



# STEREOCHEMISTRY

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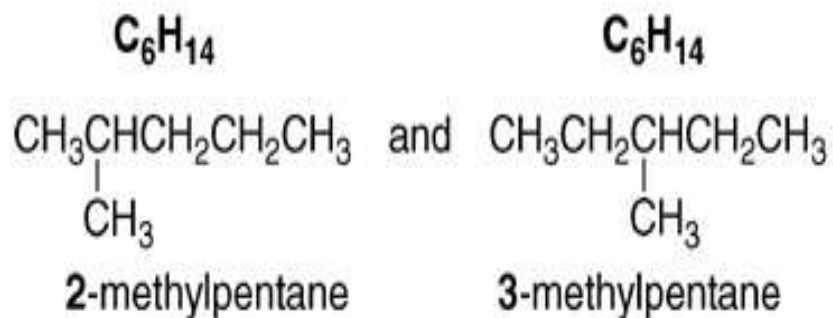
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# STEREOCHEMISTRY

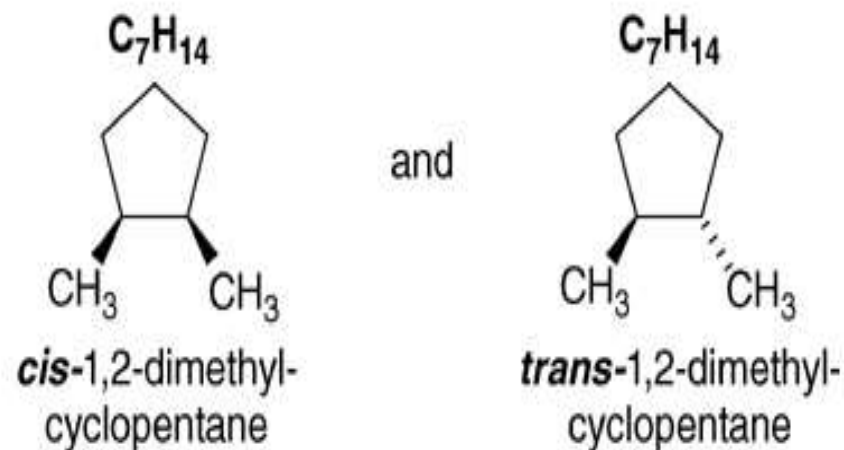
- Isomers are different compounds with the same molecular formula.
- The two major classes of isomers are **constitutional isomers** and **stereoisomers**.
  - ➡ **Constitutional/structural isomers** have different IUPAC names, the same or different functional groups, different physical properties and different chemical properties.
  - ➡ **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.

## A comparison of constitutional isomers and stereoisomers.....



same molecular formula  
different names

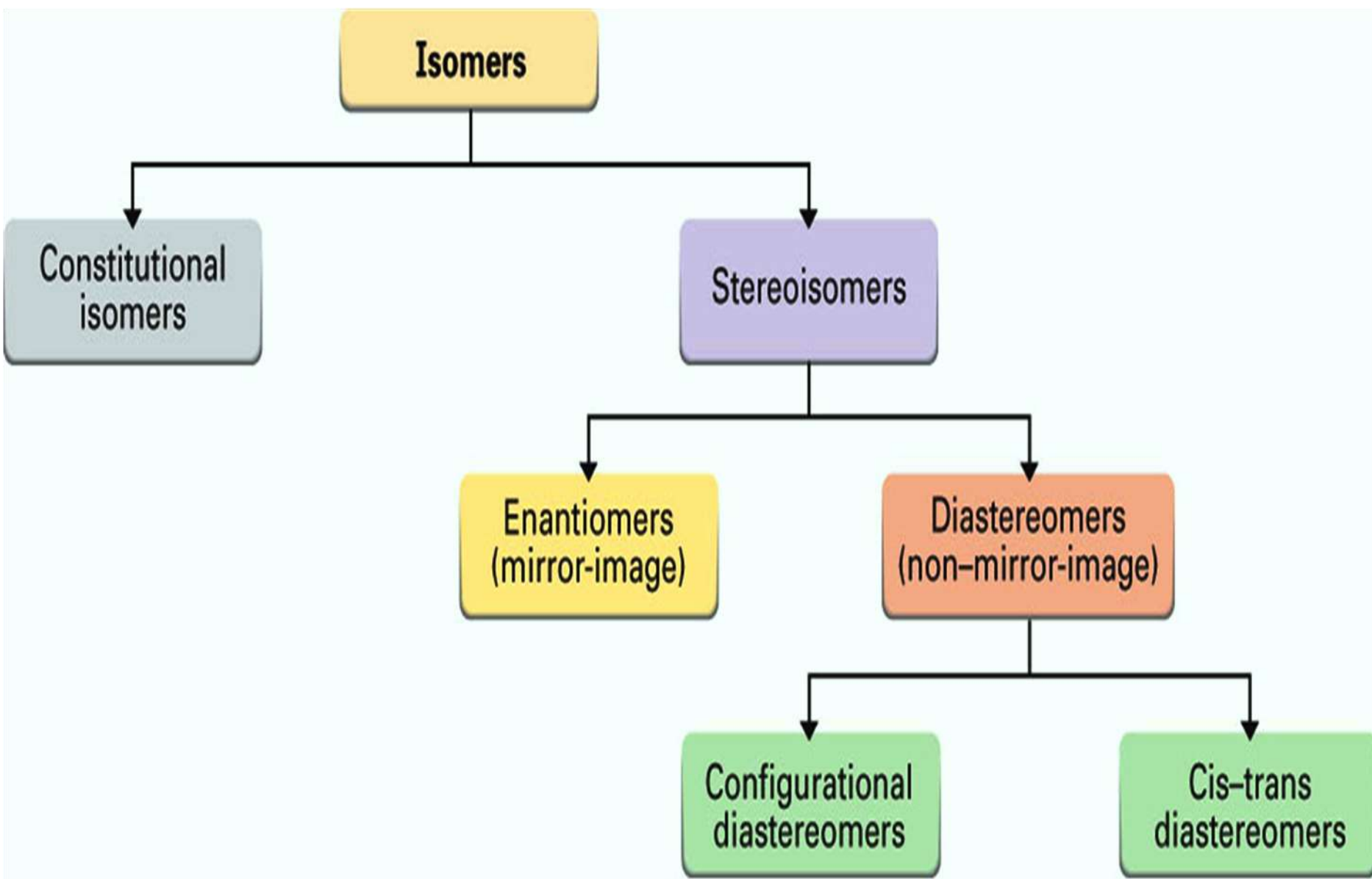
**constitutional isomers**



same molecular formula  
same name except for the **prefix**

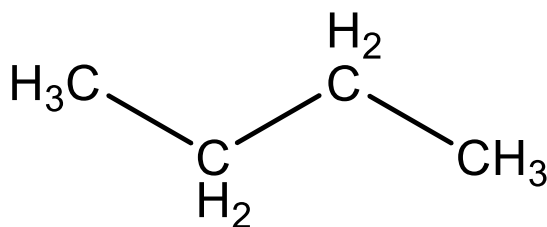
**stereoisomers**

## Classification of Isomers:



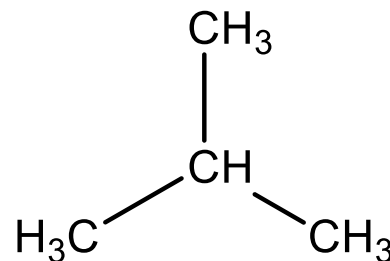
# Constitutional Isomers

Constitutional isomers are isomers which have the same molecular formula but differ in the way their atoms are connected.



butane

Chemical Formula: C<sub>4</sub>H<sub>10</sub>



2-methylpropane

Chemical Formula: C<sub>4</sub>H<sub>10</sub>

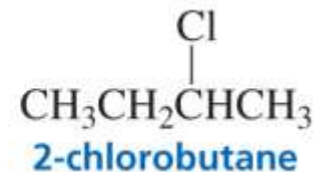
constitutional isomers



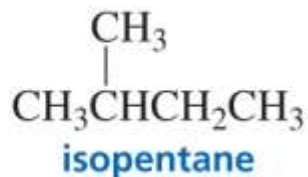
and



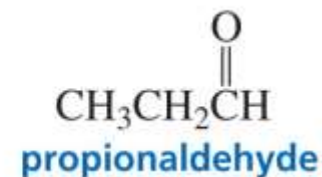
and



and



and



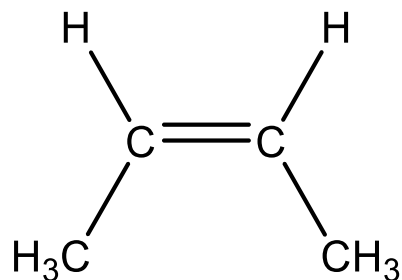
## GEOMETRICAL ISOMERS

The  $\pi$ -bond in an alkene does not permit rotation, thus all of the atoms attached directly to the alkene lie in a plane.

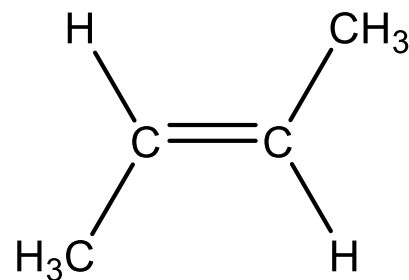
Groups attached to the alkene could be positioned on the same side of the alkene (or) on opposite sides of the alkene. Such compounds are different in chemical and physical properties as well as in their geometry, and are called geometrical isomers.

**Ex:**

In 2-butene the methyl groups can be located on the same side or on the opposite side of the double bond, giving rise to two geometrical isomers.



*cis*-2-butene



*trans*-2-butene

The isomer with the groups on the same side is called the **Cis isomer**, while the isomer with the groups located on opposite sides is called the **Trans isomer**.

**Trans isomers of compounds are usually more stable than Cis isomers.**

Geometric (Cis and Trans) Isomers result from **restriction rotation**.

### Compounds with double bonds:

*Cis* isomer – have same substituents on the same side of the double bond (*Z-zusammen (together)* with more complex molecules having high priority groups on the same side).

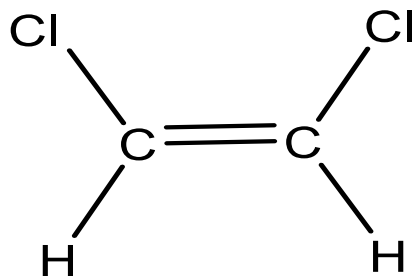
*Trans* isomer – have the same substituents on the opposite side of the double bond (*E - entgegen (opposite)* with more complex molecules having high priority groups on opposite sides).

### Compounds with bonds in a ring:

*Cis* isomer – have the same substituents on the same side of the ring.

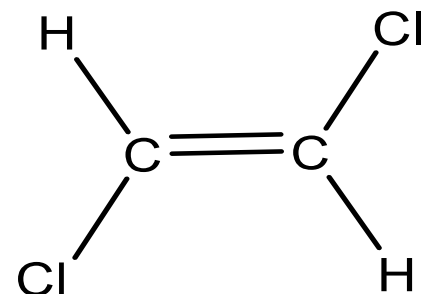
*Trans* isomer - have the same substituents on the opposite side of the ring.

