

STEREOCHEMISTRY II

SEM-1, CC-1B

PART-8, PPT-8

Part-8: Configurations-I

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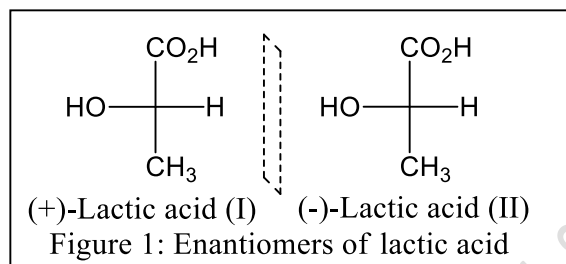
Kolkata

Stereochemistry (PART-8, PPT-8)

Configurations-I

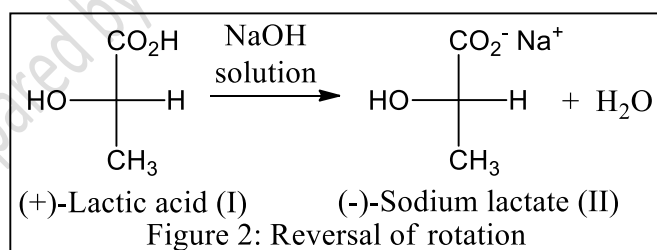
Configuration

By “configuration” is meant the arrangement in space of the atoms or groups around the dissymmetric or rigid part of a molecule-in the simplest case, around an asymmetric carbon. For example, the formulae for (+)- and (-)-lactic acid (Figure 1) represent molecules of identical structure but different configuration.

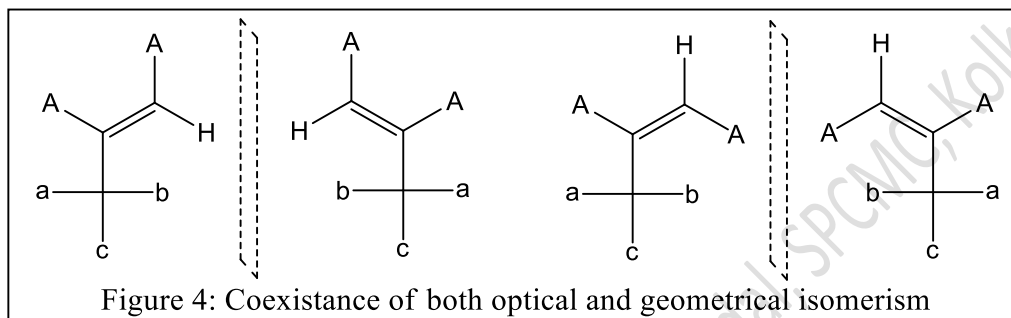
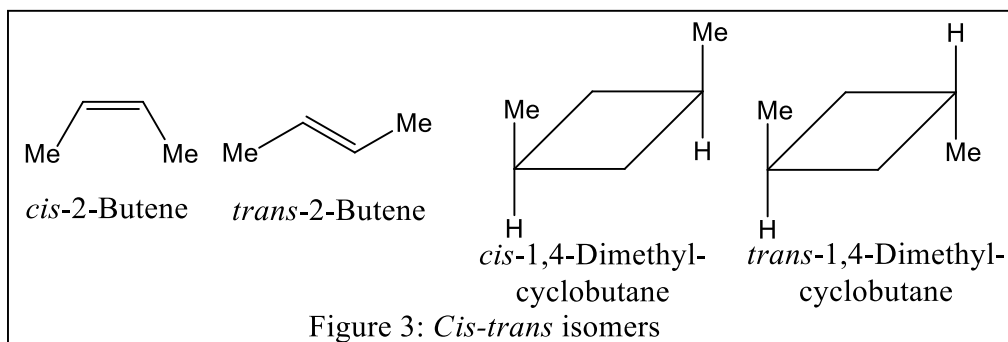


Rotation is an experimental property, measured in a polarimeter. Configuration is a theoretical concept related to molecular architecture, expressed by a (three-dimensional or projection) formula. While configuration is less tangible than rotation, it is more fundamental.

When (+)-lactic acid (Figure 2) is dissolved in aqueous sodium hydroxide, the resulting solution of sodium lactate is *levorotatory* and would have to be called (-)-sodium lactate. Nevertheless, the arrangement of the groups about the asymmetric carbon is not changed by the abstraction of the ionisable hydrogen. Asymmetric carbon atom is untouched during the course of the reaction. Both lactic acid and sodium lactate can be represented by the same molecular architecture (with CO_2^- instead of CO_2H).



Cis-trans isomers (Figure 3) also differ in configuration, namely, in the arrangement of the groups about the (rigid) double bond or ring. No additional complication is introduced in cases where both optical and geometrical isomerism coexist (Figure 4).



By specifying the configuration at each asymmetric atom and pertinent double bond, one specifies also their relative configuration; in other words, one specifies with which optical isomer one is dealing and to which geometrical configuration has corresponds.

Glossary

Absolute configuration: The spatial arrangement of the atoms of a *chiral* molecular entity (or group) that distinguishes it from its from image, and its stereochemical description e.g. *R* or *S*. Absolute configuration is reflection-variant.

Relative configuration: The configuration of any stereogenic (asymmetric) centre with respect to any other *stereogenic* centre contained within the same molecular entity. Unlike absolute configuration, relative configuration is reflection-invariant.

Reflection invariant: This term is applied to a structure or substructure (part of a structure) that remains unchanged by reflection, such as an *achiral* or *meso* compound).

Configurational Nomenclature

Relationship between two molecules of same molecular formula giving rise to different stereochemical or structural terms. The configuration of a molecule is completely specified either by an appropriate three-dimensional model or formula drawing or by the corresponding projection formula. Fischer projection formula are preferred for this particular purpose.

