STEREOCHEMISTRY II

SEM-1, CC-1B
PART-10, PPT-10

Part-10: Stereogenecity

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Stereochemistry (PART-10, PPT-10)

Stereogenecity and Chirotopicity

Nature of Stereoisomers

Isomers were defined as compounds having the same molecular formula but differing in structure. The isomers were subdivided according to whether they differ in constitution, in configuration, and / or in conformation. Isomers differing only in configuration and / or conformation were recognized as stereoisomers. The stereoisomers can be alternatively subdivided into enantiomers and diastereomers. Enantiomers may differ in configuration or only in conformation; the same is true of diastereomers (diastereoisomers).

Enantiomers are pairs of isomers related as an object is to its mirror image. This relationship may stem from a configurational difference, as in CHFClBr (Figure 1) or in ethylmethylbenzylamine (Figure 2) or from a conformational (sign of torsion angle) difference, as in a tetra-*o*-substituted biphenyl (Figure 3), the *gauche* forms of 1,2-dichloroethane (Figure 4; A and C), or the two *chair* forms of *cis*-1,2-dimethylcyclohexane (Figure 5).

Different Types of Stereoisomers

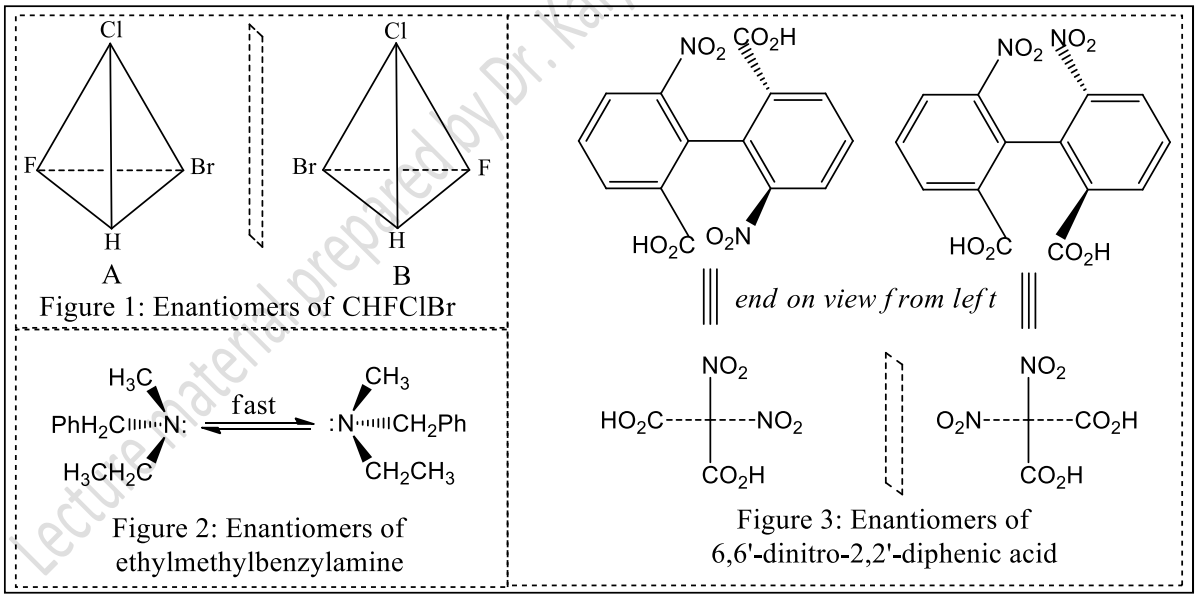


Figure 1: Enantiomers of CHFClBr

Figure 2: Enantiomers of ethylmethylbenzylamine

Figure 3: Enantiomers of 6,6'-dinitro-2,2'-diphenic acid

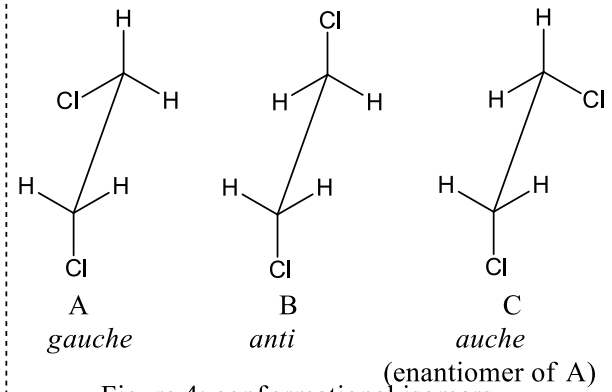


Figure 4: conformational isomers of 1,2-dichloroethane

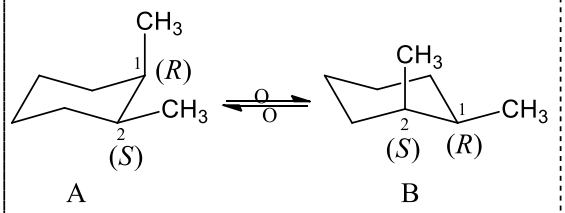


Figure 5: Conformational isomers of *cis*-1,2-dimethylcyclohexane

The stability to interconversion of the enantiomers, which is high in the case of CHFClBr and appropriately tetra-*o*-substituted biphenyls (considered as an *axially chiral* molecules) but fleeting in the other three examples (shown in Figures 2, 4 and 5). Conceptually, the structures that are compared are considered as being rigid.