# Cis-trans (Geometric) isomerism in Alkenes



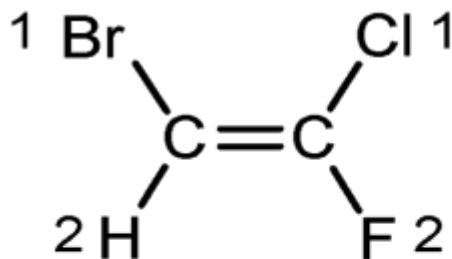
*cis*-1,2-dichloroethene

(*Z*)-1,2-dichloroethene



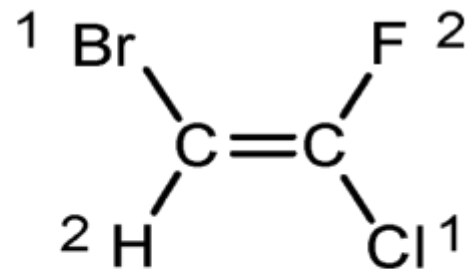
*trans*-1,2-dichloroethene

(*E*)-1,2-dichloroethene



groups with higher priority  
on the same side

**Z-isomer**

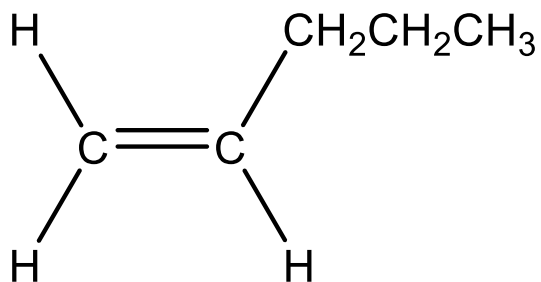


groups with higher priority  
on opposite side

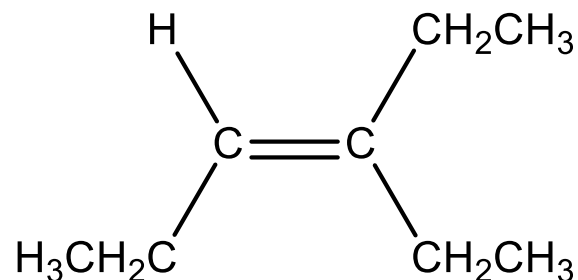
**E-isomer**



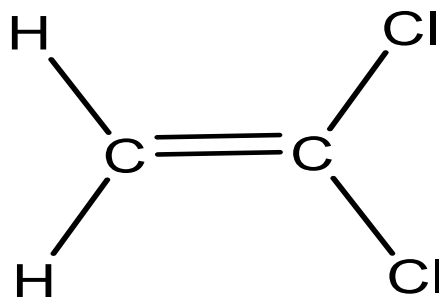
\*If one of the two carbon atoms of the double bond has **two identical substituents**, there are **no cis-trans isomers** for that molecule



1-pentene



3-ethyl-3-hexene

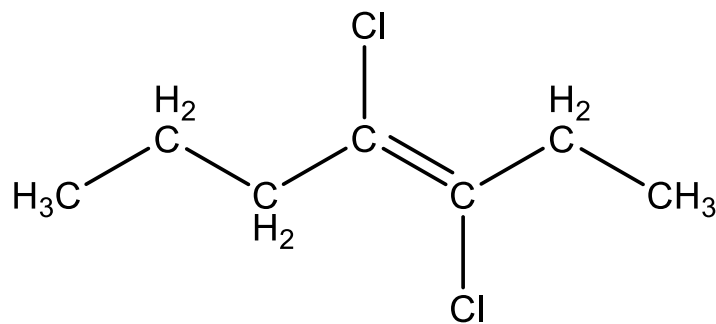


1,1-dichloroethene

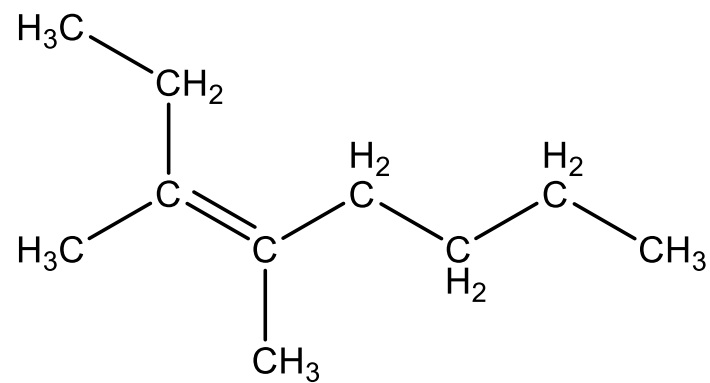
# Identifying cis and trans isomers of Alkenes

Example:

Name the following geometric isomers.



*trans*-3,4-dichloro-3-heptene



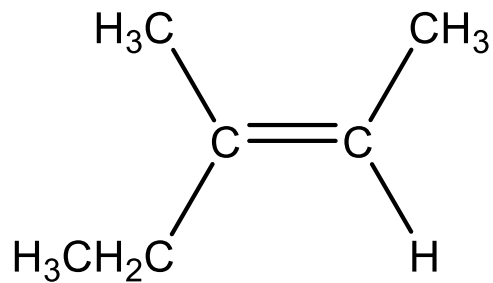
*cis*-3,4-dimethyl-3-octene

## Identifying Geometric Isomers

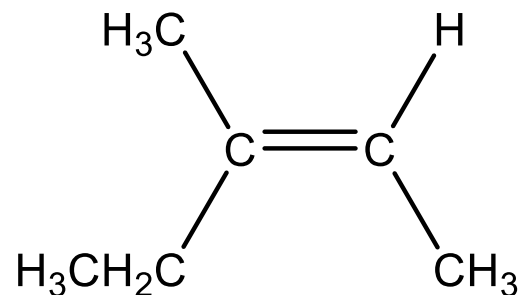
Example:3

Determine whether each of the following molecules can exist as cis-trans isomers:

(1) 3-methyl-2-pentene



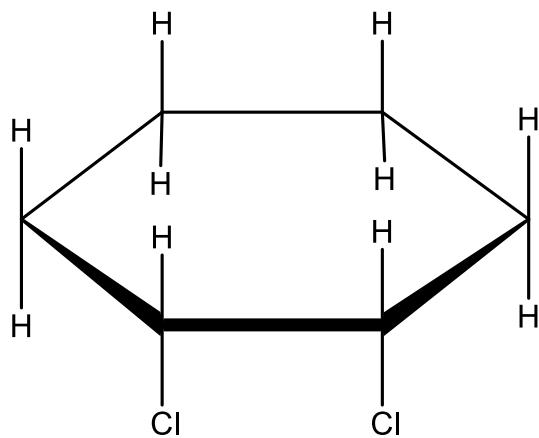
*cis*-3-methyl-2-pentene



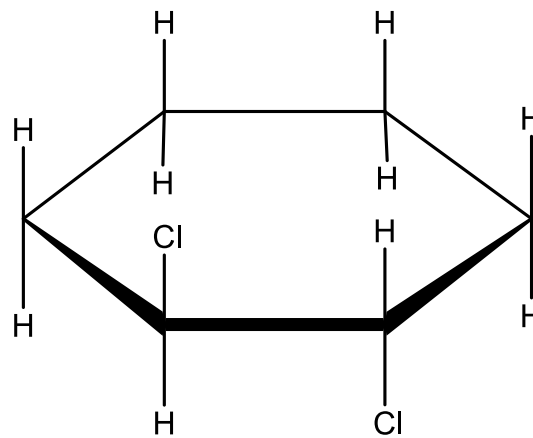
*trans*-3-methyl-2-pentene

## Cis-trans (Geometric) isomerism in Cycloalkanes

**Cis-trans isomers** are molecules having the same arrangement of atoms but differ in the spatial orientation of their substituents.



*cis*-1,2-dichlorocyclohexane

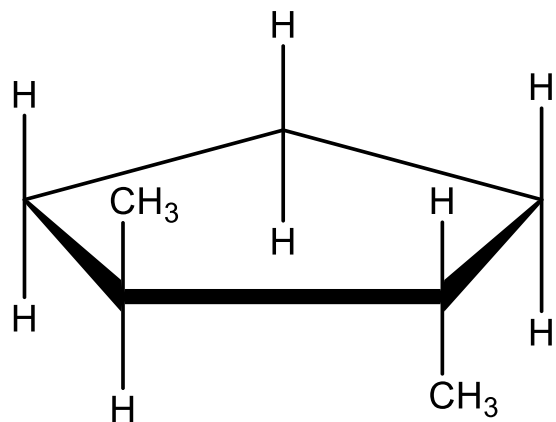


*trans*-1,2-dichlorocyclohexane

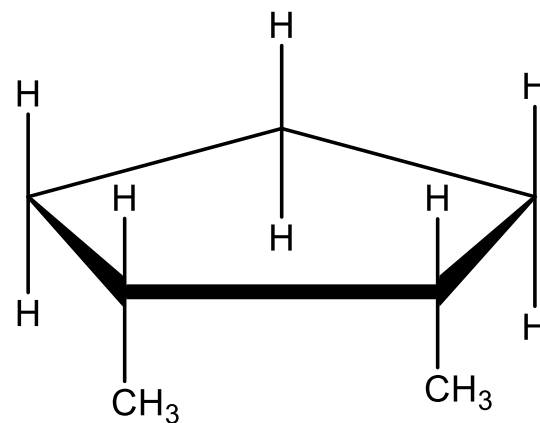
# Naming *cis-trans* Isomers of Substituted Cycloalkanes

## Example:3

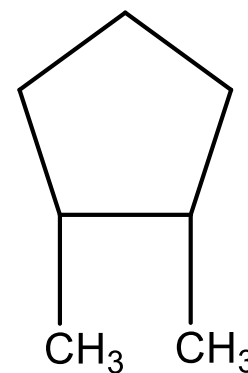
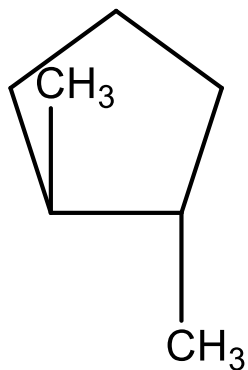
Determine whether the following substituted cycloalkanes are *cis* or *trans* isomers.



*trans*-1,2-dimethylcyclopentane



*cis*-1,2-dimethylcyclopentane

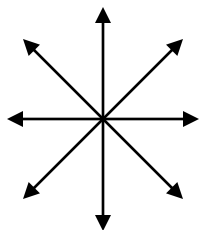


## OPTICAL ACTIVITY:

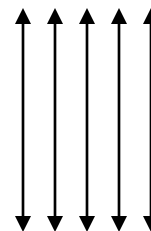
**Optical activity** is the ability of a Chiral molecule to rotate the plane of plane-polarised light, measured using a **polarimeter**.

## PLANE POLARIZED LIGHT:

light that has been passed through a nicol prism or other polarizing medium so that all of the vibrations are in the same plane.



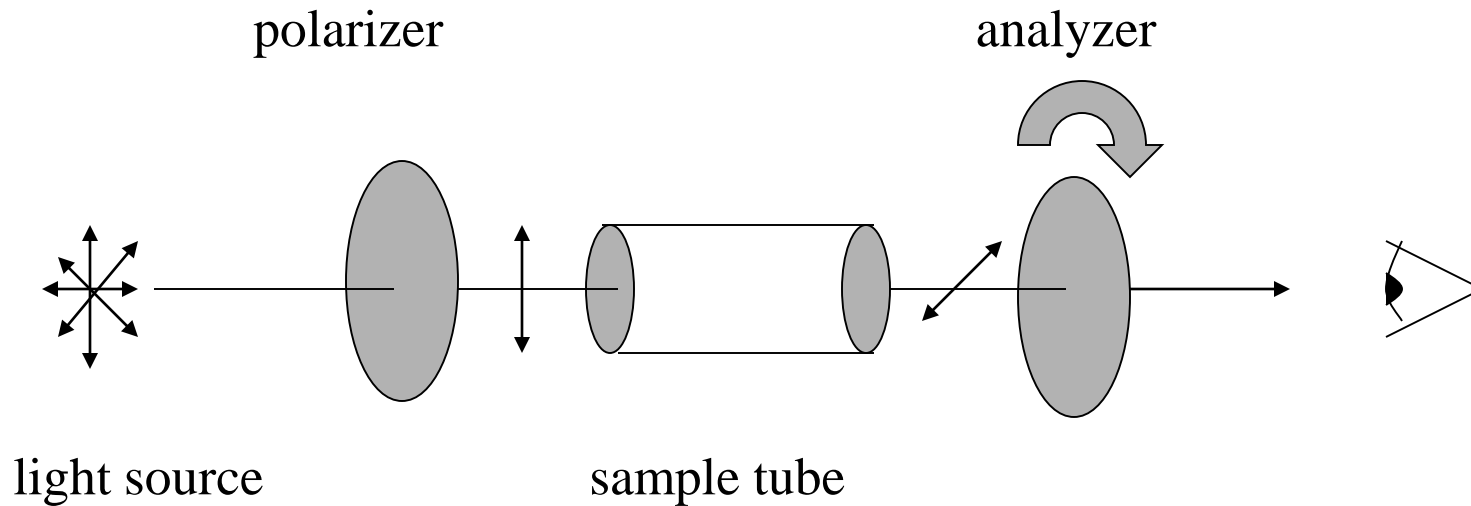
non-polarized



polarized

**Polarimeter** – an instrument used to measure optical activity.

A simple polarimeter consists of a light source, polarizing lens, sample tube and analyzing lens.



