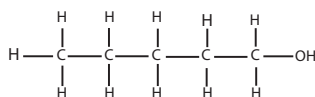


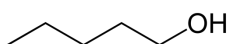
Year 2, Organic Chemistry, Chapter 23:

Differing Sorts of Isomerism

- Before we start on the subject matter of this Chapter, let me remind you that
- An **Empirical** formula is the *smallest* whole number ratio of atoms of the elements in a **compound** e.g. the Molecular Formula of Butane is C_4H_{10} , but the Empirical Formula is C_2H_5 . [There is no such thing as a fraction of an atom, therefore " $C_1H_{2.5}$ " is not a permissible formula.]
- A **Molecular** formula is the *actual* whole number ratio of atoms of the elements in a **compound** but it does not attempt to show how the molecule is constructed e.g. the Molecular Formula of Butane (C_4H_{10}) does not attempt to show how the atoms have been linked together.
- A **Structural** formula is the minimum amount of detail that will define the simplest combination of atoms that form that molecule e.g. " $CH_3CH_2CH_2CH_2CH_2OH$ " = $CH_3(CH_2)_4CH_2OH$ = Pentan-1-ol.
- A **Displayed** formula sets out the interrelationship between the different atoms and the associated functional groups in an Organic molecule e.g. this is the displayed formula for Pentan-1-ol.



- A **Skeletal** formula sets out to describe the interrelationship between all the Carbon atoms (and their associated functional groups) in an Organic molecule – but it does not show any of the Carbon nor any of the Hydrogen atoms in the molecule, and it therefore shows none of the C–H bonds in the molecule e.g. the molecule below is the skeletal representation of pentan-1-ol.

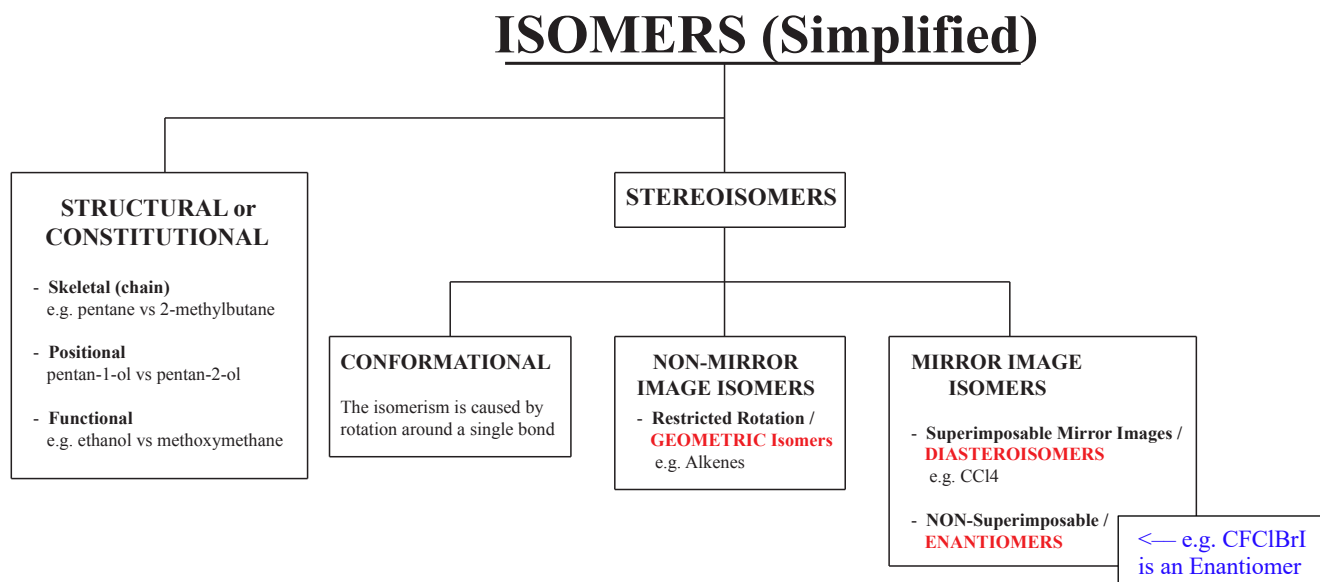


- A **Functional** Group identifies that part of a compound that is responsible for its characteristic reactions e.g. the " $-OH$ " in Alcohols.
- **Homologous Series** in Organic Chemistry are groups of Organic compounds that
 - contain the same functional group
 - have the same general formula, and
 - differ in composition by a multiple of CH_2 .

All three conditions must be fulfilled e.g. ethanol (C_2H_5OH) and cyclohexanol ($C_6H_{11}OH$) are both alcohols, but they are NOT members of the same homologous series because they do not differ from each other by a function of CH_2 .
- I would urge you in the strongest terms possible to revise the whole of the Chemistry that I taught you last year. In your final exams you will be tested on everything that you have learnt in your two years in the Sixth Form (Years 12 and 13). There is a considerable lack of clarity when it comes to the teaching of Isomers. Students spend hours studying the subject without understanding the distinctions involved. I therefore intend to start by talking about the terms that are used in the analysis of Isomerism.

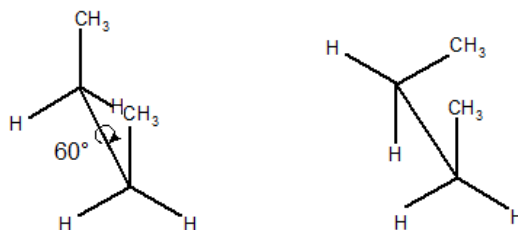
NB For the details of classification Systems that you will see but on which you will NOT be tested please go to the Appendix.

- The chart on page 3 showing the detailed classification of Isomers by different categories is **essential** for a Second Year student. Everything in the diagram (except for “Conformational” Isomers) is in the syllabi/syllabuses of all the major Examining Boards. The chart below is a simplified version of that detailed chart.



Conformational Isomers

- I have included Conformational Isomers in this diagram because in your First Year I told you that Isomerism did not include *saturated* Carbon compounds. That was not the truth, but merely an over-simplification for your First Year (because I did not want to introduce the subject of Conformational Isomers at that time). Now, in your Second Year, I have to point out that it is possible for a saturated Carbon compound to have an isomer that is created simply by **rotation around a single bond**. However, Conformational Isomers are **not** part of the UK ‘A’ Level syllabus. (*Rotation around a **double bond** would break the π bond and thus destroy the molecule – but if the rotation is continued through 180° , then the π bond will be re-established and a **cis-trans isomer** will be created*).
- Saturated Carbon compounds **can** form isomers (Conformational isomers) – as you can see from the following diagram where rotation around a single bond has resulted in a different 3-Dimensional arrangement.



Source: Wikipedia

- However, Conformational isomers do not form part of any of the Examining Boards’ syllabi/syllabuses, therefore I am not going to talk about them.
- At ‘A’ level, “Geometric Isomerism” refers to the **cis/trans or E/Z isomers in Alkenes**.

ISOMERS

Just as twins look alike but are actually different people, so also can it be with some chemical substances. *If the molecules of two substances have the same molecular formula but have one or more different physical or chemical properties, then the two substances are **ISOMERS** of each other.*

STRUCTURAL or CONSTITUTIONAL ISOMERS

Structural isomers have the same molecular formula but differing structural formulae e.g. pentane $\text{CH}_3(\text{CH}_2)_3\text{CH}_3$ and 2-methylbutane $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_3$. However, if rotation around one or more single bonds converts the wedge and dashed-line diagram of one substance into the other, then the substances under consideration are NOT structural isomers (but are a form of stereoisomer called “conformational” isomers).

