Stereoisomerism

- ❖ **Isomers** are **compounds** with the same molecular formula but different linkages or **spatial arrangements of atoms** (which differ in physical and chemical properties). C_2H_6O
- ❖ **Isomerism** is the **phenomenon** of exhibiting two or more compounds with the same molecular formula but different physical and chemical properties.

Two main types of isomerism:

1. Structural isomerism (constitutional isomerism)
2. **Stereoisomerism**

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1. Structural isomerism

– Different linkages of atoms

Same molecular formula

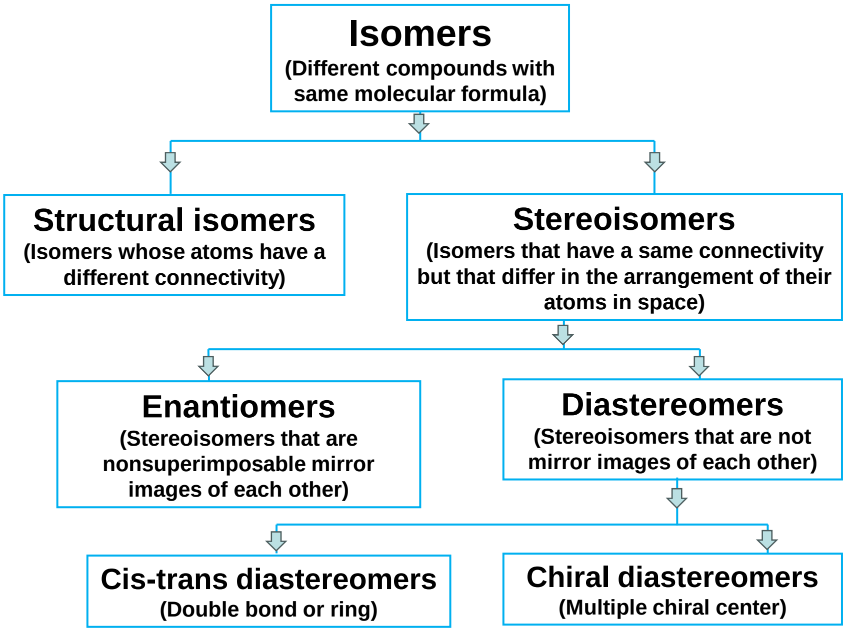
Different structural formulas

2. Stereoisomerism

– different spatial arrangements of atoms

Same molecular formula

Same structural formula



Isomers
(Different compounds with same molecular formula)

Structural isomers
(Isomers whose atoms have a different connectivity)

Stereoisomers
(Isomers that have a same connectivity but that differ in the arrangement of their atoms in space)

Enantiomers
(Stereoisomers that are nonsuperimposable mirror images of each other)

Diastereomers
(Stereoisomers that are not mirror images of each other)

Cis-trans diastereomers
(Double bond or ring)

Chiral diastereomers
(Multiple chiral center)

Structural isomers

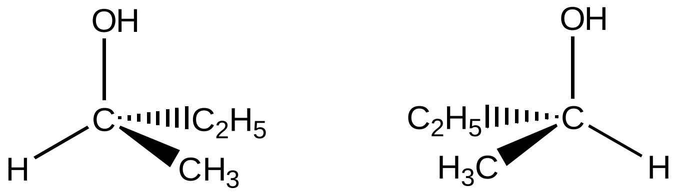
- ❖ Differ in the way the atoms are connected to each other
- ❖ Structural isomers have:
  - ○ Different IUPAC names
  - ○ The same or different functional groups
  - ○ Different physical properties, so they are separable by physical techniques such as distillation
  - ○ Different chemical properties. They behave differently or give different products in chemical reaction

Structural isomerism

- Chain isomerism
- Position isomerism
- Metamerism
- Tautomerism
- Functional group isomerism

Stereomerism

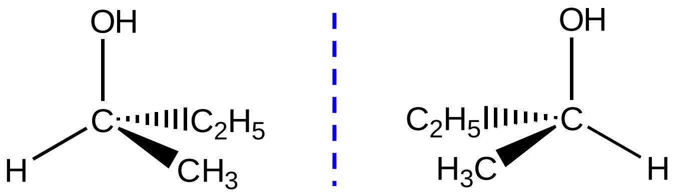
- When isomerism is caused by the different arrangement of atoms or groups in space, the phenomenon is called stereoisomerism.



(+) or (-)butan-2-ol

Enantiomers

- **Enantiomers**: stereoisomers that are non-superimposible mirror images; the only difference is the direction (+ or -) of optical rotation.