However, just as there are names as well as structural formulae to specify structure, it is desirable to have symbols as well as three-dimensional or projection formulae to specify

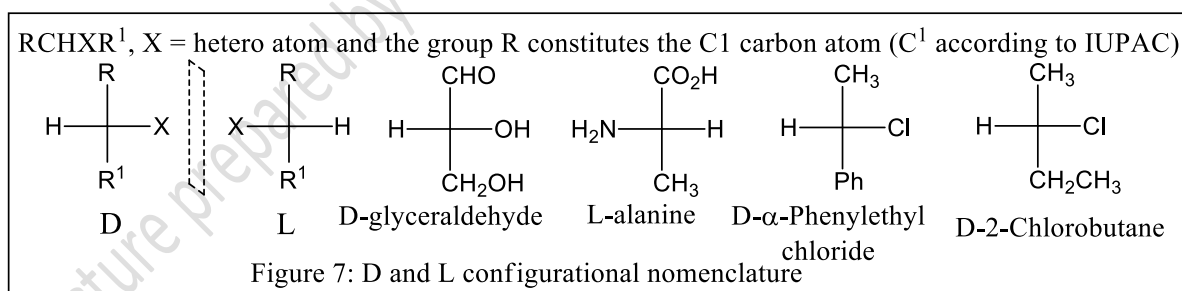
configuration. Two different methods are in use for completely specifying the absolute configuration of a *chiral* centre in a molecule. These are:

1. Fischer's D, L-Nomenclature
2. R, S-Nomenclature (CIP Rule)

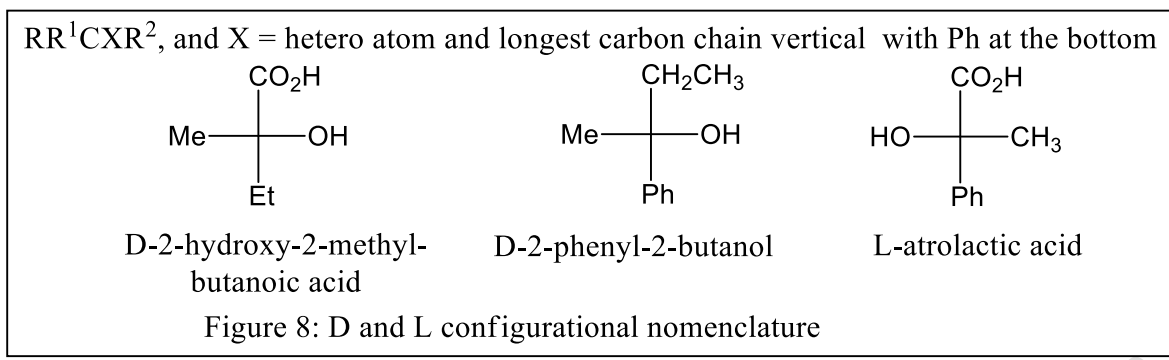
Fischer's D, L-Nomenclature

This oldest system of nomenclature of *chiral* compounds was introduced by Emil Fischer in 1891, while working with carbohydrates. Rosanoff modified the system in 1906 and suggested the following conventions for a projection nomenclature of D, L system.

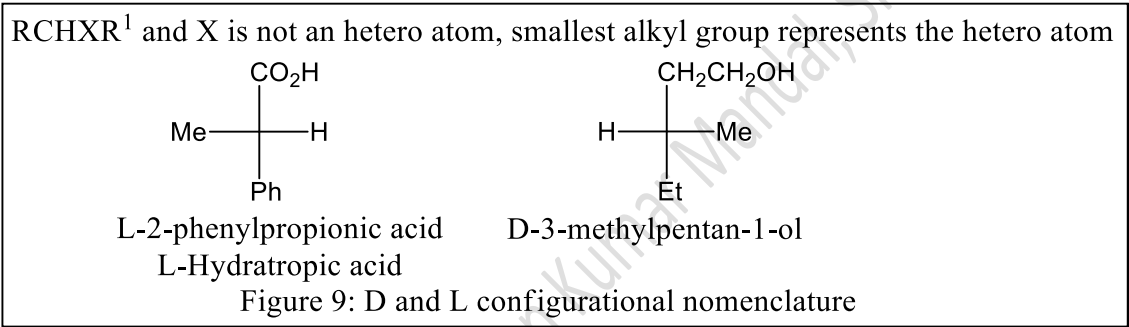
1. As in Fischer's system, the molecule is written with the longest carbon chain placed vertically. When the *chiral* centre contains a ring system, then total numbers of carbon atoms including the ring are taken into consideration to right down the main chain in Fischer projection.
2. The C1 carbon or the most highly oxidized end of the chain is placed at the top, following Fischer's convention, e.g., $-\text{COOH} > -\text{CHO} > -\text{CH}_2\text{OH}$ (according to IUPAC also).
 - (a) The system works well for compounds of the type RCHXR^1 , where R-C-R¹ constitutes the main chain of the molecule and X is a hetero atom. The molecule is so oriented that the No. 1 carbon of the main chain is at the top in Fischer projection formula. Then if X is on the right, the molecule is called "D" and if X is on the left, the molecule is called "L". When phenyl or aryl group is attached to the *chiral* centre, it is generally placed at the bottom in Fischer projection (Figure 7).



- b) In compounds of the type RR^1CXR^2 (here, X represents the hetero atom and R¹ represents the smallest alkyl group), this system is also applicable (Figure 8). The molecule is D when X (hetero atom) is on the right, and the small alkyl group R¹ is to the left. The molecule is L when X (hetero atom) is on the left, and the small alkyl group R¹ is to the right. The enantiomer of D is L.

