Molecules with a single chiral centre

Molecules containing a single tetracoordinate or tricoordinate chiral centre exist as two stereoisomers. The two stereoisomers are non-superimposable mirror images of each other, which means they exist as a pair of enantiomers. Let us discuss the stereochemistry of a molecule with one chiral centre taking Mandelic acid, PhCH(OH)(COOH) as an example. The Wedge formulae and Fischer projections of the two stereoisomers are:

I II

The isomers I and II are mirror image to each other but non-superimposable, i.e. they are enantiomers. They are optically active-one rotates the plane of polarised light towards left and the other rotates the plan of polarised light towards right.

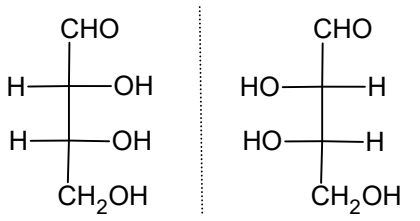
Fischer projections of the two stereoisomers along with their R, S-nomenclature is shown below:

R **S**

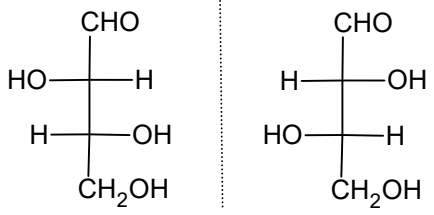
Molecules with two or more chiral centres

A. Stereochemistry of Constitutionally unsymmetrical chiral molecule

(i) A molecule with two or more chiral centres is constitutionally unsymmetrical if the two end groups are non-equivalent. An example of such molecule is aldotetrose [CHO-CH(OH)-CH(OH)-CH_2OH] which is having two chiral centres-C2 and C3. It has four stereoisomers which exist as two pairs of enantiomers.



I **II**

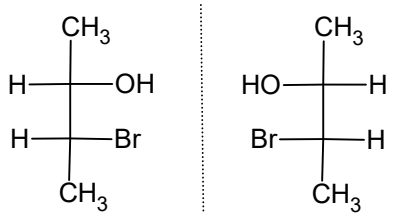


III **IV**

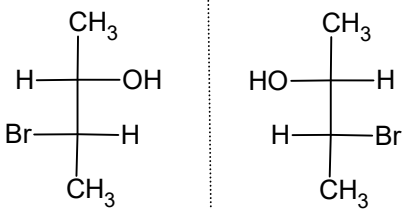
I and II are enantiomers, hence optically active. Similarly, III and IV are enantiomers and optically active. Stereoisomer I is diastereomeric to III and IV, similarly, stereoisomer II is also diastereomeric to III and IV.

R,S-nomenclatures to the configurations of C2 and C3: **I**-2R, 3R; **II**-2S, 3S; **III**-2S,3R; **IV**-2R, 3S

(ii) If each of the chiral centre is substituted differently then also the molecule is said to be constitutionally unsymmetrical. e.g., 3-bromobutanol-2. The molecule is having two chiral centres-C2 and C3. It has four stereoisomers which exist as two pairs of enantiomers.



I **II**



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I and II are enantiomers, hence optically active. Similarly, III and IV are enantiomers and optically active. Stereoisomer I is diastereomeric to III and IV, similarly, stereoisomer II is also diastereomeric to III and IV.

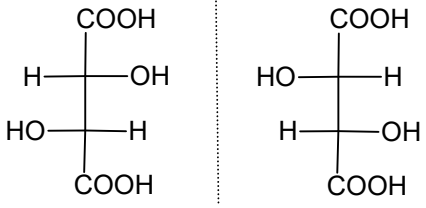
R, S-nomenclatures to the configurations of C2 and C3: **I**-2S, 3R; **II**-2R, 3S; **III**-2S,3S; **IV**-2R, 3R

In a constitutionally unsymmetrical molecule, each chiral centre is capable of exhibiting in two configurations R and S, and the total number of stereoisomers is thus 2^n, where n is the number of non-equivalent chiral centres.