## Dextrorotatory (+):

An optically active compound that rotates plane polarized light in a clockwise direction.

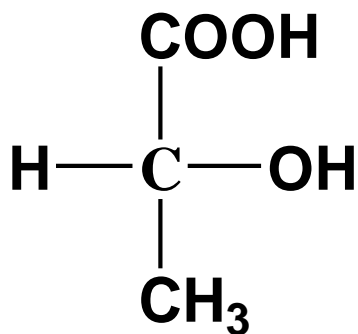
(+) or (*d*) do not confuse with D

## Levorotatory (-):

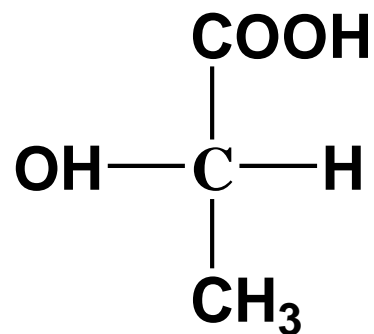
An optically active compound that rotates plane polarized light in a counterclockwise direction.

(-) or (*l*) do not confuse with L

The angle of rotation of plane polarized light by an optically active substance is proportional to the number of atoms in the path of the light.



(+)/*d* - Lactic Acid



(-)/*l* - Lactic Acid



## SPECIFIC ROTATION:

The angle of rotation of plane polarized light by a 1.00 gram per cm<sup>-3</sup> sample in a 1 dm tube.

$[\alpha]_D$  (D = sodium lamp,  $\lambda = 589 \text{ m}\mu$ ).

$$[\alpha]_D = \frac{\alpha}{l \times d}$$

where  $\alpha$  = observed rotation

$l$  = length (dm)

$d$  = concentration (g/cc)

(+)-alanine  $[\alpha]_D = +8.5$

(-)-lactic acid  $[\alpha]_D = -3.8$

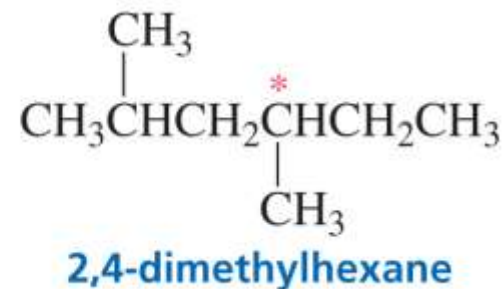
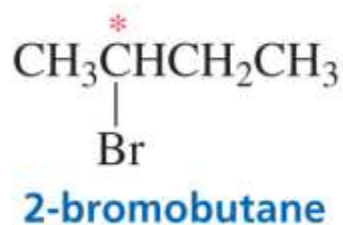
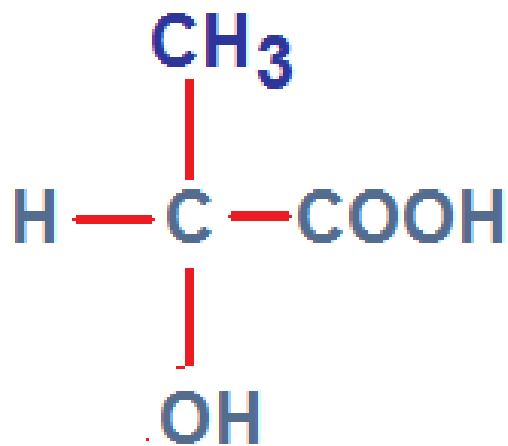
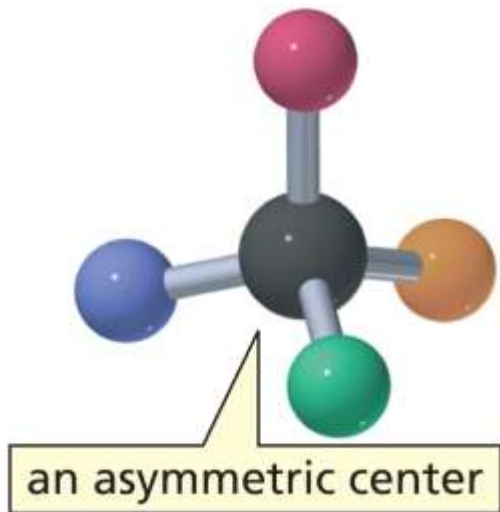
Specific Rotation depends on the nature of substance, wavelength of light used, concentration of the solution, thickness of the layer, nature of the solvent and temperature at which experiment is conducted.

# Assymmetric Center

Chirality is not reserved just for objects - *molecules can be chiral*

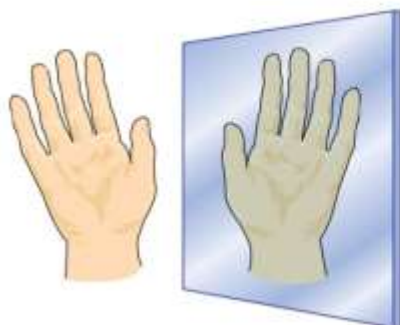
**Chiral molecules** - generally molecules containing an assymmetric center

**Assymmetric (chiral) center** - tetrahedral atom bonded to four different groups - indicated with an *asterisk* (\*)

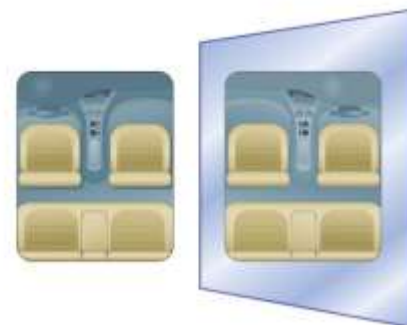


# Chirality

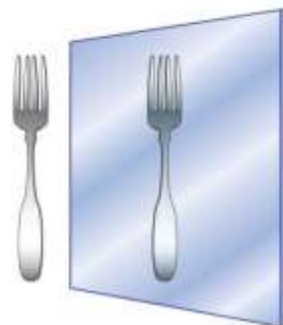
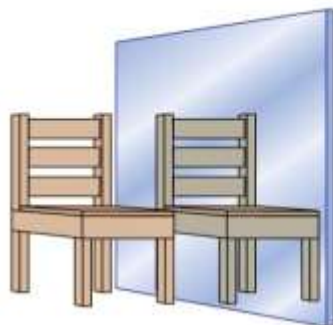
## chiral objects



right hand      left hand



## achiral objects



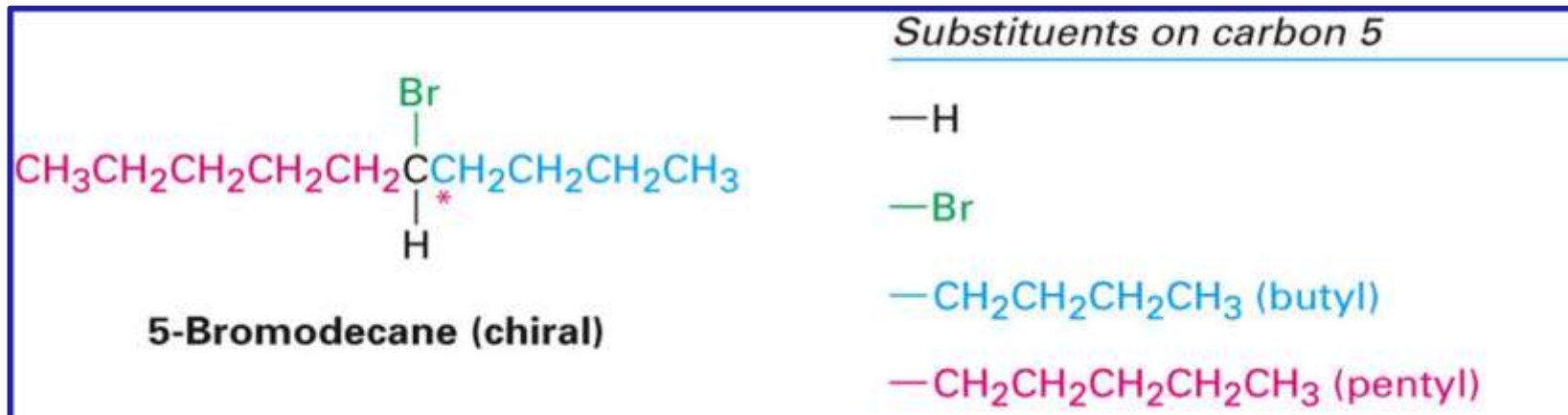
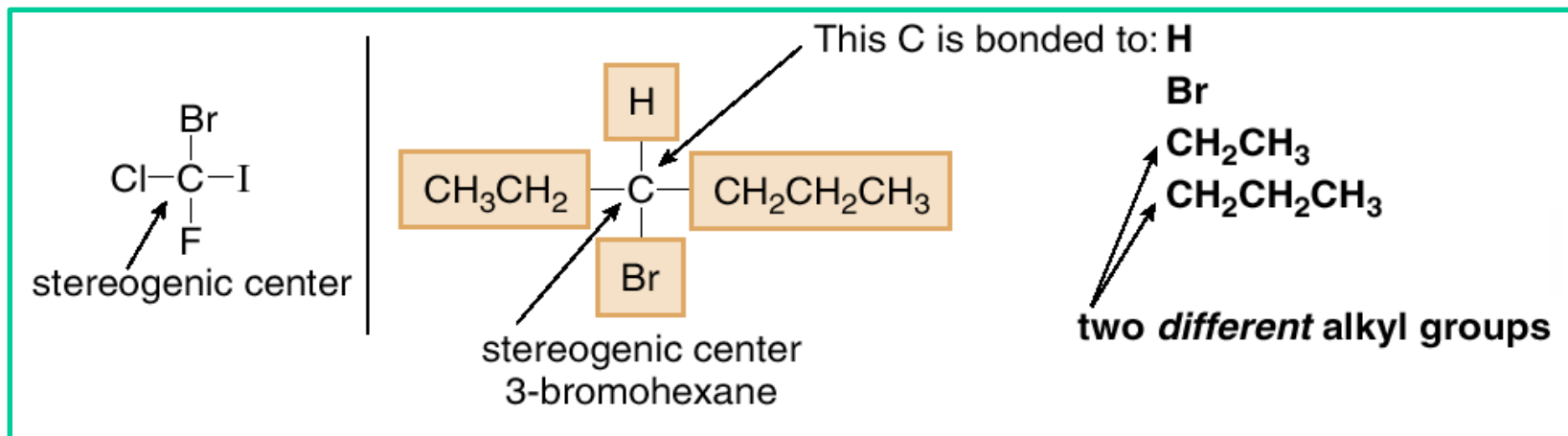
**Chiral objects are objects with left-handed and right-handed forms**

