Chemistry I (Organic): Stereochemistry

Fischer Projections, Absolute Configuration and (*R*)/(*S*) Notation

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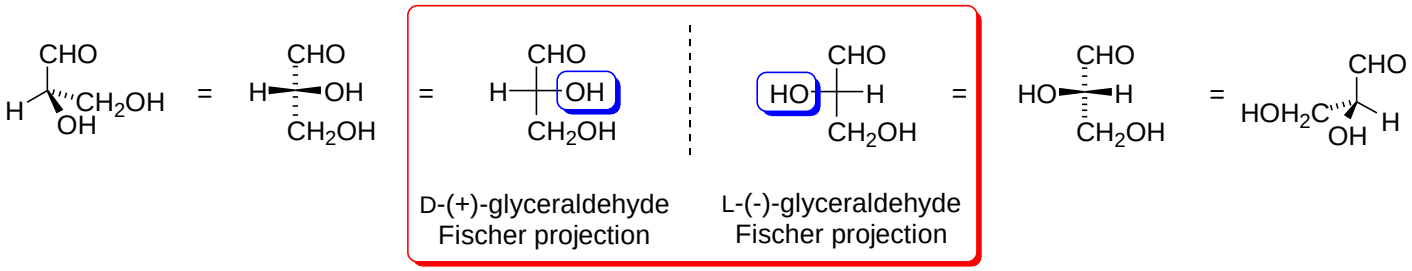
Notation for Designating the Configurations of Stereogenic Centres:

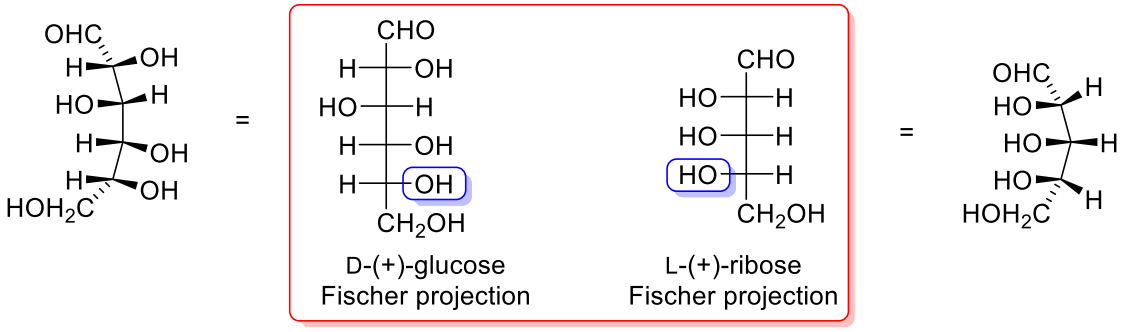
It is obviously necessary, as a matter of convenience, to be able to describe the configuration of a chiral molecule by an unambiguous symbol rather than have to draw a three-dimensional perspective figure.

Fischer Projections and the D/L Notation:

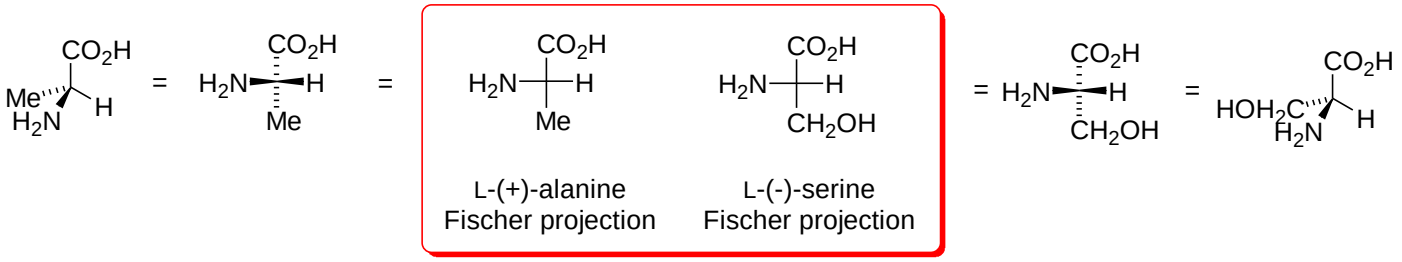
The first system for doing this was developed by **Fischer** and **Rosanoff** around **1900**. Fischer first developed a method for drawing carbohydrates in two-dimensions, and a convention with respect to orientation, so as to indicate their three dimensional structures, so-called ***Fischer projections*** (see below). Fischer and Rosanoff then devised a notation for designating the configurations of stereogenic centres, depicted in Fischer projections, as either D or L. *Totally arbitrarily, (+)-glyceraldehyde was defined as being D because the OH group attached to the C-2 is on the right hand side (RHS) of the molecules when drawn in its correct Fischer projection (in which the CHO or most highly oxidised group appears at the top)*. Its enantiomer [(-)-glyceraldehyde] was defined as L because the OH group is on the left hand side (LHS).