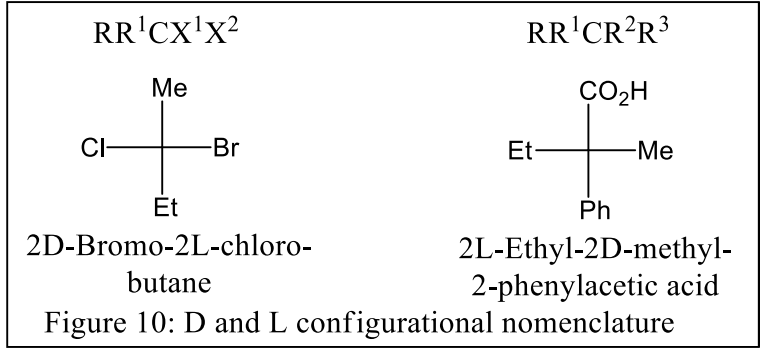


The system may be applied also to cases where X is an alkyl group, i.e., the molecule (of the type $RCHXR^1$) does not have a hetero atom directly attached to the *chiral* carbon atom. Now, if $R-C-R^1$ constitutes the main carbon chain of the molecule and that D means that X [the smallest alkyl group (usually Me) becomes the *fiducial* group] is to the right, if to the left it is L. Figure 9 illustrates the situation.



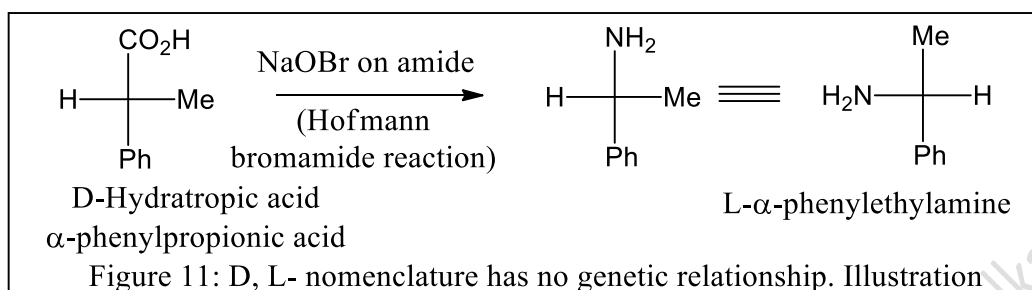
d) When the *chiral* centre carries two different substituents of comparable electronegativity, D- and L-notations are generally used separately for each substituent to specify the configuration. This is also true when two different alkyl groups are present in horizontal bonds.

Thus, the system may be applicable to compounds of the types $RR^1CR^2R^3$, having asymmetric quaternary carbon, e.g., 2L-methyl-2D-ethyl-2-phenylacetic acid. Figure 10 illustrates the situation.



The configurational (D, L or R,S) nomenclature is conventional rather than based on genetic relationship. Thus, the $-\text{COOH}$ group of D-hydratropic acid when converted to $-\text{NH}_2$ gives L- α -phenylethylamine, although no bond to the *chiral* centre is broken.

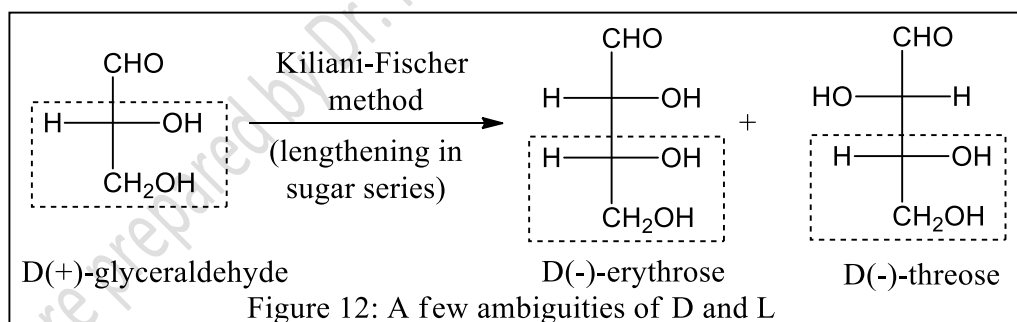
The Hofmann bromamide reaction as applied to D-hydratropic acid is known to proceed without change (*retention*) of configuration. Nevertheless, the nomenclature convention is such that the product must be labeled L- α -phenylethylamine (Figure 11).



