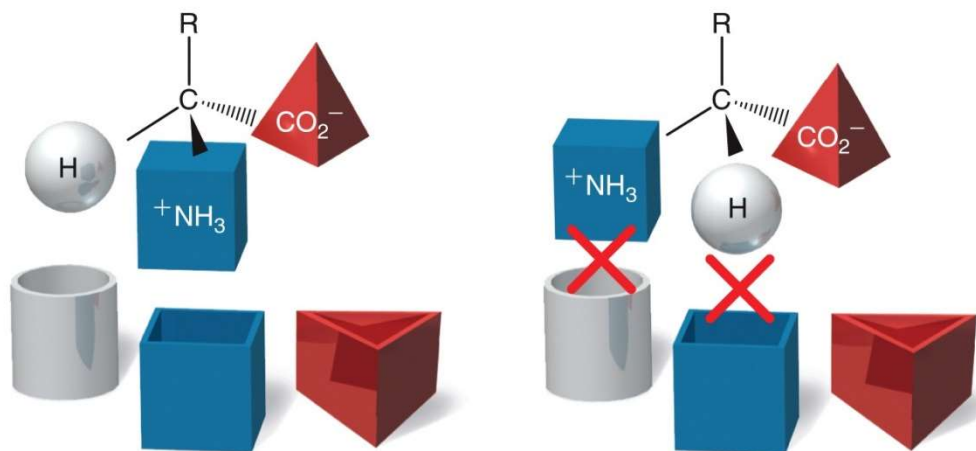


Chapter 3: Stereochemistry

- **Stereochemistry**, involves the study of the relative spatial arrangement of atoms that form the structure of molecules. An important branch of stereochemistry is the study of **chiral** molecules.

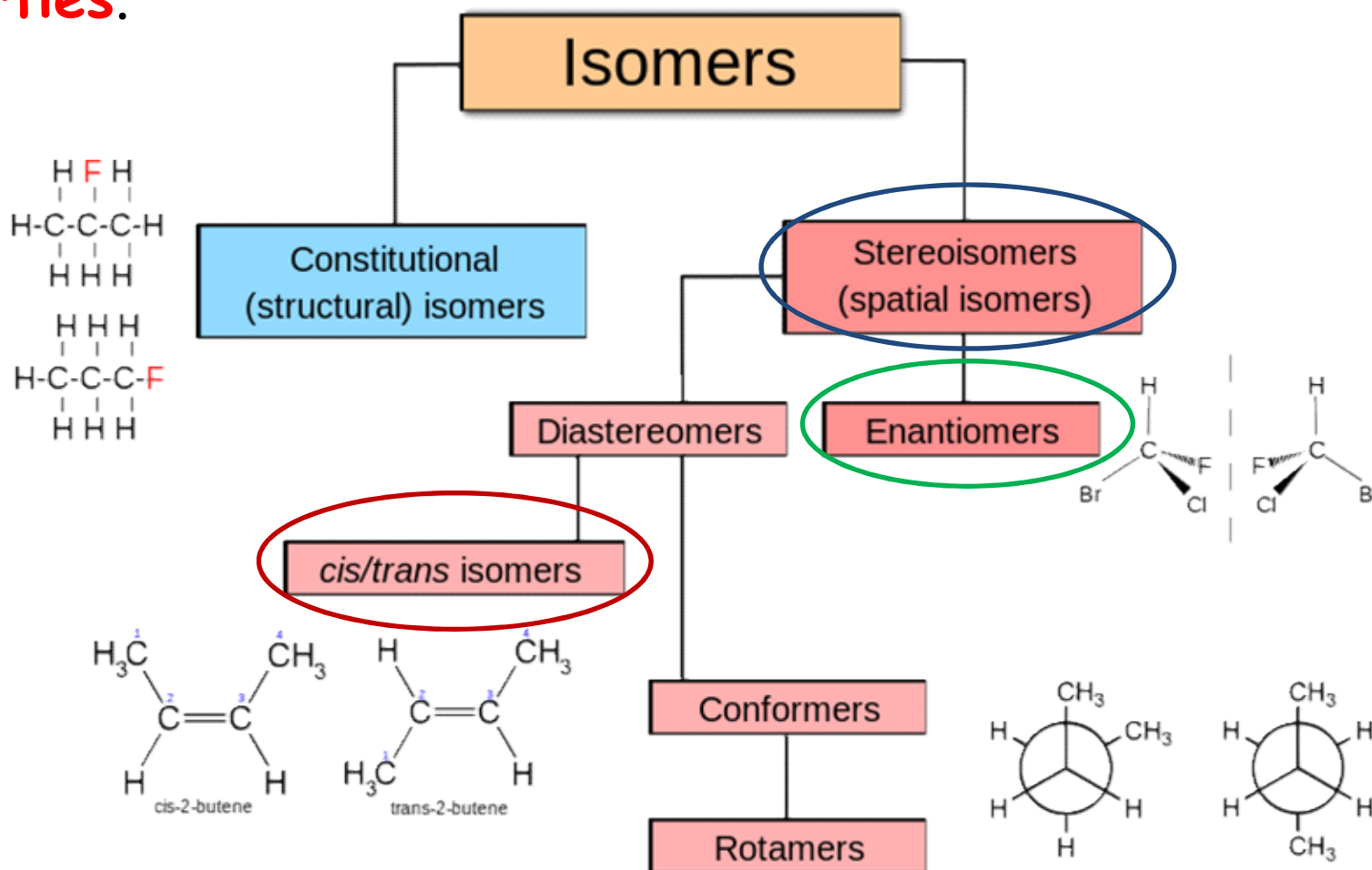
- Stereochemistry is also known as 3D chemistry because the **prefix "stereo-"** means "three-dimensionality".



- The **study** of stereochemistry focuses on stereoisomers and links to the entire spectrum of **organic**, **inorganic**, **biological**, **physical** and especially **supramolecular** chemistry.

Different Types of Isomerism

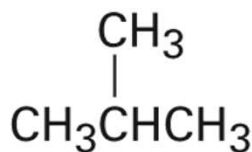
Isomerism relates to the existence of different compounds which have the **same molecular formula** but **different properties**.



Constitutional Isomers

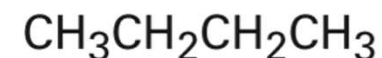
Constitutional Isomers: **Different order** of connections gives different carbon **backbone** and/or different **functional groups**

Different carbon skeletons



2-Methylpropane

and



Butane

Different functional groups



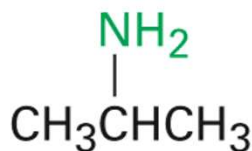
Ethyl alcohol

and



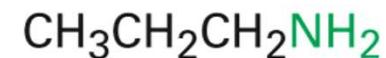
Dimethyl ether

Different position of functional groups



Isopropylamine

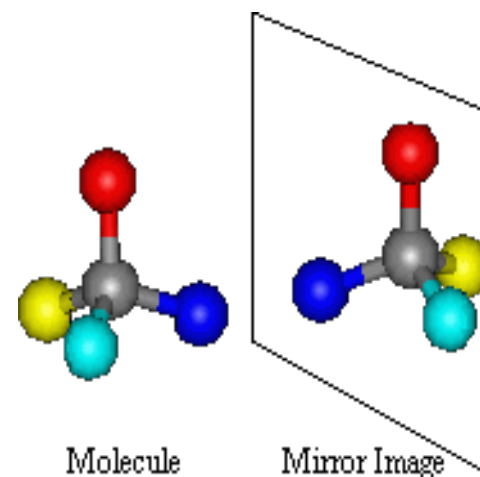
and



Propylamine

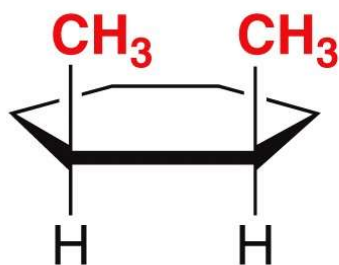
Stereoisomerism

- ❑ The isomeric compounds which differ from each other only in the relative **arrangement** of atoms in **space**
- ❑ There are **two** types of stereoisomerism: **Geometrical** isomerism and **Optical** isomerism.
 - **Geometrical isomerism:** Because **rings** and **C=C double** bonds can not freely rotate, It forms to two different isomers. **cis-trans** notation is used to distinguish between stereoisomers
 - **Optical isomerism:** In this the isomeric compounds **resemble** one another in their **chemical reactions** and most of the **physical properties** but **differ** in their effect on **polarized light**.