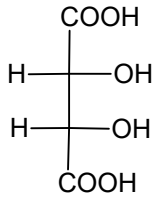
B. Stereochemistry of constitutionally symmetrical chiral molecule

An acyclic molecule containing multiple chiral centers are called constitutionally symmetrical, if chiral atoms equidistant from the geometrical centre of the molecule are identically substituted. The two end groups of such a molecule are necessarily equivalent. When 'n', the number of chiral centres, is even, and the geometrical centre is located at the centre of a bond, then the number of stereoisomers are given by $2^{n-1}(optically\ active) + 2^{\frac{n-2}{2}}(meso\ form)$. When 'n' is odd, the geometrical centre lies on an atom and the number of stereoisomers is given by 2^{n-1} with $2^{n-1} - 2^{\frac{n-1}{2}}$ optically active and $2^{\frac{n-1}{2}}$ optically inactive (meso) forms.

(i) 2,3-Dihydroxysuccinic acid (Tartaric acid): It has three stereoisomers-two of them exists as enantiomeric forms and third one is a meso form.



I **II**

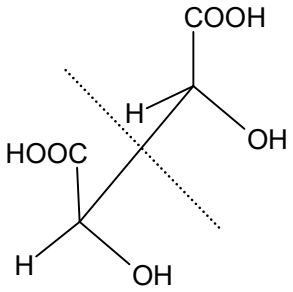


III

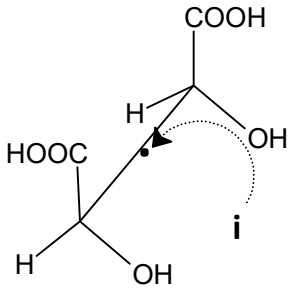
Stereoisomers I and II are enantiomers and III is a meso compound.

R, S-nomenclatures to the configurations of C2 and C3: **I**-2R, 3R; II-2S, 3S; **III**-2R,3S (considering numbering from the top of Fischer projection).

The meso form III is superimposable with its mirror image. It has got a plane of symmetry in its eclipse sawhorse representation (S_1 axis) and a centre of symmetry (S_2 axis), therefore, it is not dissymmetric, i.e., it is achiral and hence optically inactive. A stereoisomer which is achiral and optically inactive in spite of having chiral carbon atoms, is called a meso compound.

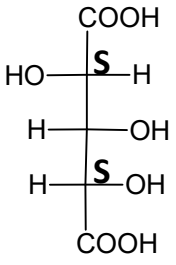


meso-tartaric acid
(eclipsed sawhorse)

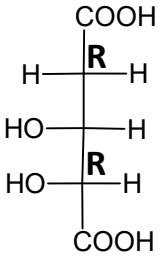


meso-tartaric acid
(staggered sawhorse)

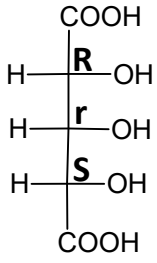
(ii) 2,3,4-Trihydroxyglutaric acid: This is a constitutionally symmetrical molecule having three chiral centres and exists as four(2^{3-1}) stereoisomers.



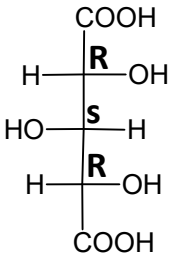
I



II



III



IV

Two of them I and II are enantiomers and the remaining two III and IV are optically inactive meso forms. In the enanatiomers I and II, the C3 centre is not a chiral centre because, two of the ligands [-CH(OH)COOH] are identical (R, R). No configurational assignment R or S may be given to C3. Moreover, C3 is also non-stereogenic; the interchange of H and OH at this centre in one enantiomer does not generate the other enantiomer. The molecule is chiral due to the presence of other two chiral centres C2 and C4. As the C3 centre is present in an overall chiral environment, it is chirotopic.

