

Chemistry I (Organic)

Stereochemistry ***LECTURE 3***

***Stereochemical notation, absolute configuration &
(R)/(S) notation***

Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College
London

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Format & scope of lectures

- ***Notation for designation of stereochemistry***
- ***Fischer projections and the D/L notation***
- ***Absolute configuration determination***
 - anomalous dispersion X-ray crystallography (Bijvoet's method)
- ***The (R)/(S) notation***
 - CIP Sequence rules
 - assigning (R) & (S) using the CIP sequence rules

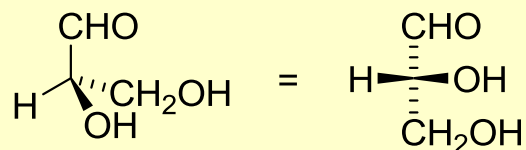
NB. For 3D Jmol models of molecules **A-D** see link @ <http://www.ch.ic.ac.uk/spivey/?q=firstyear>

Notation for designating the configurations of stereogenic centers

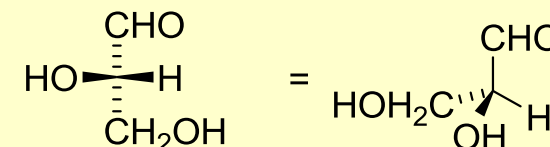
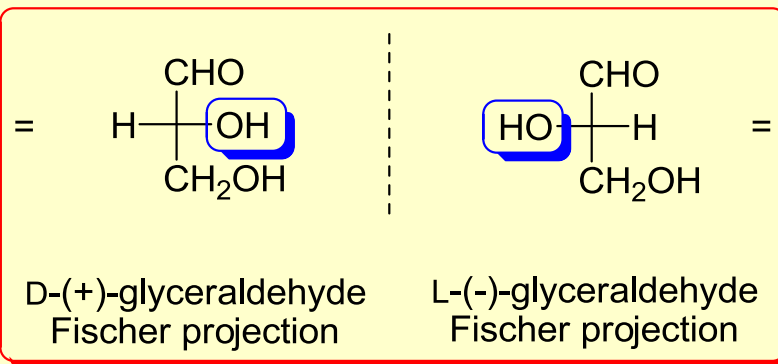
- *It is obviously necessary, as a matter of convenience, to be able to describe the configuration of a chiral molecule by an unambiguous symbol rather than have to draw a three-dimensional perspective picture*
- *There are two systems used:*
 - *The D/L notation* (associated with Fischer projections of sugars but also used for α -amino acids)
 - *The Cahn, Ingold & Prelog (CIP) notation* (a systematic nomenclature that can be applied to most stereoisomers)
- *The following 2 slides overview Fischer projections and the D/L notation. This notation has been superseded by the CIP notation but is still used in catalogues and text books etc. so it is useful to know about...*

Fischer projections and the D/L notation

- **Around 1900, Fischer developed a method for drawing carbohydrates in 2D, and a convention with respect to orientation, so as to indicate their 3D structures, so-called Fischer projections**
- **Fischer and Rosanoff then devised a notation for designating the configurations of stereogenic centers, depicted in Fischer projections, as either D or L**
- **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 group appears at the top)**
- **Its enantiomer [(-)-glyceraldehyde] was defined as L because the OH group is on the left hand side (LHS)**