Enantiomers

(+) or (-)butan-2-ol

- Mirror images of each other
- Non-superimposable with each other
- Rotate plane-polarized light to the same extent but in opposite directions

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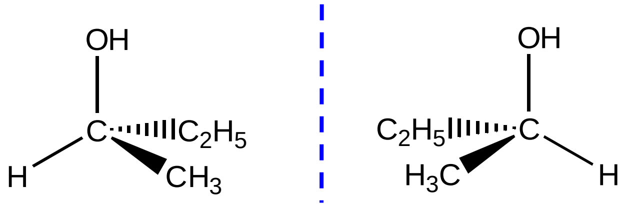
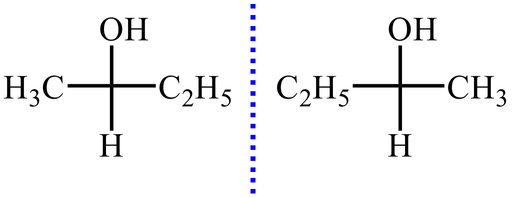


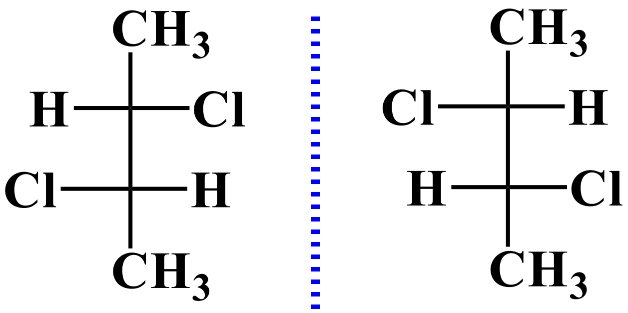
Enantiomers

- The direction of optical rotation cannot be predicted from the structural formulae.
- It can only be determined experimentally.



Fischer mirror images

- ❖ Easy to draw, easy to find enantiomers



Enantiomers

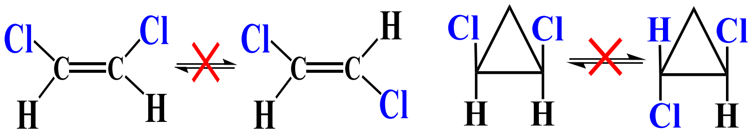
Diastereomers

Diastereomers: Stereoisomers that are not mirror images; different compounds with different physical properties.

Geometrical Isomerism

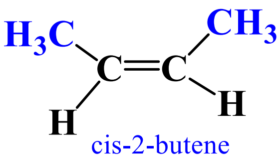
Arises due to the

- ❖ restricted rotation about a C=C double bond in alkene
- ❖ restricted rotation about a single bond in a cyclic/ring like compound.

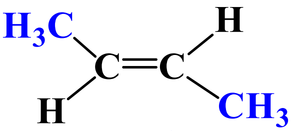


Geometrical Isomerism

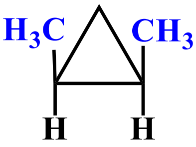
- It is also called cis-trans isomerism.
- **Cis isomer**, two similar groups are on the same side of the double bond
- **Trans isomer**, two similar groups are on the opposite sides of the double bond



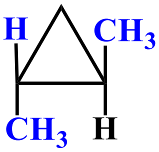
cis-2-butene



trans-2-butene



cis-1,2-dimethylcyclopropane

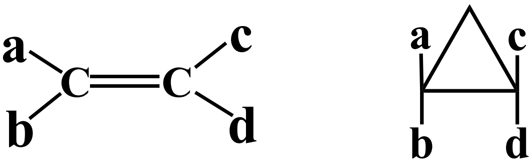


trans-1,2-dimethylcyclopropane

Conditions for geometrical isomerism

Two conditions are necessary for any compounds to show geometrical isomerism:

- There should be restricted (not allowed) rotation about a bond in a molecule.
- Both substituent/atoms on each carbon about which rotation is restricted should be different.



where **a** $\neq$ **b** and **c** $\neq$ **d**

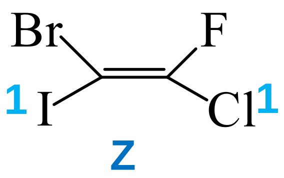
E/Z notation

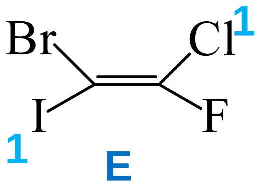
If there are three or four different groups attached to the carbons of C=C double bond.

