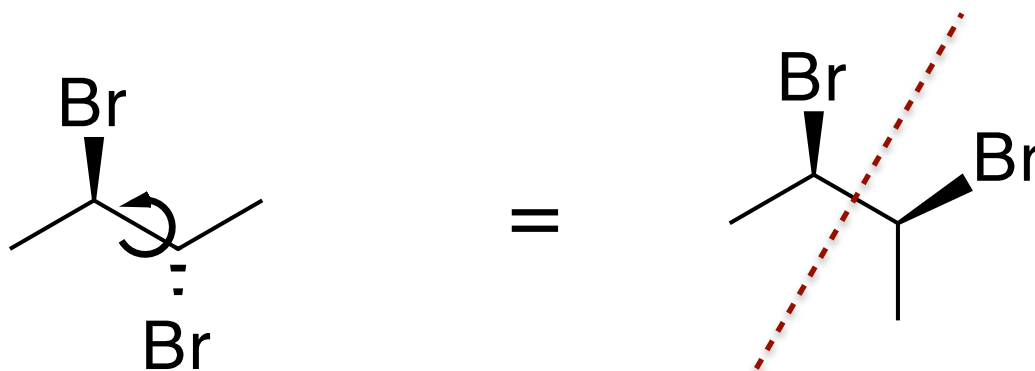
(2*S*,3*R*)-2,3-dibromopentane

In general: n stereogenic centers $\Rightarrow 2^n$ stereoisomers

Meso Compounds



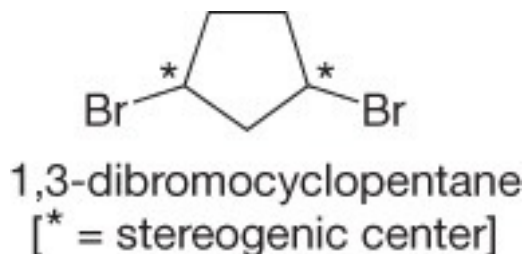
Meso Compounds



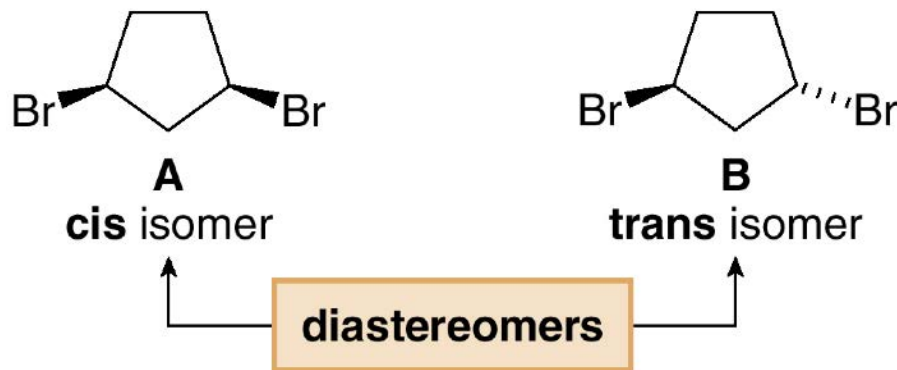
- Meso compounds contain a plane of symmetry, and are achiral.

Diastereomers

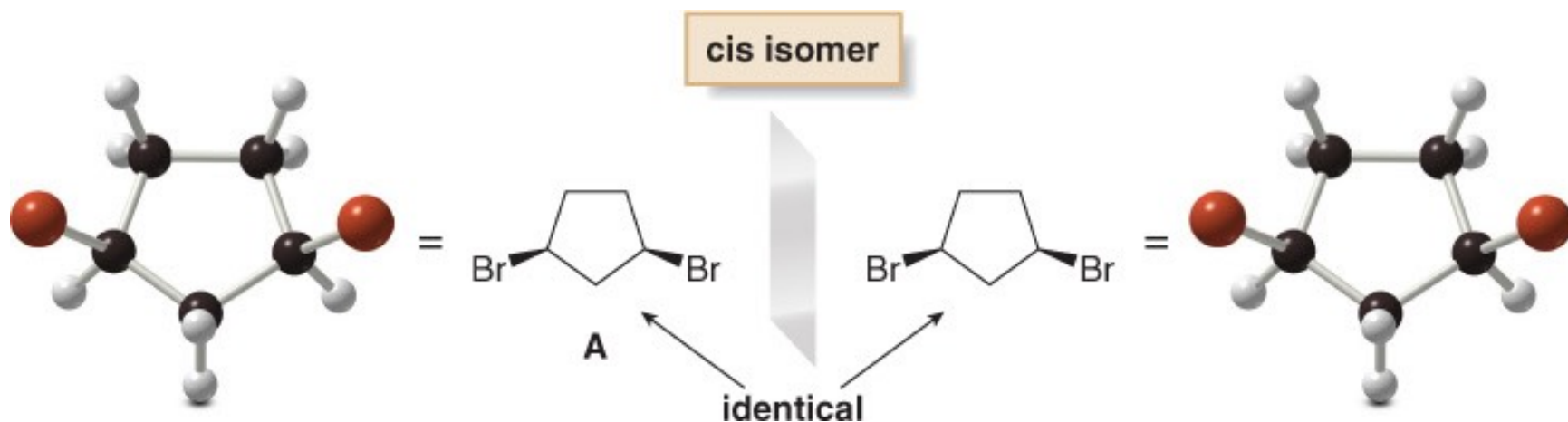
- Consider 1,3-dibromocyclopentane. Since it has two stereogenic centers, it has a maximum of four stereoisomers.