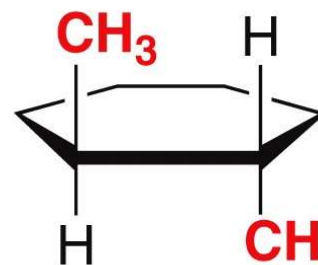


Geometrical Isomers (Cis-trans or Z-E)

- C-C bonds that are constrained in a **cyclic** structure can **not freely rotate**

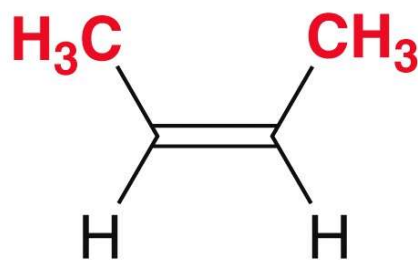


Cis (Z)

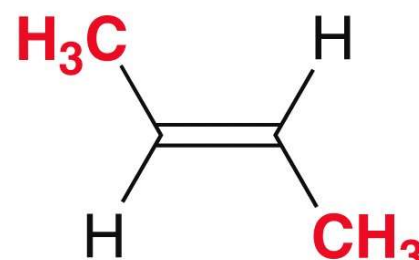


Trans (E)

- To maintain orbital overlap in the pi bond, **C=C** double bonds can **not freely rotate**.



Cis (Z)

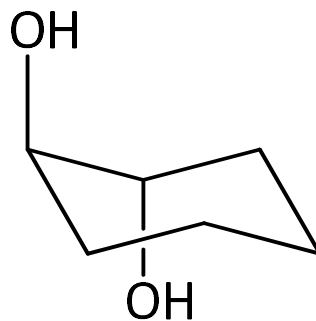
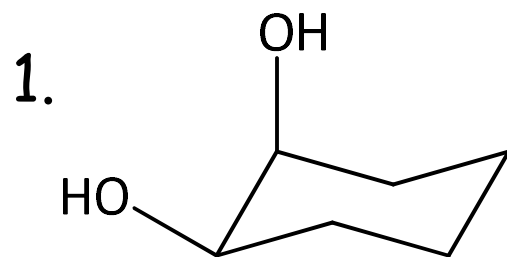


Trans (E)

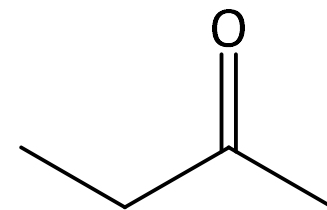
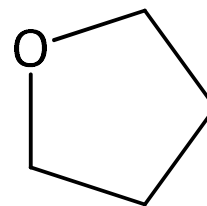
Cis (or Z)– identical groups are positioned on the **SAME** side of a ring
Trans (or E)– identical groups are positioned on **OPPOSITE** sides of a ring

Examples

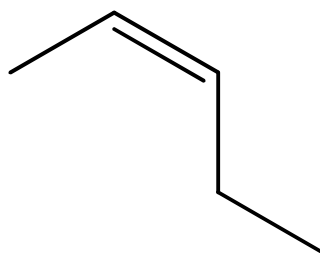
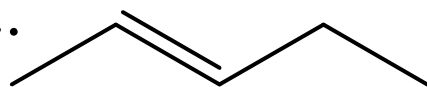
Identify the following pairs as either **constitutional isomers**, **stereoisomers**, or **identical**



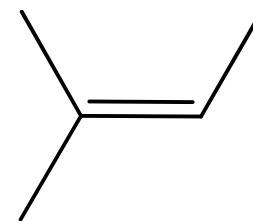
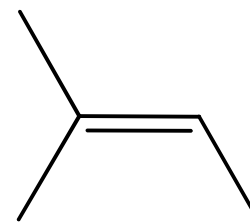
3.



2.

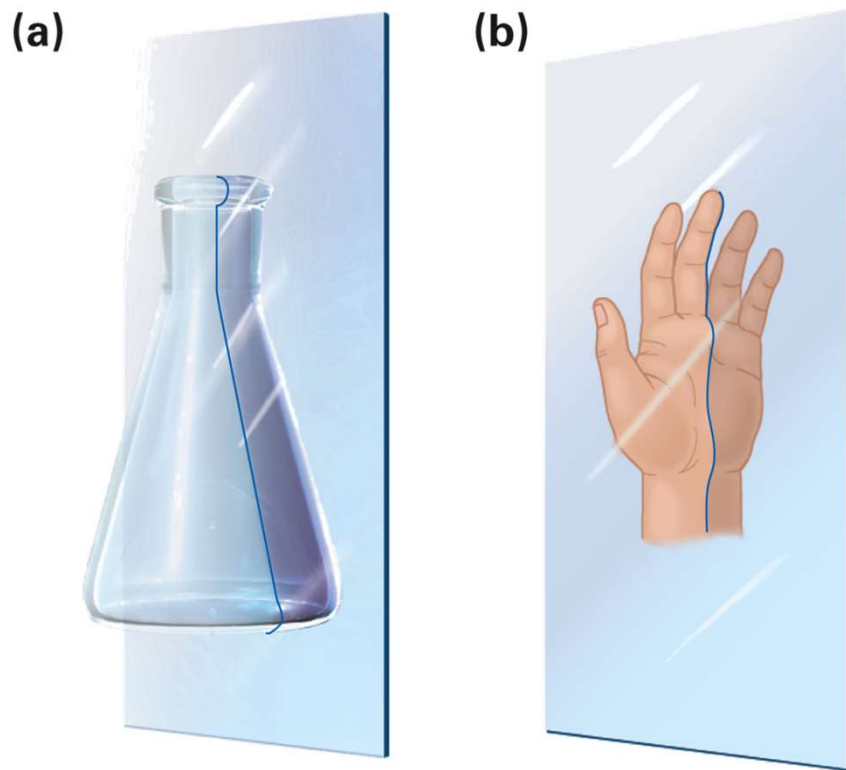


4.



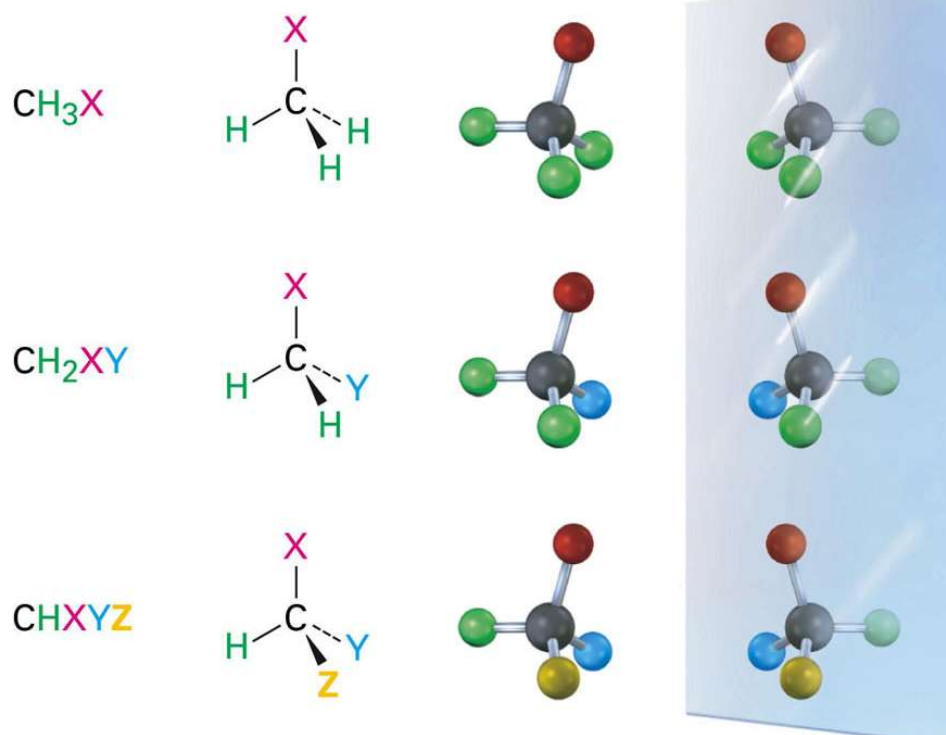
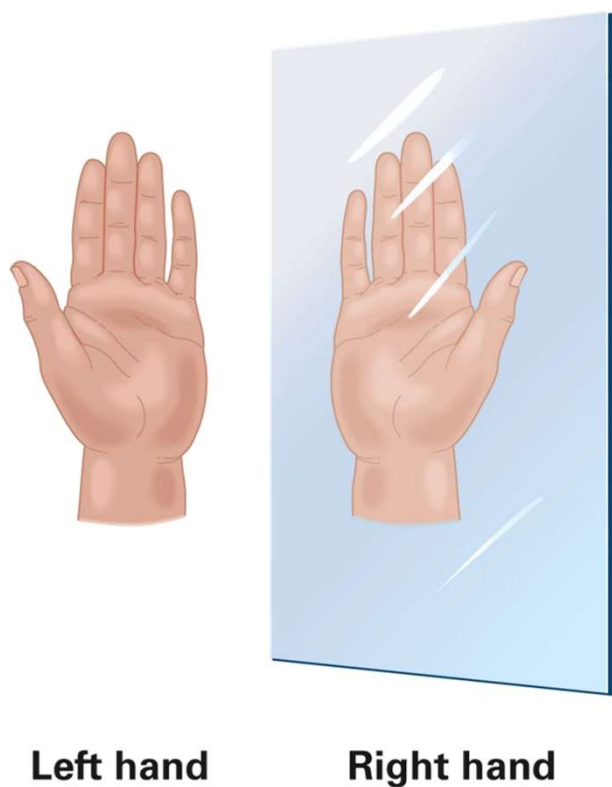
Chirality

- ❑ Beyond *cis-trans* isomers, there are many other important stereoisomers which must contain **chiral** object, having **no plane of symmetry**
- ❑ If an object has a plane of symmetry, it is necessarily the **same as its mirror image**.
- ❑ The lack of a plane of symmetry is called "**handedness**". They have a "left" and a "right" version
- ❑ A **chiral** object is **NOT identical** to its mirror image
- ❑ A molecule with a plane of symmetry is the same as its mirror image and is said to be **achiral**.