Ambiguities/Shortcomings of D, L Nomenclature

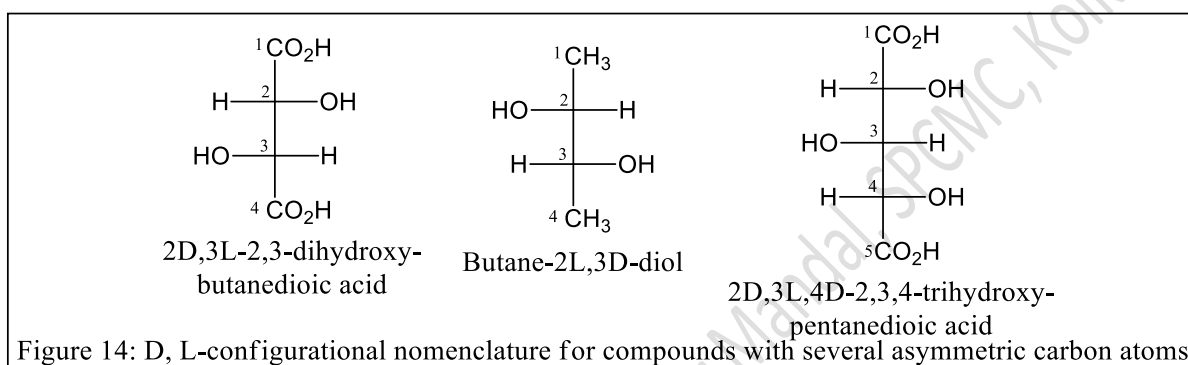
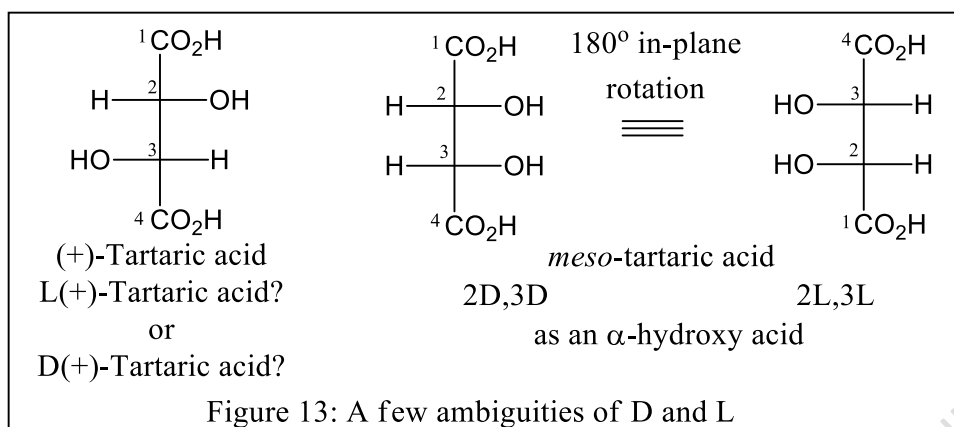
Difficulties in the use of D, L-nomenclature arise when it is to be applied to compounds with more than one asymmetric atom. For example, in (-)-threose (Figure 12) the hydroxyl group on the lower (No.3) asymmetric carbon atom is on the right, but that on the upper (No. 2) asymmetric carbon atom is on the left when the formula is written in the Fischer projection (more oxidized carbon being at the top). Should this compound be called D or L?

An additional convention has been developed according to which in the sugars (in carbohydrate chemistry) the asymmetric carbon next to the primary alcohol group (not the aldehyde group) is the one that specifies convention (Figure 12). Therefore, the (-) threose is D(-)-threose and the (+) threose is D(+)-threose. It is to be noted that, D and L do not have any formal correspondence with *d* (or +) or *l* (or -), respectively.



There seems to be no agreement whether the (+)-tartaric acid (Figure 13) should be called “L(+)-tartaric acid” using the bottom asymmetric carbon as reference, or “D(+)-tartaric acid” using the top asymmetric carbon as reference. Ambiguity also arises for D and L designation of tartaric acid diastereomers.

Useful extensions of the D,L-nomenclature to compounds containing more than one asymmetric carbon have been proposed. This system specifies that each asymmetric carbon in a compound possessing more than one is to be given a configurational symbol (Figure 14).



Specification of Absolute Configuration

The D, L nomenclature of Fischer applies to the Fischer projection. In spite of the shortcomings/ambiguities, the Fischer nomenclature has proved particularly useful for sugars or amino acids. However, one should avoid confusion between *d*, *l* (*dextrorotatory* or *levorotatory*) and D, L (absolute configuration). A *d*-compound may have the absolute configuration either D or L, e.g., (*d*)-L-alanine and (*d*)-D-glyceraldehyde, which are now expressed as L-(+)-alanine and D-(+)-glyceraldehyde.

D, L nomenclature is, thus, not generally useful to some types of compounds with *chiral* centers. Cahn, Ingold, and Prelog (CIP) developed *R-S* nomenclature, generally applicable to *chiral* compounds of all three different types having (i) a *centre of chirality*, (ii) an *axis of chirality*, and (iii) a *plane of chirality*. However, each of these chirality elements requires a particular method of nomenclature.

The CIP sequence rules are a standard process used to completely and unequivocally name a stereoisomer of a molecule. The purpose of the CIP system is to assign an *R* or *S* descriptor (Absolute configuration) to each stereocenter and an *E* or *Z* descriptor (Relative configuration) to each double bond so that the configuration of the entire molecule can be specified uniquely by including the descriptors in its systematic name.

A molecule may contain any number of stereocentres and any number of double bonds and each usually gives rise to two possible isomers. A molecule with an integer '*n*' describing the

number of its stereogenic centres will usually have 2^n stereoisomers, and 2^{n-1} diastereomers each having an associated pair of enantiomers. The CIP sequence rules contribute to the precise naming of every stereoisomer.

R, S Nomenclature: Centre of Chirality

A centre of chirality is usually associated with an asymmetric carbon atom, $Cabcd$. A self-consistent and unambiguous system of configurational nomenclature based on the three-dimensional structures of molecules was first introduced by Cahn and Ingold (1951) and subsequently elaborated by Cahn, Ingold and Prelog (1956, 1966). The system is known as CIP nomenclature after the names of the authors.

According to this system, the configuration of a molecule is specified uniquely either as R (for *rectus*, Latin for right) or S (for *sinister*, Latin for Left) which is independent of nomenclature and numbering. Like D and L , R and S also have nothing to do with the signs of rotation. R and S are usually put within parenthesis.

Assignment of configuration is done by the application of two rules: the sequence rule (consisting several standard sub rules) and the chirality rule.