Enantiomers must be isomers as well as mirror images, that is, they must not be superimposable. There are many structures (one is shown in Figure 6) which bear a mirror-image relationship but, upon rotation of the entire model (rigid rotation) around an appropriate axis, turn out to be superimposable with the original structure. Such structures are identical (or homomeric) and not enantiomeric.

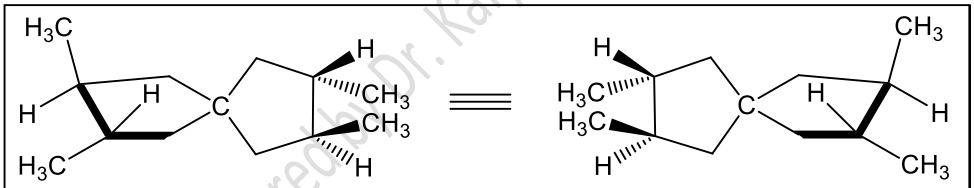


Figure 6: Identical mirror-image structures (structures containing S_4 axis)

Diastereomers are stereoisomers (i.e., isomers of identical constitution but differing three-dimensional architecture) which do not bear a mirror-image relation to each other. Diastereoisomerism may be due to differences in configuration (or conformation) at several sites of the molecule, as in the tartaric acids (Figure 7).

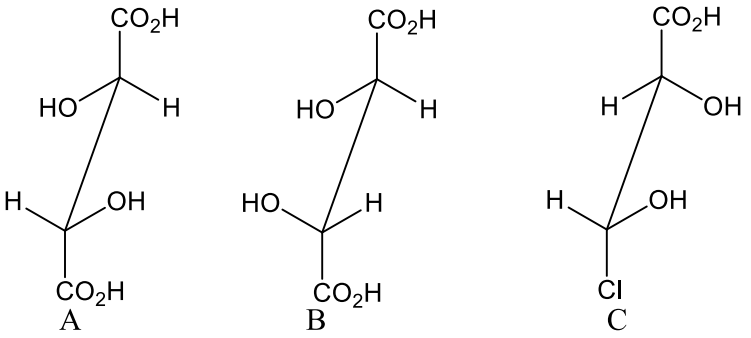


Figure 7: Stereoisomers of tartaric acid; enantiomers are B and C; diastereomers are A, B and A, C

In this particular case, the barriers between the diasteromers are high and each isomer is stable, at least at room temperature. However, this is not essential: The rapidly interconverting isomers of tertiary amines shown in Figure 8 and the *gauche* and *anti*-form of 1,2-dichloroethane (Figure 4; A and B) are also diastereomers.

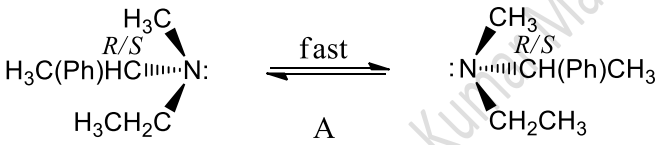


Figure 8: Diastereomers of *N*-ethyl-*N*-methyl-1-phenylethanamine

In case of the *gauche* and *anti*-form of 1,2-dichloroethane, the difference between the diastereomers is in the magnitude of the torsion angle (60° *vs.* 180°) rather than in a difference of sign of several torsion or bond angles. The terms enantiomer and diastereomer relate to molecules as a whole. Thus, if two molecules have the same constitution (connectivity) but different spatial arrangements of the atoms (i.e., if they are stereoisomeric), they must either be related as mirror images or not. In the former case they are enantiomers, in the latter case they are diastereomers.

The differentiation can be made without considering any particular part of the molecule. However, in viewing and specifying enantiomers and diastereomers one often focuses on particular sites in the molecule, such as the carbon atom in CHFClBr or the torsion axis containing the phenyl-phenyl bond in the biphenyls shown in Figures 3. In the tradition of van't Hoff, one considers stereoisomerism by attributing it to a "*chiral* center" or a torsion axis.

A *chiral* centre (or, centre of chirality) is a focus of chirality; in the case of carbon, at least, it corresponds to the asymmetric tetrahedral atom of van't Hoff (1874) as shown in Figure 9. The existence of enantiomers is usually, but not invariably, associated with at least one *chiral* centre or *chiral* torsion axis (axis of chirality).