E/*Z* notation rather than the *cis*/*trans* notation is used to name the stereoisomers of a molecule.

E* : in opposition to → *trans

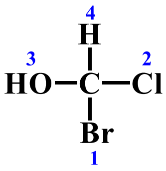
Z* : together → *cis



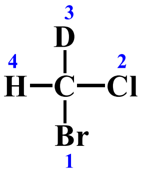


Cahn-Ingold-Prelog (CIP rule)

1. If directly attached atoms are different, priorities are determined by their atomic number. Higher atomic number is given higher priority. For same element, isotope with higher mass number has the higher priority.

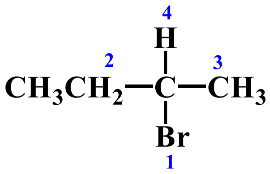


$\mathrm{HO{-}\overset{H}{\underset{Br}{C}}{-}Cl}$



$\mathrm{H{-}\overset{D}{\underset{Br}{C}}{-}Cl}$

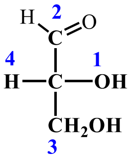
2. If the attached atom has same atomic number, priority is assigned by comparing next atoms/group.



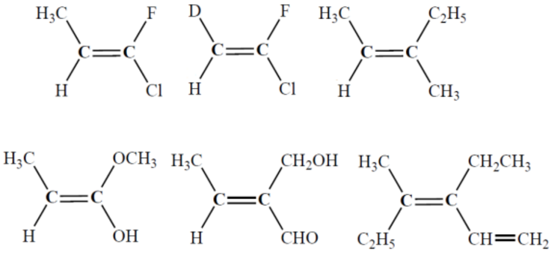
$\mathrm{CH_3CH_2{-}\overset{H}{\underset{Br}{C}}{-}CH_3}$

Cahn-Ingold-Prelog (CIP rule)

3. Atom linked via double and triple bonds are considered to be duplicate or triplicate. Triple bond gets priority over double bond, double bond gets priority over single bond.

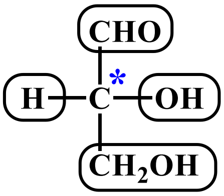


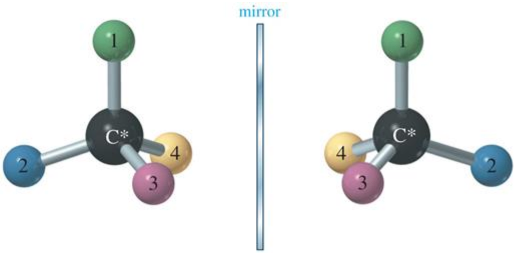
Identify the following as E/Z nomenclature



Chiral Compound

- If a compound is not superimposable on its mirror image then it is said **chiral compound** (usually the compound contains a carbon atom with four different groups attached to it).
- It's mirror image will be non-superimposible mirror images).

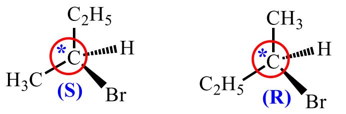




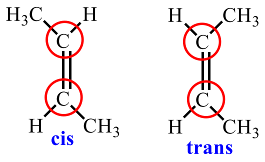
- The carbon is called **chiral** or **chiral center** or **asymmetric center** or **stereocenter** or **stereogenic center**

Stereocenter

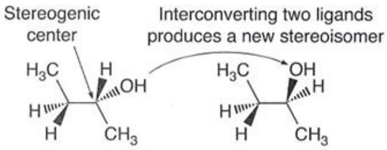
- ***Stereocenter*** (or stereogenic atom*):* any atom *at* which the interchange of two groups gives a stereoisomer.
  - Chirality center (chiral carbon)
  - Double-bonded carbon atoms in cis-trans isomers.