**Achiral objects - objects that have superimposable mirror images**

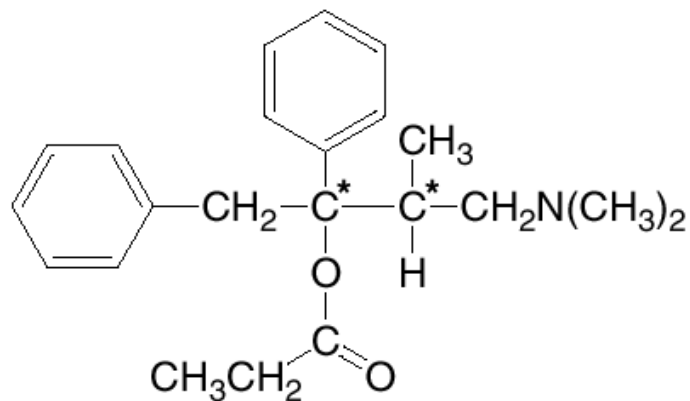
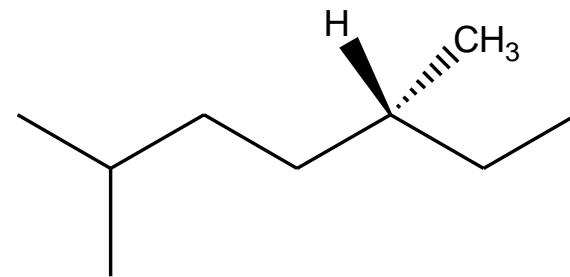
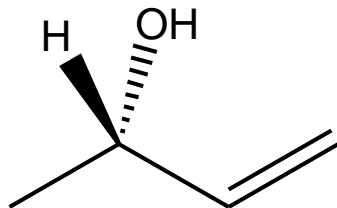
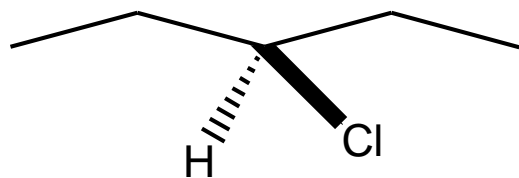
**Nonsuperimposable mirror images - a mirror image that is not the same as the image itself - *chiral objects have nonsuperimposable mirror images***

# CHIRAL CENTERS

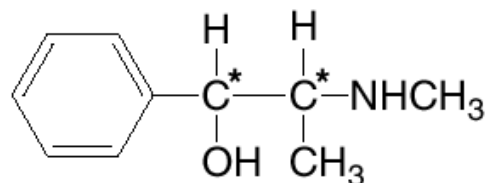
- A point in a molecule where four different groups (or atoms) are attached to carbon is called a **Chiral center**.
- If two groups are the same, then there is only one way
- A Chiral molecule usually has at least one Chiral center.



Label the stereogenic centers in each molecule and decide if it is chiral....?

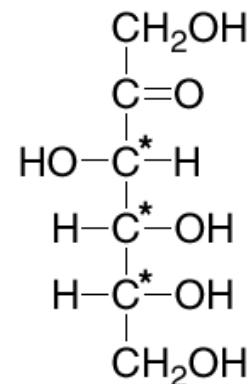


propoxyphene  
Trade name: Darvon  
(analgesic)



ephedrine  
(bronchodilator, decongestant)

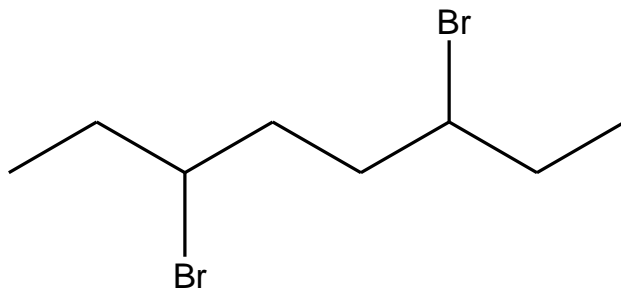
[\* = stereogenic center]



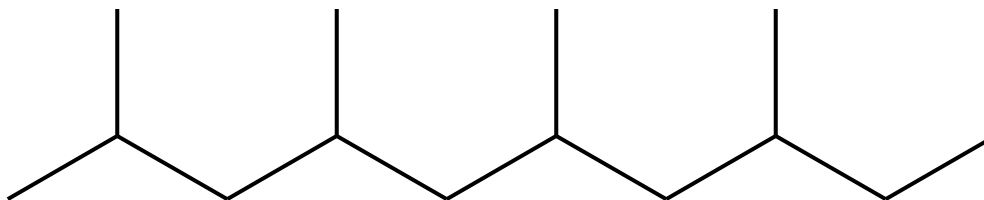
fructose  
(a simple sugar)

**How many stereogenic centers does each molecule have?**

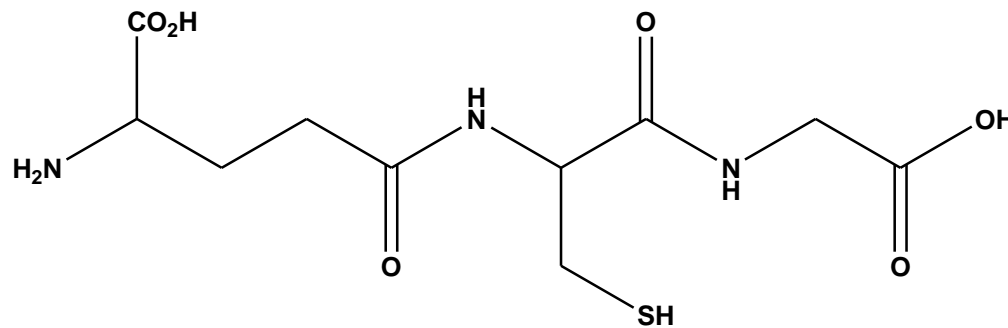
**A)**

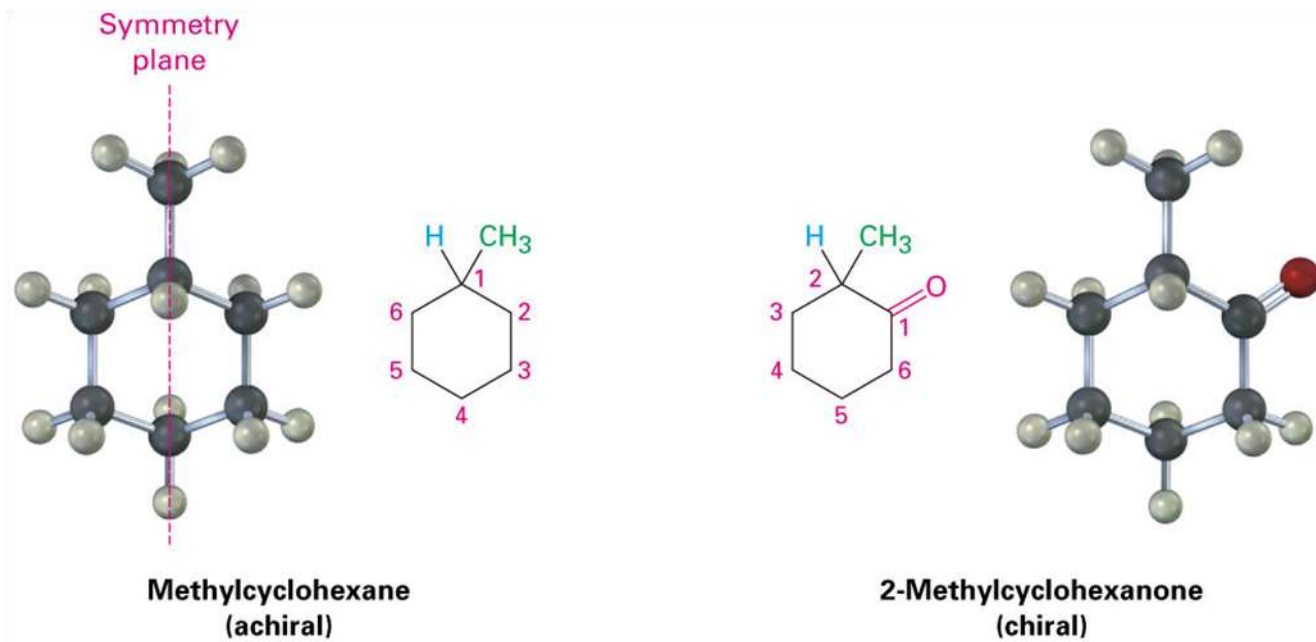
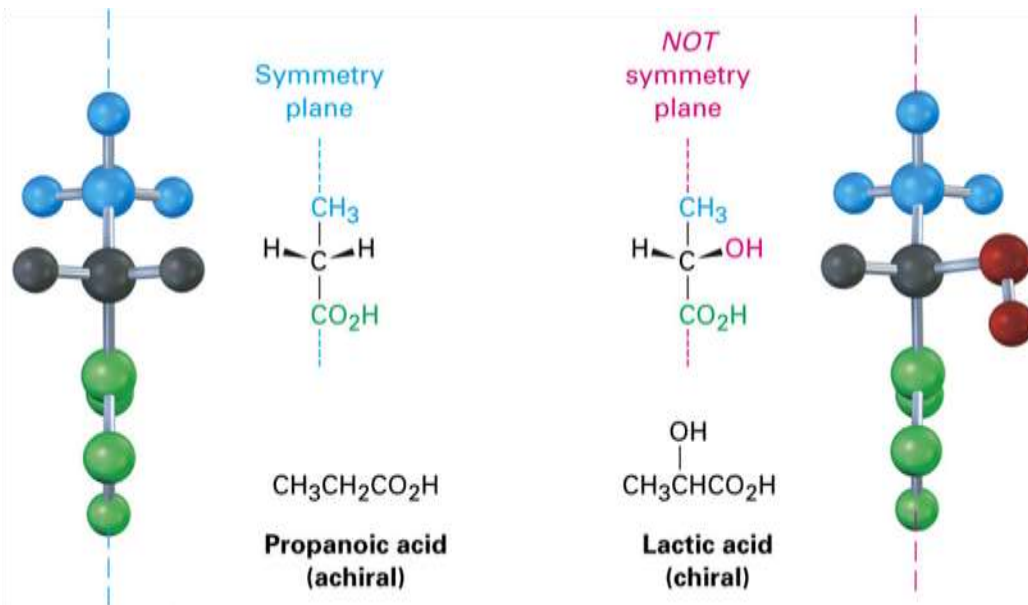


**B)**



**C)**





# CONFIGURATION

The arrangement of atoms that characterizes a particular stereoisomer is called its Configuration.

The following methods are used to assign configuration.

**A. Absolute configuration [R and S system]**

**B. Relative configuration [D and L system]**



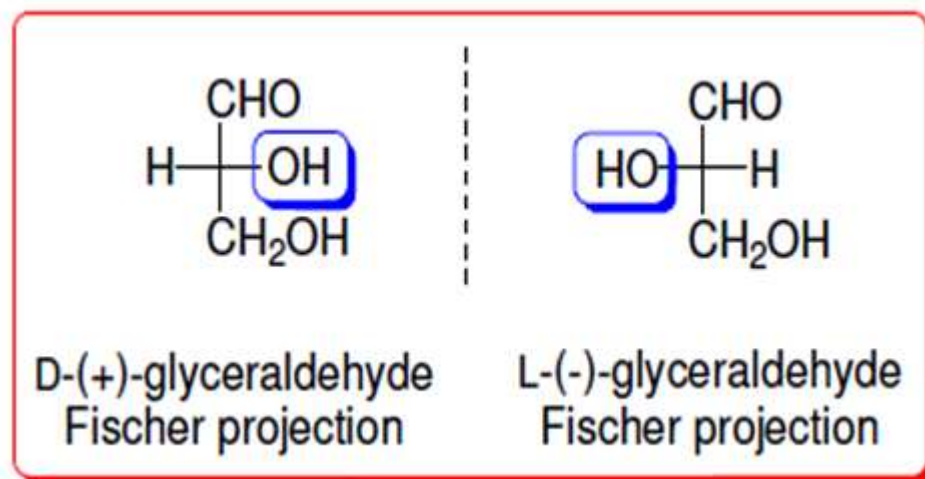
## Fischer Projections and the D/L Notation:

- ✓ The first system for doing this was developed by **Fischer and Rosanoff** around **1900**.
- ✓ **Fischer first** developed a method for drawing carbohydrates in two-dimensions, and a convention with respect to orientation, so as to indicate their three dimensional structures, so-called *Fischer projections*.
- ✓ Fischer and Rosanoff then devised a notation for designating the configurations of stereogenic centres, depicted in Fischer projections, as either **D or L**.