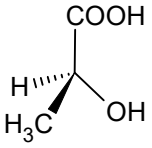
In the two meso forms III and IV, C3 is a chiral centre according to common definition because the two ligands [-CH(OH)COOH] are not identical (R, S). However, a plane of symmetry passes through this centre. Due to this local symmetry C3 is achirotopic. This centre is also stereogenic because the interchange of H and OH at this centre in one diastereomer generates the other diastereomer. Thus, in the enantiomers of 2,3,4-Trihydroxyglutaric acid, C3 is chirotopic but non-stereogenic; in the meso forms, C3 is achirotopic but stereogenic. Due to stereogenic property of the C3 centre in the meso forms, it can be given configurational descriptor 'r' in III and 's' in IV.

Chirotopic and Achirotopic Centre:

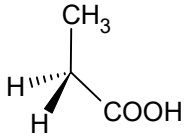
Any atom within a molecule is said to be chirotopic if its local symmetry (site symmetry) is chiral; i.e., the atom resides in a chiral environment. The molecules bearing a chirotopic centre need not be as a whole chiral.

An atom is said to be achirotopic when its site symmetry is achiral, that is, a point or atom located on a plane of symmetry or a centre of symmetry, or at the point where an alternating axis of symmetry intersects a reflection plane is achirotopic.

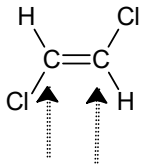
All segments or points in a chiral molecule are chirotopic because chirality affects all parts of a molecule. In lactic acid, all atoms/groups are chirotopic, All the ligands in Propanoic acid [CH_3CH_2COOH] are achirotopic:



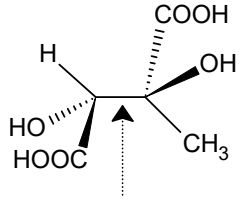
Lactic acid



Propanoic acid



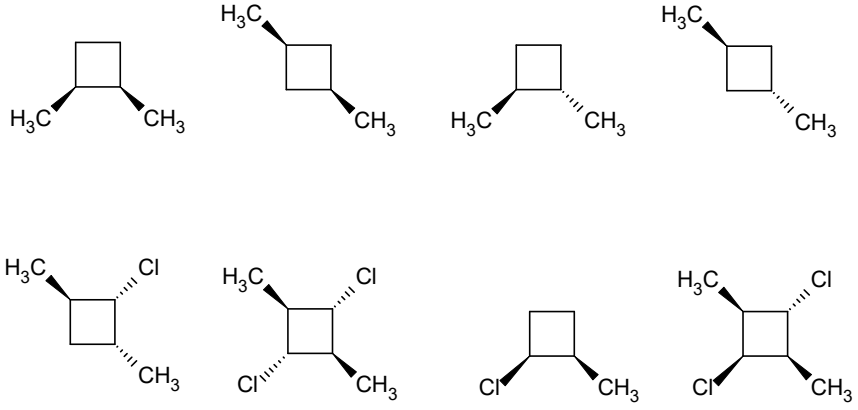
achirotopic centres



achirotopic point
(meso tartaric acid)

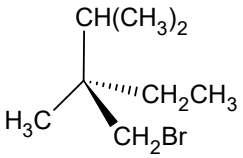
Questions

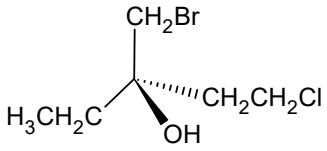
1. Which of the following compounds have a chirality centre? Identify the centre wherever it exists.
   (a) $CH_3CH_2CH_2CH(OH)CH_2CH_2CH_2CH_3$
   (b) 2-Bromobutane
   (c) 2,4-Dimethylhexane
   (d) $CH_3CH_2CH(Cl)CH_3$
   (e) $CH_3CH_2CH(CH_3)CH_3$
   (f) CH_3CH_2OH
   (g) $CH_3CH_2BrCH_2CH_3$
   (h) $CH_3CH_2CHBrCH_2CH_3$
   (i) $CH_2{=}CHCH(NH_2)CH_3$
2. Does the molecule 2-bromobutane have a chirality centre? If so, show it. How many stereoisomers exist for 2-bromobutane?
   - Draw their three-dimensional structure and the corresponding Fischer Projection.
   - What stereoisomeric relationships exist between them?
   - Are they optically active?
3. Which of the following are chiral and why?