In carbohydrates, in general, the OH group attached to the penultimate carbon atom from the bottom in the chain, when drawn as described above, determines the assignment of D or L. Thus (+)-glucose has the D-configuration and (+)-ribose has the L-configuration.



The notation was extended to α-amino acids: L enantiomers are those in which the NH_2 group is on the LHS of the Fischer projection in which the carboxyl group appears at the top. Conversely, the D enantiomers are those in which the NH_2 group is on the RHS. Thus (+)-alanine and (-)-serine are L-amino acids.

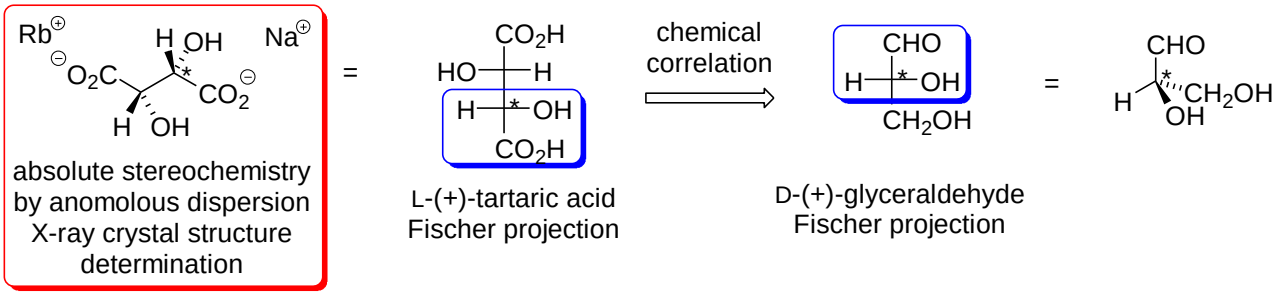


NB. The symbols D and L *DO NOT* relate to the sign of rotation of an optically active molecule which is designated (+) (or *d*) and (-) (or *l*).

Although the D/L nomenclature appears satisfactory for carbohydrates and α-amino acids it suffers from serious defficiencies when trying to extend the notation to molecules with multiple stereogenic centres and molecules that differ structurally from these standards. Assignment of the configurational symbols D or L will not therefore automatically allow the unambiguous construction of a three-dimensional model for most molecules.

Bijvoet's Determination of the Absolute Configuration of (+)-Tartaric Acid

As explained above, Rosanoff ***arbitrarily*** assigned (+)-glyceraldehyde as having the D configuration. It was not until 50 years later that this arbitrary assignment was able to be tested experimentally. In **1951**, ***Bijvoet*** performed a structure determination on the sodium rubidium double salt of (+)-tartaric acid using ***anomalous dispersion X-ray crystallography***.



Although X-ray crystal structure determination will *NOT* normally destinguish between enantiomers the incorporation of a heavy atom (in this case rubidium) results in an anomolous dispersion of the X-rays which allows the ***absolute three-dimensional structure*** to be determined. Since chemical synthesis had already been carried out to correlate one of the stereogenic centres in (+)-tartaric acid with that in (+)-glyceraldehyde it was possible to verify Rosanoff's assignment. ***Fortunately, the configuration was the same as that arbitrarily assigned!***

Nowadays, anomalous dispersion X-ray crystallography can be carried out fairly routinely on crystalline molecules provided >6 or so atoms with atomic number >12 (*e.g.* typically, Ns and Os) are present. Absolute configurations can also be obtained by ***circular dichroism*** (CD) and certain other techniques.

Bijvoet's breakthrough provided the impetus for the development of a totally unambiguous notation for defining absolute configuration: the (*R*)/(*S*) notation.

(R)/(S) Notation: The Cahn Ingold Prelog (CIP) Sequence Rules

Cahn, Ingold and Prelog introduced this systematic notation during the period **1951-1956**. The notation allows us to define in an unambiguous manner the absolute configuration of a drawn stereogenic centre by assigning it as either (*R*) or (*S*). Correlation with an arbitrary standard is not involved.