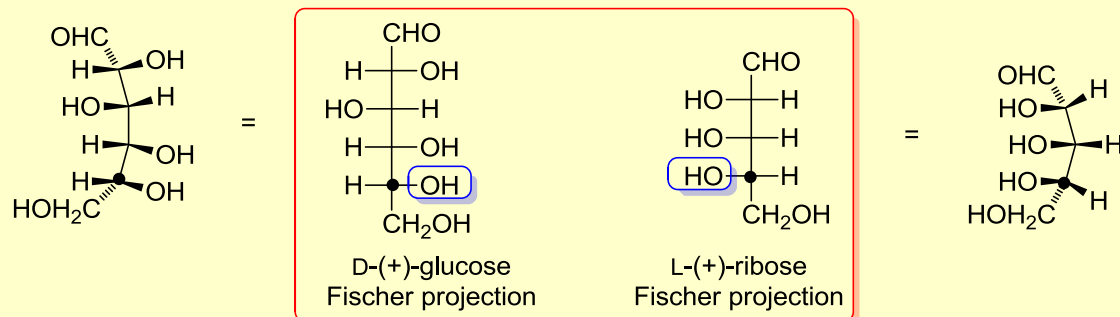
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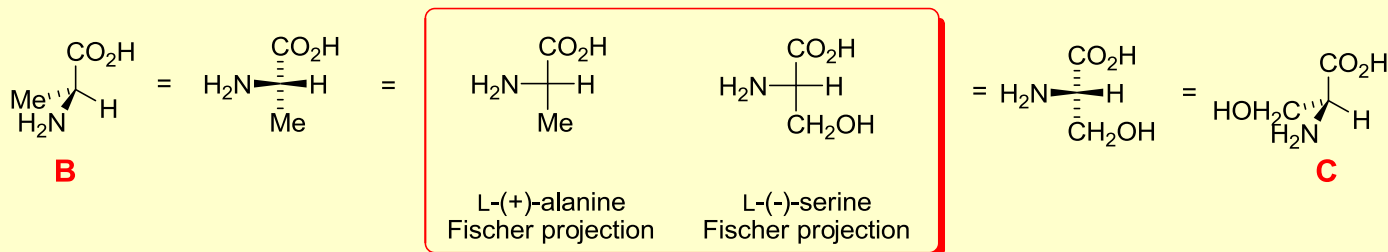
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Fischer projections and the D/L notation

- For carbohydrates in general, the OH group attached to the penultimate carbon atom in the chain 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

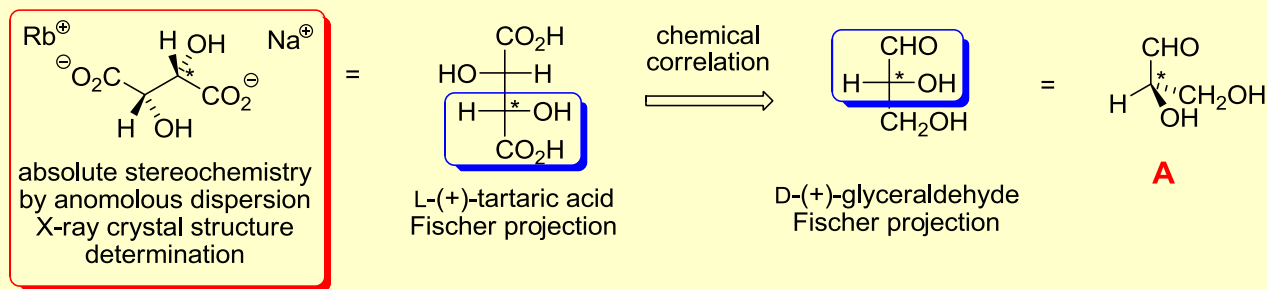


- NB.** The symbols D and L do NOT relate to the sign of rotation of an optically active molecule which is designated (+) (or d) and (-) (or l)

Absolute configuration - *Bijvoet's X-ray method*

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

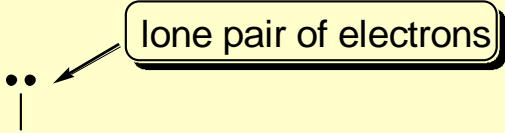
- As explained above, Rosanoff **arbitrarily** assigned (+)-glyceraldehyde as having the D configuration around 1900. It was not until **1951**, that **Bijvoet** tested this experimentally by performing a structure determination on the sodium rubidium double salt of (+)-tartaric acid using **anomalous dispersion X-ray crystallography**