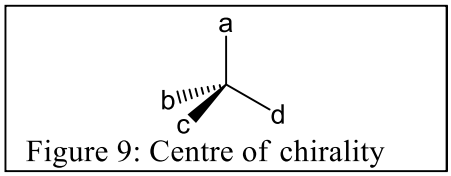
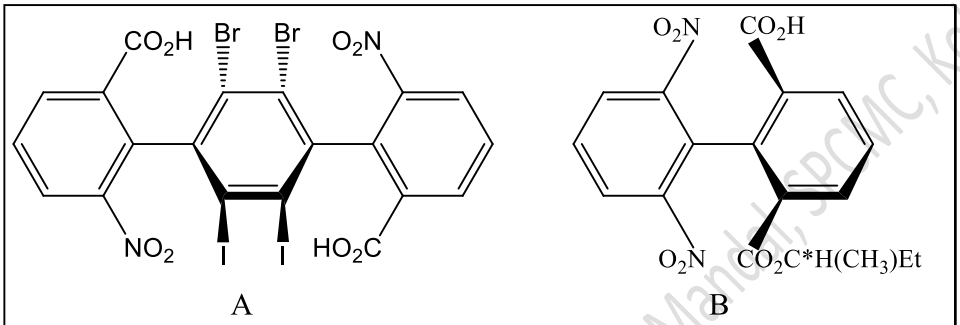


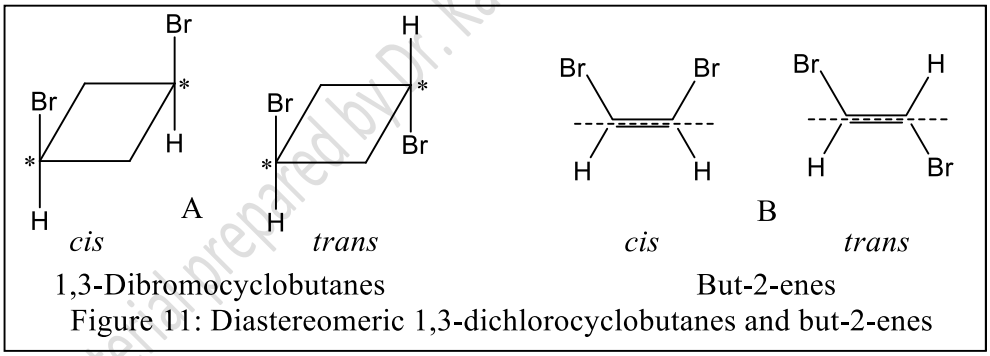
Figure 9: Centre of chirality

Diastereomers often contain two or more *chiral* centres (Figure 7), *chiral* (torsion) axes (Figure 10; A), or a combination there of (Figure 10; B). However, there are cases where diastereomers are neither *chiral* nor contain *chiral* centres; alkene diastereomers (B; Figure 11) are of this type.



A B
Figure 10: Diastereomers in terphenyl and biphenyls

Diastereoisomerism is not necessarily associated with *chiral* centres or *chiral* torsion axes; a general scheme for factorizing diastereoisomerism must go beyond consideration of these *chiral* elements.



A B
cis *trans* *cis* *trans*
1,3-Dibromocyclobutanes But-2-enes
Figure 11: Diastereomeric 1,3-dichlorocyclobutanes and but-2-enes

The starred carbon atoms (C*) in Figure 11 (A) (which are the foci of the diastereoisomerism but are not *chiral*, since each bears two identical ligands) have been called "centres of stereoisomerism" or *"stereogenic centres"*. Interchange of two ligands at a *stereogenic centre* leads to a stereoisomer. Similarly, the axis containing the olefinic double bond (dashed in B; Figure 11) may be called a *"stereogenic axis."* The axis containing the phenyl-phenyl bonds in the terphenyl shown in Figure 10 (A) is also a *stereogenic axis*.

Concept of Stereogenecity and Chirotopicity

Stereogenic centres thus may be or may not be *chiral* (i.e., centres of chirality). Conversely, however, all *chiral* centres are *stereogenic*. The subject of stereogenicity is distinct from chirality. A point in a molecule (it need not be a material point coincident with an atom) is *chirotopic* if it is located in a *chiral* environment. Any point in a *chiral* molecule is *chirotopic*, but even in an *achiral* molecule there may be many *chirotopic* points or atoms. For example, in *meso*-tartaric acid (Figure 7; A) all atoms are *chirotopic*; only the centre of symmetry [midway between C(2) and C(3)] is *"achirotopic"* (i.e., not *chirotopic*).

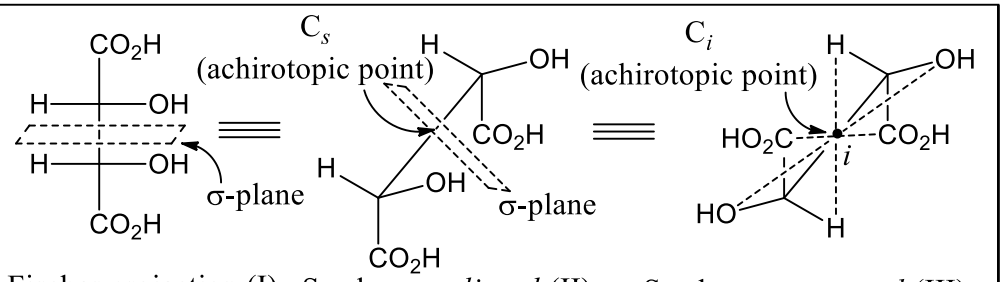
In general, "all points in a model that remain invariant under a rotation-reflection operation are *achirotopic*"; thus, all points on a plane of symmetry in a molecule are *achirotopic*. It is to be noted that van't Hoff's asymmetric atom has two separate aspects: one, that it is a focus of dissymmetry or chirality (*chirotopic*), the other, that the exchange of two ligands at the asymmetric atom gives rise to stereoisomers (it is *stereogenic*). With carbon, these two aspects are usually linked, although, this is not always the case.