chiral centers
stereocenter



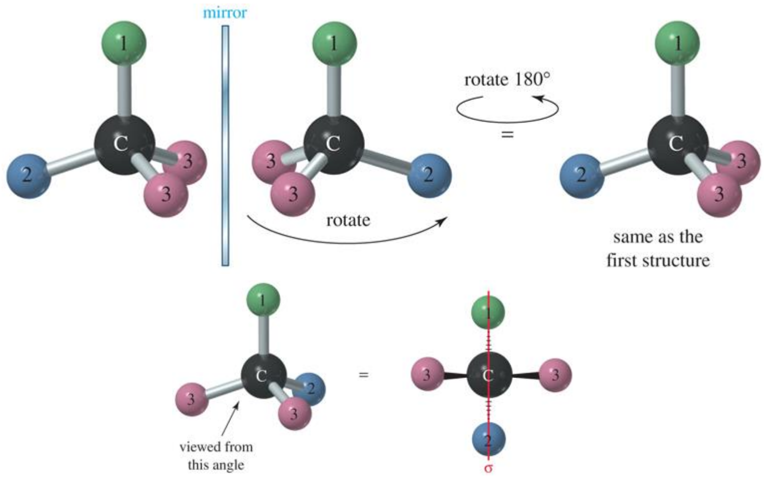
stereocenter



(*R*)-2-Butanol (*S*)-2-Butanol

Achiral Compound

If any symmetry is present in the compound and it's mirror image can be superimposed on it then the compound is ***achiral*** or **symmetric.**

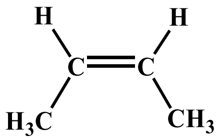


Chiral and achiral compound

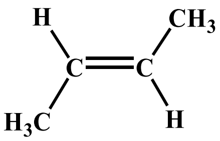
- Compounds with **one chiral center** will show optical activity.
- Compounds without chiral centers do not normally show optical activity.
- Compounds with more than one chiral center may or may not show optical activity depending on whether or not they are **non-superimposable on their mirror image (chiral)** or **superimposable (achiral)**.

Diastereomers

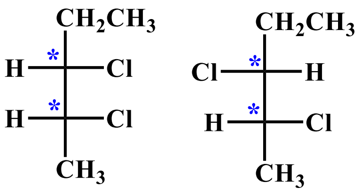
- **Diastereomers**: Stereoisomers that are not mirror images; different compounds with different physical properties
- Geometric isomers (cis-trans)
- Molecules with 2 or more chiral carbons.



cis-2-butene



trans-2-butene

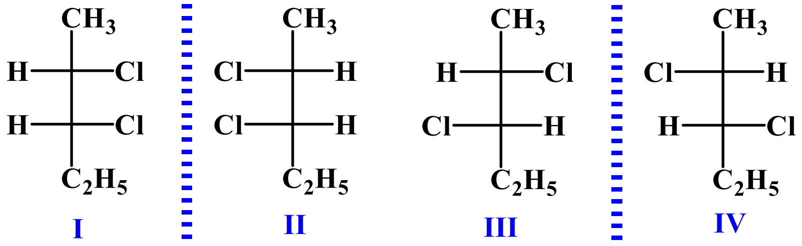


- Cis-trans isomers are not mirror images, so these are diastereomers.

- RULE - a compound can have a maximum of 2^n stereoisomers, where n = the number of asymmetric centers (not counting cis-trans isomeric centers)

2,3-dichloropentane $CH_3\overset{*}{C}H(Cl)\overset{*}{C}H(Cl)CH_2CH_3$

n = 2 → 2^2 = 4 stereoisomers



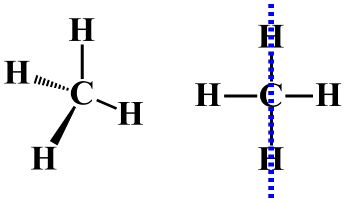
I & II are enantiomers; III & IV are enantiomers;
I & III; I & IV are diastereomers;
II & III; II & IV are diastereomers

Properties of enantiomers and diastereomers

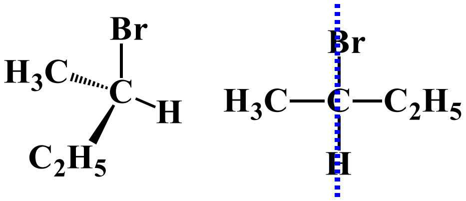
- Diastereomers have different physical properties: m.p., b.p.
- They can be separated easily.
- Enantiomers differ only in reaction with other chiral molecules and the direction in which polarized light is rotated.
- Enantiomers are difficult to separate.

Symmetric, Asymmetric and Dissymmetric molecules

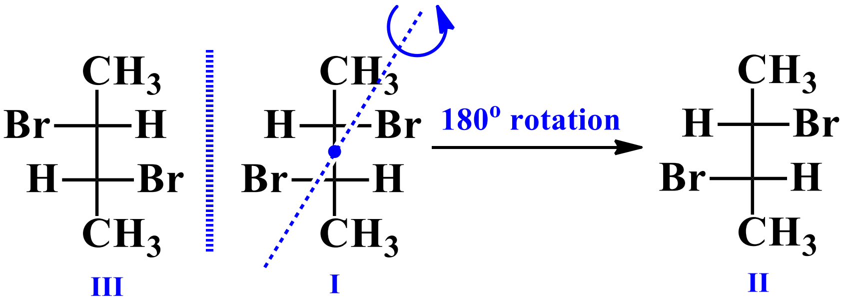
- **Symmetric molecules:** If any symmetry is present in a molecule then the molecule will be symmetric molecule.