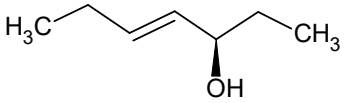


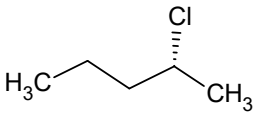
4. Draw enantiomers for each of the following compounds using: (a) Perspective formulas (3D) (b) Fischer projections:
   (a) $CH_3CH(Br)CH_2OH$
   (b) $ClCH_2CH_2CH(CH_3)CH_2CH_3$
   (c) $CH_3CH(CH_3)CH(OH)CH_3$

5. Indicate whether the following structures have the (R)-configuration or the (S)-configuration:

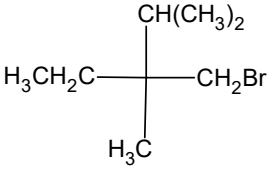


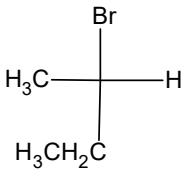


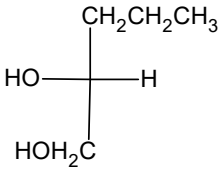


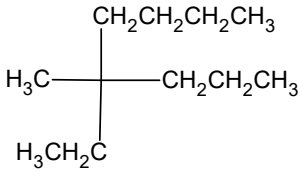


6. Assign priority numbers to the following groups:
   (a) $-CH_2OH$ $-CH_3$ $-CH_2CH_2OH$ $-H$
   (b) $-CH{=}O$ $-OH$ $-CH_3$ $-CH_2OH$
   (c) $-CH(CH_3)_2$ $-CH_2CH_2Br$ $-Cl$ $-CH_2CH_2CH_2Br$
   (d) $-CH{=}CH_2$ $-CH_2CH_3$ -Ph $-CH3$
7. Indicate whether each of the following structures has the (R)-configuration or the (S)-configuration









8. Draw perspective formulas for the following compounds:
   a. (R)-2-butanol
   b. (2S, 3R)-3-chloro-2-pentanol
   c. (S)-3-chloro-1-pentanol
   d. (2S, 3R)-3-methyl-2-pentanol
   e. (R)-1,2-dibromobutane

9. Draw Fisher projections of all the stereoisomers of 2, 3-dibromobutanal. Mention stereoisomeric relationship between them. Assign R, S-nomenclature to the configurations of the chiral centres in all the stereoisomers. Classify the stereoisomers as threo and erythro. Take one stereoisomer and convert its Fisher projection to Sawhorse and Newman projections.

Racemic modifications:

The racemic modification is an equimolecular mixture of a pair of enantiomers, independent of whether it is crystalline, liquid, or gaseous.

Difference between racemic modification and meso compound:

1. A meso compound is a single active substance, while racemate is a 50:50 combination of a pair of enantiomers.
2. The racemic modification is optically inactive due to external compensation, that is, (+)-rotation of one enantiomer is compensated by the (−)-rotation of the other. A meso compound is optically inactive due to internal compensation, that is, the (+)-rotation of one part of the molecule is nullified by the (−)-rotation of the other part within the same molecule.
3. Since racemic modification is a mixture, it can be separated into pure enantiomers. Meso compounds cannot be resolved.

Resolution of racemic modification:

When a racemic modification is separated by a process into its constituent enantiomers, the process is known as resolution.