- In **skeletal** (also called “chain”) isomers, the skeletons of the Carbon molecules are different e.g. as in pentane and 2-methylbutane above.
- In **positional** isomers, the carbon skeletons are exactly the same but the locations of the same functional group in each molecule are different e.g. as in pentan-1-ol, and pentan-2-ol.
- In **functional** isomers, the same molecular formula is used to construct a different functional group in each substance e.g. ethanol $\text{CH}_3\text{CH}_2\text{OH}$ and methoxymethane $\text{CH}_3\text{-O-CH}_3$.

STEREISOMERS

Substances that have the same molecular and structural formulae but whose atoms have different spatial orientation in the three dimensional space **within** their molecules, are stereoisomers of each other. Stereoisomers are divided into **Enantiomers** and **Diastereoisomers** (or non-enantiomers).

A) ENANTIOMERS (non-superimposable mirror image isomers)

If a substance can change the plane of mono-planar light passing through it, then the substance is said to be “optically active”. **Enantiomers** are optically active substances that have exactly the same molecular and structural formulae but which change the plane of mono-planar light in opposing directions [clockwise (ie “d” or “+”) or counter-clockwise (ie “l” or “-”)]. *The symbols “d” and “D” and “l” and “L” do NOT signify the same thing!* Enantiomers are non-superimposable **mirror images** of each other, and for two substances to be enantiomers, they must be “**chiral**” or “asymmetric” i.e. they cannot have any plane/nor any axis/nor any centre of symmetry. In Organic Chemistry a central carbon atom with four different attachments is called a **chiral centre**. (An **achiral** Carbon atom would have at least two similar attachments and thus it could NOT have enantiomers.) Substances that have equal amounts of two enantiomers of the same concentration are not optically active (because the opposing optical effects cancel each other out) and such mixtures are called “racemic” or “racemate”.

B) DIASTEREOISOMERS (Stereoisomers that are not mirror images of each other)

B.1) Diastereoisomers with restricted rotation (Configurational diastereoisomers)

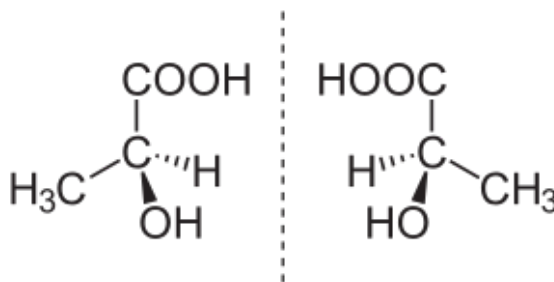
Certain structures do not allow one part of a molecule to be rotated freely against the other part of the molecule and this can occur with (for example) double bonds and ring molecules. Substances where free rotation to convert one isomer to the other is restricted are called **geometric** isomers and they can be classified according to two systems viz the **E/Z** classification and the less structured **cis/trans** classification. It is possible for a molecule to be **both** “E” (for “entgegen” in German) in one system and yet “cis” in the other system!

B.2) Diastereoisomers with unrestricted rotation (Conformational diastereoisomers)

Where rotation is not restricted and is thus possible (e.g. around a single bond), then diastereoisomers are said to be **conformational** and the Cahn-Ingold-Prelog system of prioritisation (the same system as in the E/Z system) is used to determine whether the molecule is classed as an R (for clockwise priority) or an S (for anticlockwise priority) type of isomer. The order of priority system (ie the R/S system) does not say anything at all about which way the mono-planar light will be turned.

Chirality/Enantiomers/Plane-polarised light/Optical activity/Racemic mixtures

- In Isomerism, the word “**chiral**” is used to indicate that the central Carbon atom (in a tetrahedral grouping of five species with a Carbon atom at the centre of the tetrahedron), has four **DIFFERENT** species attached to it. In the diagram from Wikipedia below, the central Carbon atom is chiral (i.e. it has four different species attached to it). One tetrahedral grouping of five species is the mirror image of the other, and two mirror images that are not superimposable on each other are given the name “**Enantiomers**”. An **enantiomer** is a stereoisomer where the species and its mirror image cannot be imposed on each other. I will discuss ‘impossibility’ later on.



- A Carbon species which is a “>CH₂” or a “-CH₃” species, **cannot be chiral**. If there are 2 Hs or 3Hs in the grouping, then the central C atom **cannot** be attached to **four different** species. The species above are two forms of CH₃.CH(OH).COOH (3-methyl-2-hydroxy propanoic acid). The “-CH₃” and “-COOH” species cannot be chiral because they do not have four different species attached to them. It is only the C atom in “CH₃CH(OH)COOH” that is chiral.
- Any Carbon compound that has a chiral centre will be optically active.** In Isomerism, the phrase “optically active” indicates that a substance will alter the plane of polarised light. The mirror image compound of a chiral compound will alter the plane of polarised light: counter-clockwise would be signified by the symbol ‘l’ (for “levorotatory”) or ‘-’; and, if the compound altered the light clockwise then ‘d’ (for “dextrorotatory”) or ‘+’. (The two symbols indicate the same transformation.)
- A **racemic** mixture has equal amounts of a chiral compound and its *companion* enantiomer. Such racemic mixtures are optically **inactive** because the optical effect of the two compounds is to cancel each other out, and polarised light passes through unaltered. (This piece of knowledge has been tested at ‘A’ Level in recent years.)

A) Structural (or Constitutional) Isomers

NB Structural isomers **do** exist in three dimensions, but they are **NOT** classed as “**stereoisomers**”.

- **Skeletal or Chain isomers** where the atoms of the molecules of the two isomeric substances are *connected* in a different way e.g. pentane and 2-methyl butane.
- **Positional** where the isomeric molecules have the same functional group, but the groups are located in different positions in the molecules e.g. pentan-1-ol and pentan-2-ol.
- **Functional** where the isomeric molecules possess different functional groups e.g. ethanol and methoxymethane.

B) Stereoisomers¹

B1 Mirror Image Isomers viz. where the isomeric molecules are mirror images of each other. Chemists describe some mirror images as being **superimposable** on each other (e.g. CHBrClCl and its mirror image) and other (chiral) molecules (e.g. CFCIBrI) as being **non-superimposable**. **The non-superimposable mirror images are called enantiomers.** (Any Carbon molecule that has four different species bonded to the central Carbon atom is termed “chiral”.)

B2 Diastereoisomers where the isomeric molecules are **not** mirror images of each other.

B2.1 Restricted-rotation diastereoisomers Here **rotation is constrained** because of (i) multiple-bonds in molecules such as Alkenes and Alkynes and (ii) ring-molecules such as some Cycloalkanes and Arene compounds. These isomers are also known as **Configurational Isomers**.

B2.2 Unrestricted-rotation diastereoisomers Here rotation is **not** constrained (*e.g. Conformational isomerism in a saturated Carbon compound*).

- OK, that is the structure on which the discussion of this Chapter will be based. If at any stage you feel that you have got lost, then please come back to pages 2 and 3 to get your bearings.
- If I were you, I would commit the table on page 2 to memory (just as I have advised you to commit to memory the information trees for Alcohols/Halogenoalkanes/Benzene/etc).
- For a Carbon species to have optical isomers, the central Carbon atom must be chiral i.e. it must be bonded to four different species. **Therefore the most helpful simple rule for isomerism in Organic Chemistry is**
 “A Carbon species which is a “>CH₂” or a “–CH₃” species, cannot be chiral.”
- **Isomers are of enormous importance when it comes to medicinal drugs.** This is so because of something called the “lock-and-key” system where a given drug might have a certain effect, but almost exactly the same drug (but with a miniscule difference) will not. The most tragic example of this in modern times was with a drug called Thalidomide. **If you are doing Biology, and want to go on and read Medicine – then you really ought to read about Thalidomide on the internet.**
- In Chemistry, do not worry about words from foreign languages (or symbols that stand for foreign words). I am not going to discuss etymology here. It is simpler to just learn how such words are used in Chemistry.
 - A **mirror image** is the reflection of an object in a mirror. If a Carbon atom is attached to four different species, then the mirror image will be **non-superimposable** on the original object. Mirror images can be superimposable or non-superimposable, and the latter are called enantiomers. **Enantiomers are non-superimposable mirror images of each other.**
 - “**cis**” means on the same side of, and “**trans**” means on opposite sides of (mainly of a double bond).
 - “**Z**” (from the German word “*zusammen*”) stands for on the same side of and “**E**” (from the German word “*entgegen*”) stands for on opposite sides of (mainly of a double bond).
 - A “+” or “**d**” enantiomer rotates plane-polarised light clockwise (when viewed from the light source) and a “–” or “**l**” enantiomer rotates light counter-clockwise.