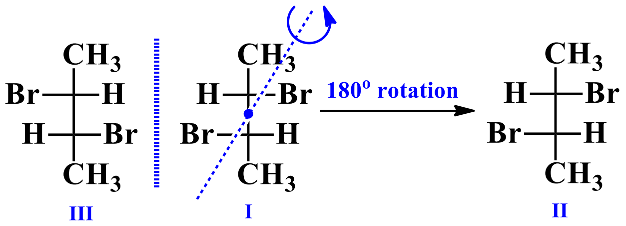
- **Asymmetric molecules:** In general the term asymmetry is used for those optically active compounds which have none of the **four elements of symmetry**.



- **Dissymmetric molecules:** The term dissymmetry is used for optically active compounds those are capable of existing as pairs of non-superimposable mirror images despite the presence of element of symmetry (usually dissymmetric molecule contains a simple axis of symmetry).



Possesses a C_2 axis of symmetry in the molecule at right angle to the plane of the paper.



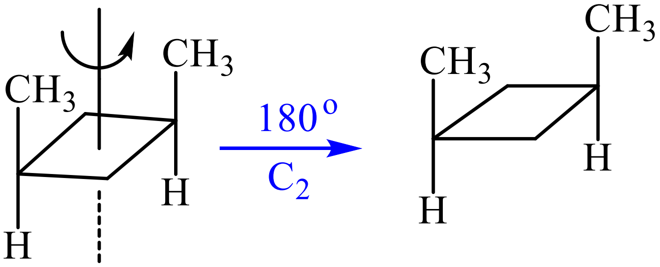
- ❖ Since structures I and II are indistinguishable, the molecule has C_2 axis of symmetry. But it is non-superimposable on its mirror image so it is dissymmetric and not asymmetric, and exhibits optical activity.
- ❖ Thus, while all asymmetric molecules are chiral, not all chiral molecules are asymmetric. Hence, to avoid any confusion, in using these terms, asymmetry or dissymmetry, the term **chirality is used**.

Chirality and symmetry

A necessary and sufficient criterion for chirality is an absence of S_n axes; the existence of any S_n axis renders an object achiral.

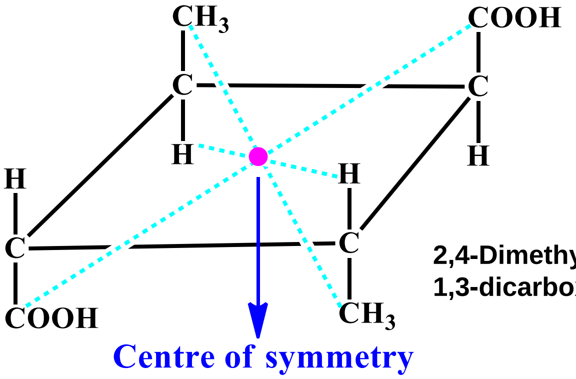
Simple axis of Symmetry (C_n):

A molecule has a n fold simple axis of symmetry, if it is rotated by an angle of 360°/n around the axis, it looks the same.



Centre of symmetry or *inversion* (i) or (C_i)

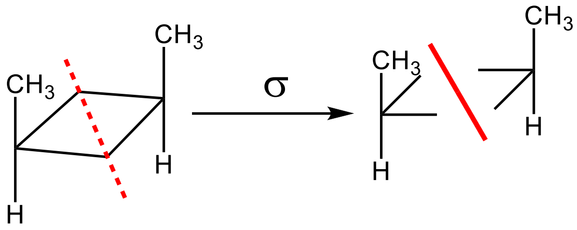
- It is defined as a point within the molecule at which an atom/group connected to it by a straight line meets the same atom/group in the opposite direction when extrapolated from it.

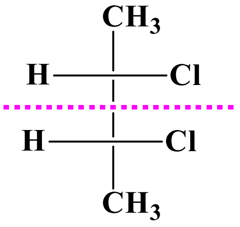


2,4-Dimethyl cyclobutane - 1,3-dicarboxylic acid

Plane of symmetry (σ):

An imaginary mirror plane dividing the molecule into two halves such that one half is the mirror image of the other half.