- Although X-ray crystal structure determination will **NOT** normally distinguish between enantiomers the incorporation of a heavy atom (in this case rubidium) results in an anomalous 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 optical techniques

Cahn Ingold Prelog (CIP) - *sequence rules*

- ***During 1951-1956 Cahn, Ingold and Prelog developed of a totally unambiguous notation for designating (absolute) configurations: the (R)/(S) notation [DOI]***
- ***The absolute configuration of a drawn stereogenic centre can be assigned as either (R) or (S) without recourse to an arbitrary standard***
- ***Designation requires assignment of an order of priority to the groups directly attached to a stereogenic centre using the following (simplified) sequence rules:***
 - **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

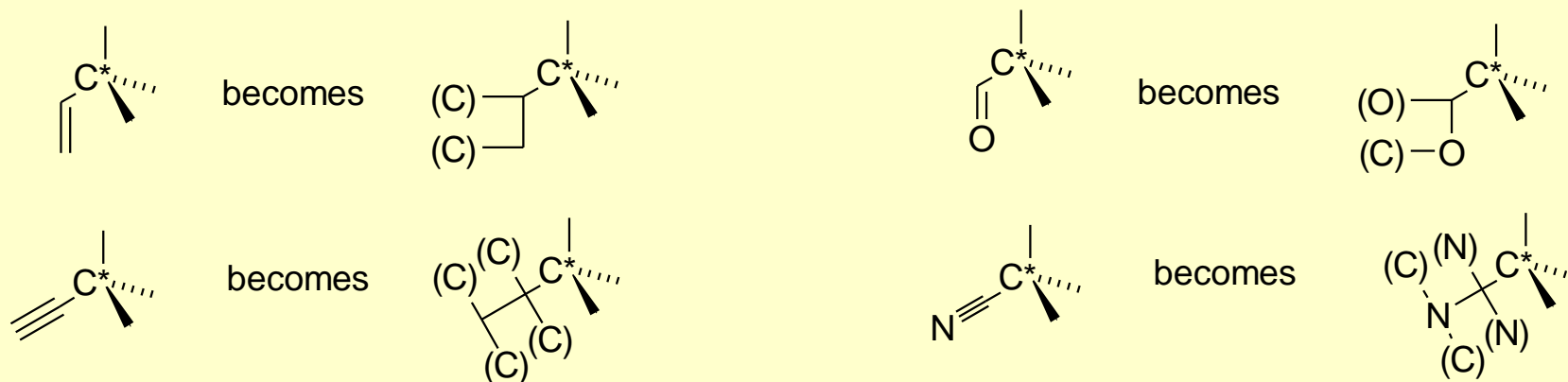
order of priority: I > Br > Cl > F > O > N > C > H > 
 - **Rule 2**: is that isotopes of higher atomic weight take precedence

order of priority: ³H (tritium) > ²H (deuterium) > ¹H (hydrogen)
 - **Rule 3**: when the difference between substituents is in configuration then (R) takes precedence over (S)
- ***Where two or more of the atoms directly attached to the stereogenic centre are the same then, additionally, we need to establish the order of priority of the next atoms along those chains - the 'principle of outward exploration' (see next slide)***
- ***NB. For a detailed account of the method see IUPAC recommendations 1974 [DOI]***

Cahn Ingold Prelog (CIP) - *sequence rule application*

- The Principle of Outward Exploration:

- To decide between two atoms of identical priority we work outwards to the atoms to which they in turn are *directly attached*
- For molecules bearing unsaturated groups attached to the stereogenic central atom we convert the π -system into a hypothetical saturated 'equivalent' system using **ghost atoms** (in parenthesis) as follows (*NB.* C* is the stereogenic carbon)