¹ There is an **R/S** system for naming isomers, and also a **Cis/Trans** and **E/Z** system for naming Alkenes. Both the **R/S** and the **E/Z** systems are based on the Cahn-Ingold-Prelog (CIP) priority rules.

- “D” means right, and “L” means left. (“d” and “l” are **not** the same classification system as “D” and “L”.)
- “R” also means right, and “S” means left. However, the R/S system involves something called **absolute configuration** whereas the D/L system is about configuration **relative to the manner in which the two different isomers of glyceraldehyde rotate plane-polarised light**.
- The D/L system is not as precise as the R/S classification system (and both are described in this Chapter). The D/L system is still used (mainly in Biology with regard to amino acids and carbohydrates, and in the naming of medicinal drugs). If you are doing Biology, then you might want to have a look at <http://www.masterorganicchemistry.com/2017/05/24/d-and-l-sugars/> where you will find the attached (*and much more*). (I, however, know nothing about Biology. The stuff below is all Greek to me.) A chemist would identify the first four species below as Aldehydes, while the fifth one is a Ketone.

Please remember that “D” and “L” (quite arbitrarily) refer back to the manner in which the isomers of glyceraldehyde alter the plane of polarised light. (It is a classification system that lacks precision.)

For a sugar drawn in the Fischer projection with the most oxidized carbon at the top:

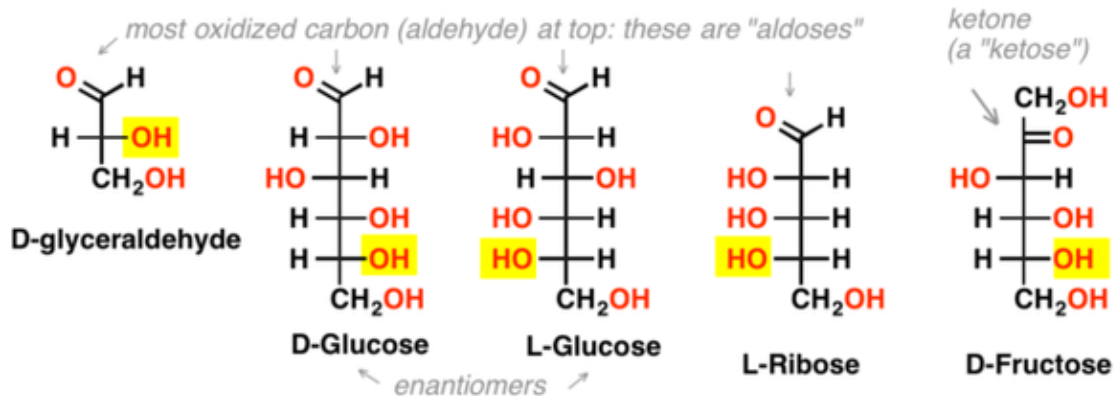
- if the OH on the bottom chiral centre points to the right, it is referred to as D-
- if the OH on the bottom chiral centre points to the left, it is referred to as L-.

D- and L- Sugars

For a sugar drawn in the Fischer projection with the most oxidized carbon at the top:

- If the OH on the bottom chiral center points to the **right**, the sugar is **D**
- If the OH on the bottom chiral center points to the **left**, the sugar is **L**

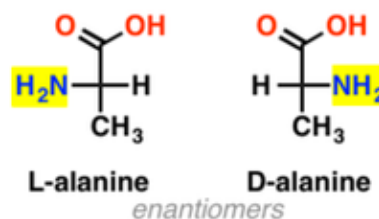
↓



L- and D- is a means of describing the **absolute configuration** of a molecule that pre-dates *R* and *S* but is still used for some biological molecules (sugars, amino acids). It's a quick way of denoting enantiomers: e.g. L-glucose and D-glucose are enantiomers.

L- and D- have no relation to the optical rotation of a molecule.

The D- L- system can also be applied to other chiral molecules, e.g. amino acids:



An explanation of some of the terms that are used

a) Left and Right

- **There is no up/down nor left/right in space.** If I stand in front of a molecule and you stand behind it, then my left is your right. Referring to left and right would therefore be entirely relative, and confusing. **Left and right do not exist in space.** However, the convention in Chemistry is that if you are looking at a piece of paper on which a molecule has been drawn, then left and right are taken to mean “left and right as you perceive them on the piece of paper that is in front of you”.

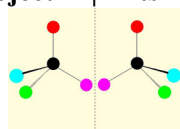
b) Isomers

- If two chemical compounds possess exactly the same molecular formula but have one or more physical or chemical differences (no matter how minute the difference), then they are **isomers** of each other. The different types of isomers (most of which arise from how the atoms in a molecule are connected to each other) are explored below.

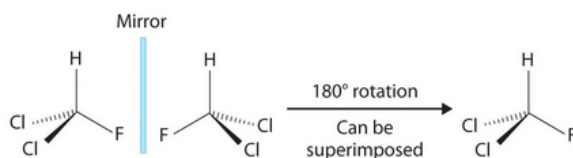
c) Mirror images and Superimposability

- If an object is placed in front of a mirror, then the reflection of that object is seen in the mirror. By close inspection it can be seen that a *left hand* placed in front of a mirror will be reflected as a *right hand* in the mirror. It might appear to be exactly the same object, but in reality it is **not**.

An object | Its mirror image



- The difference between an object and its mirror image is that the two objects are not superimposable. Please put your left hand face down on a table in front of you, and now put your right hand on top of it (your right hand being what, by close inspection, you realised was the mirror image of your left hand). Is your right hand the same as your left hand? No, and you realise this **because they are not superimposable**. The thumb of one hand will point in exactly the opposite direction to the thumb of the other hand.
- Those of you who are doing Optics in Physics will know why a mirror image can never be the same as the original object. **Even if it appears to be so, it cannot be so.** In Physics, even if two objects appear to be superimposable, then that is the result merely of the inability of human beings' eyes to distinguish the difference that their brains know to be the case. (In Physics, an object and its mirror image can never be imposed on each other. **Superimposability is an illusion of the eye.**) In contrast to physicists, chemists make imprecise statements e.g. that dichlorofluoromethane and its mirror image are superimposable. This of course is not true. It is just that the eyes of a human being cannot distinguish the difference between the two **DIFFERENT** Chlorine atoms in the molecule. **Twins may look exactly like each other but they are not the same as each other.** For example, the mirror images below are superimposable **ONLY** if one ignores the fact that the two Chlorine atoms are in fact different Chlorine atoms. **The definition of superimposability is thus best confined to discussions about symmetry (cf. “chirality” on the next page).**



(b) Dichlorofluoromethane

d) Chirality

- Robert Boyle defined the term “chiral” as “..... I call any geometrical figure, or group of points, ‘chiral’ **if its image in a plane mirror cannot be brought to coincide with itself.**”
In other words, Boyle defined chirality in terms of enantiomers (cf. below).
- **Any object that is not symmetrical in three-dimensional space is ‘chiral’.** Chirality can be extraordinarily complicated (and I therefore do not intend to go into the subject in any detail). However, at its simplest, any central object in a configuration such as **a Carbon atom that is attached to four different species is chiral.** The defining characteristic of a ‘chiral’ object is that **it is not symmetrical.** ‘Chirality’ stems from the lack of **symmetry**.

e) Enantiomers

- Enantiomers are a sub-set of the larger group of ‘chiral’ objects. Enantiomers are
 - **non-superimposable**
 - **mirror images** of each other.

