Configurational Nomenclature

D–L Nomenclature

While studying carbohydrates and amino acids (around 1890), Emil Fischer recognized the need to establish configurational relationships within a family of compounds. He arbitrarily assigned a configuration to (+)-glucose and designated it D-(+)-glucose. The letter D therefore does not indicate optical rotation, but a configurational relationship. Any sugar that could be chemically interconverted with D-(+)-glucose, regardless of whether it rotated plane-polarized light to the right or left, was assigned D-configuration. For example, (+)-mannose or (–)-fructose) was placed in the D-family. Their mirror images were placed in the L-family. Because D-glucose can be synthesized from, or degraded to, glyceraldehyde, the latter was assigned the same configuration as D-glucose, i.e. D-glyceraldehyde. Because most of the sugars can be synthesized from, or degraded to, glyceraldehyde, the configurations of most sugars were defined by genetic (chemical) relationship to either D- or L-glyceraldehyde.

In D, L-method configuration to a stereoisomer is assigned with respect to a reference compound. So, the method assigns relative configuration to a stereoisomer.

Limitation of Genetic Correlation

This genetic approach sometimes fails. In several cases, both enantiomers of a compound can be chemically correlated to the same glyceraldehyde. For example, both (+)- and (–)-lactic acid can be derived from D-glyceraldehyde through suitable oxidation–reduction steps. Hence, configurational assignment based purely on chemical interconversion becomes ambiguous.

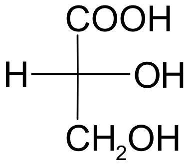
Fischer–Rosanoff Projection Rules (1906)

To overcome this difficulty, Rosanoff modified Fischer's system and proposed a projection nomenclature, now universally used for sugars and similar molecules.

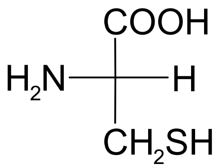
The conventions are:

1. The molecule is drawn in a Fischer projection with the longest carbon chain vertical.
2. The most highly oxidized end of the chain is placed at the top.
3. The configuration is determined by the bottom-most (highest-numbered) chiral carbon.
    - If the OH group (or a characteristic substituent X) at this carbon is on the right, the molecule is assigned the D-configuration.
    - If it is on the left, the molecule belongs to the L-configuration.

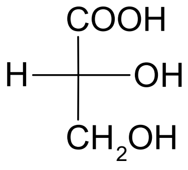
Following examples follows these conventions:



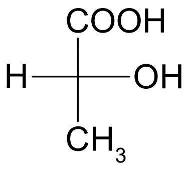
D-Glyceraldehyde



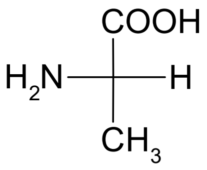
L-Cystein



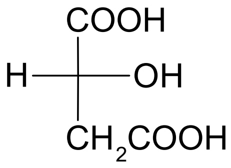
D-Glyceric acid



D-Lactic acid



L-Alanine



D-Malic acid

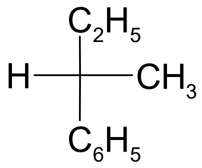
This assignment is independent of optical rotation and independent of the origin of the compound (non-genetic).

Limitation

Compounds that do not fit these projection requirements (longest carbon chain vertical, the most oxidized end of the chain at the top) cannot be assigned D or L configuration using this system. e.g., 1-phenylbutyric acid.

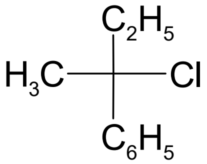
Some other rules of D, L-nomenclature

1. When the chiral centre contains a ring system, then the total number of carbon atoms including the ring are taken into consideration to draw the main carbon chain in Fischer projection**.**

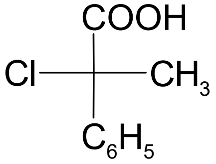


D-2-Phenylbutane

2. When the chiral centre does not contain H atom as one of the ligands, the naming is done with respect to the more electronegative group:

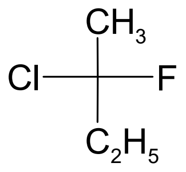


D-2-Chloro-2-phenylbutane

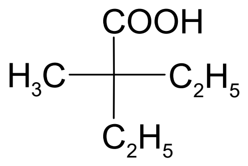


L-2-Chloro-2-phenylpropanoic acid

3. When the chiral centre contains two different substituents of comparable electronegativity, then D- and L- may be used separately:



2L-Chloro-2D-flurobutane



2-D-Ethyl-2L-methyl-2-phenylbutanoic acid

R, S nomenclature (Absolute Configuration)

The R–S nomenclature (also called absolute configuration) is a standardized method for specifying the three-dimensional arrangement of groups around a chiral (stereogenic) centre in a molecule. It was developed by Robert Sidney Cahn, Christopher Ingold, and Vladimír Prelog, and is widely known as CIP nomenclature. This system does not depend on the direction of optical rotation; it strictly describes spatial arrangement.