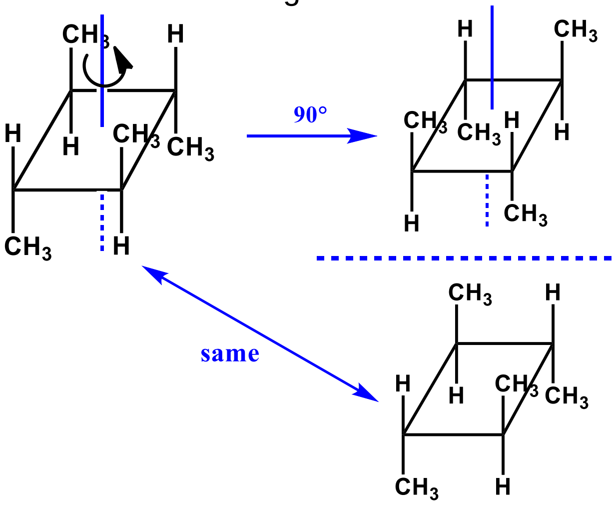




Plane of symmetry

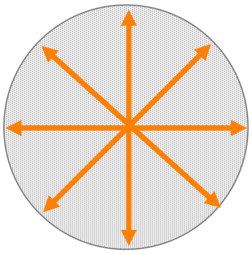
Alternating axis of symmetry (S_n)

A molecule rotated around an axis by 360°/n ⟶ an image taken through a mirror placed perpendicular to the axis ⟶ the mirror image looks identical with the original.

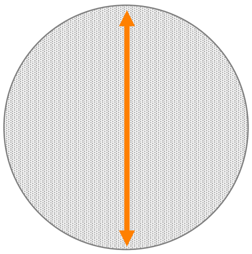


Polarized Light

- ❖ Ordinary (nonpolarized) light consists of many beams vibrating in different planes.

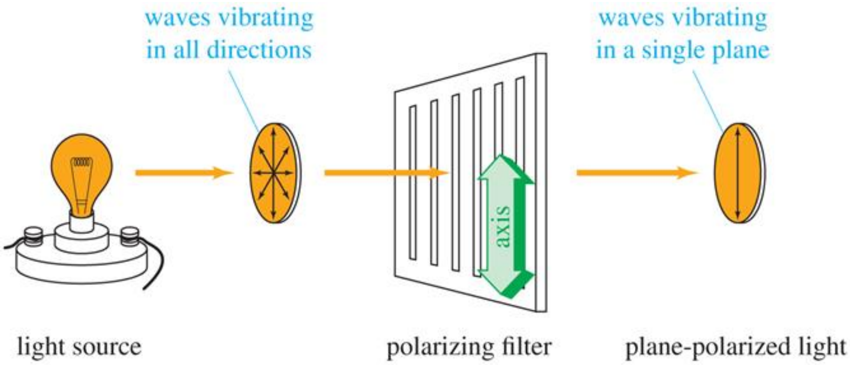


- ❖ Plane-polarized light is composed of waves that vibrate in only one plane.

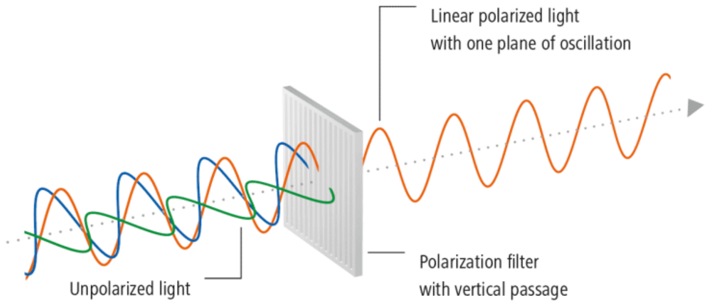


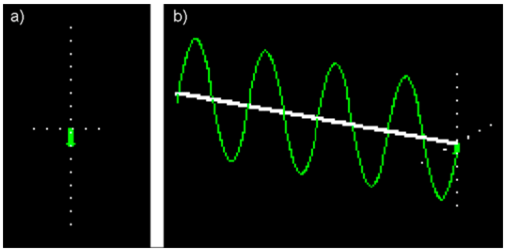
Polarized Light

- Plane-polarized light is composed of waves that vibrate in only one plane.