Method of resolution:

Chemical method:

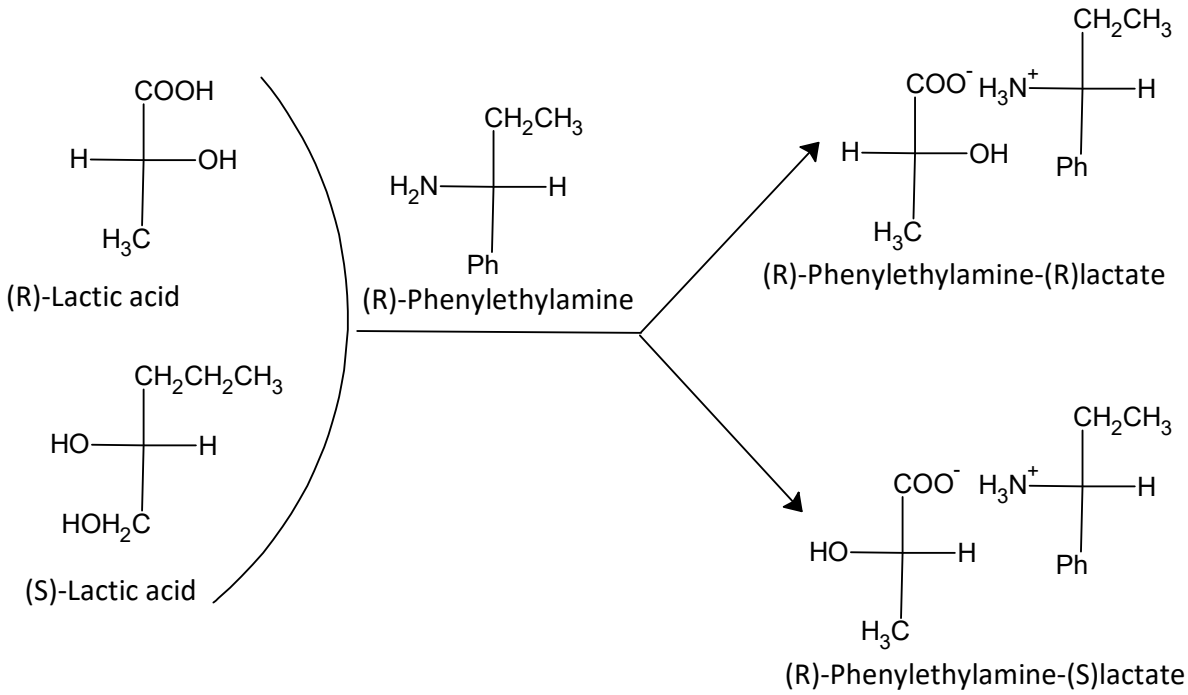
In this method, resolution is done with the formation of diastereomers. In the resolution of a racemic acid (±)A with an optically pure base (+)-B, the following two diastereomeric salts are formed:

$$(\pm)\text{−A} + (\pm)\text{−B} \longrightarrow (+)\text{−A}\mathbf{.}(+)\text{−B} + (-)\text{−A}\mathbf{.}(+)\text{−B}$$

Being diastereomers, the two salts differ in properties such as solubility, boiling point, etc. When crystallized from a solvent, one of them would separate first. Thus, the two diastereomers can be separated. Decomposition of the salts with mineral acid would furnish (+)-A and (−)-A in pure form. e.g.,

Resolution of an acid (Lactic acid):

The mixture reacts with (R)-phenylethylamine to yield a mixture of phenylethyl ammonium lactates, which can be separated by a physical method.



After separation of the diastereomeric salts, each of them on treatment with mineral acid liberates the optically pure enantiomers:

(R, R)-salt + HCl → (R)-Lactic acid + (R)-Phenylethylammonium chloride

(S, R)-salt + HCl → (S)-Lactic acid + (R)-Phenylethylammonium chloride