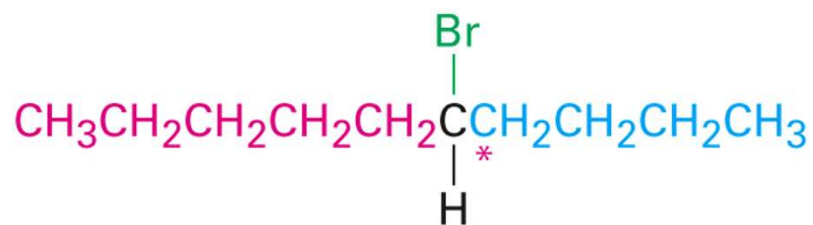
Chirality molecules

- ❑ **Organic** molecules (including many drugs) have handedness that results from **substitution** patterns on sp^3 hybridized carbon.
- ❑ **Chirality** most often results when a carbon atom is bonded to **4 different groups** of atoms.

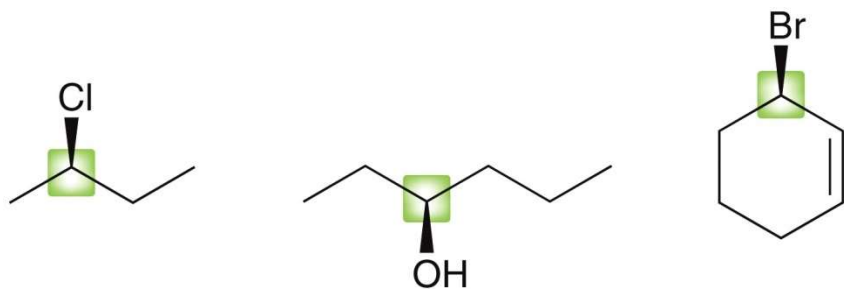


Chirality centers

- ❑ A **point** in a molecule where four different groups (or atoms) are attached to carbon is called a **chirality center (stereocenter)**.
- ❑ There are two **non-superimposable** objects that 4 different groups (or atoms) can be attached to one carbon atom
- ❑ A **chiral** molecule usually has **at least** one chirality center



5-Bromodecane (chiral)



Substituents on carbon 5

—H

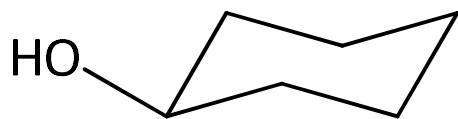
—Br

—CH₂CH₂CH₂CH₃ (butyl)

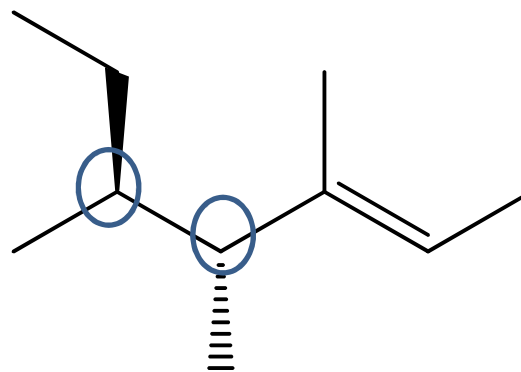
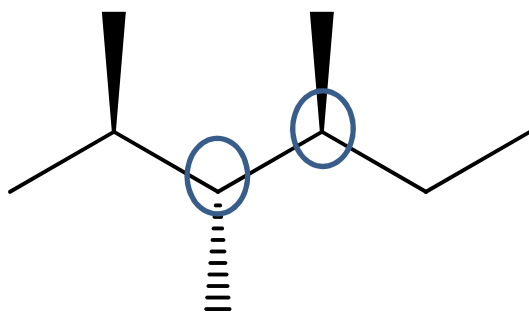
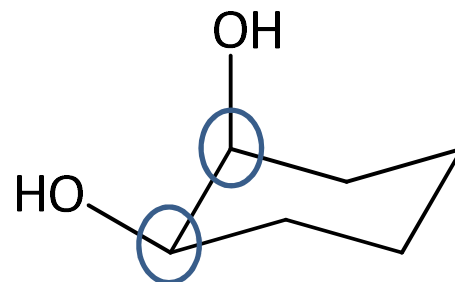
—CH₂CH₂CH₂CH₂CH₃ (pentyl)