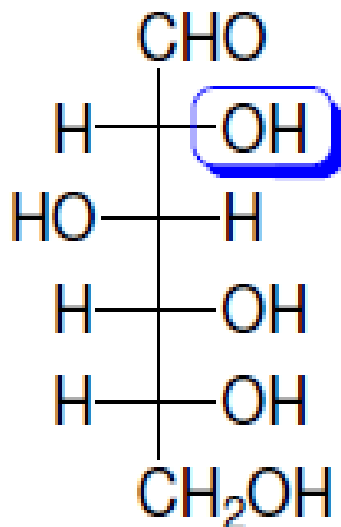
The symbols **D and L** *DO NOT* relate to the sign of rotation of an optically active molecule which is designated (+)- (or *d*) and (-)- (or *l*).

**Example:** D (+)-glyceraldehyde was defined as being D because the OH group attached to the C-2 is on the right hand side (RHS) of the molecules when drawn in its correct Fischer projection (in which the CHO group appears at the top).

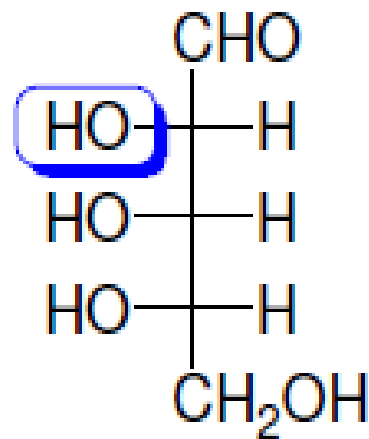
Its enantiomer L (-)-glyceraldehyde was defined as L because the OH group is on the left hand side (LHS).



In carbohydrates, in general, the OH group attached to the penultimate carbon atom in the chain determines the assignment of D or L. Thus (+)-glucose has the D-configuration and (+)-ribose has the L-configuration.

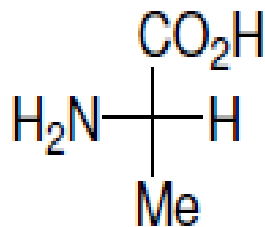


D-(+)-glucose  
Fischer projection

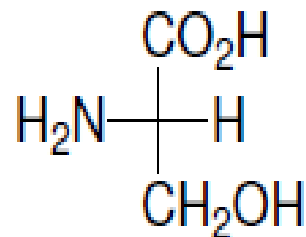


L-(+)-ribose  
Fischer projection

The notation was extended to  $\alpha$ -amino acids : L enantiomers are those in which the  $\text{NH}_2$  group is on the LHS of the Fischer projection in which the carboxyl group appears at the top. Conversely, the D enantiomers are those in which the  $\text{NH}_2$  group is on the RHS. Thus (+)-alanine and (-)-serine are L-amino acids.



L-(+)-alanine  
Fischer projection



L-(-)-serine  
Fischer projection

# Cahn-Ingold-Prelog sequence rules /R-S Notational System(R/S)

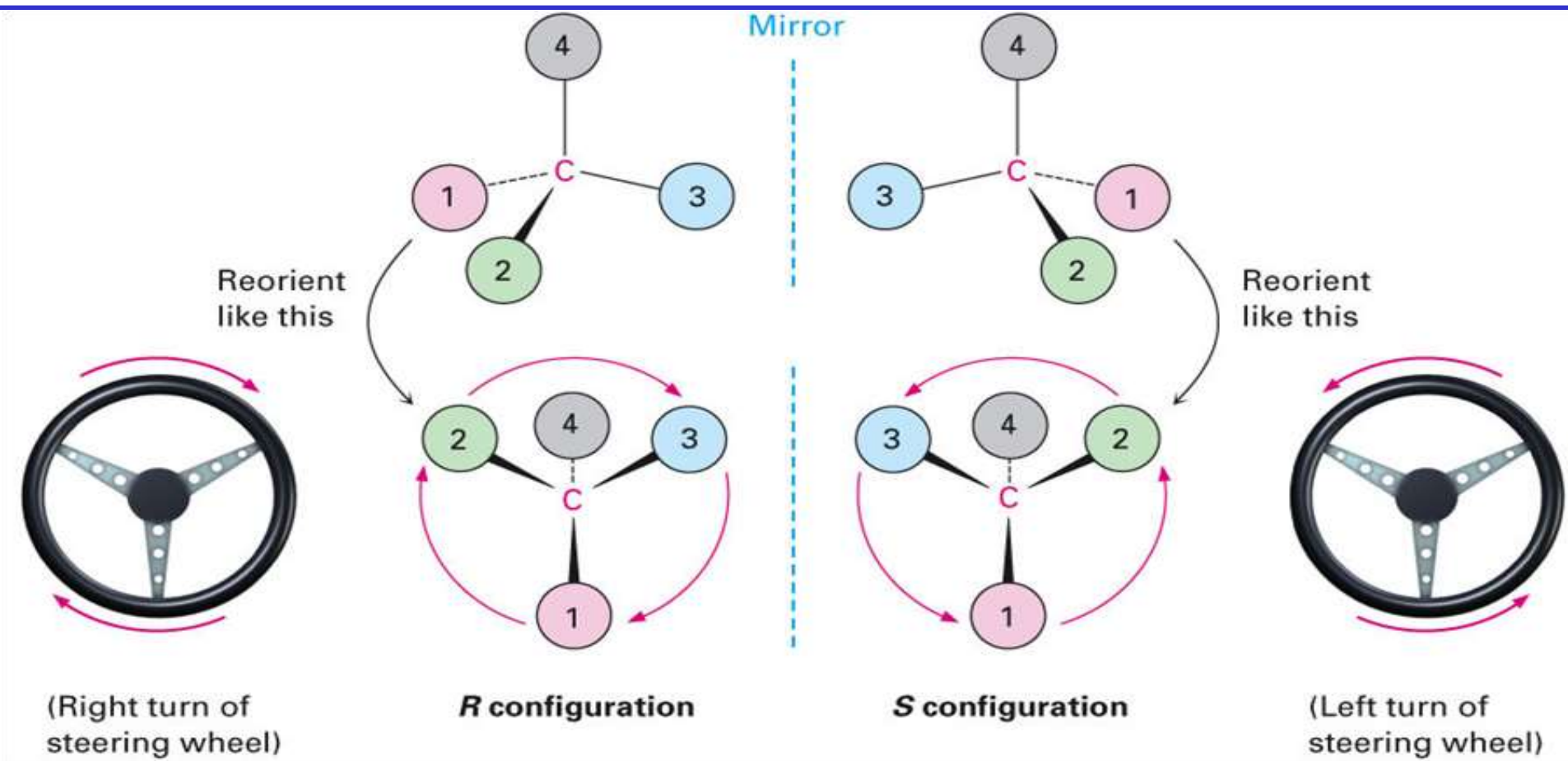
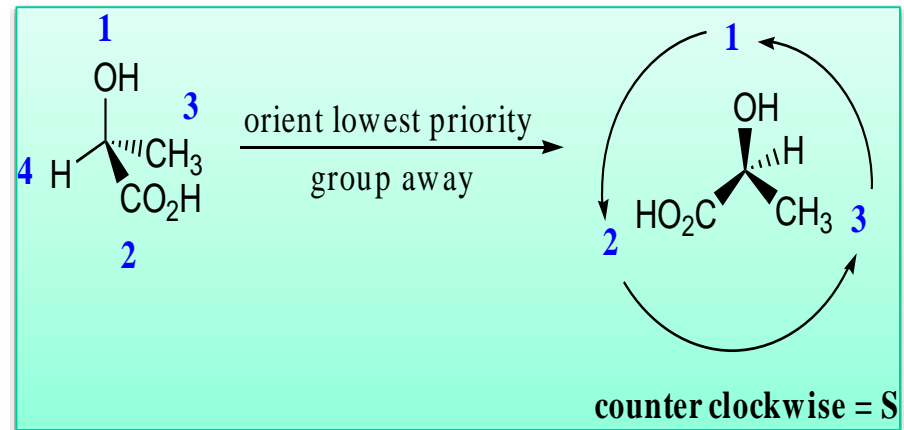
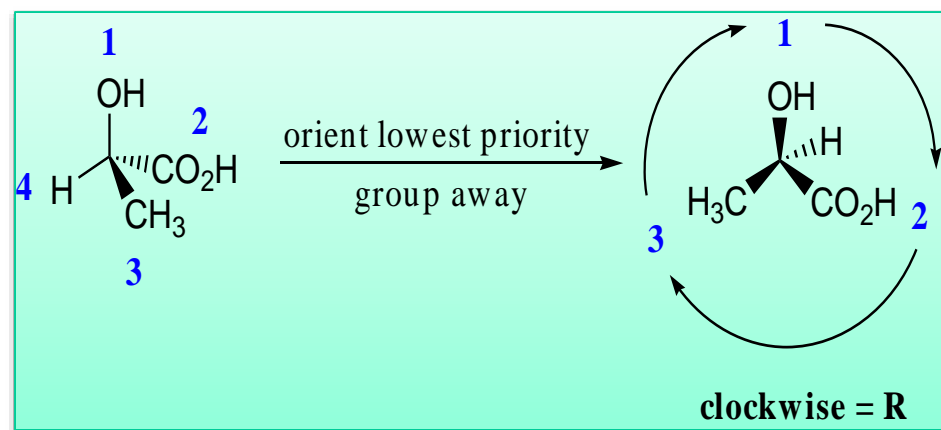
## Assigning the Absolute Configuration

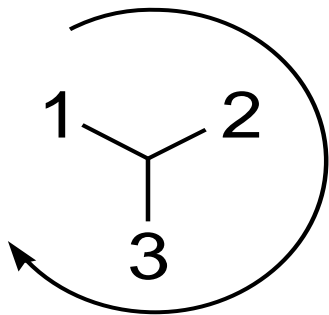
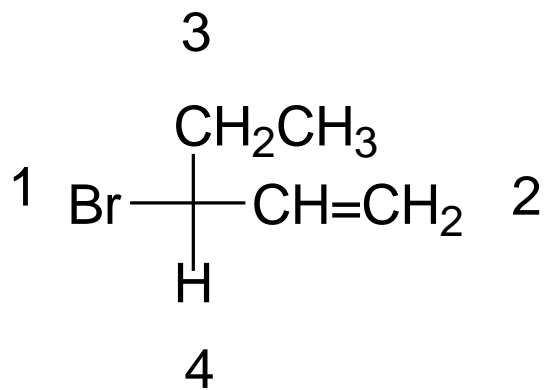
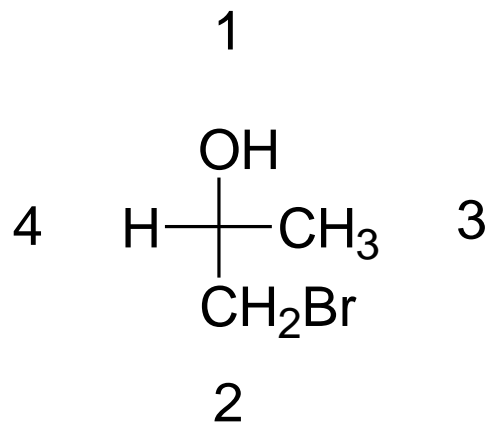
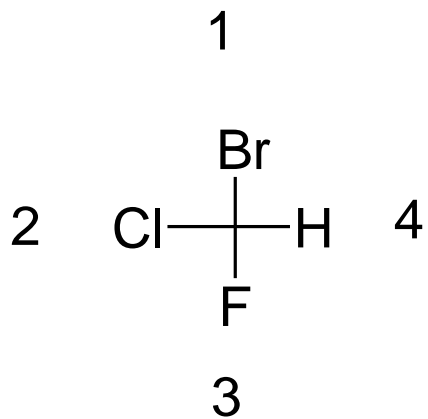
1. Use the Cahn-Ingold-Prelog priority rules to assign priority (one through four) to the four groups on the “chiral” atom.
2. Orient the molecule so that the lowest priority atom is in the back (away from you). Look at the remaining three groups of priority 1-3. If the remaining three groups are arranged so that the priorities 1→2→3 are in a *clockwise* fashion, then assign the chiral center as **R** (“**rectus**” or **right**). If the remaining three groups are arranged 1→2→3 in a *anti-clockwise* manner, then assign the chiral center as **S** (“**sinister**” or **left**).