The description of an atom (or point, group, face, etc. in a molecular model) that resides within a *chiral* environment is *chirotopic*. The description of an atom (or point, group, face, etc. in a molecular model) that resides within an *achiral* environment has been called *achirotopic*.

The site symmetry of atoms in molecules falls into two classes, *chiral* and *achiral*. It is important to note that main classification of chirality and achirality is a function of geometric shape. Any atom within a molecular framework is said to be *chirotopic* if its site symmetry is *chiral*, i.e., the atom resides in a *chiral* environment. The molecules bearing *chirotopic* centre need not be as a whole *chiral*.

An atom within a molecular framework is said to be *achirotopic* when its site symmetry is *achiral*, i.e., the atom resides in an *achiral* environment, such as 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 interacts in reflection plane. All segments or points in a *chiral* molecule are *chirotopic* because chirality is in all-inclusive property, as it affects all parts of a *chiral* molecule. For example, in lactic acid [$CH_3CH(OH)CO_2H$], all ligands are *chirotopic* but in propanoic acid [$CH_3CH_2CO_2H$], the ligands are *achirotopic*, i.e., they do not reside in *chiral* site symmetry.

It is sometimes possible to divide an *achiral* molecule to two *chirotopic* segments, and then there will always be at least one point in an *chiral* conformation of the molecule which is *achirtopic* point, even though the *achirotopic* point may not contain an atomic nucleus. For example, *meso*-tartaric acid can have two *achiral* conformations one with C_i and the other with C_s point group of symmetry, i.e., *achirotopic* points. However, many *chiral* conformations of tartaric acid are also possible. Figure 12 illustrates the *achirotopic* points.



Fischer projection (I) *meso*-tartaric acid | Sawhorse *eclipsed* (II) *achiral* conformation with C_s point group | Sawhorse *staggered* (III) *achiral* conformation with C_i point group

Figure 12: *meso*-Tartaric acid in different projections

Stereogenic Unit (stereoelement)

Stereogenic unit is a grouping within a molecular entity that may be considered a focus of stereoisomerism. At least one of these must be present in every enantiomer (though the presence of *stereogenic* units does not conversely require the corresponding chemical species to be *chiral*). Three basic types are recognized for molecular entities involving atoms having not more than four substituents:

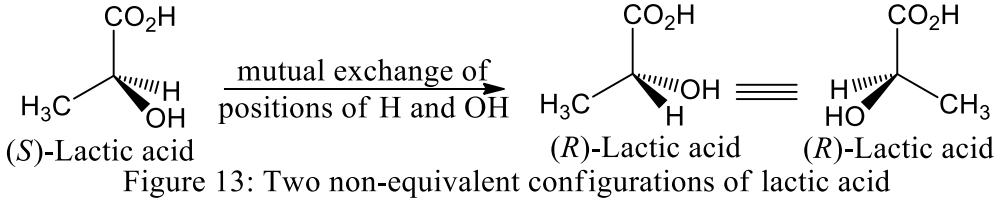
1. A grouping of atoms consisting of a central atom and distinguishable ligands, such that the interchange of any two of the substituents leads to a stereoisomer. An *asymmetric atom* (chirality centre) is the traditional example of this *stereogenic unit*.
2. A chain of four non-coplanar atoms (or rigid groups) in a stable conformation, such that an imaginary or real (restricted) rotation (with a change of sign of the torsion angle) about the central bond leads to a stereoisomer.
3. A grouping of atoms consisting of a double bond with substituents which give rise to *cis-trans* isomerism.

The term, *stereogenic* atom or centre, may be defined as follows:

a) An atom (usually carbon) of such nature and bearing of groups of such nature that it can have two non-equivalent, i.e., non-superposable configurations.

b) An atom bearing several groups of such nature that mutual exchange of any two groups on that atom generates a new stereoisomer.

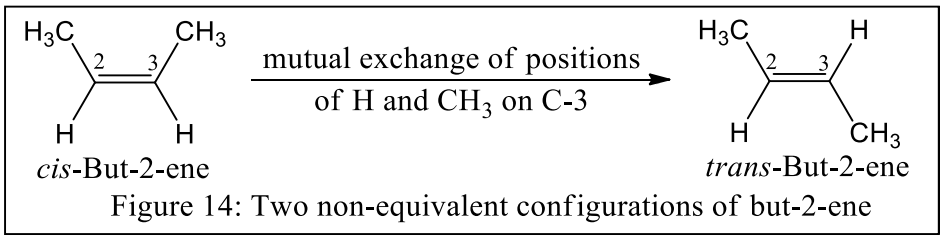
In molecules like Cabcd, lactic acid for example (Figure 13), carbon atom is *stereogenic* because the molecule can exist in two non-equivalent configurations.