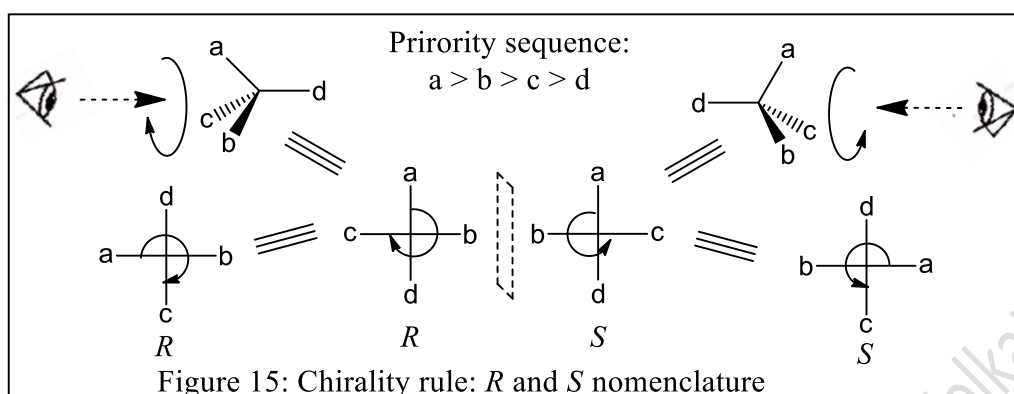
Sequence Rules: The four ligands attached to the *chiral* centre ($Cabcd$) are first ordered according to the sequence rule. According to this rule, the ligands are arranged in decreasing atomic number of the atoms by which they are bound to the asymmetric carbon atom. If two or more of these atoms have the same atomic number, then the relative priority of the ligands is determined by a similar comparison of the atomic numbers of the next atoms in the group are considered. Thus, one works outwards from the asymmetric carbon atom until a selection can be made for the sequence of the ligands.

CIP Chirality rule

Chirality Rule: The path of the sequence of precedence/priority $a \rightarrow b \rightarrow c$ is followed from the preferred side of the model (containing the three preferred ligands a , b , and c), i.e., remote from the ligand of the lowest precedence d . If the path turns right (traces clockwise, which is the entire sense of direction of abc) the element is assigned *chiral* label " R ". If the said path turns left (traces anticlockwise, which is the entire sense of direction of abc) then the stereogenic center is assigned the *chiral* label " S ".

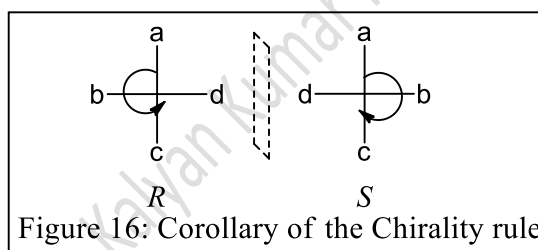
It is evident from Figure 15 that in the Fischer projection formula, if d (the least priority group) is at the bottom or top: $a \rightarrow b \rightarrow c$ makes a clockwise movement in the R -configuration; $a \rightarrow b \rightarrow c$ makes an anticlockwise movement in the S -configuration.

Specification of Absolute Configuration



Corollaries of the Chirality Rule

If *d* is on the right or left side of the Fischer projection formula, or above the plane containing the two in-plane bonds in the *flying wedge* formula, the anticlockwise movement from $a \rightarrow b \rightarrow c$ (or $1 \rightarrow 2 \rightarrow 3$) will define *R*-configuration, and clockwise movement will define *S*-configuration.



CIP Sequence Rules or Standard Sub-Rules for Ascertaining the Priority Sequence of Ligands

The Sequence rules or standard sub-rules are applied considering different aspects, as needed. They must be applied in succession, i.e., one after the other in the order stated:

1. **Sub-rule 0:** Nearer end of an axis or a plane precedes the farther end (proximity rule).
2. **Sub-rule 1:** Higher atomic number precedes lower, e.g., $I > Br > Cl > S > P > Si > F > O > N > C > H$
3. **Sub-rule 2:** Higher atomic mass number precedes lower, e.g., $T > D > H$
4. **Sub-rule 3:** *Cis* precedes *trans* and *sequential cis* (*Z*) precedes *sequential trans* (*E*) (*cis* > *trans* and *Z* > *E*).
5. **Sub-rule 4:** Like pair *R,R* or *S,S* precedes unlike pair *R,S* or *S,R*.
6. **Sub-rule 5:** *R* precedes *S* ($R > S$)

'Sub-rule 0' gets the topmost priority but is applicable to *axially chiral molecules* to be discussed later (Semester-II).

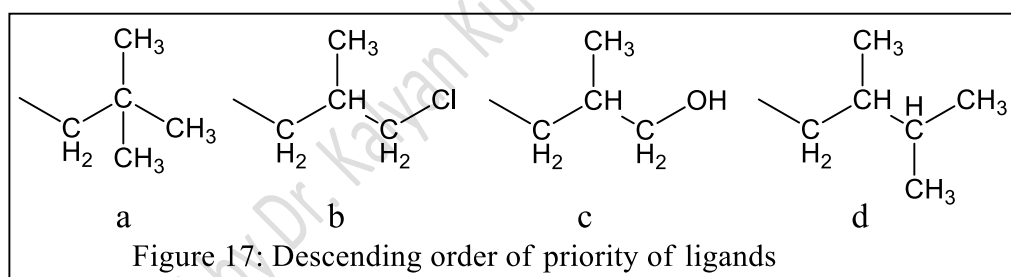
For the majority of compounds, only “sub-rules (1) and (2)” are important. The other sub-rules apply only to special cases. Sub-rule (1) needs further elaboration which is done in the following paragraphs:

- Atoms directly attached to the *chiral* carbon atom must be sequenced first according to sub-rule (1). If the two atoms directly linked to the asymmetric carbon atom are different, the atoms of higher atomic number get precedence. If the priority still remains undecided for some of the ligands, one passes over to the next atom in the ligands and the exploration continues until a decision is reached on the basis of the sub-rules, e.g.,