## Cahn Ingold Prelog (CIP) sequence rules:

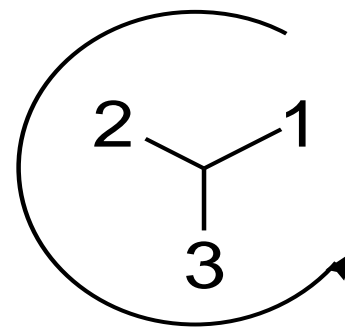
**Sequence rule 1:** The atom attached to the chiral center with the highest atomic number = 1, next = 2, etc.

**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.



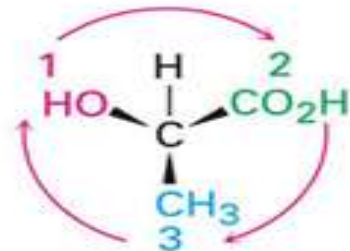
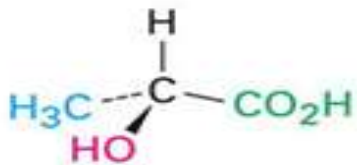
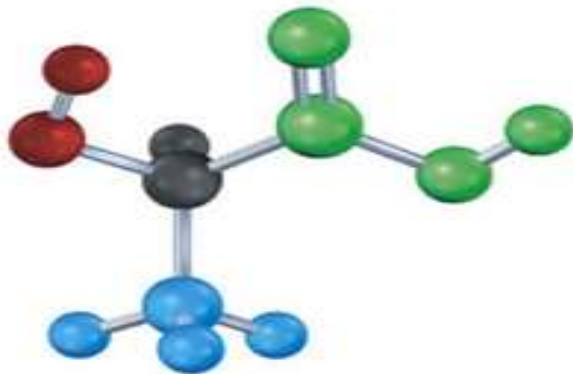


R



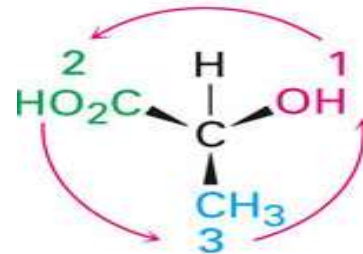
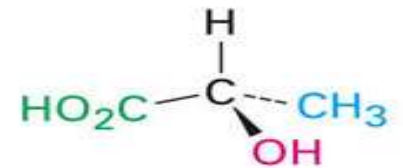
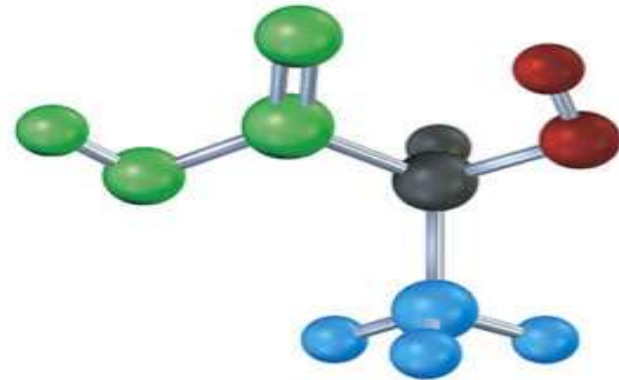
S

(a)



**R configuration**  
(-)-Lactic acid

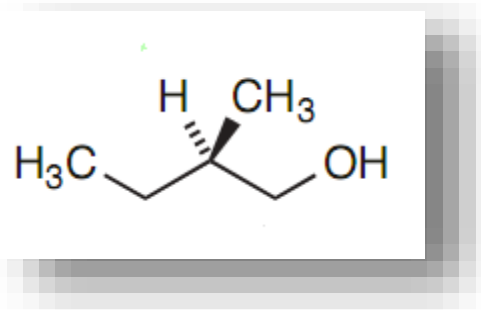
(b)



**S configuration**  
(+)-Lactic acid

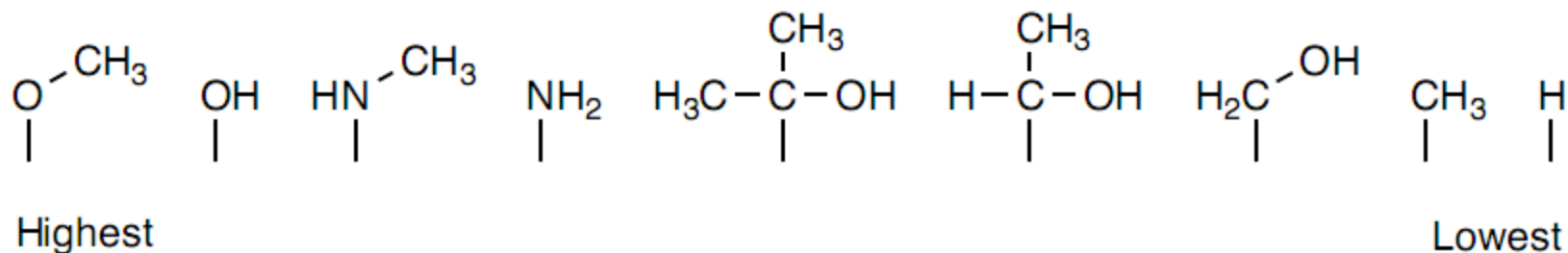


## Assigning Priorities to Groups

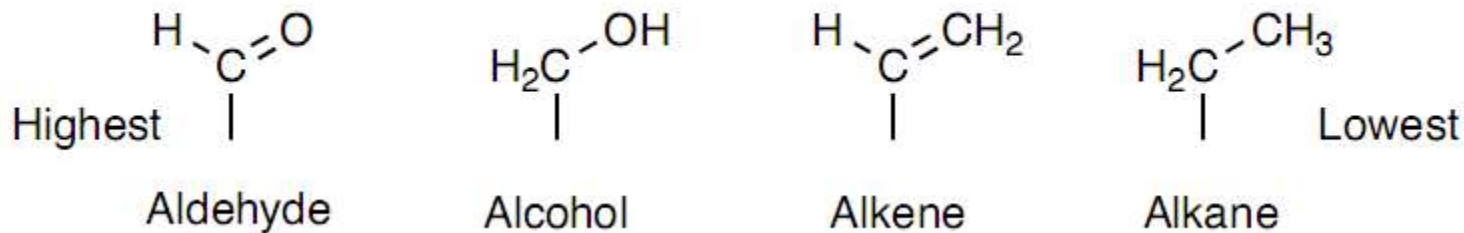


1. Oxygen (from CH<sub>2</sub>OH) = 16
2. Carbon (from CH<sub>2</sub>CH<sub>3</sub>) = attached to carbon
3. Carbon (from CH<sub>3</sub>) = attached to hydrogen
4. Hydrogen = 1

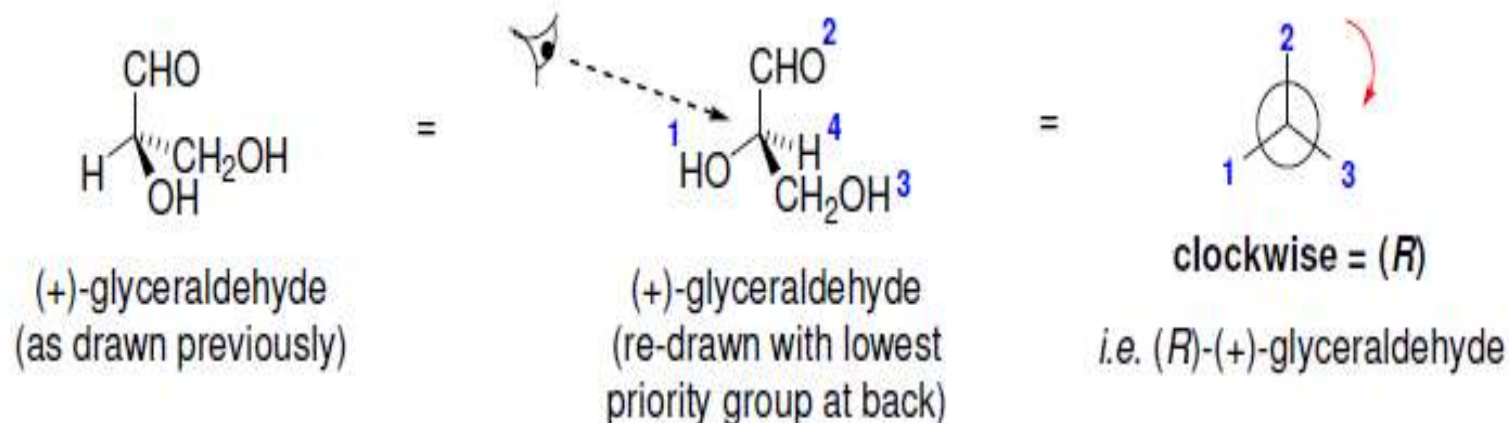
**Figure 4.** Some example groups in order of priority (highest to lowest).



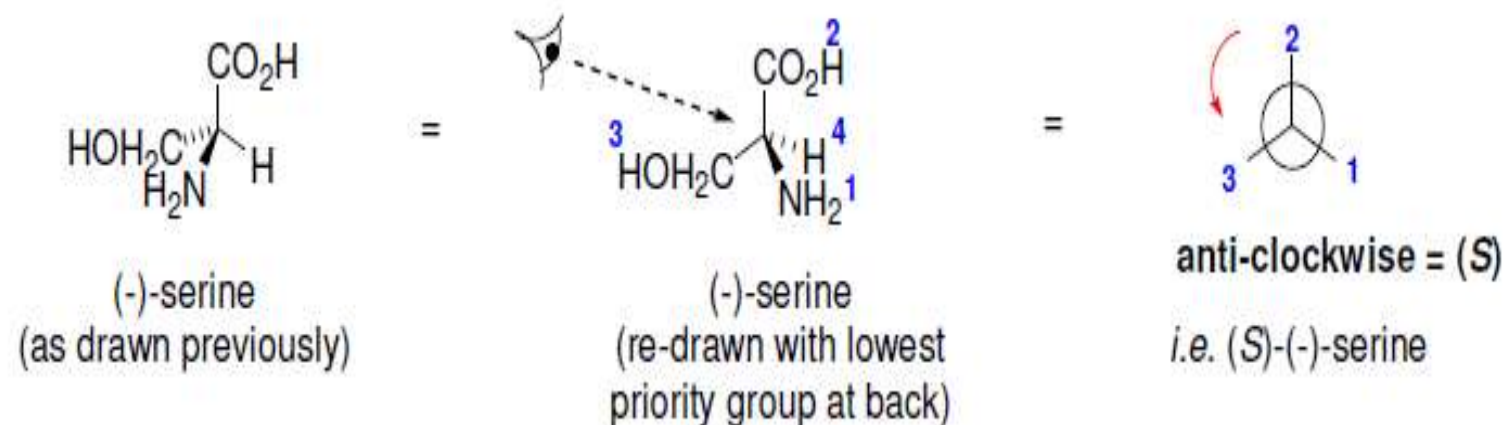
**Figure 5.** Some groups with double bonds



For example, in (+)-glyceraldehyde the order of priority of the groups is  $\text{OH} > \text{CHO} > \text{CH}_2\text{OH} > \text{H}$  and the configuration is (*R*).