(*S*)-Lactic acid | (*R*)-Lactic acid | (*R*)-Lactic acid

Figure 13: Two non-equivalent configurations of lactic acid

Again, C-2 and C-3 carbon atoms of *cis*-and *trans*-but-2-ene (Figure 14) are *stereogenic* because interchange of H and CH_3 on any of these atoms gives a new stereoisomer.



cis-But-2-ene *trans*-But-2-ene

Figure 14: Two non-equivalent configurations of but-2-ene

In case of olefins like Cab=Cab or Cab=Cac, the axis joining two carbon atoms is called *stereogenic axis* (Figure 15), because stereoisomerism by interchange of positions of substituents on each carbon atom is made possible due to the rigid axis joining two carbon atoms by a double bond.

In case of allene like Cab=C=Cab, the axis passing through carbon atoms is also called stereogenic axis.

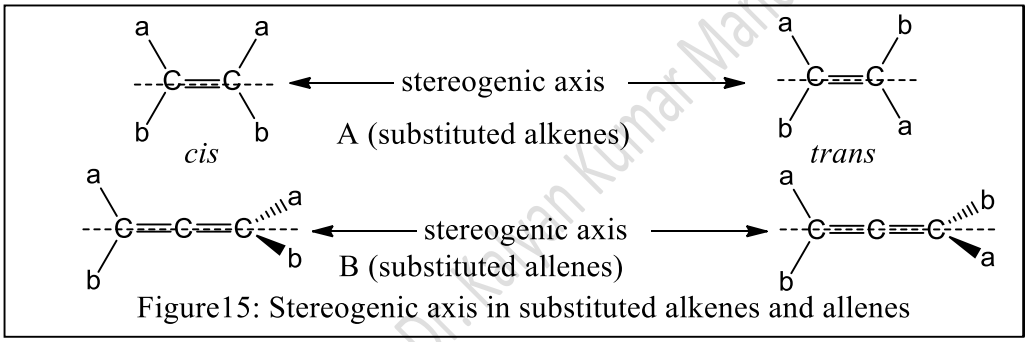


Figure15: Stereogenic axis in substituted alkenes and allenes

Difference between Stereogencity and Chirotopicity

The terms stereogenecity and chirotopicity may not coincide in many centres. In molecules like Cabcd, a ≠ b ≠ c ≠ d, the carbon centre is *chirotopic* as well as *stereogenic* where the ligands a, b, c, and d are *chirotopic* but *non-stereogenic*. Carbon atoms in 1,2-dibromo-1,2-dichloroethane (Case I, B; Figure 16) are *chirotopic* as well as *stereogenic*.

Both the carbon atoms in *cis*-but-2-ene (Case II, A; Figure 16) are *stereogenic* but *achirotopic*. In CH_2X_2 type molecules, such as in dibromomethane, propan-2-ol, etc., the carbon centre is *achirotopic* as well as *non-stereogenic* (Case IV; Figure 16).

In all stereoisomers of 2,3,4-trihydroxyglutaric acid, C-2 and C-4 centres are *chirotopic* as well as *stereogenic* (Case I, C; Figure 16), but C-3 is *stereogenic* but *achirotopic* in the *meso*-isomers (Case III, B; Figure 16) whereas *chirotopic* but *non-stereogenic* in the *active*-isomers (Case IV; Figure 16).