Examples

Identify all of the chirality centers (if any) in the following molecules

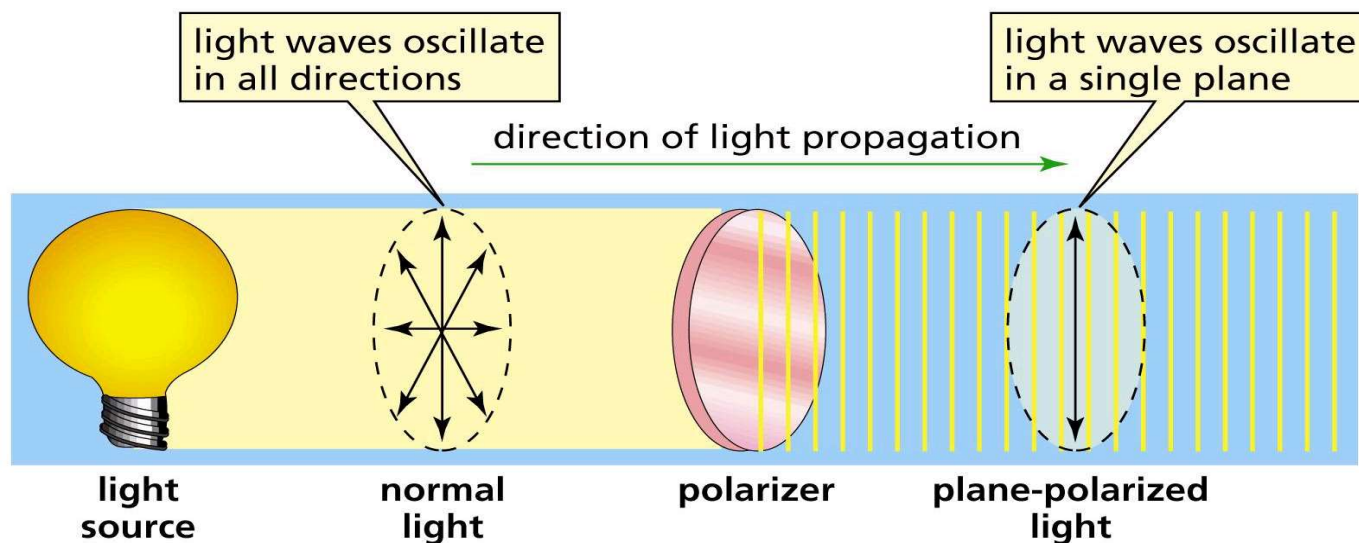


No

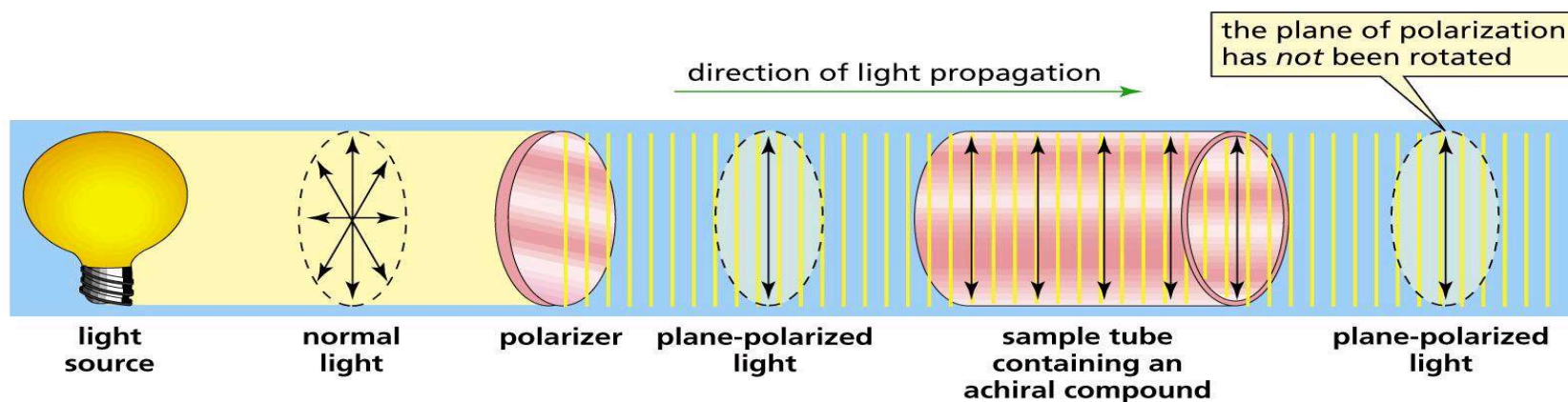


Optical Activity

Plane-Polarized Light

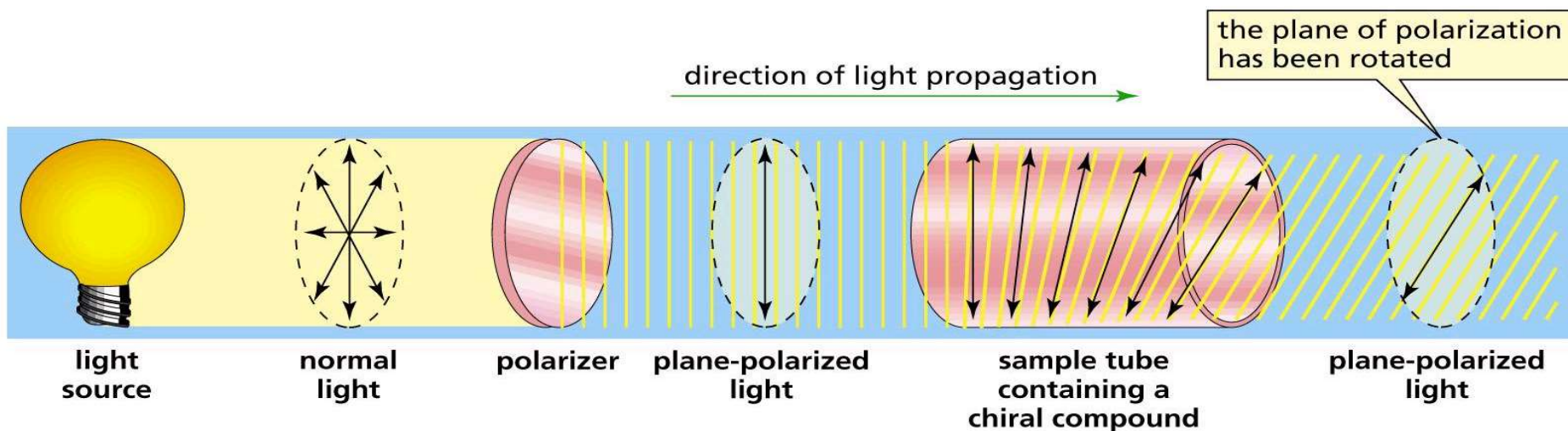


Plane-Polarized Light through an **Achiral** Compound



Optical Activity

Plane-Polarized Light through a **chiral** Compound



- ❑ A **polarimeter** measures the rotation of plane-polarized light that has passed through a solution
- ❑ The **angle** between the **entrance** and **exit** planes is the optical **rotation**.

Specific Rotation, $[\alpha]$

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

Where,

α = observed rotation

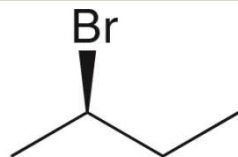
c = concentration in g/mL

l = length of tube in dm

- ❑ $[\alpha]$ depends on the sample concentration and the pathlength of the light
- ❑ **Standard** optical rotation measurements are taken with **1 gram** of compound dissolved in **1 mL** of solution, and with a pathlength of **1 dm** for the light
- ❑ **Temperature** and the **wavelength** of light can also affect rotation and must be reported with measurements that are taken

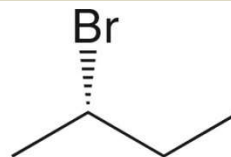
$$[\alpha]_{\lambda}^T$$

Specific Rotation, $[\alpha]$



(*R*)-2-Bromobutane

$$[\alpha]_{\text{D}}^{20} = -23.1$$



(*S*)-2-Bromobutane

$$[\alpha]_{\text{D}}^{20} = +23.1$$

- (+) and (-) signs refer to the direction that the plane of light is rotated
 - **Dextrorotary** designated as ***d*** or (+), **clockwise** rotation
 - **Levorotary** designated as ***l*** or (-), **counter-clockwise** rotation

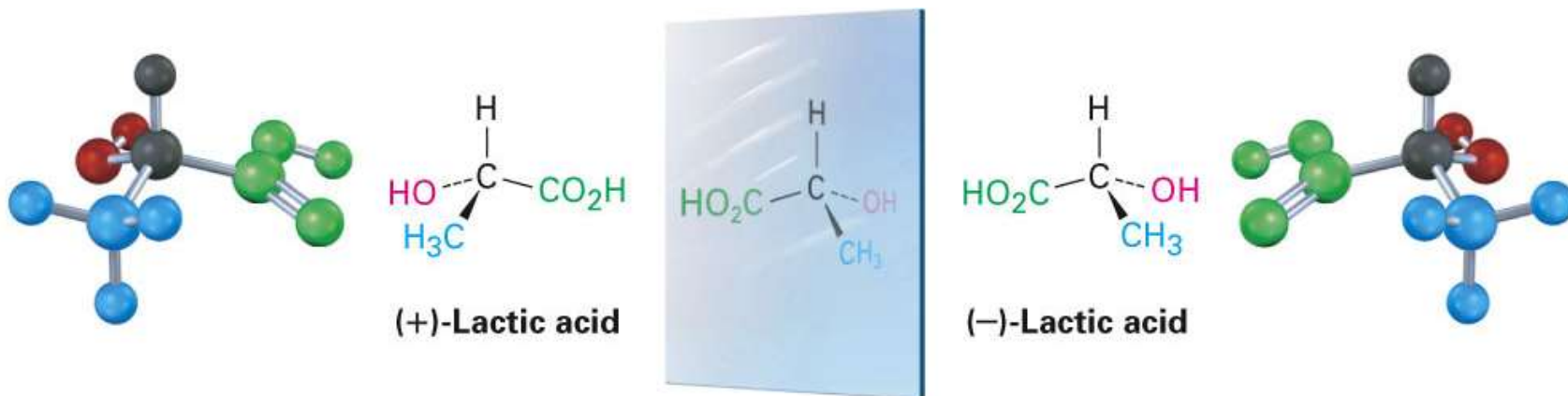
Compound	$[\alpha]_{\text{D}}$	Compound	$[\alpha]_{\text{D}}$
Penicillin V	+233	Cholesterol	-31.5
Sucrose	+66.47	Morphine	-132
Camphor	+44.26	Cocaine	-16
Chloroform	0	Acetic acid	0

□ **Note:** Having **NO** relationship between (*R*), (*S*) and (+)/(-)

Types of optical isomerism

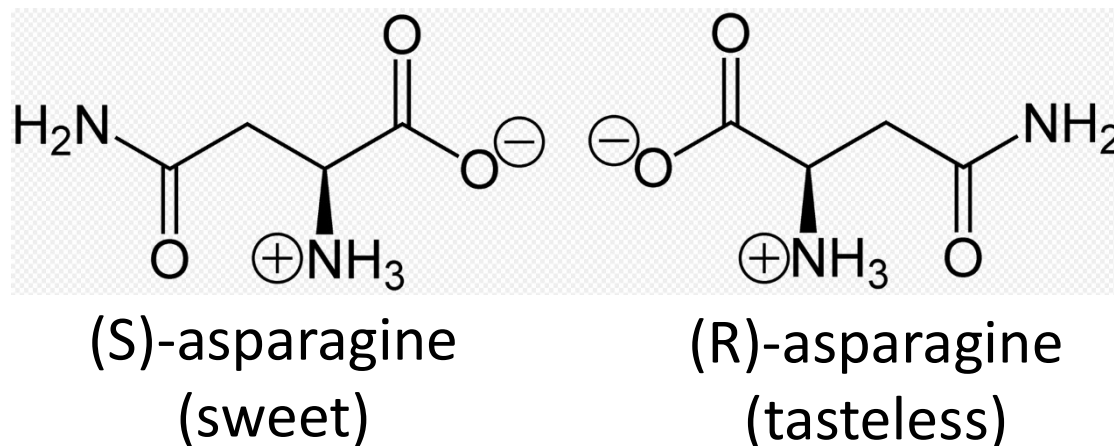
There are two types: **Enantiomerism** and **Diastereomerism**

- **Enantiomerism:** An **enantiomer** is one of the two stereoisomers that are mirror images of each other that are non-superimposable and which rotate the plane polarized light equally but in opposite directions. The phenomenon of mirror image isomerism is called **enantiomerism**.
- **Fundamental condition of enantiomerism:** A molecule must have **NO** symmetric object or in the other words **chirality**.