Two main steps in assigning R or S

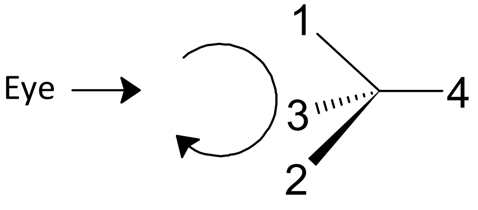
A. Sequence Rule (Priority Rules)

Priorities are given to the four groups/atoms attached to a chiral centre based on the Cahn-Ingold-Prelog (CIP) priority rules.

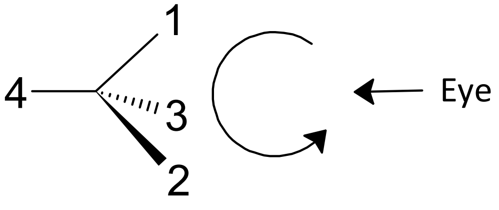
B. Chirality Rule — Assigning R or S

After priority ranking:

1. the molecule is oriented in such a way so that the lowest priority group (4) points away from the observer.
2. a path from highest priority 1 → 2 → 3 is traced.
3. If the path is clockwise → (R) configuration.
   If the path is counterclockwise → (S) configuration.



R



S

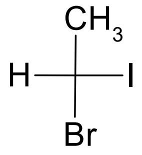
Sequence Rules (Cahn–Ingold–Prelog Priority Rules)

1. The four different atoms or groups directly attached to a chiral centre are assigned priorities according to the atomic number of the atom directly bonded to the chiral centre.
    - Higher atomic number → higher priority
    - Lower atomic number → lower priority
    - If one of the four "groups" is a lone pair of electrons, the lone pair is always assigned the lowest priority.

Example:

In 1-bromo-1-iodoethane (CH_3CHIBr), the chiral carbon is attached to:

- I ($Z = 53$)
- Br ($Z = 35$)
- C (of CH_3, $Z = 6$)
- H ($Z = 1$)



Hence, the priority order is: $I > Br > CH_3 > H$

2. When two or more groups are attached through the same atom (usually carbon), priorities cannot be decided using Rule 1 alone. In such cases:

- Compare the next set of atoms bonded to those identical atoms
- Move outward step by step along each group
- The priority is decided at the first point of difference

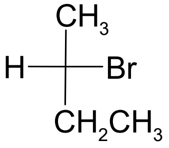
Example: 2-Bromobutane (CH_3–$CHBr$–C_2H_5)

The four ligands attached to the chiral carbon are:

- Br (highest priority)
- H (lowest priority)
- CH_3
- CH_2CH_3

To compare CH_3 and CH_2CH_3:

- CH_3 has attached atoms: H, H, H
- CH_2CH_3 has attached atoms: H, H, C



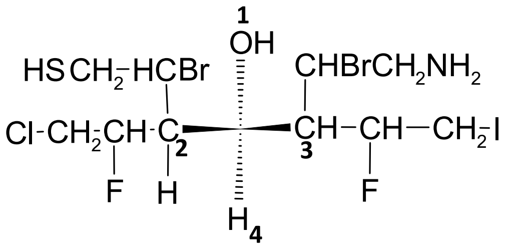
Since C > H, the ethyl group gets higher priority than methyl. Thus: $Br > CH_2CH_3 > CH_3 > H$

3. When substituents are branched carbon chains, priority determination requires a systematic hierarchy of paths. The guiding principles are:

(a) All atoms at a given "distance" from the chiral centre must be compared before moving further outward.

(b) Once one path is found to have higher priority at a given level, that precedence is retained at subsequent levels until the final decision is reached.

See the sequencing in the following examples:



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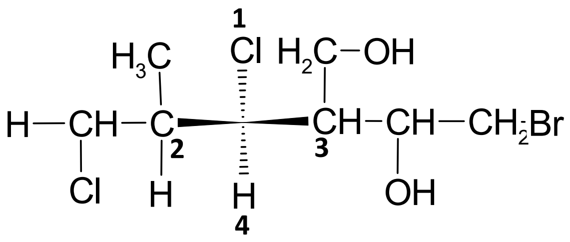


S

4. **When isotopic atoms are directly attached to the chiral centre, priority is assigned according to mass number.**

   The isotope with the higher mass number gets higher priority.