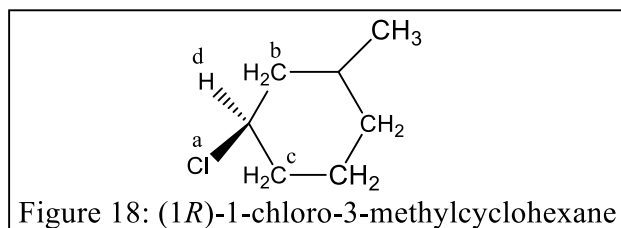


It is to be noted that the *sub-rule* (2) must not be used until the *sub-rule* (1) is completely exhausted: thus $-\text{CH}_2\text{CH}_2\text{CH}_3 > -\text{CD}_2\text{CH}_3$ because propyl $>$ ethyl (*sub-rule* 1); but $-\text{CH}_2\text{CD}_2\text{CH}_3 > -\text{CH}_2\text{CH}_2\text{CH}_3$ (*sub-rule* 2).

- In case a ligand bifurcates, one must proceed along the branch providing the highest precedence until a difference is encountered. The decision must be made at the *earliest* opportunity and once made, cannot be changed from consideration of substituents farther along the chain. These points are illustrated in Figure 17.

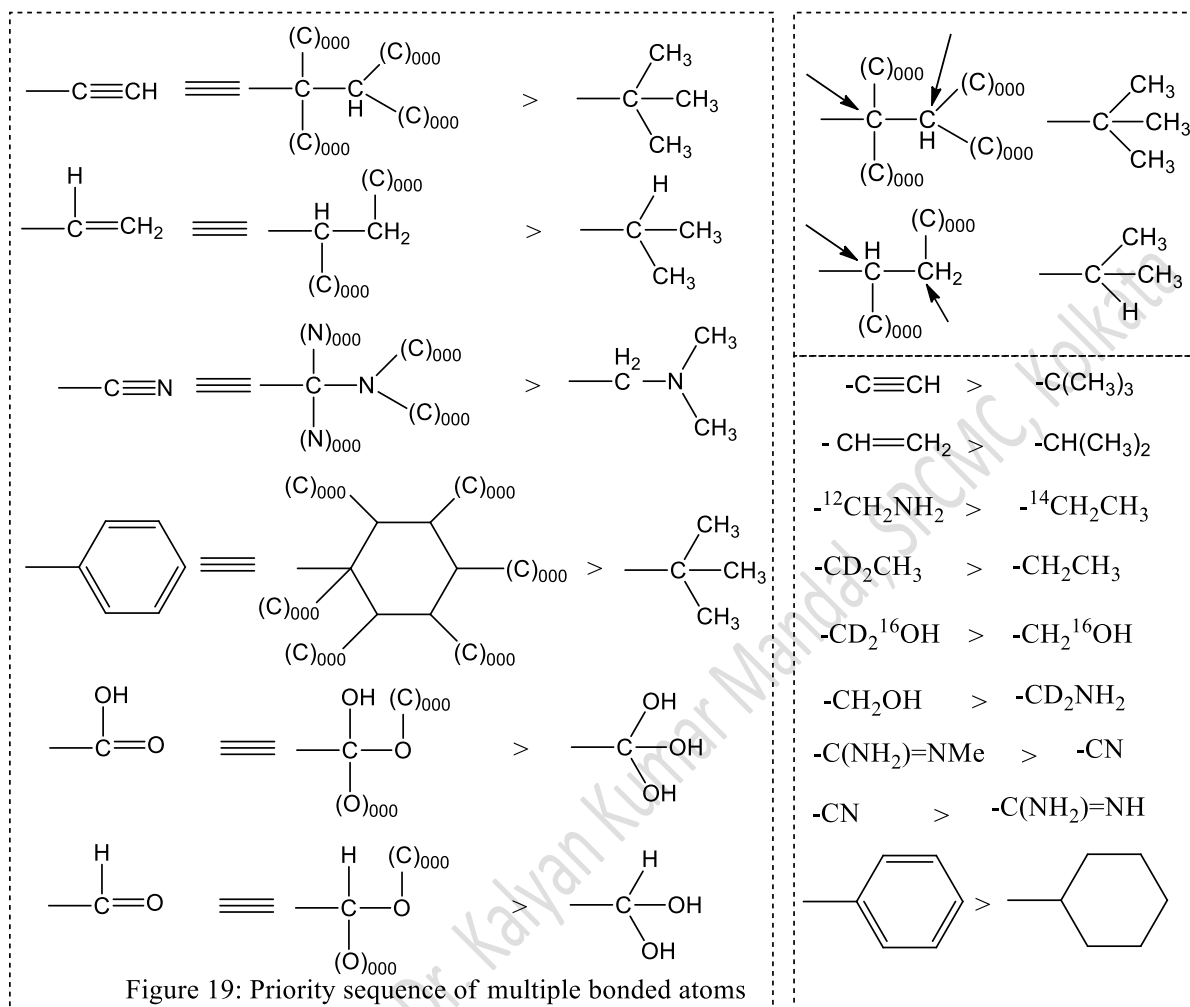


- If the ligands attached to the asymmetric centre are composed of only C and H atoms, then the ligand with a smaller number of H atom gets priority. For example:
 $-\text{CR}_3 > -\text{CHR}_2 > -\text{CH}_2\text{R} > -\text{CH}_3$



- When the *chiral* carbon atom is a part of a ring system, each branch is followed until a decision is reached as shown in Figure 18.
- Multiple bonded atoms are treated as four-coordinated ones by adding replica atoms of the same type (duplications or triplications) which are bracketed to signify that they are surrounded by phantom atoms of atomic number zero. Both atoms attached to the

multiple bonds are considered to be duplicated (for a double bond) or triplicated (for a triple bond) as shown in Figure 19.