Characteristics of enantiomers

- ❑ They have **identical physical** properties such as m.p, b.p, densities, solubility, refractive index.
- ❑ They have **identical chemical** properties except in reactions with other optically active compounds.
- ❑ They have **different biological** properties.

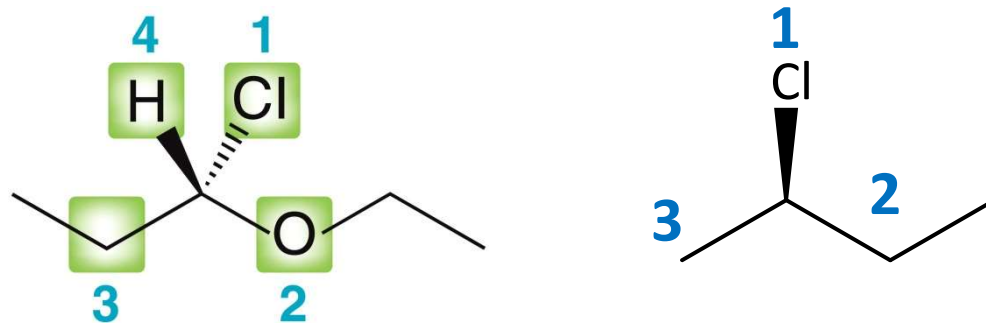


- ❑ When **equal quantities** of enantiomers are mixed together it results in the formation of an **optically inactive** form called **racemate**.

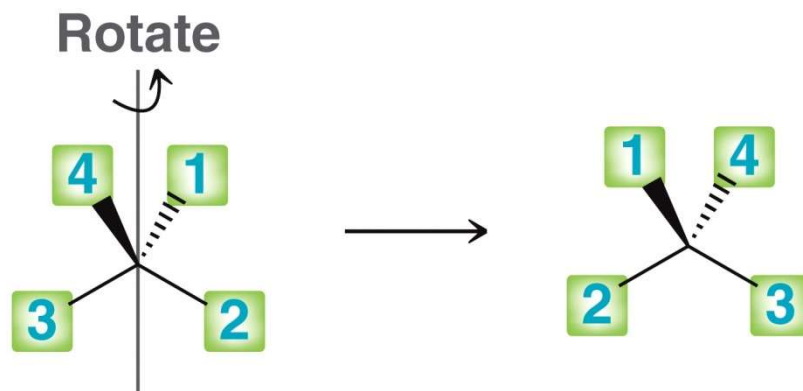
Designating Configurations

Methods

Step 1. Assign each group priority 1-4 according to Cahn-Ingold-Prelog rule.

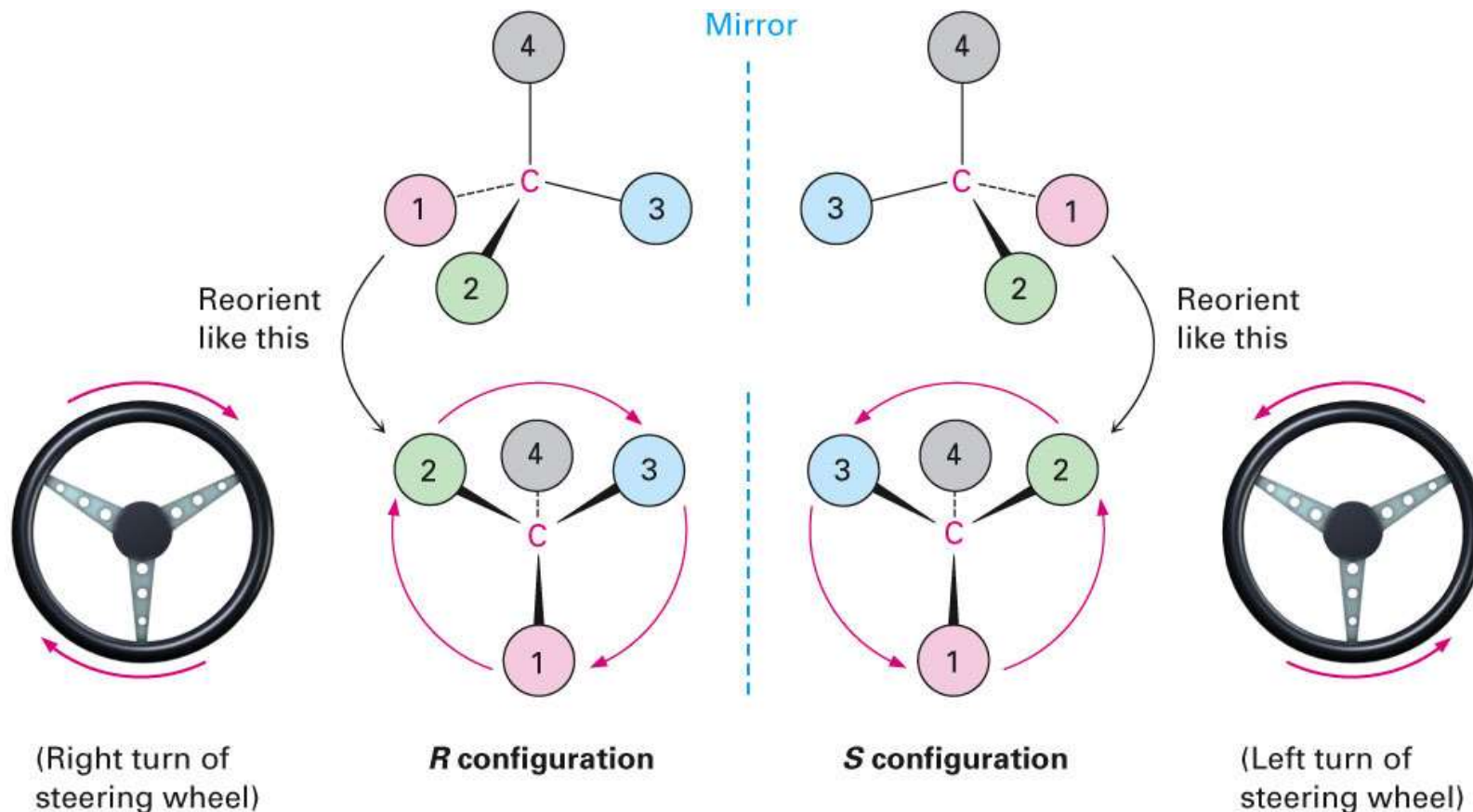


Step 2. Rotate the assigned molecule until the **lowest priority** group (4) is in the back, look at remaining 3 groups in a plane



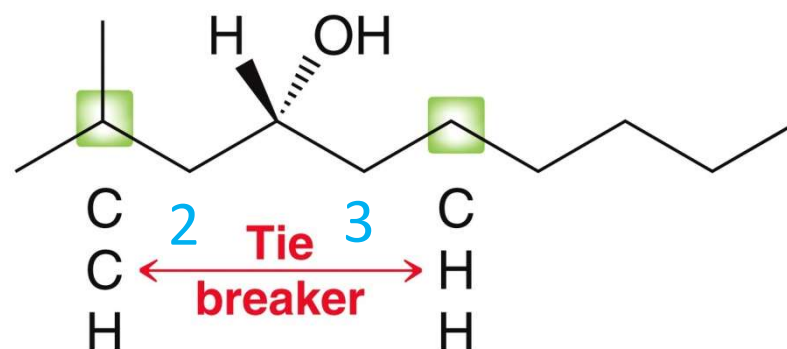
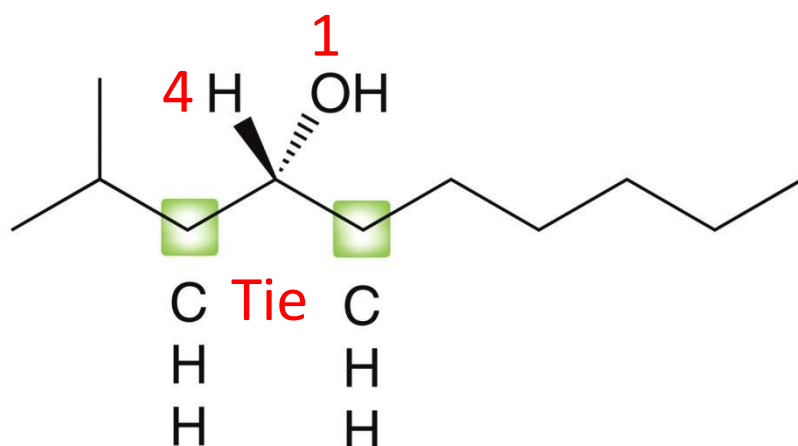
Designating Configurations

Step 3. Clockwise 1-2-3 movement is designated **R** (from Latin for “right”). **Counterclockwise** is designated **S** (from Latin word for “left”).



Cahn-Ingold-Prelog (C.I.P) sequence rules

- ❑ **Sequence rule 1:** the atom attached to the chiral center with the **highest atomic number** = 1, next = 2, etc.
- ❑ **Sequence rule 2:** if the four atoms attached to the chiral center are not all different, the sequence is determined at **the first point of difference**.