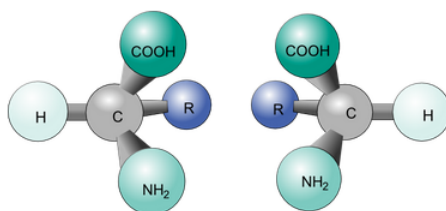


Figure 1: Two enantiomers of a tetrahedral complex.

f) Plane-polarised light and “Optical Activity”

- “Light” is the tiny part of the spectrum of electro-magnetic radiation (emr) that human beings can see. The **wavelengths** of the emr spectrum extend from the very small (as in gamma rays) to the very large (as in radio waves). The science of “light” belongs in Physics, and if you go to https://science-edu.larc.nasa.gov/EDDOCS/Wavelengths_for_Colors.html you will find a nice little discourse by NASA on light.
- Light waves vibrate in many different directions at right angles to the direction of travel of the light wave. My knowledge of Physics is limited, but as I understand it, the fact that the light from a point-source travels **in an expanding funnel** can be explained only if the light is vibrating in many different directions at right angles to the direction of travel.
- **Plane-polarised light** is light that has been reduced to just one direction of vibration perpendicular to the direction of travel (i.e. to one single plane). **You will of course now immediately deduce that plane-polarised light will be propagated **not** as an expanding funnel but as a mono-planar expanding SHEET of light.**
- If a substance (mainly natural, but including some man-made substances) can alter the angle of vibration of a plane-polarised beam of light (i.e. **rotate** the plane of vibration), then it is said that the substance is **optically active**.
- Please be sure that you understand **plane-polarisation** and **optical activity** before you read about the “+” / “-” / “D” and “L” / and the “R” and “S” classification systems on the next page.

g) “+” (clockwise) and “-” (anticlockwise) rotation, and the D/L and R/S classification systems

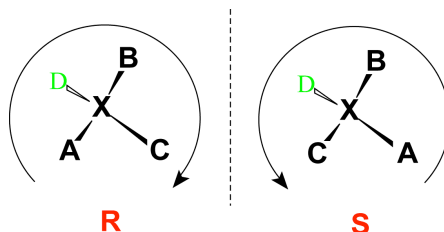
In common with a large number of students (who have gone before us since Emil Fischer), I had enormous difficulty in grasping this bit of Chemistry when I did my ‘A’ Levels. Please read the stuff below again and again until you get it.

- The D/L system of classification was devised at the turn of the last (the 20th) century by the Nobel Laureate Emil Fischer, a German organic chemist who worked extensively with carbohydrates. He chose the compound glyceraldehyde, $\text{HOCH}_2\text{CH}(\text{OH})\text{CHO}$, as the standard for defining **configuration**. *Please stop there and read that sentence again. Fischer chose Glyceraldehyde as his benchmark/his yardstick.* This was a purely arbitrary decision on his part.
- There are two sorts of glyceraldehyde in nature. Both of them have the same molecular formula, but one isomer just happens to rotate plane-polarised light in one direction (i.e. clockwise, and he called this isomer “D-glyceraldehyde”) while the other isomer happens to rotate plane-polarised light in the opposite direction (i.e. anti-clockwise, and he called this “L-glyceraldehyde”).
- **The D-L system has no direct connection to the (+)/(-) notation.** It just so happens that D-glyceraldehyde rotates plane-polarised light in the clockwise (+) direction, and L-glyceraldehyde rotates plane-polarised light in an anticlockwise (-) direction.
- Now comes the crucial bit (and if you get this bit, then you will have cracked the “D/L” system and its anomalies). Fischer then said “if the constituent parts of an isomer of another substance have the same **CONFIGURATION** in space as D-glyceraldehyde, then the isomer of that substance will be given the prefix “D”, and if the constituent parts of another isomer of that substance have the same configuration in space as L-glyceraldehyde, then the isomer of that substance will be given the prefix “L”. *(If you did not get that the first time that you read it, then please read it again.)*
- Fischer did **NOT** say anything about the way that the isomers of the second substance altered the direction of plane-polarised light. **It did not enter into his thinking at all.** The naming was based purely on whether or not the constituents parts of the isomers **were configured/connected in the same way** as D-glyceraldehyde and L-glyceraldehyde.
- I hope that you will now see very clearly that if the D-isomer of the second substance rotates plane-polarised light in a different direction to D-glyceraldehyde, then Fischer would just shrug his shoulders and say “So what. That has nothing to do with the way that I have named the substance. The direction of deflection of plane-polarised light is not crucial to my naming system” – and he would be absolutely right to say that.
- I hope that you can now see that in Biology (and mainly with regard to sugars and α -amino acids) the naming system of a substance relates to the stereochemistry of that substance in relation to that of the stereochemistry of D-glyceraldehyde and L-glyceraldehyde, and says nothing whatsoever about its optical activity. *It is possible for its constituent part to have the same relative configuration as D-glyceraldehyde (and therefore it is given the prefix “D”), and yet the compound might rotate plane-polarised light counterclockwise (-) e.g. D-(-)-ribose², i.e. in the opposite direction to the deflection by D-glyceraldehyde.*
- The (R) and (S) classification system also is not determined by the direction in which a molecule rotates plane-polarised light. Instead it is primarily about **the sequence of the priorities³ given to the species that are attached to a chiral centre.** *In the R/S system also, it is possible for an isomer to have an S-prefix while its optical activity to be (+) i.e. clockwise.*

² The minus sign in the brackets indicates the direction of deflection of plane-polarised light by D-(-)-Ribose.

³ Where the priority is determined by the Cahn-Ingold-Prelog (CIP) priority rules. The Chemistry building at UCL is named after Sir Christopher Ingold.

- In the example below, the naming procedure is as follows:
 - Assign priorities to the species A/B/C/D according to the CIP rules (explained later).
 - Point the species with the lowest priority away from you in space.
 - Starting from A, if the order of priorities for A/B/C takes you clockwise then the species is termed “R”, but if the order of priorities takes you anticlockwise then the species is “S”.



- Please stop there and just read all that again, *and again and again* until you have understood clearly the difference between the two designation (D/L and R/S) systems.
- Both are totally arbitrary designation systems. One relates the name of an isomer of a molecule in relation to the configuration in space of the two isomers (D and L isomers) of glyceraldehyde, and the other system is based on the priorities assigned by the CIP rules. **BOTH ARE TOTALLY ARBITRARY DESIGNATIONS!**
- The D/L system and the R/S are totally different classification systems.** The D/L system labels the *WHOLE* molecule, whereas the R/S system labels the *absolute configuration* of *each chiral centre* (cf. masterorganicchemistry on the next page).
- Those of you who are doing Biology and who are going on to do Medicine will **still** see medicines that are named using the old D/L classification system (now not much used in Chemistry). The reason for this is that it is an extremely useful classification system for sugars but possibly not much else (but please remember that I know absolutely nothing about Biology).
- I do not intend to say any more than that, but if you want to understand why the D/L system was abandoned in Chemistry, then you could go to the University of Maine’s webpage <http://chemistry.umeche.maine.edu/CHY251/dlwrong.html>.
- There is also a very good explanation of D/L and +/- on <https://chemistry.stackexchange.com/questions/44260/what-is-the-difference-between-d-and-l-configuration-and-and-%E2%88%92>
If I were doing Biology and I wanted to go into Medicine, then I would read it.