   Example:

   - D > H
   - $^{18}O > {}^{16}O$
   - $^{15}N > {}^{14}N$

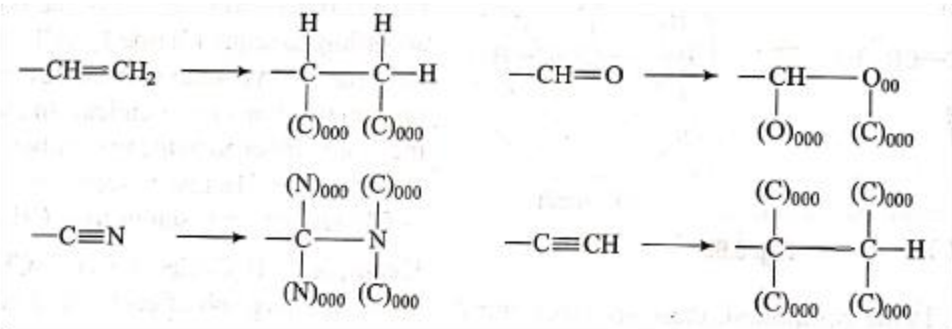
When isotopes occur within substituent groups:

- —$^{12}CH_2NH_2$ > —$^{14}CH_2CH_3$

  because the second atom in $^{12}CH_2NH_2$ is N (Z = 7), which has higher atomic number than C (Z=6) in —CH_2CH_3; atomic number comparison takes precedence over mass comparison).
- —$CH_2{}^{18}OH$ > —CD_2OH

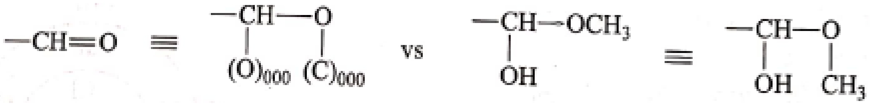
  because ^{18}O has a higher mass number than D.

5. **For assigning priority to groups containing double or triple bonds, multiple bonds are treated as if the atoms are replicated (duplicated or triplicated). Replicated atoms are enclosed in parenthesis in the expanded form of the group. Each replicated atom, except for H atom, is converted to single bond tetravalency by adding phantom atoms having atomic number zero.**

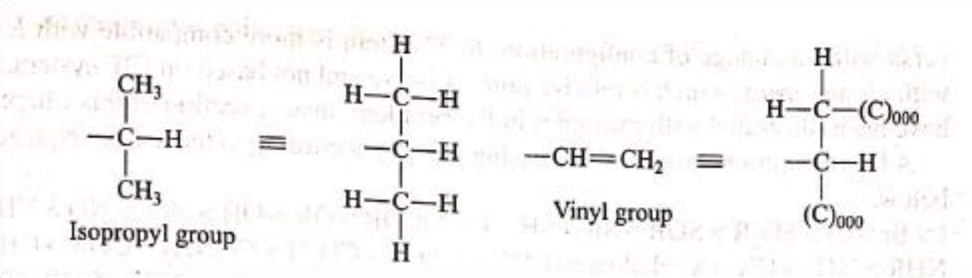


Examples

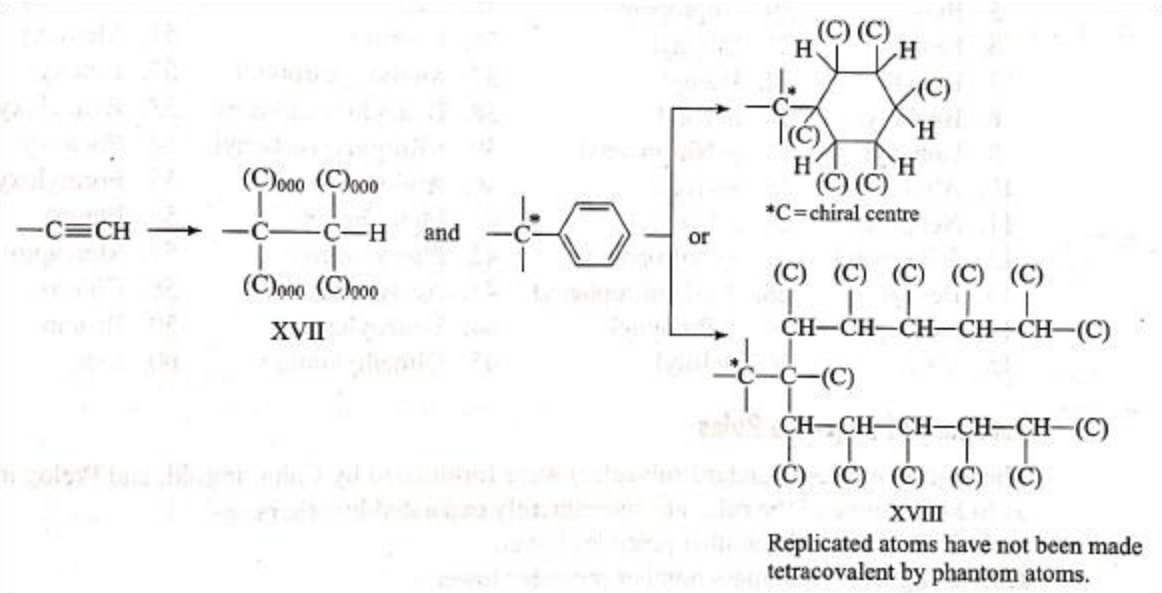
- Hemiacetal group (—CH(OH)OCH$_3$) has priority over aldehyde group (—CHO)