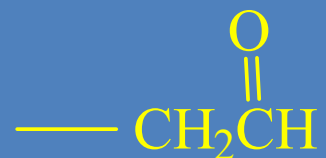
- ❑ **Sequence rule 3:** =X is equal to two -X, etc.



C.I.P. Priorities

Low

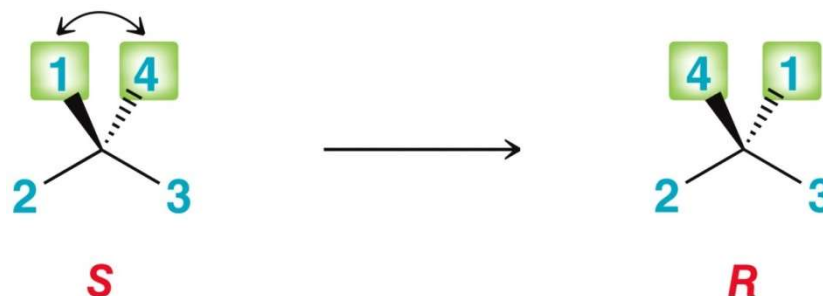
High



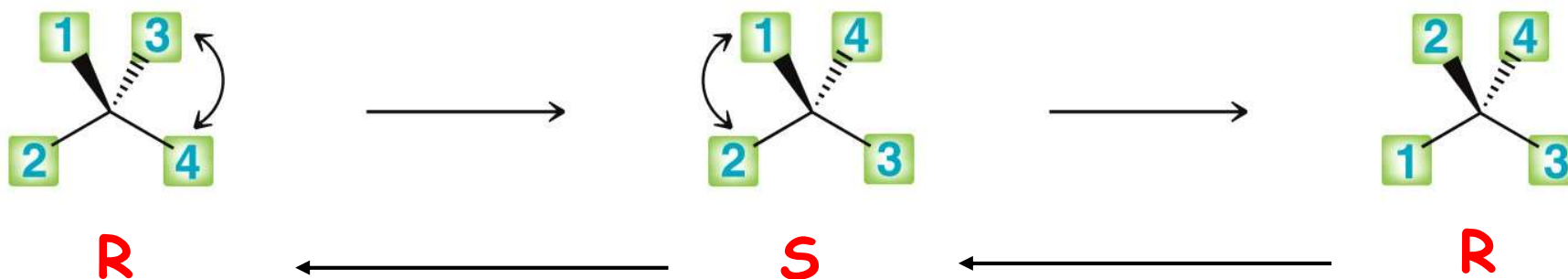
Designating Configurations (Tips)

❑ **Tip 1:** Handheld molecular models can be very helpful when arranging the molecule in space so **the lowest priority** group faces **away** from you

❑ **Tip 2: Switching two groups** on a chirality center will produce its **opposite** configuration

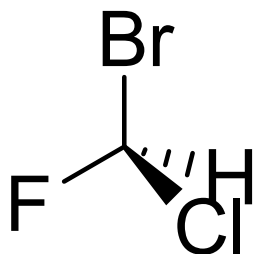


➡ You can use this trick to **adjust** a molecule so that the lowest priority group faces away from you

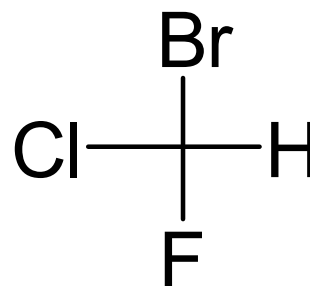


Configuration Images

- There are **two ways** to show a configuration for one structure: “**Wedge**” formulas (3D structure) and **Fisher** projection (cross structure)

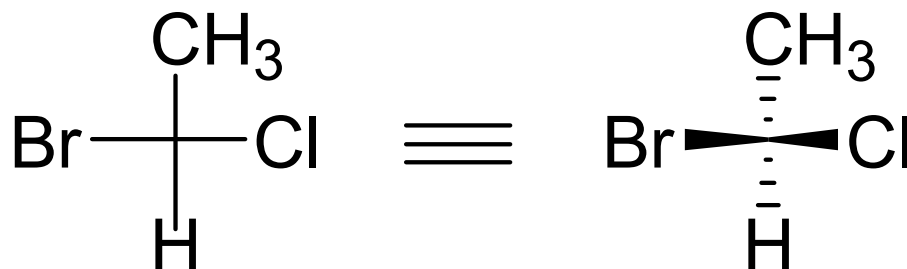


Wedge

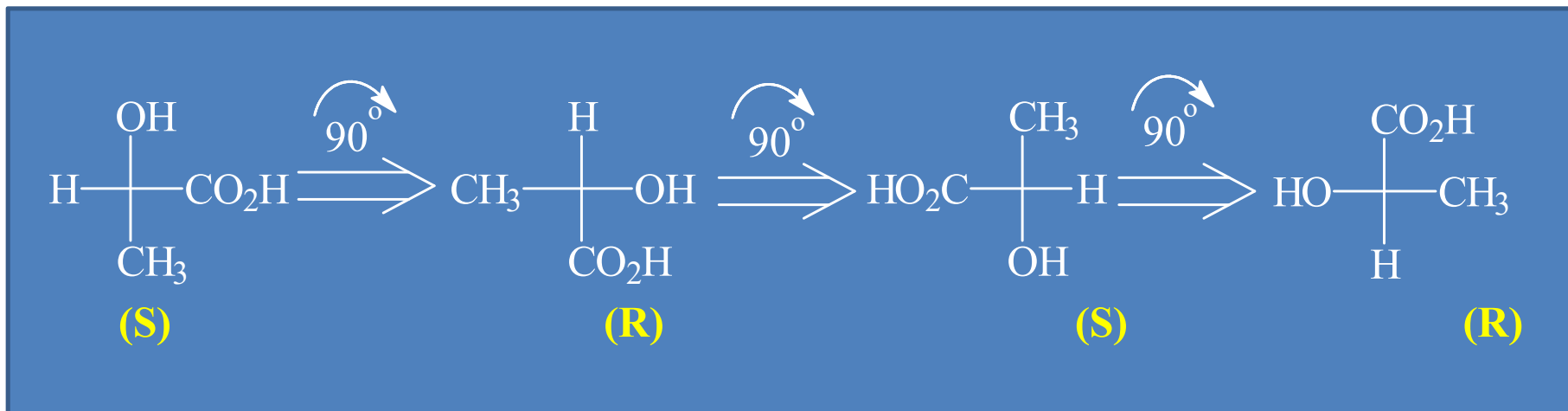
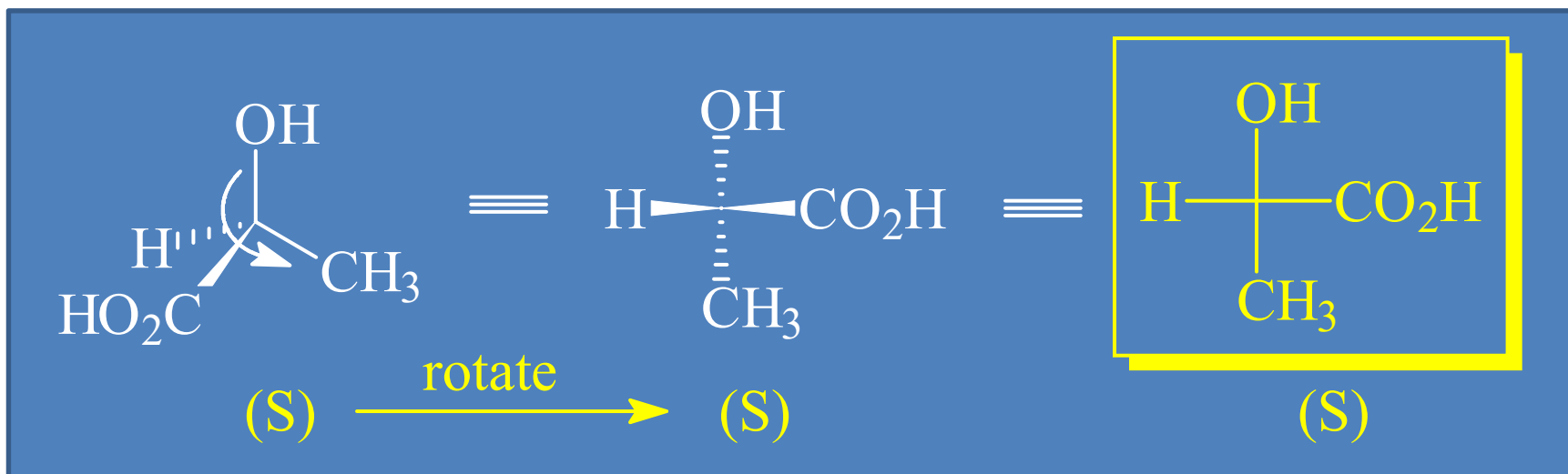


Fisher projection

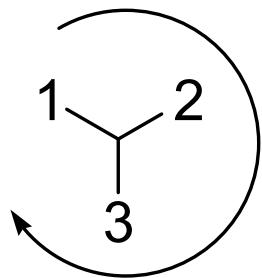
- In the **Fischer** projection, the **horizontal** bonds to the chiral center are always **above** the plane and the **vertical** bonds to the chiral center are **below** the plane. (the horizontals are “hugging you.”)