h) The CIP (Cahn-Ingold-Prelog) Priority rules for the R/S classification of absolute configuration

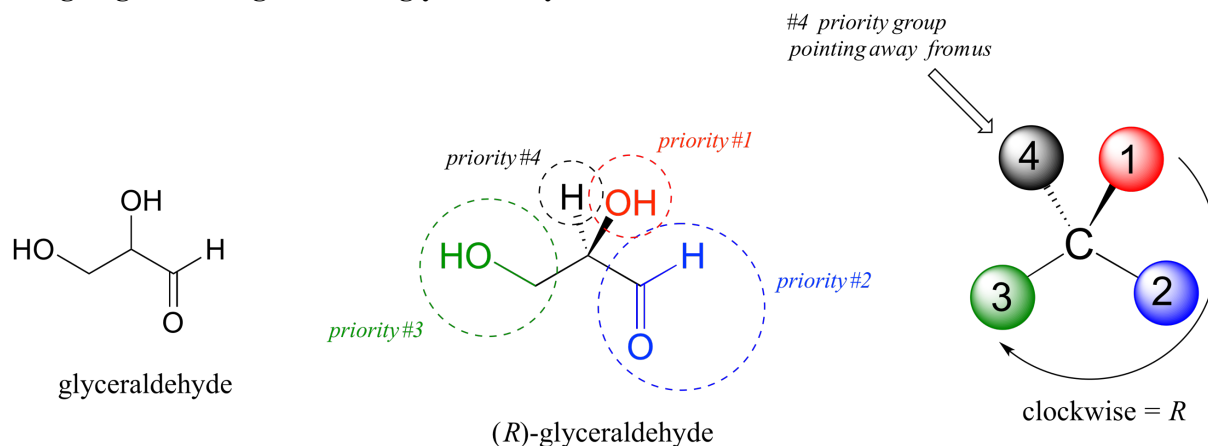
- At its simplest there are three CIP rules for determining priority. Masterorganicchemistry gives the following *simplified* rules at <http://www.masterorganicchemistry.com/2016/10/20/introduction-to-assigning-r-and-s-the-cahn-ingold-prelog-rules/>
- I am going to quote Chemistry LibreTexts and Dr James Ashenhurst of masterorganicchemistry for the easy rules of priority in the R/S classification system.

a) This is a quote from Chemistry LibreTexts

Please remember that “atomic number” = proton number (and not the atomic mass)

- We'll use the 3-carbon sugar (glyceraldehyde) as our first example. The first thing that we must do is to assign a **priority** to each of the four substituents bound to the chiral center. We first look at the atoms that are directly bonded to the chiral center: these are H, O (in the hydroxyl species), C (in the aldehyde), and C (in the CH₂OH group).

Assigning R/S configuration to glyceraldehyde:



- Two priorities are easy: hydrogen, with an atomic number of 1, is the lowest (#4) priority, and the hydroxyl oxygen, with atomic number 8, is priority #1. Carbon has an atomic number of 6. Which of the two 'C' groups is priority #2, the aldehyde or the CH₂OH? To determine this, we move one more bond away from the chiral center: for the aldehyde we have a *double* bond to an **oxygen**, while on the CH₂OH group we have a *single* bond to an **oxygen**. If the atom is the same (and here it is Oxygen), double bonds have a higher priority than single bonds. Therefore, the aldehyde group is assigned #2 priority and the CH₂OH group the #3 priority.
- With our priorities assigned, we look next at the #4 priority group (the hydrogen) and point it away from us, into the plane of the page - thus step 4a from the procedure above applies. Then, we trace a circle defined by the #1, #2, and #3 priority groups, in increasing order. The circle is clockwise, which by step 4a tells us that this carbon has the 'R' configuration, and that this molecule is (R)-glyceraldehyde. Its enantiomer, by definition, must be (S)-glyceraldehyde.

b) Next is a quote from Dr James Ashenhurst of masterorganicchemistry

(Chemistry LibreTexts explains the priority rules better, but Dr Ashenhurst applies them more 'visually' below).

1. Prioritise the four groups around a chiral centre **according to atomic number** in the Periodic Table. The highest/largest atomic number is assigned priority #1, and the lowest atomic number is assigned priority #4.
 2. Orient the chiral centre so that the #4 priority substituent is pointing **away** from you. For our purposes, it's enough for it merely to be shown by a “dashed” bond (cf. overleaf).
 3. Now just look at the three groups with the highest atomic numbers. Trace the path of priorities #1, #2 and #3. (For this part **ignore** #4).
- If the path traced from 1-2-3 is **clockwise**, then the chiral center is assigned the label (R).
 - If the path traced is **counter-clockwise**, then the chiral center is assigned the label (S).

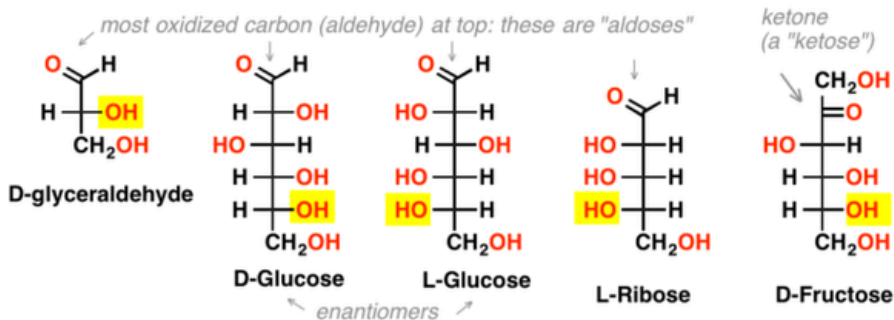
For a sugar drawn in the Fischer projection with the most oxidized carbon at the top:

- if the OH on the bottom chiral centre points to the right, it is referred to as **D-**
- if the OH on the bottom chiral centre points to the left, it is referred to as **L-**.

D- and L- Sugars

For a sugar drawn in the Fischer projection with the most oxidized carbon at the top:

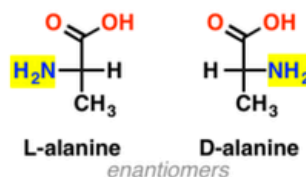
- If the OH on the bottom chiral center points to the **right**, the sugar is **D**
- If the OH on the bottom chiral center points to the **left**, the sugar is **L**



L- and D- is a means of describing the **absolute configuration** of a molecule that pre-dates *R* and *S* but is still used for some biological molecules (sugars, amino acids). It's a quick way of denoting enantiomers: e.g. L-glucose and D-glucose are enantiomers.

L- and D- have no relation to the optical rotation of a molecule.

The D- L- system can also be applied to other chiral molecules, e.g. amino acids:



Source: masterorganicchemistry

- You may find it difficult to believe, but so far I have talked merely about the preliminaries to Isomerism, but now that we have got the preliminaries out of the way let us start to talk about Isomerism itself – and please remember that Diastereoisomers are **not** mirror images of each other.

A) ISOMERISM

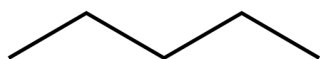
NB Please never lose sight of the fact that as Chemistry developed we have discovered more and more about different substances, and things that we thought were different (they had different chemical properties/different physical properties) turned out to be *almost* exactly the same as each other, and things that we thought were the same (or that we did not realise were different) in fact turned out to be **very different indeed**. During my lifetime, the saddest case of this was the drug Thalidomide, and you can read for yourselves (on the web) about what happened.