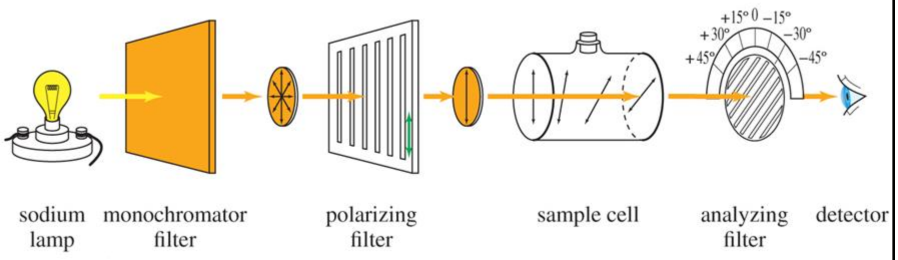
Polarized Light





Polarimeter

- ❖ **Polarimeter**: Device that measures the optical rotation of the optically active substance.



Clockwise
Dextrorotatory (+)

Counterclockwise
Levorotatory (-)

Not related to (*R*) and (*S*)

Optical activity

- ❖ Substances which can rotate the plane of polarised light are said to be **optically active**.
- ❖ **Dextrorotatory** (Latin: dextre means right) and is indicated by (+) sign.

	new	**older**
Dextrorotatory	**(+)**	***d***

- ❖ Rotates the plane of plane-polarized light to the right.

Optical activity

- **Laevorotatory** (Latin: laeves mean left) and is indicated by (-) sign.

Levorotatory

new	older
(-)	***l***

- Rotates the plane of plane-polarized light to the left.
- Those substance which do not rotate the plane of polarised light are called **optically inactive**.

Specific Rotation $[\alpha]_D$

It *is defined as the number of degrees of rotation caused by a solution of 1.0 g of compound per mL of solution taken in a polarimeter tube 1.0 dm (10 cm) long at a specific temperature and wavelength*.

The specific rotation is calculated from observed angle of rotation, as below:

$$[\alpha]_D^t = \frac{\alpha}{c \times l}$$

Specific rotation calculated in this way is a physical property of an optically active substance.

You always get the same value of $[\alpha]_D^t$

α = observed rotation
c = concentration (g/mL)
l = length of cell (dm)
D = yellow light from sodium lamp
t = temperature (Celsius)

Angle of rotation (α) is the angle **(degrees)** by which the analyser is rotated to get maximum intensity of light. It depends upon:

(i) Nature of the substance;
(ii) Concentration of the solution in g/mL;
(iii) Length of the polarimeter tube;
(iv) λ of the incident monochromatic light (598 nm).
(v) Temperature of the sample.

Racemic modification/mixtures

- A mixture containing equal amounts of a pair of enantiomers is called a **racemic mixture**.
- Equal quantities of *d*- and *l*- enantiomers.
- Notation: (*d,l*) or (±)
- No optical activity.
- The mixture may have different b.p. and m.p. from the pure enantiomers!
- The clockwise rotation caused by the (+)isomer is cancelled by the anti-clockwise rotation caused by the (-)isomer

external cancellation

Racemic mixture (racemate)

- The (+)isomer and (-)isomer are **different** structures
- One serves as the impurity of the other in a racemic mixture.
- A racemic mixture has a lower m.p. than its components.

	(+)butan-2-ol	(-)butan-2-ol	(±)butan-2-ol
m.p.	99.5°C	99.5°C	< 99.5°C

Meso compounds

A compound with 2 or more asymmetric centers, and a **plane of symmetry** - cuts molecule in half so that one half of the molecule is the mirror image of the other

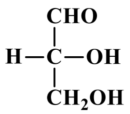
Symmetry plane not drawn through ***asymmetric centers***

Note this plane of symmetry does not eliminate the presence of stereocenters.

Configuration

- **Relative configuration** compares the arrangement of atoms in space of one compound with those of another (glyceraldehyde, amino acid). **Until the 1950s, all configurations were relative.**
- **Absolute configuration** is the precise arrangement of atoms in space.

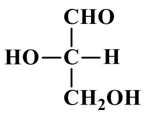
- The configuration of carbohydrates, amino acids and some other compounds is commonly designated by the ***D,L* system proposed by Emil Fischer in 1891**. At that time, it was known that one enantiomer of glyceraldehyde has a specific rotation of + 13.5; the other has a specific rotation of -13.5. Fischer proposed that these enantiomers be designated *D* and *L* (for dextro and levorotatory) but he had no experimental way to determine which enantiomer has which specific rotation. Fischer, assigned the dextrorotatory enantiomer an arbitrary configuration and named it *D*-glyceraldehyde. He named its enantiomer *L*-glyceraldehyde.
- Fischer could have been wrong, but by a stroke of good fortune he was correct, as proven in 1952 by a special application of X-ray crystallography.
- D- and L-glyceraldehyde serve as reference points for the assignment of relative configuration to all other aldoses and ketoses.