- Vinyl group gets preference over isopropyl group.



- Phenyl group gets preference over ethynyl group.



XVII

XVIII

Replicated atoms have not been made tetracovalent by phantom atoms.

6. When two substituents attached to a chiral centre are themselves chiral centres and are identical in constitution but differ only in configuration (i.e., they are enantiomorphic groups), priority is assigned as follows:

- A substituent with R-configuration gets priority over the corresponding substituent with S-configuration.
- Similarly:
  - (R, R) > (R, S)
  - (R, S) > (S, S)

7. When substituents contain double bonds and differ in geometrical configuration, priority is assigned according to the following order:

- **cis** configuration gets priority over **trans** configuration.
- **Z** has priority over **E**.

R, S nomenclature in Fischer projections

Epling's very good method

1. Assign priorities to the four groups attached to the chiral centre:

   1 > 2 > 3 > 4

   where 4 is the lowest priority group.
2. Trace the path from (ignoring 4):

   1 → 2 → 3

Case 1: If the lowest priority group (**4**) is on one of the **vertical bonds** of the Fischer projection:

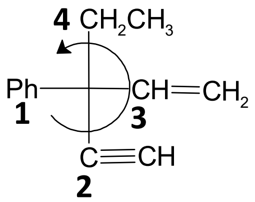
- Clockwise path → **R**
- Anticlockwise path → **S**

Case 2:

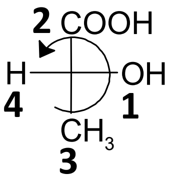
If the lowest priority group (**4**) is on a **horizontal bond**:

- Clockwise path → **S**
- Anticlockwise path → **R**

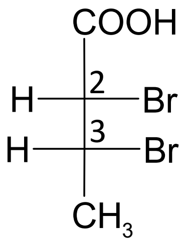
Examples:

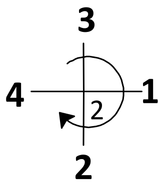


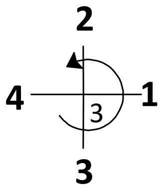
1 → 2 → 3 anticlockwise path and the lowest priority group (**4**) is on one of the vertical bonds → **S**



1 → 2 → 3 anticlockwise path and the lowest priority group (**4**) is on one of the horizontal bonds → **R**



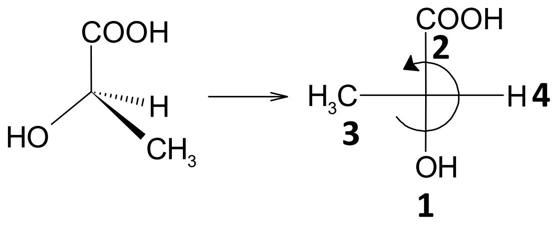




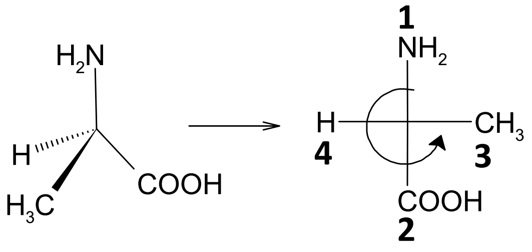
S

R

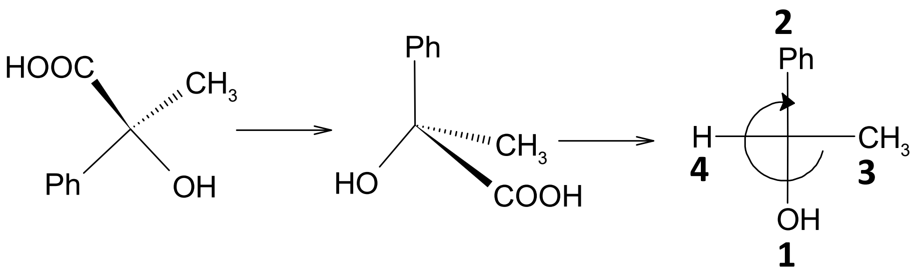
R, S nomenclature in Flying wedge projections



R



R



S