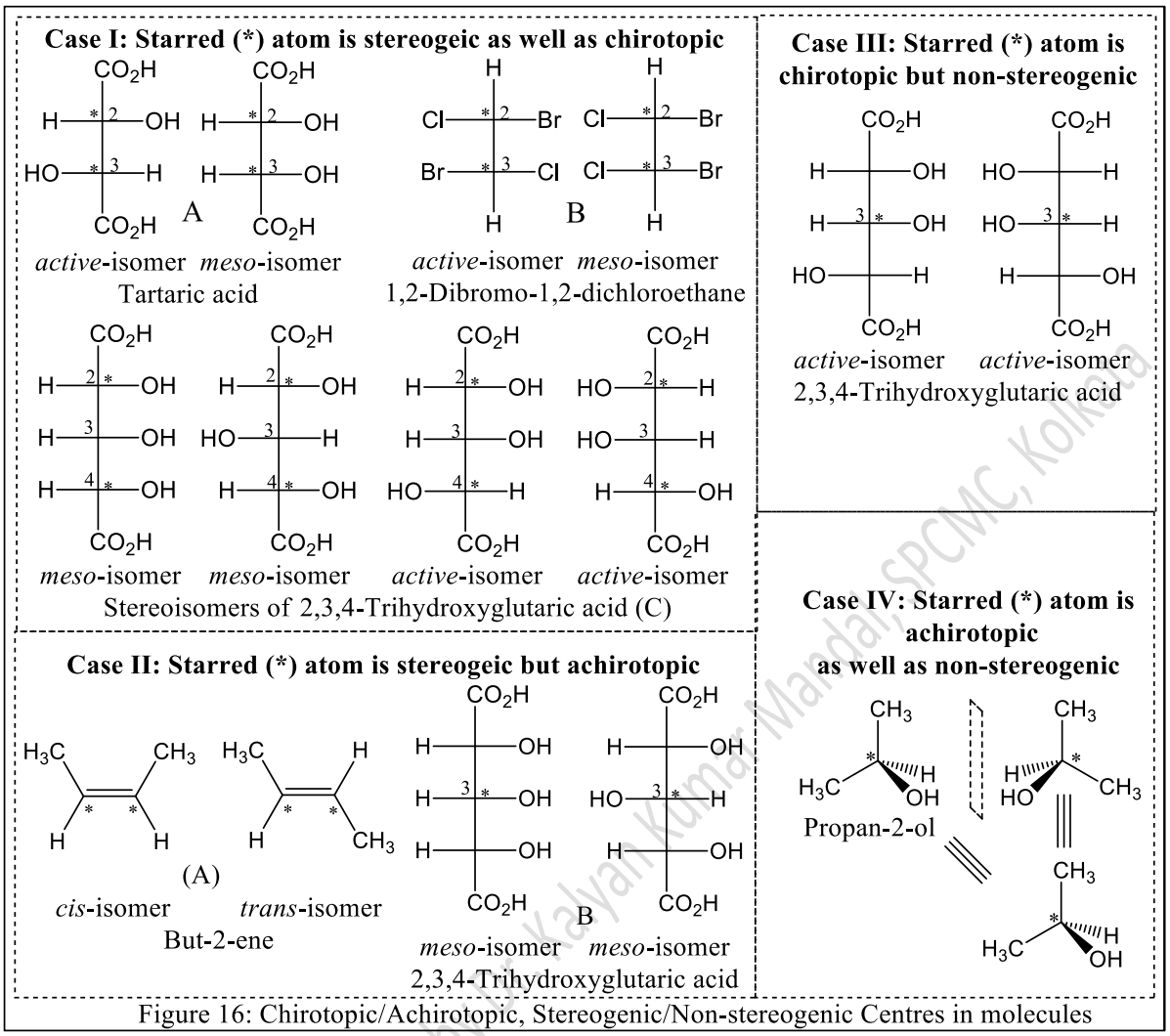


Figure 16: Chirotopic/Achirotopic, Stereogenic/Non-stereogenic Centres in molecules

Difference between Stereogencity and Chirotopicity

In this set of isomers, trihydroxyglutaric acids, there are two *meso* forms (I and II; Figure 17) and one pair of enantiomers (III and IV). In the *active* isomers of 2,3,4-trihydroxyglutaric acid, C-2 and C-4 are *chirotopic* because their site symmetry is C_1, i.e, they do not lie on a σ-plane, or on a *centre* of symmetry or no alternating axis of symmetry passes through them that intersects its reflection plane. They are *stereogenic* as well, because interchange of H and OH on these atoms separately leads to a new stereoisomer, a *meso*-isomer. Figure 18 illustrates this statement.

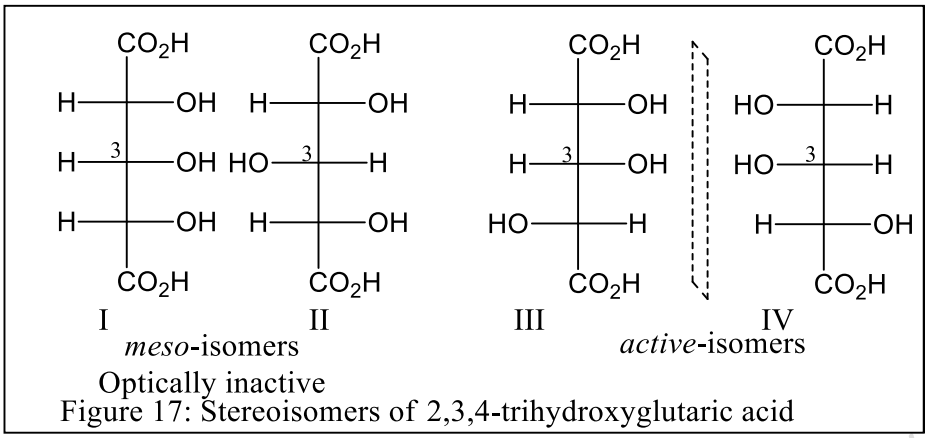


Figure 17: Stereoisomers of 2,3,4-trihydroxyglutaric acid

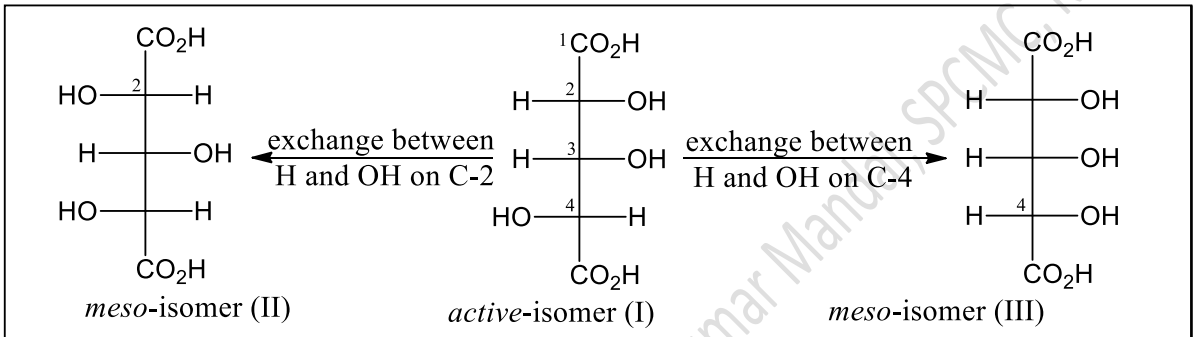


Figure 18: C-2 and C-4 atoms in 2,3,4-trihydroxyglutaric acid *are chirotopic and stereogenic*