6. *Sub-rule 3: Higher atomic mass number precedes lower:* When a *chiral* centre contains isotopic atoms directly attached to the *chiral* centre then the atom with the higher mass number gets the priority. For example, in case of H and D, deuterium will get preference over H. Similarly, $^{18}\text{O} > ^{16}\text{O}$ and $^{15}\text{N} > ^{14}\text{N}$.

In case of $^{-12}\text{CH}_2\text{NH}_2$ and $^{-14}\text{CH}_2\text{CH}_3$, $^{-12}\text{CH}_2\text{NH}_2$ will get preference over $^{-14}\text{CH}_2\text{CH}_3$. This is due to the fact that atomic number of second atom (here first atoms being the same) in the group of $^{-12}\text{CH}_2\text{NH}_2$ is higher than that of second atom in $^{-14}\text{CH}_2\text{CH}_3$ group, although mass number of carbon of CH_2 in $^{-14}\text{CH}_2\text{CH}_3$ is greater than that in CH_2 of $^{-12}\text{CH}_2\text{NH}_2$.

By the same token, it can be said that $-\text{CH}_2\text{CH}_2\text{CH}_3$ will get preference over both $-\text{CD}_2\text{CH}_3$ and $-\text{CH}_2\text{CD}_3$ prior. However, the priority of $-\text{CD}_2\text{CH}_3$ is higher than that of $-\text{CH}_2\text{CD}_3$.

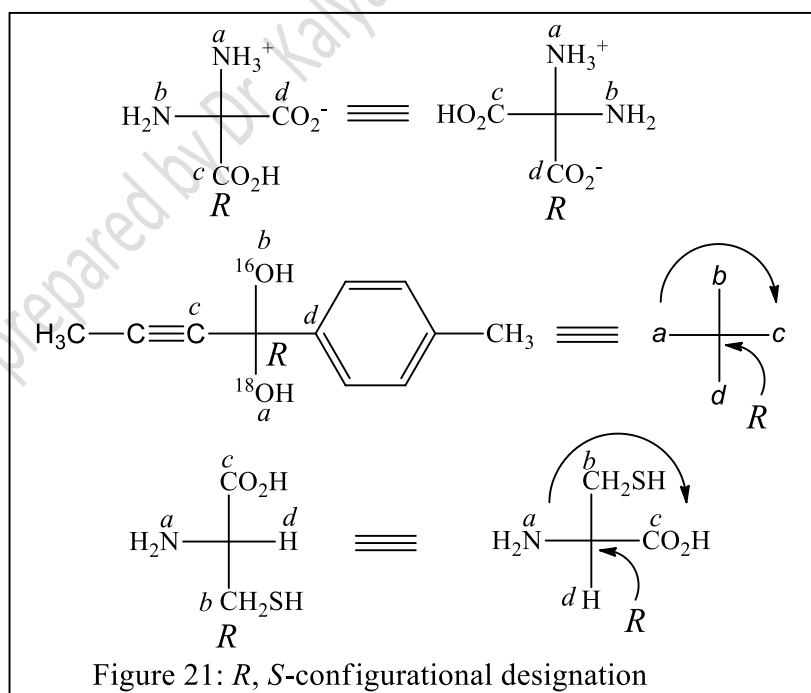
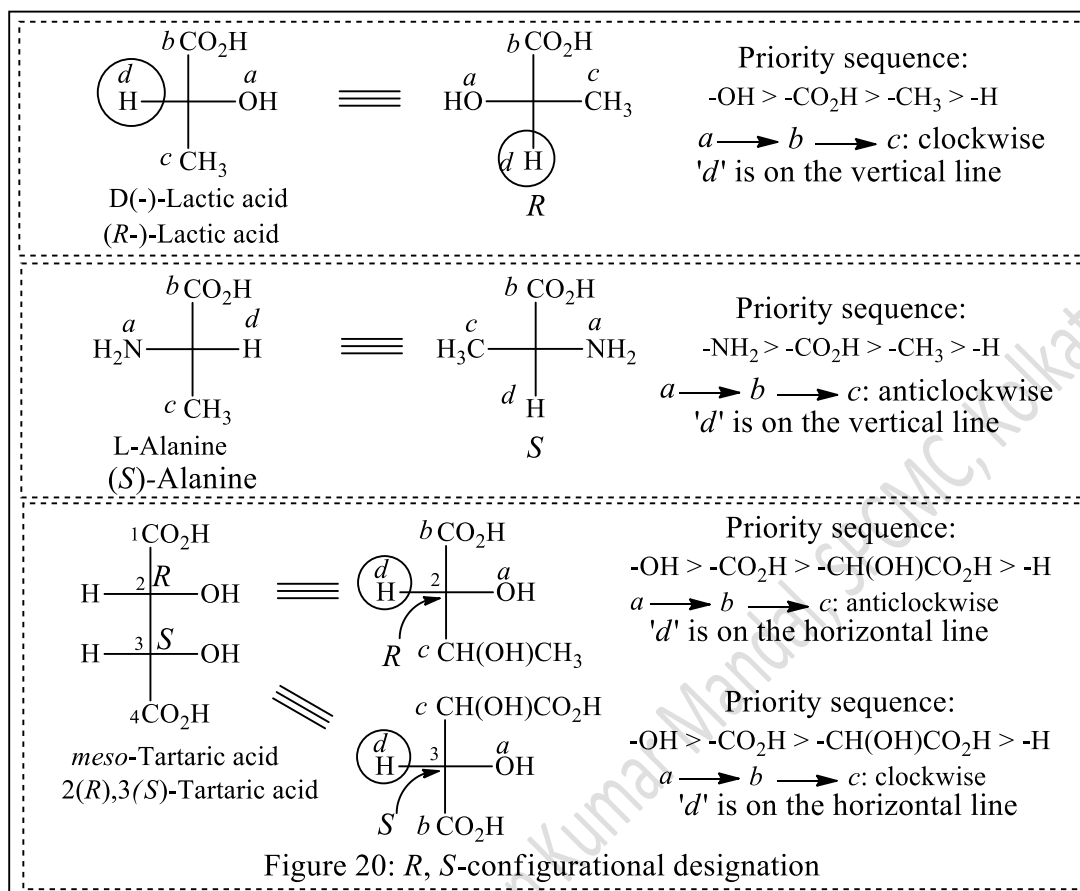
Priority of Ligands