In order to use this notation the first thing to do is to assign an ***order of priority*** to the atoms of the groups directly attached to a stereogenic centre. In order to make this easy to remember a few simple ***sequence rules*** were adumbrated:

Rule 1: is that atoms of higher atomic number take precedence over those of lower atomic number. Lone pairs of electrons are assigned the lowest priority.

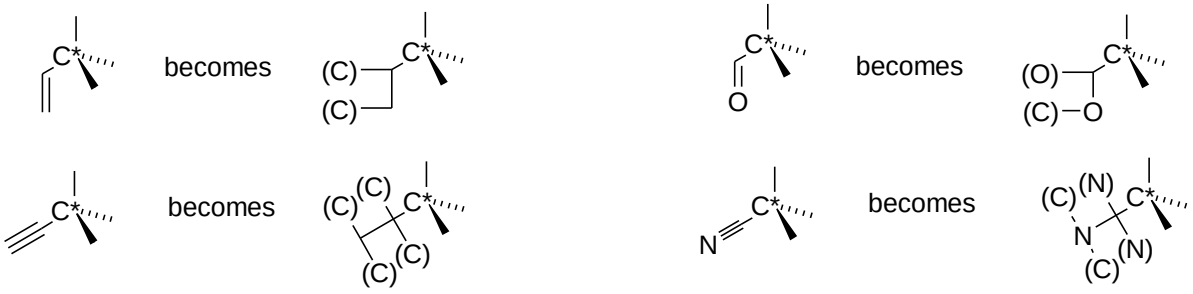
Rule 2: is that isotopes of higher atomic weight take precedence.

order of priority: ^{3}H (tritium) > ^{2}H (deuterium) > ^{1}H (hydrogen)

Rule 3: relates to molecules where two or more of the atoms directly attached to the stereogenic centre are the same *e.g.* in the compounds below in which three of the atoms attached to the stereogenic central carbon are carbon. In such cases we establish the order of priority of the next atoms along the chain adhering to the 'principle of outward exploration' (see later).

(-)-isomer (+)-isomer

Rule 4: relates to molecules bearing unsaturated groups attached to the stereogenic central atom. In these cases we convert the π-system into a hypothetical saturated 'equivalent' system using ghost atoms (in parenthasis) as follows (*NB.* C* is the stereogenic carbon).



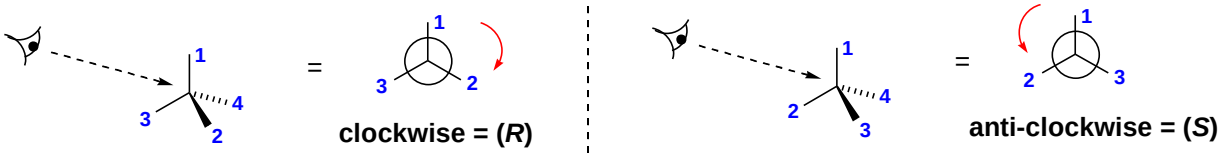
The ghost atoms are then used to decide the priority. In this way we get:

order of priority: $CO_2Me > CO_2H > CONH_2 > COMe > CHO > CH_2OH$

Rule 5: when the difference between substituents is in configuration then (*R*) takes precedence over (*S*).

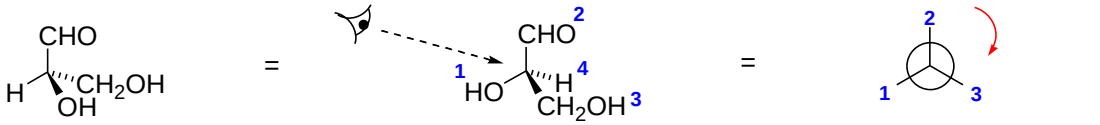
Having established the priorities, ***we now view the molecule so that the atom/group with lowset priority is pointing away from us in space***. Finally, we count around the face of the molecule which is pointing towards us the three other groups ***in order of decreasing priority***.

A ***clockwise*** decreasing order is assigned the ***(R)-configuration*** (*cf.* Latin, *rectus*).
An ***anti-clockwise*** decreasing order defines an ***(S)-configuration*** (*cf.* Latin, *sinister*)



NB. group 1 is highest priority, group 4 is lowest priority

For example, in (+)-glyceraldehyde the order of priority of the groups is OH > CHO > CH_2OH > H and the configuration is (*R*).