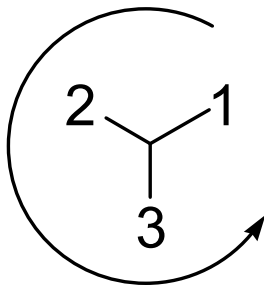
Configurations by using Fisher Projection



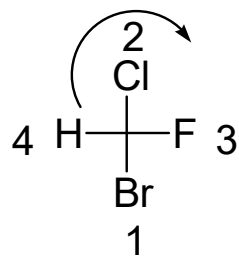
Configurations by using Fisher Projection



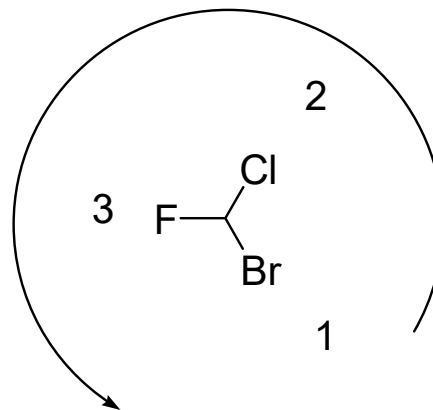
R



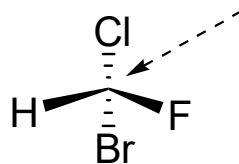
S



rotate #4 away

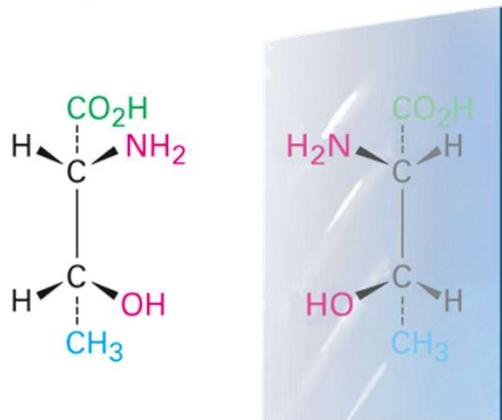


(S)-configuration

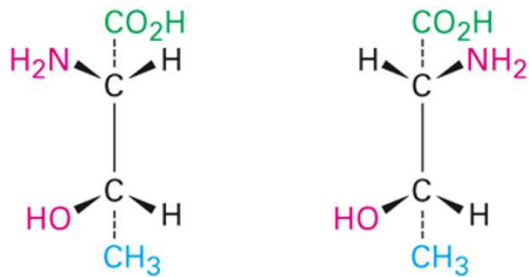


Diastereomers

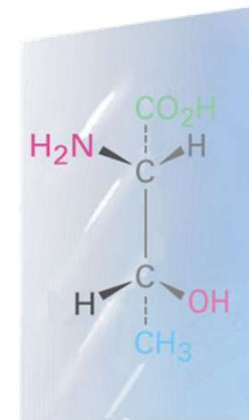
- Molecules with **more than one chirality** center usually have mirror image stereoisomers that are **enantiomers**



Enantiomers

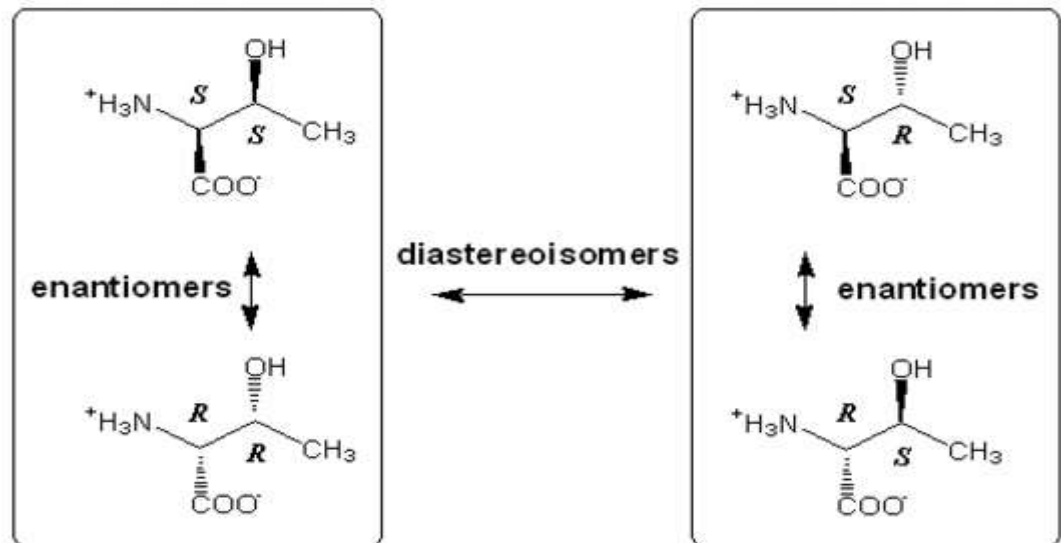


Diastereomers



Enantiomers

- In addition they can have stereoisomeric forms that are not mirror images, called **diastereomers**

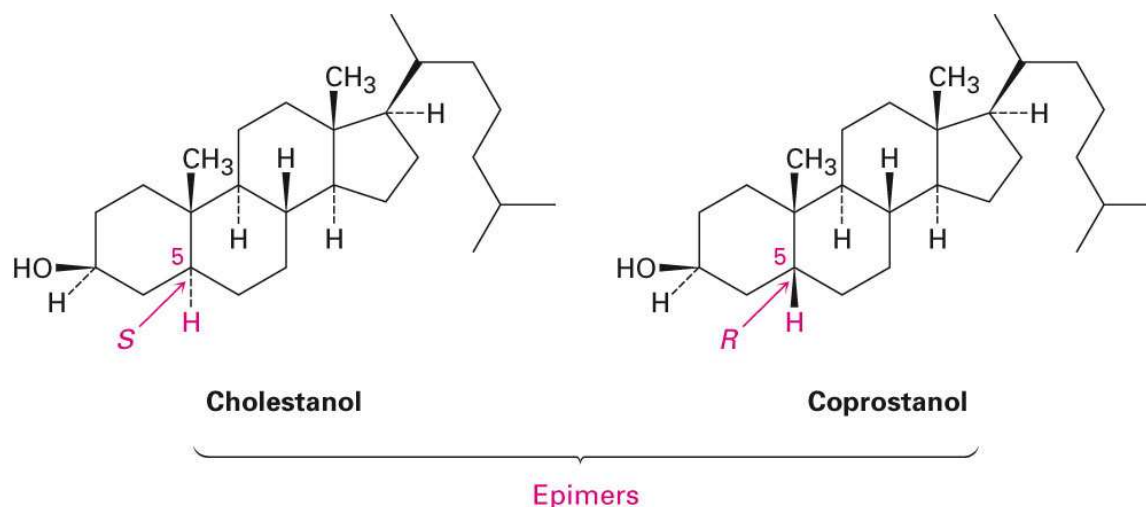


Diastereomers

□ Diastereomers are opposite at some, **but not all** chiral centers

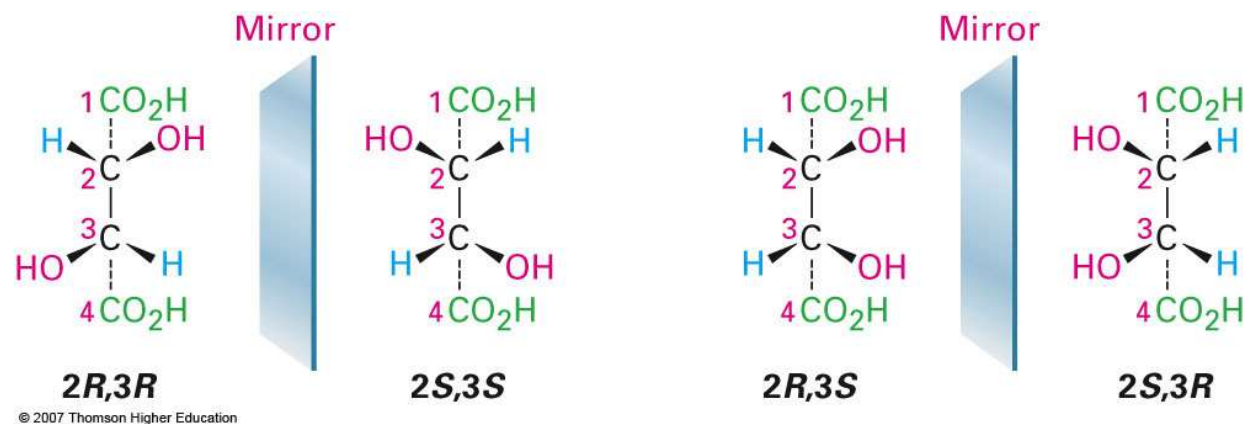
Stereoisomer	Enantiomer	Diastereomer
$2R,3R$	$2S,3S$	$2R,3S$ and $2S,3R$
$2S,3S$	$2R,3R$	$2R,3S$ and $2S,3R$
$2R,3S$	$2S,3R$	$2R,3R$ and $2S,3S$
$2S,3R$	$2R,3S$	$2R,3R$ and $2S,3S$