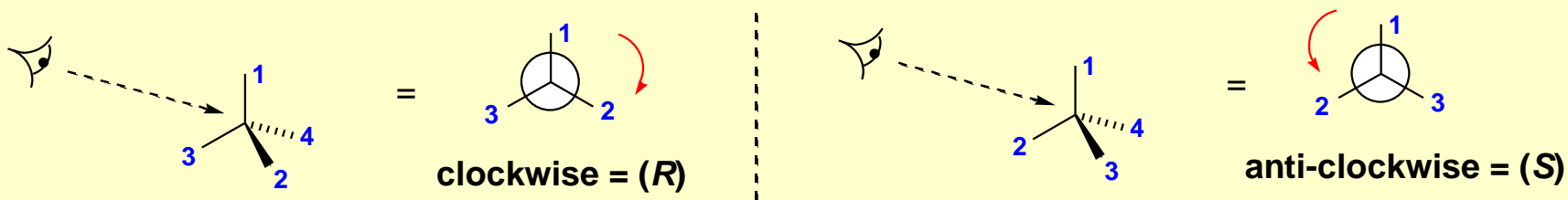
NB. a 'ghost' atom will always be of lower priority than its corresponding real atom because it will have no additional substituents

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

order of priority: CO₂Me > CO₂H > CONH₂ > COMe > CHO > CH₂OH

Assigning (*R*) & (*S*) using the sequence rules

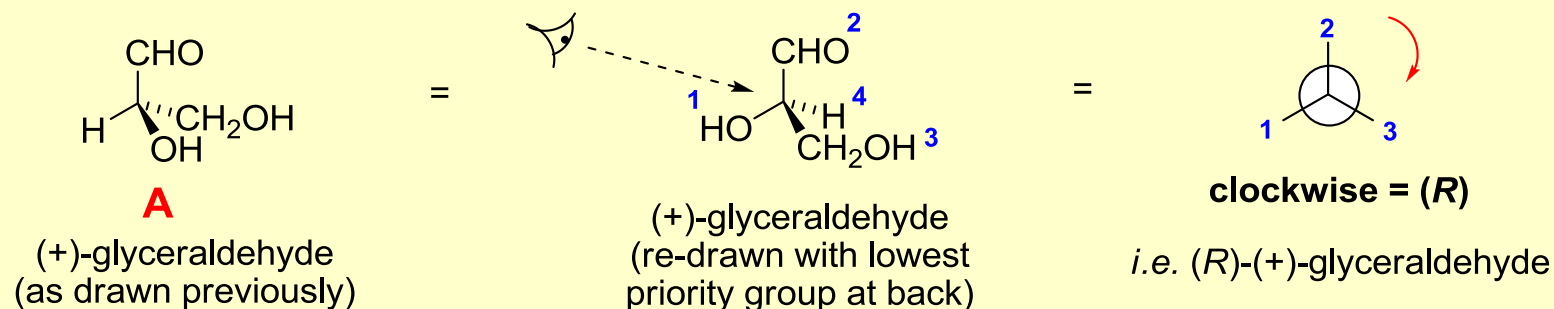
- **Having established the priorities**, we now view the molecule so that the atom/group with **lowest** priority is pointing away from us in space
- **Finally, we count around the three other groups on the face of the molecule which is pointing towards us** in order of decreasing priority
 - A **clockwise** decreasing order is assigned the (***R***)-configuration (cf. Latin, *rectus*)
 - An **anti-clockwise** decreasing order is assigned the (***S***)-configuration (cf. Latin, *sinister*)



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

Assigning (*R*) & (*S*) - examples

- For example, in (+)-glyceraldehyde the order of priority of the groups is $\text{OH} > \text{CHO} > \text{CH}_2\text{OH} > \text{H}$ and the configuration is (*R*):



- Similarly for (-)-serine the order of priority of the groups is $\text{NH}_2 > \text{CO}_2\text{H} > \text{CH}_2\text{OH} > \text{H}$ and the configuration is (*S*):