C-3 in all the stereoisomers of 2,3,4-trihydroxyglutaric acid is of particular interest. In the *chiral* members (III and IV; Figure 17) of the set, C-3 is a *non-stereogenic* centre since its two *chiral* ligands ($^{*}CHOHCO_2H$) are *homomorphic* (constitutionally and configurationally identical). The transposition of H and OH at C-3 in either enantiomer leads to an identical structure. This is seen by turning the new structure by 180°, which is an allowed operation (Figure 19). These structures are of the type $CL^{+}L^{+}XY$. In the *achiral* members of the set (type $CL^{+}L^{-}XY$), permuting the ligands at C-3 leads from one diastereomer to the other, both diastereomers being *meso* forms. This is elaborated in Figure 20.

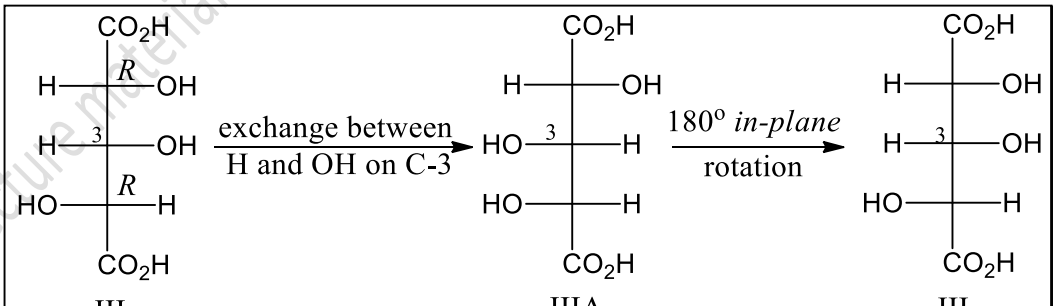


Figure 19: C-3 *is non-stereogenic in active*-2,3,4-trihydroxyglutaric acid

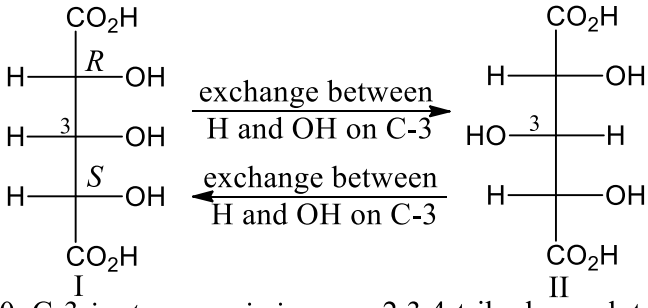


Figure 20: C-3 *is stereogenic in meso*-2,3,4-trihydroxyglutaric acid

C-3 is a centre of stereoisomerism (*stereogenic* centre), but it is not a *chiral* centre. In these isomers (*meso*), (I and II; Figure 17), the central carbon atom is *asymmetric*, but the molecule as a whole is not, since it has a *plane* of symmetry bisecting carbon atom No. 3. The central carbon atom (No. 3) in isomers I and II is said to be *"pseudoasymmetric,"* meaning that its asymmetry is due to two of the attached groups being opposite in configuration. C-3 atom of these isomers is, thus, *achirotopic*. This is because, chirality is *all-inclusive* property.

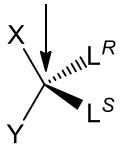
In the light of stereoisomerism, the carbon atom of the molecule of the type C*abcd should be more appropriately called *stereogenic* than *chirotopic* because *stereogenecity* is a more intrinsic property of the molecule. *Chirotopicity* of a molecule is manifested only when it encounters with external *chiral* agents like polarized light. *Stereogenic* centres of a molecule may or may not be *chiral*, but all *chiral* centres are *stereogenic*.

Pseudoasymmetric Carbon Atom and Pseudoasymmetry

The traditional name for a tetrahedrally coordinated carbon atom bonded to four different entities is *psudoasymmetric*, when two and only two of which have the same constitution but opposite chirality sense. The *r/s* descriptors of *pseudoasymmetric carbon atoms* are invariant on reflection in a mirror (i.e. *r* remains *r*, and *s* remains *s*), but are reversed by the exchange of any two entities (i.e. *r* becomes *s*, and *s* becomes *r*). An example is C-3 of ribaric (I of Figure 22; C-3 is *r*) or xylaric acid (II; C-3 is *s*). The general structure of a *pseudoasymmetric centre* may be represented as follows (Figure 21):

A *stereogenic* [but *achirotopic*] atom of whose four distinct ligands, two are enantiomorphic (i.e., opposite configuration), as in $CL^{+}L^{-}XY$ is called *pseudoasymmetric*. Molecules containing such atoms are *achiral*, but interchange of two ligands gives rise to diastereomers.

pseudoasymmetric centre



where L^R and L^S represent *chiral* groups which are constitutionally identical but configurationally different. L^R and L^S are, therefore, enantiomeric groups. X and Y represent *achiral* groups which are different.