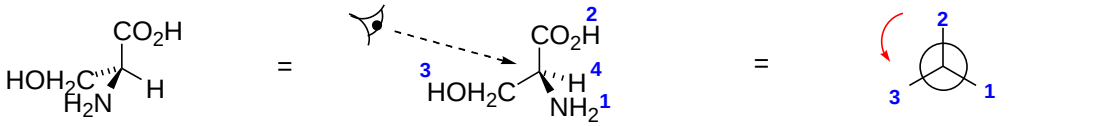


(+)-glyceraldehyde
(as drawn previously)

(+)-glyceraldehyde
(re-drawn with lowest priority group at back)

i.e. (*R*)-(+)-glyceraldehyde

Similarly for (-)-serine the order of priority of the groups is NH_2 > CO_2H > CH_2OH > H and the configuration is (*S*).



(-)-serine
(as drawn previously)

(-)-serine
(re-drawn with lowest priority group at back)

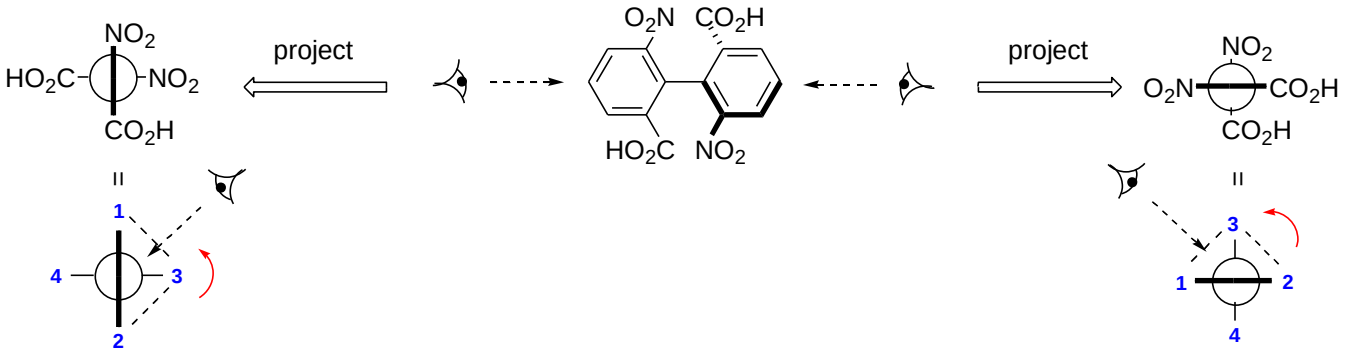
i.e. (*S*)-(-)-serine

It is important to practice and make sure you are comfortable at assigning (R) and (S) configurations to stereogenic centres. As an exercise, assign the configurations of all the chiral molecules containing a single stereogenic centre shown on page 3 of the lecture 1 handout. NB. The 'priority' of the central atom is not relavent to the assignment.

The ***(R)/(S) notation*** has also been extended to allow assignment of the configurations of some types of chiral molecules without a stereogenic centre (*e.g.* like some of those shown on page 4 of the lecture 1 handout).

For example, ***axially chiral molecules*** like allenes and hindered biaryls can be assigned provided that a couple of additional conventions are implemented. ***The molecule must be viewed along the chiral axis*** (from either end, it doesn't matter which) with the substituents giving rise to the chirality projected onto a plane at right angles to the chiral axis. The priorities of the four substituents are then assigned in the usual manner with the proviso that ***the near groups always take precedence over the far groups***.

For example, for (-)-6,6'dinitrobiphenyl-2,2'-dicarboxylic acid is (*S*)-configured:



The ***(R)/(S) notation*** has also been extended to allow assignment of *enantiotopic* and *diastereotopic* groups *etc.* This will be explored later in the degree course.

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Selected Historical Landmarks in the Development of the Field of Stereochemistry:

1848 ***Pasteur*** achieves the *first optical resolution* of the (+)- and (-)-enantiomers of tartaric acid.
1874 ***van't Hoff*** and ***Le Bel*** independently suggest that tetravalent *carbon is tetrahedral*.
1900 ***Fischer*** develops the first systematic method for depicting stereochemistry (*Fischer projections*) and a notation for designating configuration (*D/L notation*).
1905 ***Rosanoff*** arbitrarily assigns the configuration of the structure corresponding to (+)-glyceraldehyde as being D-glyceraldehyde.
1951 ***Bijvoet*** determines the *absolute configuration* of the sodium rubidium double salt of (+)-tartaric acid using anomolous dispersion X-ray crystallography.
1969 ***Hassell*** and ***Barton*** (Imperial College) jointly awarded the Nobel prize in Chemistry for their work on the *conformational analysis* of cyclohexane.