□ Diastereomers have different physical properties

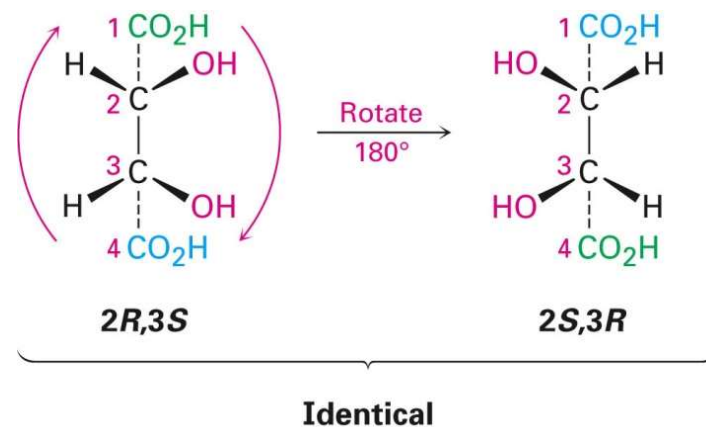
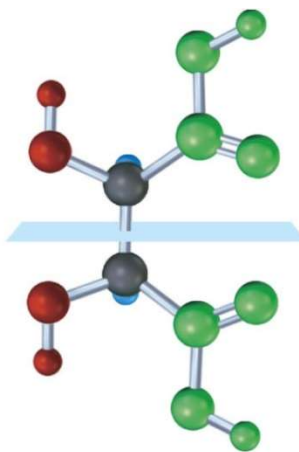
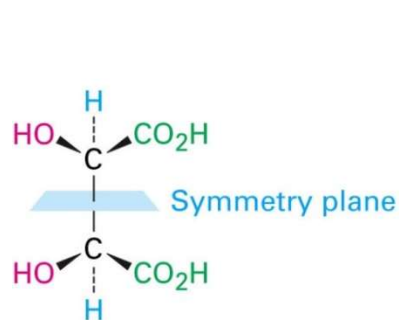


Meso Compounds

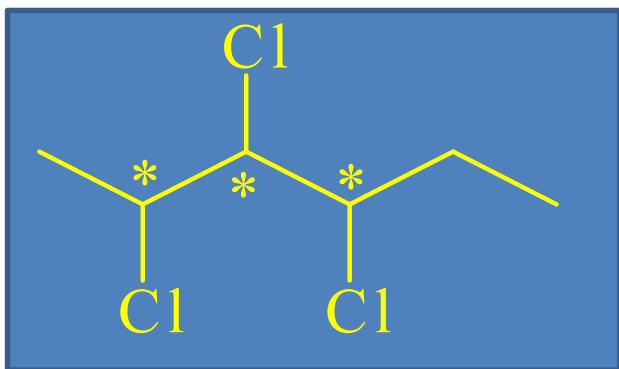
Tartaric acid



- One form is **chiral** and one is **achiral**, but both have two chiral centers
- An achiral compound with chiral centers is called a **meso compound** – it has a plane of symmetry

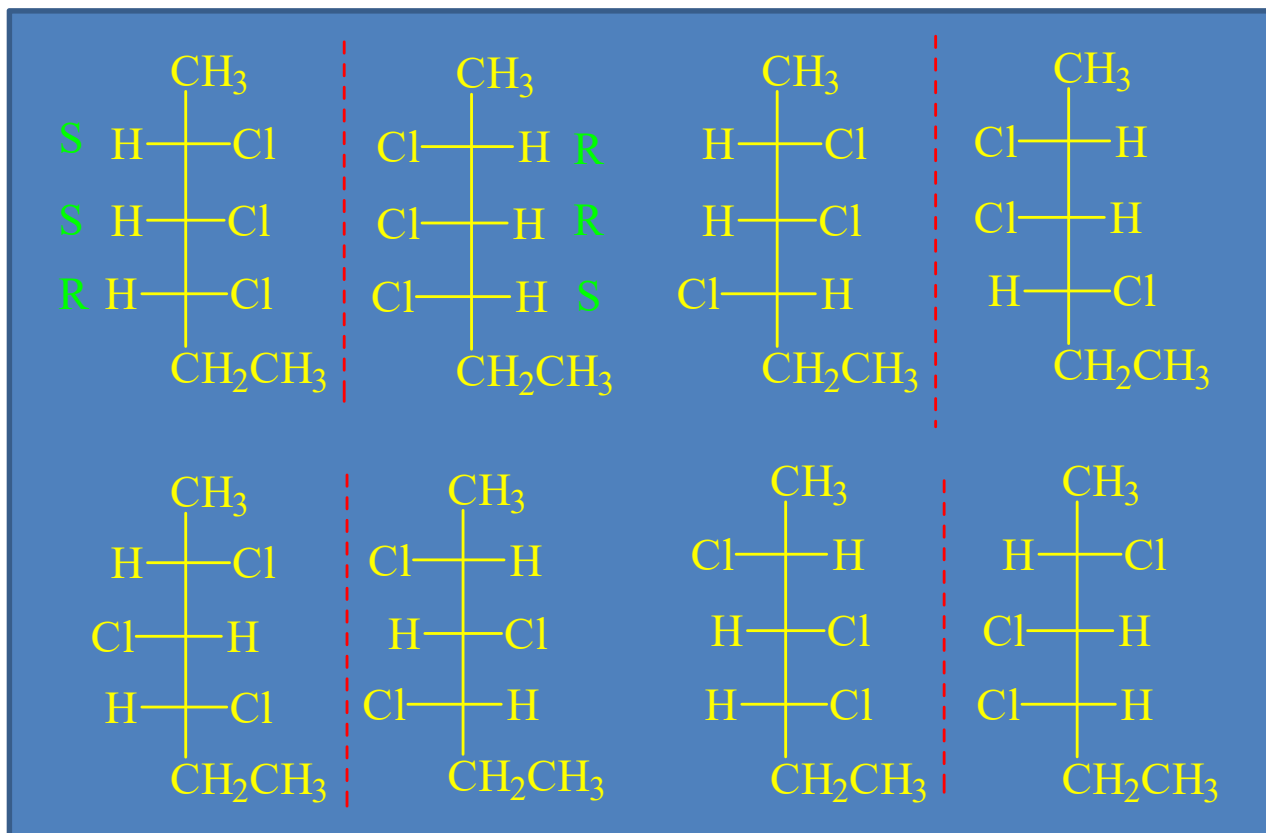


How many maximum stereoisomers?



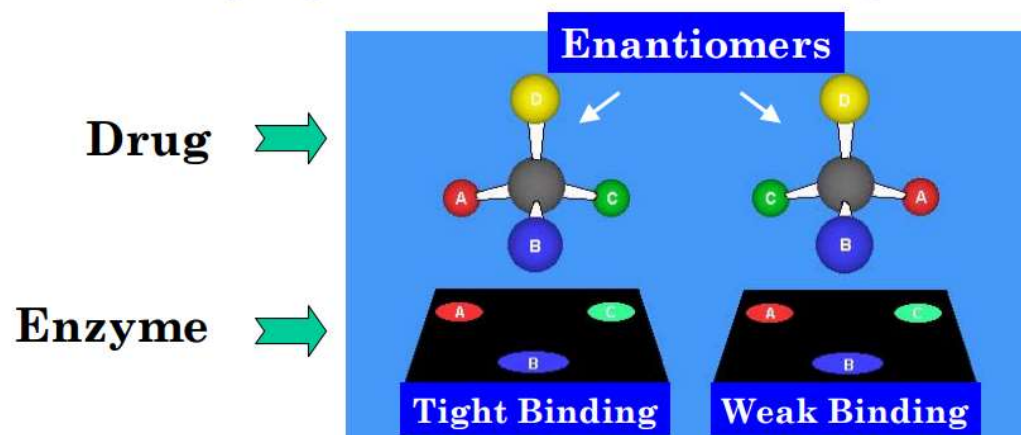
➔ 8 stereoisomers or 2^3

➔ n chiral center numbers
 2^n maximum stereoisomers



Importance of stereoisomers

❑ Stereoisomers are readily distinguished by chiral receptors in nature



❑ Properties of drugs depend on stereochemistry

❑ Think of biological recognition as equivalent to 3-point interaction