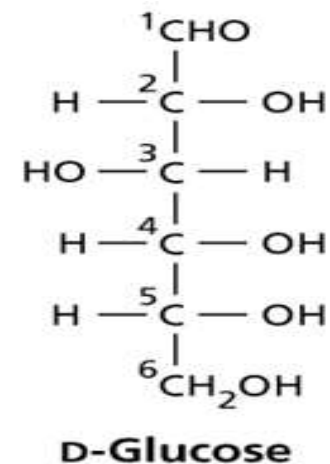
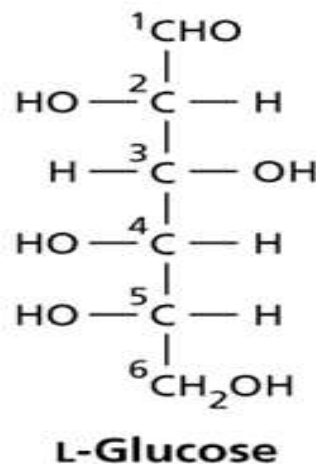
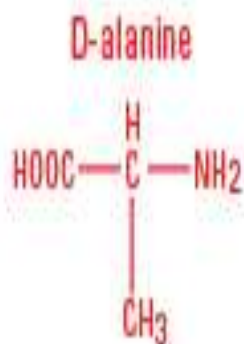
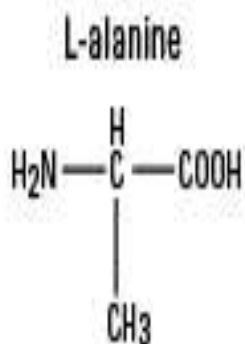


Similarly for (-)-serine the order of priority of the groups is  $\text{NH}_2 > \text{CO}_2\text{H} > \text{CH}_2\text{OH} > \text{H}$  and the configuration is (*S*).



# ENANTIOMERS

- ✓ *Enantiomers are non-superimposable mirror image isomers.*
- ✓ Enantiomers are related to each other much like a right hand is related to a left hand.
- ✓ Enantiomers are said to be *Chiral*.
- ✓ sometimes the terms right-handed and left-handed are used describe compounds with an asymmetric carbon.



## Characteristic features of enantiomers:

❖ Enantiomers have identical physical properties (bp, mp, density, solubility and refractive index) but there is a difference in direction of rotation of plane polarized light.

Property	(+)-Lactic acid	(-)-Lactic acid
Specific rotation	+2.24°	-2.24°
Melting Point	26°C	26°C

❖ They have identical chemical properties except in chemical reactions with other optically active compounds.

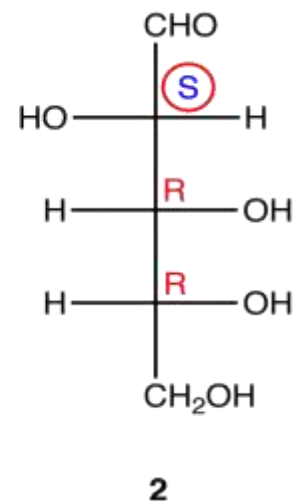
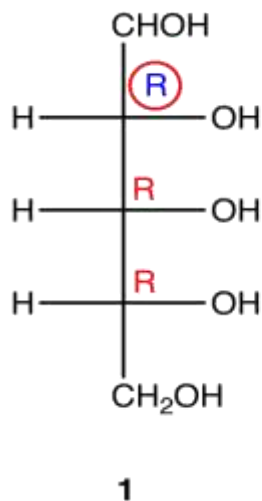
❖ They have different biological properties

E.g. (+)-Dextrose plays an important role in animal metabolism, where as (-)-Dextrose is not metabolized.

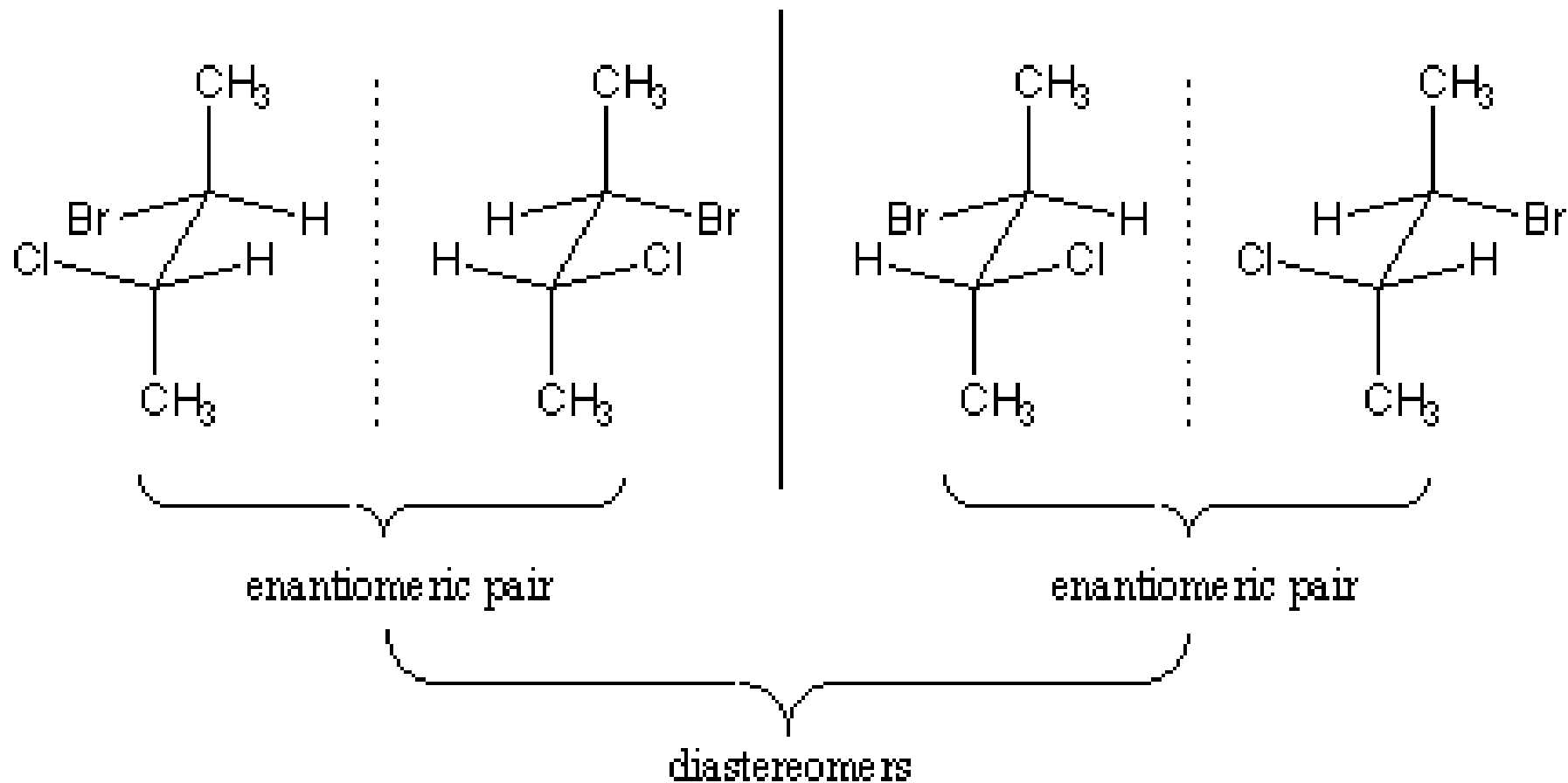
❖ When equal quantities of enantiomers are mixed an optically inactive compound racemic mixture is formed.

# DIASTEREOMERS

Stereomers of a substance that are not mirror images of each other are termed as Diastereomers.

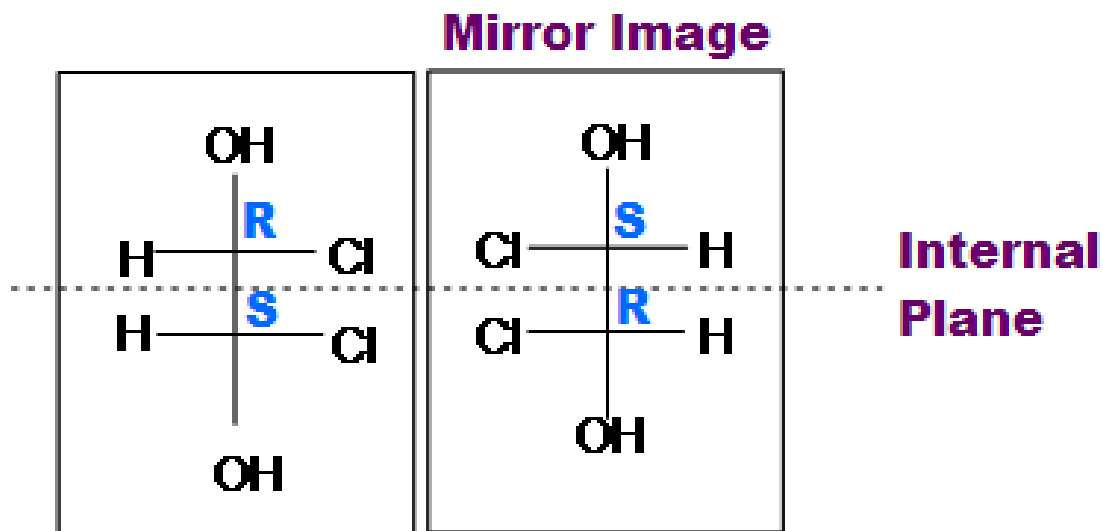


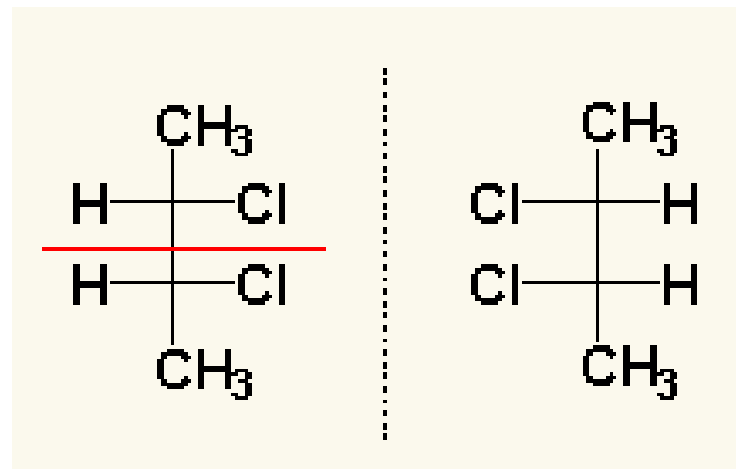
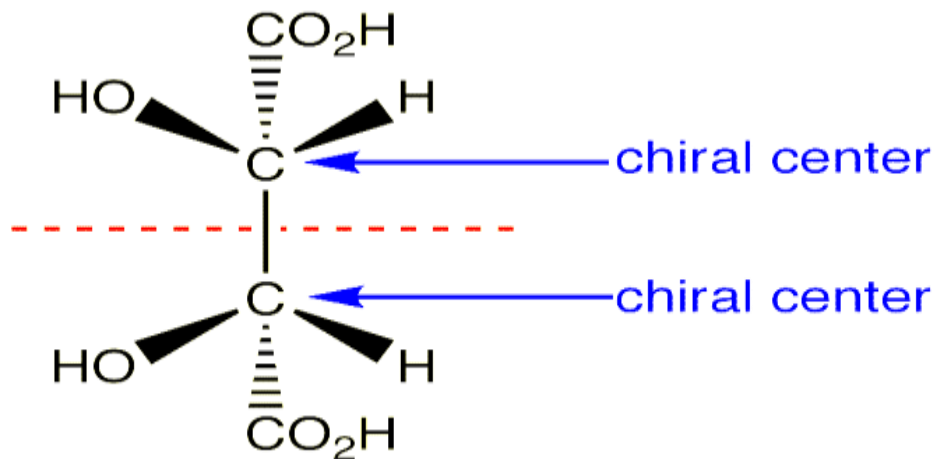
- ❖ They have different physical properties like m.p, b.p, solubility, density and refractive index, etc.
- ❖ Diastereomers have different specific rotation but they may have same or opposite sign of rotation.