- If two chemical compounds possess exactly the same molecular formula but have one or more physical or chemical differences, then they are **isomers** of each other. The challenge that chemists have had to face is to understand **how** and **why** they differ from each other. In some instances the differences have turned out to be fairly obvious, but in some instances these differences have turned out to be very subtle and very complicated (as in the case of Sugars). Luckily at 'A' Level you are not required to know about the subtle/complicated differences, and you are expected to know only the fairly basic ones.

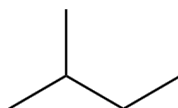
- Most chemists agree that isomerism can be divided into two broad categories (i) **Structural** (or Constitutional isomers, and (ii) **Spatial** (or Stereo isomers), and then after that the disagreement starts – not about what the different types of isomers are, but how best to name them.

- Structural isomers** can be divided into three categories viz.

- skeletal** or chain isomers where the atoms are arranged in differing ways (as with pentane , 2-methyl butane, and 2,2-dimethylpropane)



pentane

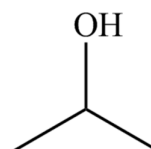
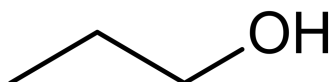


2-methyl butane

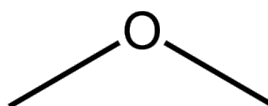
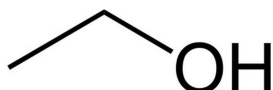


2,2-dimethylpropane

- positional** isomers possess the same functional group but with the functional group occurring in differing places e.g. as with propan-1-ol and propan-2-ol

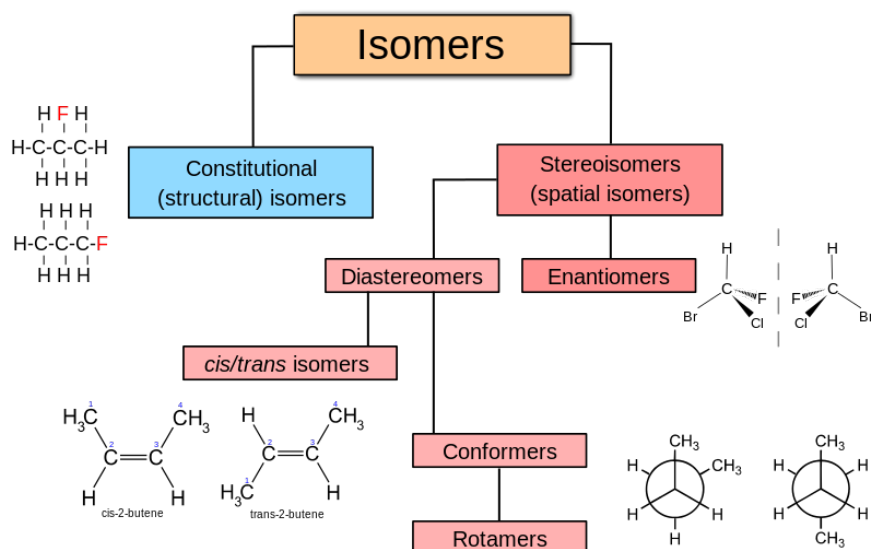


- functional** isomers possess different functional groups in their molecules (as with ethanol and methoxymethane).



methoxymethane

- I have now dealt with the basic classification of isomers into **Structural** or Constitutional Isomers (such as **Skeletal/Positional**/and **Functional**) and I have dealt with a large number of distinctions and classifications in **Stereoisomers** where there are two big divisions viz. Mirror images and non-mirror images, and if they are not mirror images then they will be called “**Diastereoisomers**”. (Mirror images of non-symmetrical objects are **chiral** and they will thus be non-superimposable on each other and they are called “**Enantiomers**”).



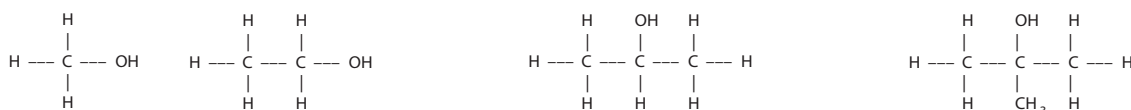
- Rotamers are a Conformational isomer and they are not in the UK 'A' Level syllabus, therefore I am not going to deal with them.
- Please remember that at 'A' Level, Geometric Isomers are unsaturated Carbon molecules (mainly Alkenes and Alkynes).

Cis/trans vs E/Z (a classification system used mainly when naming species that contain double bonds)

- When it comes to double bonds, rotation around the double bond breaks the overlap of the unhybridised 'p' orbitals that create the π bond and this destroys the molecule that contains the double bond. The basic naming system (which I told you about last year) is the Cis/Trans system.
- The only thing that I did not discuss about the Cis/Trans system with you last year was why Cis/Trans isomers have different properties (such as different boiling points), and as a matter of Revision, I should like you to re-read Chapters 21-24 on inter-molecular forces of attraction (vdW/ London/Debye forces of attraction) and then you will be able to work for yourself why a Cis configuration will have a larger inter-molecular force of attraction than a Trans configuration.⁴
- However, there are times when the Cis/Trans naming system is either cumbersome or it lacks precision/sophistication. A refinement was thus introduced, and rather like the R/S system, it was based on the CIP rules that defined priorities.
- Where the four species on a double bond are all different, then it becomes difficult (but not totally impossible) to talk with precision about Cis and Trans locations on a double bond. This is because it is extremely cumbersome to define the locations of the four species. Moreover when the molecule becomes a complicated one with many double bonds, then the Cis/Trans classification system cannot cope. However, if we were to allocate an order of priority for the different species that can attach to a double bond, then it becomes possible to standardise a naming system based on those priorities (just as the R/S system does).

⁴ If you need a hint, then think about Permanent/Momentary/ and Induced dipoles.

- The only thing that remains to tell you is that the more precise naming system is called the **E/Z** system, and I need to tell you the rules for allocating priorities under the E/Z system.
- As it happens, the rules for allocating priority in the E/Z system are exactly the same rules as those for allocating priority in the R/S system viz. the Cahn-Ingold-Prelog (CIP) rules – for which I have already given you the simple rules.
- I do not believe that the ‘A’ Level examiners will ask you anything that will require the complicated analysis of an E/Z configuration, and if you visit the Khan Academy’s website at <https://www.khanacademy.org/science/organic-chemistry/Alkene-Alkyne/naming-Alkene/v/entgegen-zusammen-naming-scheme-for-Alkene-examples> then you will see a video on E/Z which is very basic, but if you start there that will bring alive all the things that I have told you about E/Z.
- You will I am sure remember that
 - a 1° Alcohol will oxidise into an Aldehyde
 - a 2° Alcohol will oxidise into a Ketone, and
 - a 3° Alcohol will resist gentle oxidation by a dichromate ion but that a permanganate ion is so aggressive that it will break C–C bonds and then Acids will start forming.

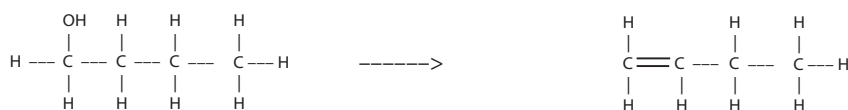


- In the ‘olden days’ (when I did my Chemistry ‘A’ Level exams), one of the things that the examiners liked to do was to ask examinees to identify the Alkene isomers that could be made from an Alcohol. I believe that in 2016 AQA asked a question that related to this, so this is what you do (and I shall use Butanol as my exemplar).

- Step 1: Write out the structural formula of the molecule as in the diagram above.
- Step 2: Look for the “H” and “OH” species that will form the molecules of water.
- Step 3: Eject/eliminate them as water molecules in a “Condensation” reaction, and then
- Step 4: Put a double bond between the respective C atoms.