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

D-Glyceraldehyde

$[\alpha]_D^{25} = +13.5$



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{CH_2OH} \end{array}$$

L-Glyceraldehyde

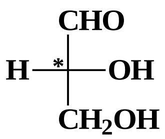
$[\alpha]_D^{25} = -13.5$

Fischer-Rosanoff convention

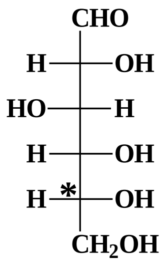
- Before 1951, only **relative** configurations could be known.
- Sugars and amino acids with same relative configuration as (+)-glyceraldehyde were assigned D and same as (-)-glyceraldehyde were assigned L.
- With X-ray crystallography, now known **absolute** configurations: D is (*R*) and L is (*S*).
- **No** relationship to **dextro- or levorotatory**.

D and L assignments for carbohydrates

- In carbohydrates, in general, the OH group attached to the **penultimate** carbon atom in the chain determines the assignment of D or L.
- OH group attached to the penultimate carbon is on the RHS, in which the CHO group appears at the top, the configuration is defined as D
- If OH group attached to LHS, it is defined as L



D-(+)-glyceraldehyde
R-(+)-glyceraldehyde



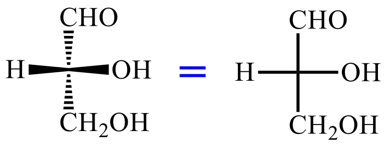
D-(+)-glucose

D, L system

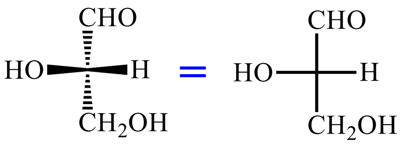
Mainly used for amino acids and carbohydrates

Fischer projection

- Horizontal lines: bonds coming out of the plane of the paper
- Vertical lines: bonds projecting behind the plane of the paper
- The most oxidized group: top
- CH_2OH (carbohydrates) or R (amino acids): bottom



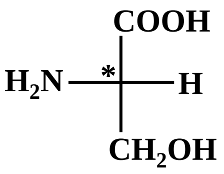
D-Glyceraldehyde



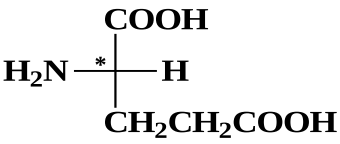
L-Glyceraldehyde

D and L assignments for amino acids

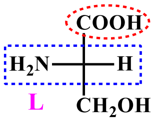
- In case of amino acids, the NH_2 group is on the LHS of the Fischer projection in which the carboxyl group appears at the top, the configuration is L conversely,
- If NH_2 group is on the RHS it is defined as D



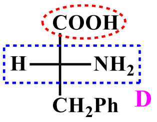
L-(-) serine
S-(-) serine



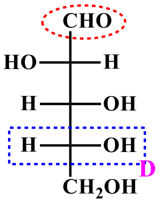
L-(+)-glutamic acid



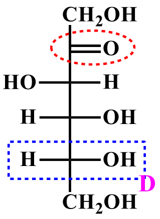
L-Senine



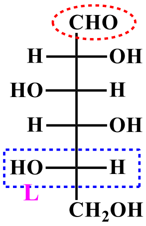
D-Phenylalanine



D-Arabinose



D-Fructose

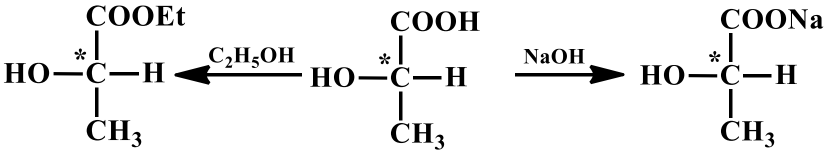


L-Idose

D: dextro, right
L: levo, left

- ❖ **No direct relationship between the R/S and D/L and the sign of optical rotation (+/-) of the molecule.**

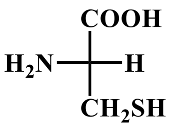
No direct relationship between D/L and (+)/(-) rotation



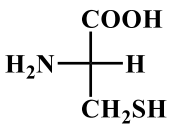
L-(-) Ethyl lactate L-(+) Lactic aci L-(-) Sodiumlactate

- ❖ Configuration of the chiral carbon is unchanged, but direction of the rotation is changed

No direct relationship between D/L and R/S



L-Crysteine



R Configuration