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

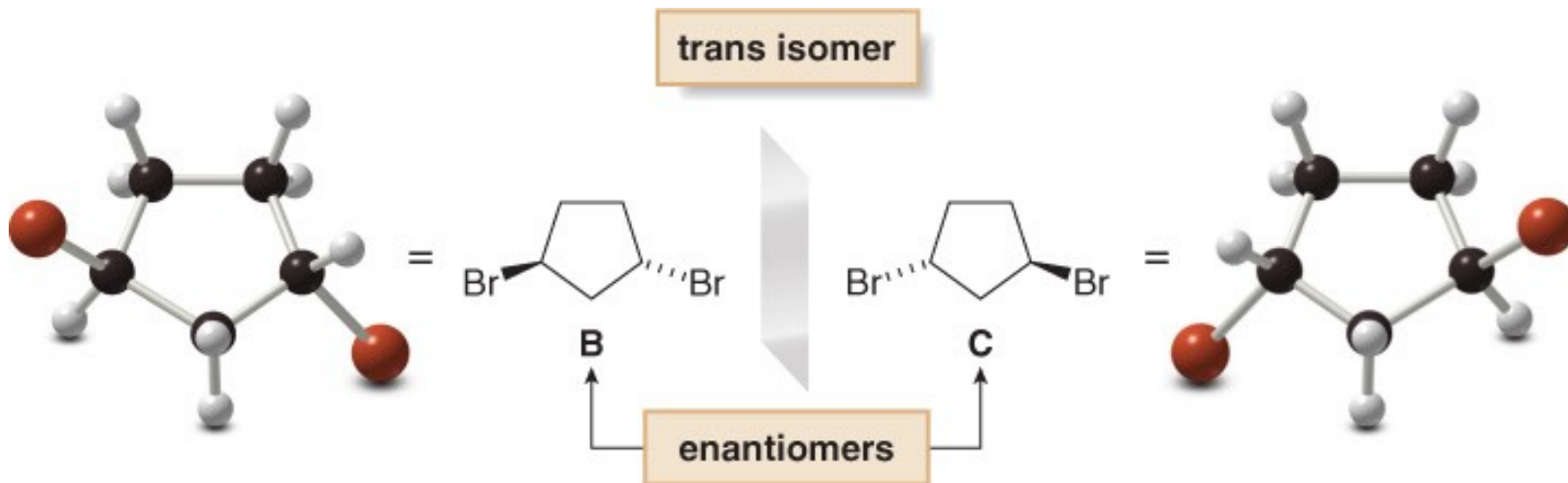


Diastereomers



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

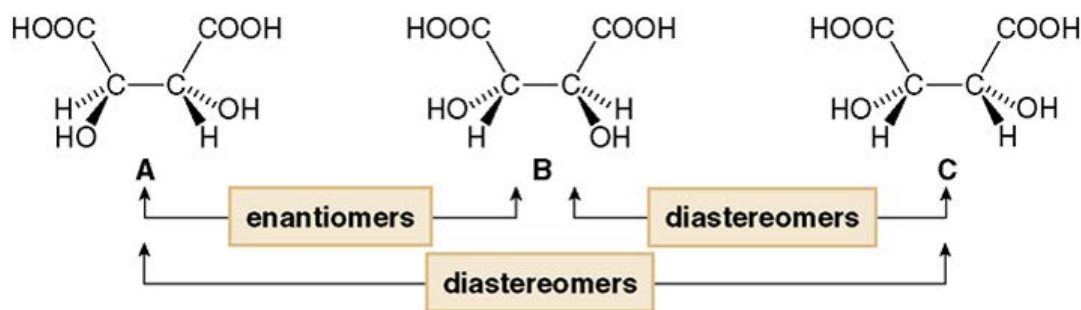
Diastereomers



- 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 ₂ O)	139	139	125	139
[α]	+13	-13	0	0
<i>R,S</i> designation	<i>R,R</i>	<i>S,S</i>	<i>R,S</i>	—
<i>d,l</i> designation	<i>d</i>	<i>l</i>	none	<i>d,l</i>

- 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.

More About Stereochemistry

[ChemTube3D - Stereochemistry](#)