This will provide the required Alkene isomers.

- Butan-1-ol will give only But-1-ene



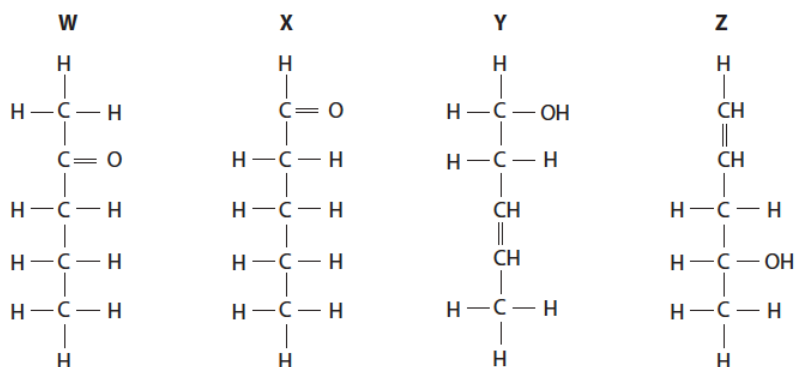
but Butan-2-ol can give both But-1-ene (as above) and But-2-ene



- I have covered a large amount of ground in this Chapter so far, so I am going to stop here and ask you to re-read all the ground that I have covered for you. You do not need to know about Conformers and Rotamers, and I will remind you that “**Enantiomers**” are **non-superimposable mirror images of each other** and I will also tell you that “**Diastereoisomers**” are not mirror images of each other.

- OK, so how do we translate all this stuff about isomers into answering exam questions? Well, let us have a look at an exam question and then we can see what to do.
- The following is Question 5 from the June 2016 Edexcel exam paper (6CH04_01_que_20160614).

5 The following molecules are structural isomers with molecular formula $C_5H_{10}O$.



(a) Which of the molecules would exhibit optical isomerism?

(1)

- ☐ A W
- ☐ B X
- ☐ C Y
- ☐ D Z

- The wording of the English used by the examiners here is rather poor because the word “optical” can refer to “optical activity” (and this question was **not** about optical activity) or it can refer to mirror-imagery which in Isomerism can refer to enantiomers or to super-imposable mirror images. In addition, the examiners are really asking a question not about the molecules ‘*per se*’ but about **individual Carbon atoms inside each molecule**. **This was a VERY poorly worded exam question.** Exam questions should contain **not even a trace** of ambiguity.
- Start with the fact that a Carbon species cannot exhibit (as the examiners called it) ‘optical isomerism’ if it contains either a CH_3 or a CH_2 species (because it then would not be chiral).
- Every single one of the four molecules W/X/Y/and Z has either a CH_3 or a CH_2 species in it, therefore clearly the examiners **did not mean “molecule”** and instead what they meant was “which of the four molecules W/X/Y/and Z **has a Carbon species in it that is chiral?**”.
- Start by quickly dismissing every C atom that is not chiral i.e. every C atom that (i) does not have four bonds (i.e. **dismiss all unsaturated C species**), and dismiss (ii) all CH_3 or CH_2 species, therefore dismiss every single C species in W/X/and Y, and then, in order to spot a **chiral C atom**, you will have to notice that the second last C atom (going from top to bottom as it is drawn) in Z has
 - a CH_2 species attached to it
 - an H species attached to it
 - an OH species attached to it, and
 - a CH_3 species attached to it,
 therefore it has four **different** species attached to it and it **is chiral** and it **will** therefore exhibit **chirality** (‘optical isomerism’), and you have to do that in less than 1 minute – and yes you can do all that in less than 1 minute, *because a huge number of candidates did precisely that in the 2016 exam* (and they were heroes to have understood the examiners’ poor English).

- OK, now can you see why I have urged you repeatedly to do masses of worked examples when you come to the end of each Chapter. **It is only the familiarity of answering questions that will enable you to answer sometimes very nice (and at other times very badly set) exam questions in the time that you will be allotted in the exam.**

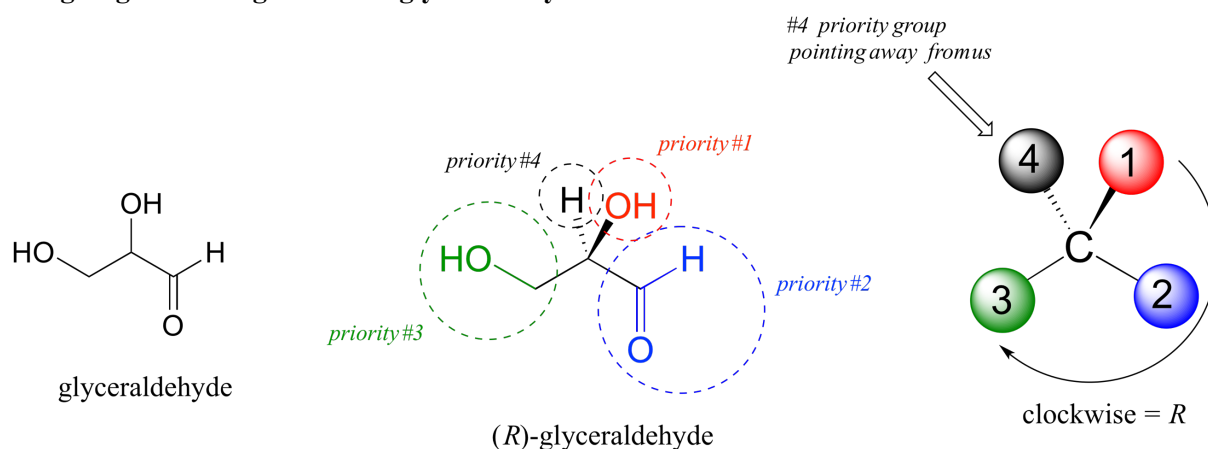
APPENDIX

Chem LibreTexts on

[https://chem.libretexts.org/Textbook_Maps/Organic_Chemistry_Textbook_Maps/Map%3A_Organic_Chemistry_with_a_Biological_Emphasis_\(Soderberg\)/Chapter_03%3A_Conformations_and_Stereochemistry/03.4%3A_Naming_chiral_centers%3A_the_R_and_S_system](https://chem.libretexts.org/Textbook_Maps/Organic_Chemistry_Textbook_Maps/Map%3A_Organic_Chemistry_with_a_Biological_Emphasis_(Soderberg)/Chapter_03%3A_Conformations_and_Stereochemistry/03.4%3A_Naming_chiral_centers%3A_the_R_and_S_system)
gives the following illustration