Figure 21: Molecules containing Pseudoasymmetric centre

Absolute Configuration of a Pseudoasymmetric Centre

To specify absolute configuration of a *pseudoasymmetric centre*, it is to be remembered that the attached chiral group having (*R*) configuration gets priority over the same *chiral* group with (*S*) configuration. On this basis, the configuration at C-3 in I and II (Figure 22) can be determined. The absolute configuration of a *pseudoasymmetric centre* is denoted by *r* or *s*.

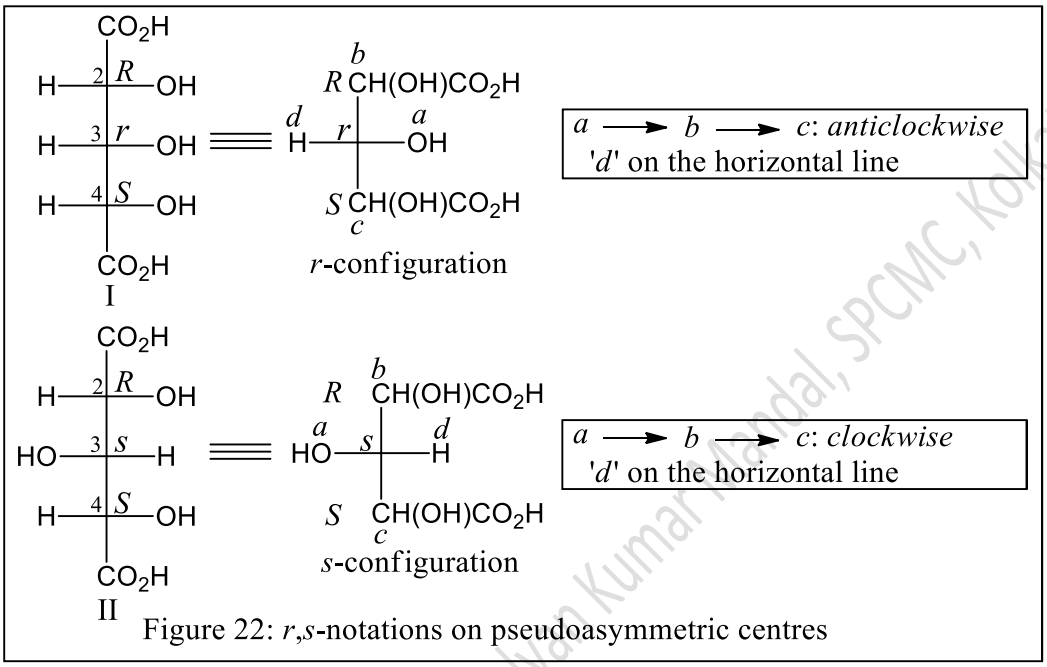


Figure 22: *r*,*s*-notations on pseudoasymmetric centres

The complete stereochemical nomenclature of I and II are (2*R*,3*r*,4*S*-2,3,4-trihydroxy-pentanedioic acid and (2*R*,3*s*,4*S*-2,3,4-trihydroxypentanedioic acid, respectively. The stereochemical descriptor of a *pseudoasymmetric centre* is reflection invariant. This can be shown in the following example (Figures 23 and 24).

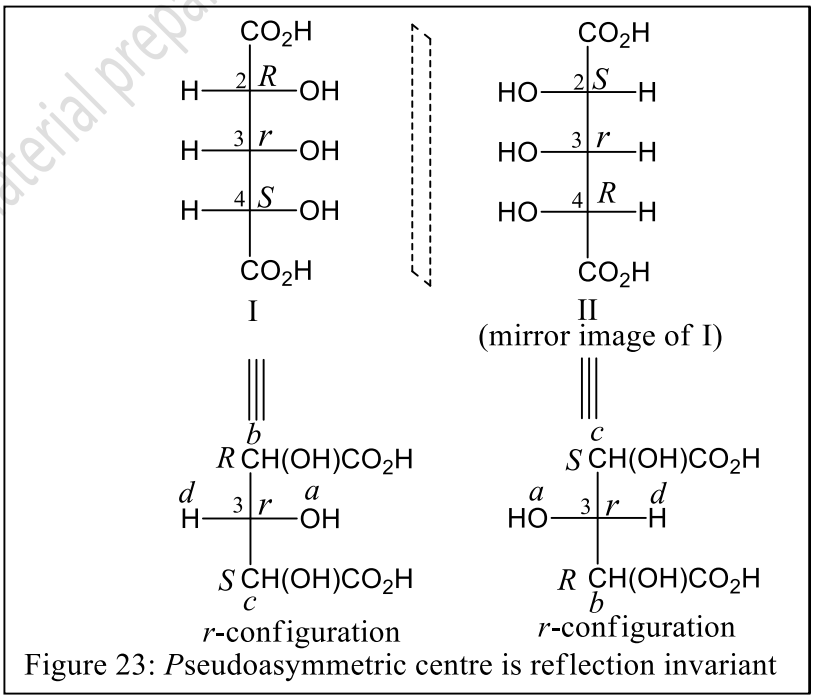


Figure 23: *P*seudoasymmetric centre is reflection invariant