For groups like $-\text{CD}_2^{16}\text{OH}$ and $-\text{CH}_2^{18}\text{OH}$, the letter gets the preference although deuterium is present in $-\text{CD}_2^{16}\text{OH}$. Here, in $-\text{CH}_2^{18}\text{OH}$, ^{18}O has higher atomic number as well as higher mass number. Similarly, $-\text{CH}_2\text{OH}$ will get preference over $-\text{CD}_2\text{NH}_2$. Thus, mass number of an isotopic atom in a group is taken into consideration only when attempt to assign priority based on atomic numbers of each atom in the group fails. This is because, CIP Rule is based on atomic number of ligands attached to the *chiral* centre.

Table 1 contains some of the most common groups in the decreasing order of precedence obtained by applications of the sequence sub-rules. The *R*, *S*-designations of some common compounds containing *chiral* centre(s) are shown in Figures 20-21.

Sl. No.	Atoms/Groups	Sl. No.	Atoms/Groups	Sl. No.	Atoms/Groups
01.	-I	17.	$-\text{NR}_2$	33.	$-\text{CH}_2\text{NH}_2$
02.	-Br	18.	$-\text{NHR}$	34.	$-\text{C}\equiv\text{CMe}$
03.	-Cl	19.	$-\text{NH}_3^+$	35.	-Ph
04.	$-\text{SO}_3\text{H}$	20.	$-\text{NH}_2$	36.	$-\text{C}\equiv\text{CH}$
05.	-SR	21.	$-\text{CX}_3$	37.	$-\text{CMe}_3$
06.	-SH	22.	$-\text{CO}_2\text{Ph}$	38.	$-\text{CH}=\text{CHMe}$
07.	-F	23.	$-\text{CO}_2\text{Et}$	39.	$-\text{CH}=\text{CH}_2$
08.	$-\text{OCOEt}$	24.	$-\text{CO}_2\text{Me}$	40.	$-\text{CHMe}_2$
09.	$-\text{OCOMe}$	25.	$-\text{CO}_2\text{H}$	41.	$-\text{CD}_2\text{Me}$
10.	-OR	26.	$-\text{CONH}_2$	42.	$-\text{CH}_2\text{Me}$
11.	-OH	27.	$-\text{COPh}$	43.	$-\text{CD}_3$
12.	$-\text{NO}_2$	28.	$-\text{COMe}$	44.	-Me
13.	$-\text{NR}_3^+$	29.	-CHO	45.	-T
14.	$-\text{NR}_2$	30.	$-\text{CH}_2\text{OR}$	46.	-D
15.	$-\text{NHCOPh}$	31.	$-\text{CH}_2\text{OH}$	47.	-H
16.	$-\text{NHCOR}$	32.	$-\text{CN}$	48.	Electron Pair

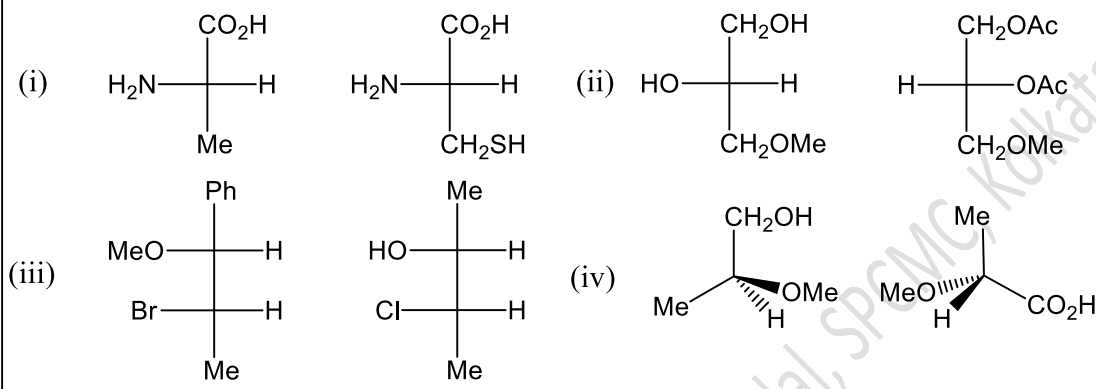
Centre of Chirality: *R, S* Nomenclature



HW: Draw the Fischer projection formulae for:

- (i) (*R*)-3-methylpentan-1-ol
- (ii) (*S*)-2,3-dimethylhexane
- (iii) (*R*)-3-methoxy-2-methylpropan-1-ol
- (iv) 2(*S*),3(*R*)-2,3-dichloropentane

HW: Label the following compounds with *R* or *S* and give your reason



Configuration of *Chiral* Centre in a Cyclic Molecule

Ligand complementation is required when there is a cyclic component to a ligand. In the present case, cyclic oxide ring (THF derivative) can be written in the disconnection form as shown in Figure 21, where the *chiral* centre itself serves as a duplicated atom at the end of the expanded chains. Duplicated atom is written within the parenthesis. Phantom atoms is inserted for tetra ligandation of the phantom atoms.