# MESO COMPOUND

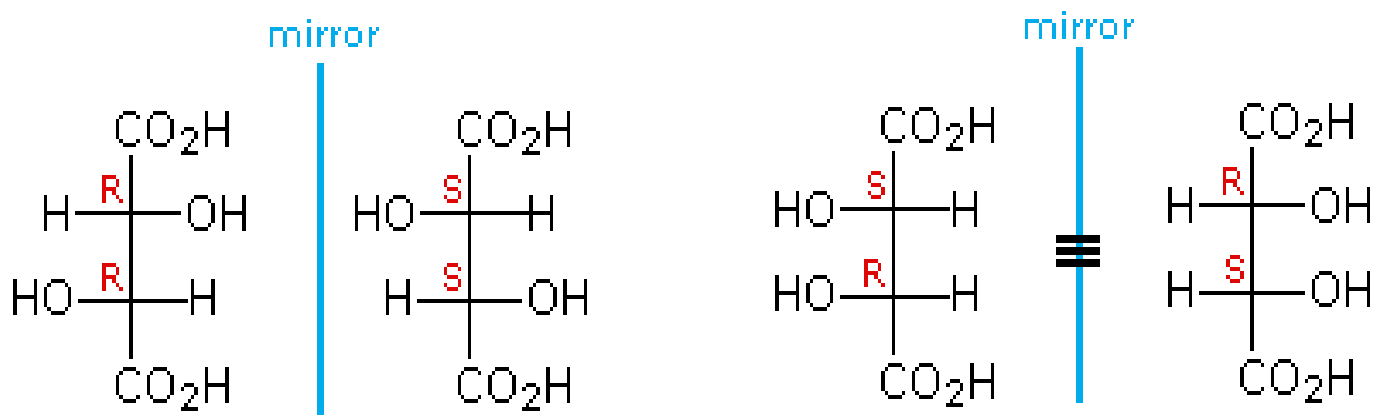
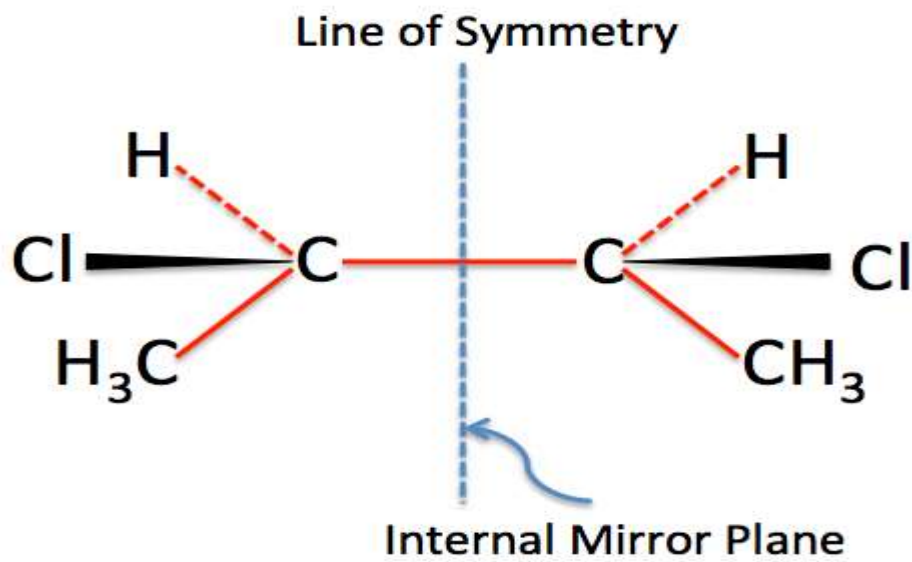
- A meso compound is a molecule with multiple stereocenters that is superimposable on its mirror image.
- Meso compounds are **achiral compounds** that has multiple chiral centers.
- Meso compounds are **optically inactive**.
- It has an internal symmetry plane that divides the compound in half.





A meso compound should contain two or more identical substituted stereocenters. Also, it has an internal symmetry plane that divides the compound in half. These two halves reflect each other by the internal mirror. The stereochemistry of stereocenters should "cancel out". What it means here is that when we have an internal plane that splits the compound into two symmetrical sides, the stereochemistry of both left and right side should be opposite to each other, and therefore, result in **optically inactive**.

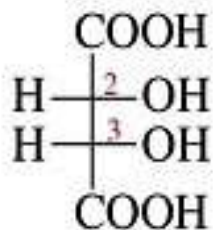




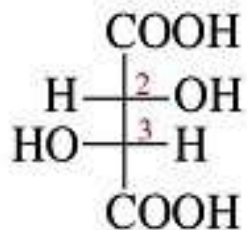
(+)-tartaric acid    (-)-tartaric acid    *meso*-tartaric acid

# RACEMIC MIXTURE

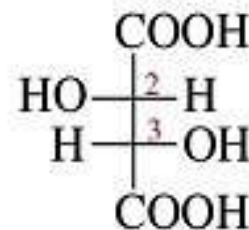
- A mixture having equal amounts of enantiomers is called **racemic mixture** or **racemic modification**.
- A **racemic mixture (or) racemate** is one that has equal amounts of left- and right-handed enantiomers of a chiral molecule. The first known racemic mixture was racemic acid, which Louis Pasteur found to be a mixture of the two enantiomeric isomers of tartaric acid.
- A racemic mixture is denoted by the prefix **(±)-** or **dl-** (for sugars the prefix **DL-** may be used), indicating an equal (1:1) mixture of dextro and levo isomers. Also the prefix symbols ***RS*** and ***SR*** (all in *italic* letters) are used.



**(2*R*,3*S*)-tartaric acid**  
a meso compound



**(2*R*,3*R*)-tartaric acid**  
a pair of enantiomers



**(2*S*,3*S*)-tartaric acid**

Fischer projections of the stereoisomers of tartaric acid

# RESOLUTION

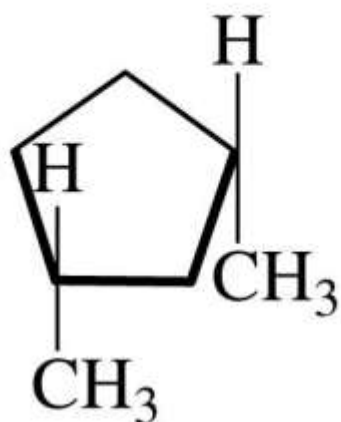
- The process of separation of racemic form into individual enantiomers is called resolution.
- The following are various methods used for resolution of racemic mixtures:

**1. MECHANICAL METHODS**

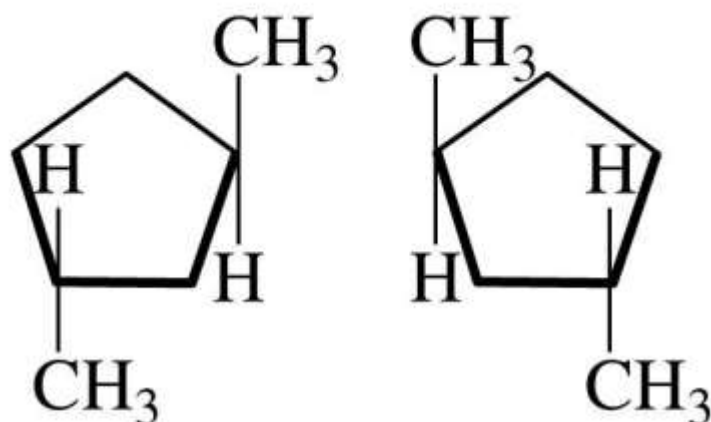
**2. BIOCHEMICAL METHOD**

**3. CHEMICAL METHOD**

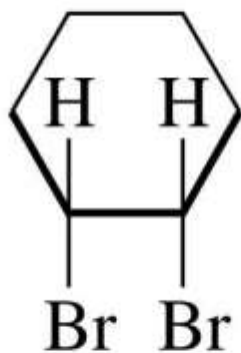
**4. CHROMATOGRAPHIC METHOD**



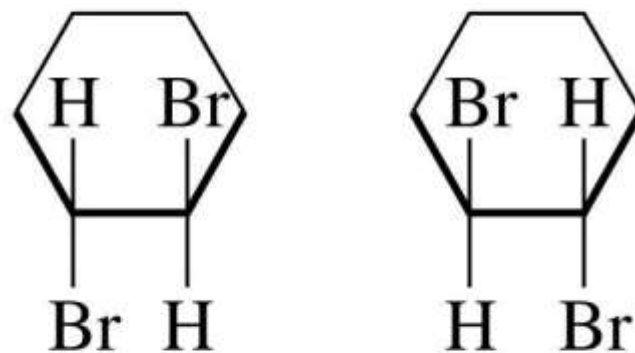
*cis*-1,3-dimethylcyclopentane  
a meso compound



*trans*-1,3-dimethylcyclopentane  
a pair of enantiomers



*cis*-1,2-dibromocyclohexane  
a meso compound

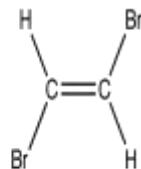
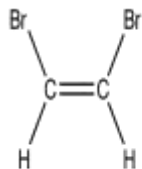


*trans*-1,2-dibromocyclohexane  
a pair of enantiomers

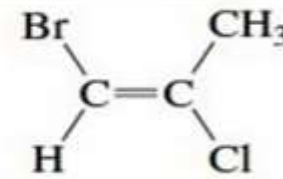
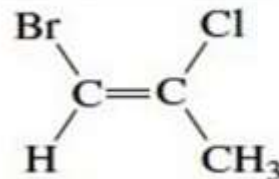
## EXCERSIZE:

Which isomer is cis isomer and which is trans.....?

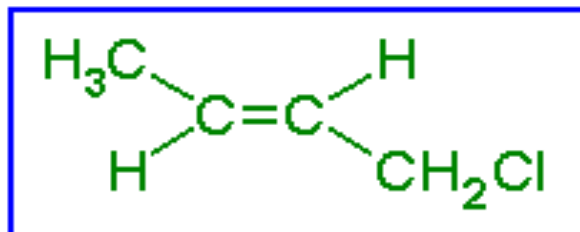
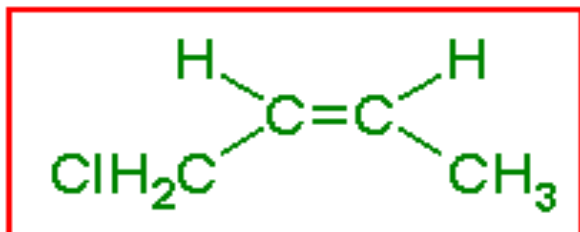
A)



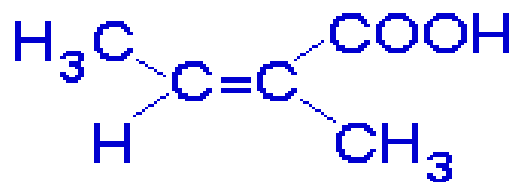
B)



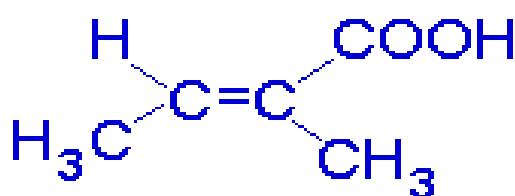
C)



D)



angelic acid



tiglic acid

### *Selected Historical Landmarks in the Development of the Field of Stereochemistry:*

- 1848 *Pasteur* achieves the *first optical resolution* of the (+)- and (-)-enantiomers of tartaric acid.
- 1874 *van't Hoff* and *Le Bel* independently suggest that tetravalent *carbon is tetrahedral*.
- 1900 *Fischer* develops the first systematic method for depicting stereochemistry (*Fischer projections*) and a notation for designating configuration (*D/L notation*).
- 1905 *Rosanoff* arbitrarily assigns the configuration of the structure corresponding to (+)-glyceraldehyde as being D-glyceraldehyde.
- 1951 *Bijvoet* determines the *absolute configuration* of the sodium rubidium double salt of (+)-tartaric acid using anomalous dispersion X-ray crystallography.
- 1969 *Hassell* and *Barton* (Imperial College) jointly awarded the Nobel prize in Chemistry for their work on the *conformational analysis* of cyclohexane.