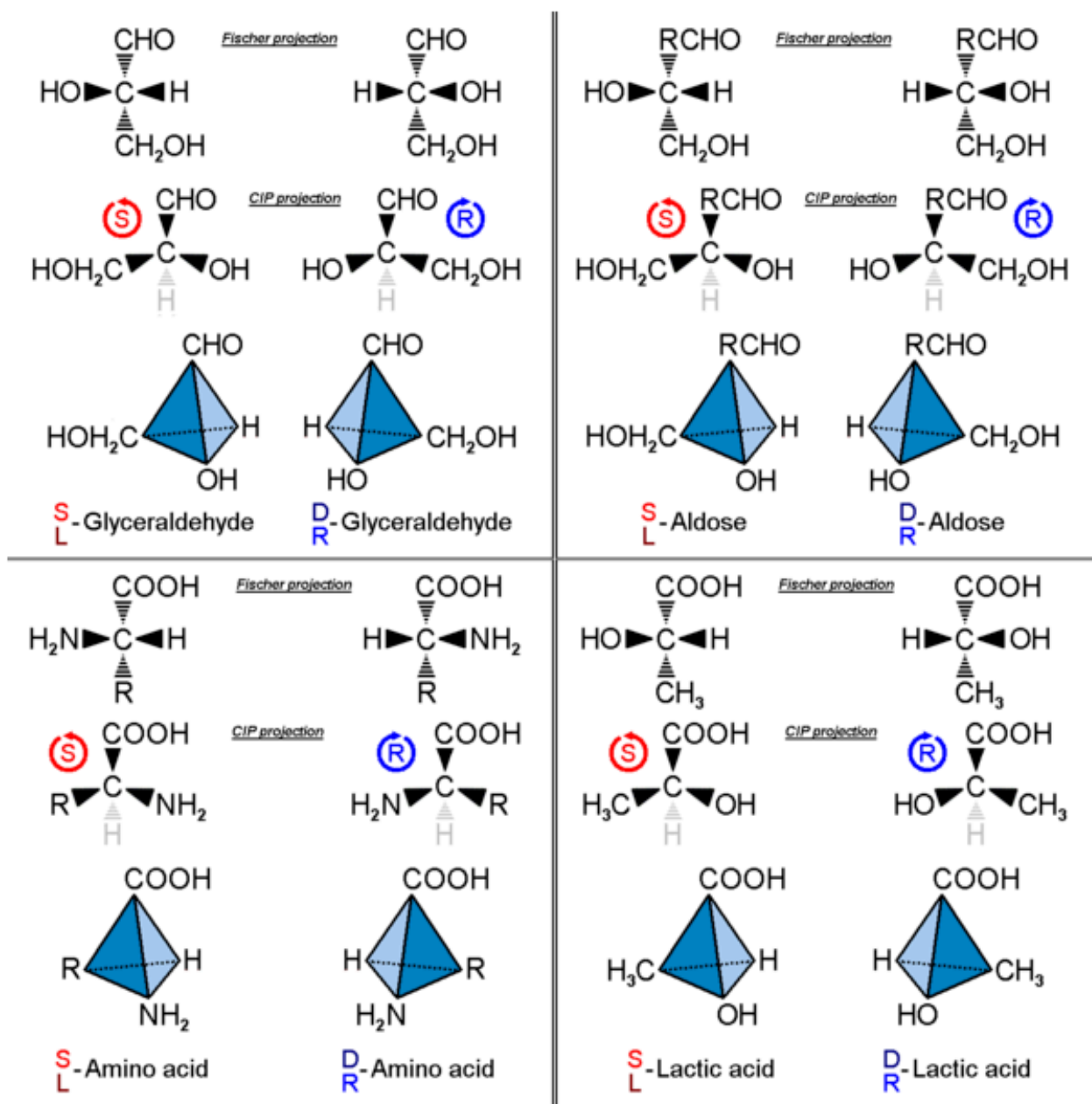
We'll use the 3-carbon sugar (glyceraldehyde) as our first example. The first thing that we must do is to assign a **priority** to each of the four substituents bound to the chiral center. We first look at the atoms that are directly bonded to the chiral center: these are H, O (in the hydroxyl species), C (in the aldehyde), and C (in the CH₂OH group).

Assigning R/S configuration to glyceraldehyde:



- Two priorities are easy: hydrogen, with an atomic number of 1, is the lowest (#4) priority, and the hydroxyl oxygen, with atomic number 8, is priority #1. Carbon has an atomic number of 6. Which of the two 'C' groups is priority #2, the aldehyde or the CH₂OH? To determine this, we move one more bond away from the chiral center: for the aldehyde we have a *double* bond to an oxygen, while on the CH₂OH group we have a *single* bond to an oxygen. If the atom is the same, double bonds have a higher priority than single bonds. Therefore, the aldehyde group is assigned #2 priority and the CH₂OH group the #3 priority.
- With our priorities assigned, we look next at the #4 priority group (the hydrogen) and point it away from us, into the plane of the page - thus step 4a from the procedure above applies. Then, we trace a circle defined by the #1, #2, and #3 priority groups, in increasing order. The circle is clockwise, which by step 4a tells us that this carbon has the 'R' configuration, and that this molecule is (*R*)-glyceraldehyde. Its enantiomer, by definition, must be (*S*)-glyceraldehyde.
- Wikipedia offers the following rather more complicated illustrations of examples of absolute configuration of some carbohydrates and amino acids according to Fischer projection (D/L system) and Cahn-Ingold-Prelog priority rules (R/S system)

(but I would not bother to try to unravel them unless you intend to read Chemistry at University)



- The *R* / *S* system is an important nomenclature system for denoting enantiomers. This approach labels each chiral center *R* or *S* according to a system by which its substituents are each assigned a *priority*, according to the Cahn-Ingold-Prelog priority rules (CIP) based on atomic number⁵. If the center is oriented so that the lowest-priority of the four is pointed away from a viewer, the viewer will then see two possibilities: If the priority of the remaining three substituents decreases in clockwise direction, it is labelled *R* (for *Rectus*, Latin for right), if it decreases in counterclockwise direction, it is *S* (for *Sinister*, Latin for left).
- (*R*) (*S*) are written in italics and parentheses. If there are multiple chiral carbons, e.g. (1*R*,4*S*), a number specifies the location of the carbon preceding each configuration.

⁵ PROTON number.

- The *R*/*S* system also has no fixed relation to the D/L system. For example, the side-chain one of serine contains a hydroxyl group, -OH. If a thiol group, -SH, were swapped in for it, the D/L labelling would, by its definition, not be affected by the substitution. But this substitution would invert the molecule's *R*/*S* labelling, because the CIP priority of CH₂OH is lower than that for CO₂H but the CIP priority of CH₂SH is higher than that for CO₂H. For this reason, the D/L system remains in common use in certain areas of biochemistry, such as amino acid and carbohydrate chemistry, because it is convenient to have the same chiral label for the commonly occurring structures of a given type of structure in higher organisms. In the D/L system, they are nearly all consistent – naturally occurring amino acids are all L, while naturally occurring carbohydrates are nearly all D. In the *R*/*S* system, they are mostly *S*, but there are some common exceptions.

By optical rotation: (+)- and (-)- or *d*- and *l*-

- An enantiomer can be named by the direction in which it rotates the plane of polarized light. If it rotates the light clockwise (as seen by a viewer towards whom the light is traveling), that enantiomer is labelled (+). Its mirror-image is labelled (-). The (+) and (-) isomers have also been termed *d*- and *l*-, respectively (for *dextrorotatory* and *levorotatory*). Naming with *d*- and *l*- is easy to confuse with D- and L- labelling and is therefore discouraged by IUPAC.

By relative configuration: D- and L-

- An optical isomer can be named by the spatial configuration of its atoms. The D/L system (named after the Latin words *dexter* and *laevus*, right and left), not to be confused with the *d*- and *l*-system, see above, does this by relating the molecule to glyceraldehyde. Glyceraldehyde is chiral itself, and its two isomers are labelled D and L (typically typeset in small caps in published work). Certain chemical manipulations can be performed on glyceraldehyde without affecting its configuration, and its historical use for this purpose (possibly combined with its convenience as one of the smallest commonly used chiral molecules) has resulted in its use for nomenclature. In this system, compounds are named by analogy to glyceraldehyde, which, in general, produces unambiguous designations, but is easiest to see in the small biomolecules similar to glyceraldehyde. One example is the chiral amino acid alanine, which has two optical isomers, and they are labelled according to which isomer of glyceraldehyde they come from. On the other hand, glycine, the amino acid derived from glyceraldehyde, has no optical activity, as it is not chiral (achiral).
- The D/L labelling is unrelated to (+)/(-); it does not indicate which enantiomer is dextrorotatory and which is levorotatory. Rather, it indicates the compound's stereochemistry relative to that of the dextrorotatory or levorotatory enantiomer of glyceraldehyde. The dextrorotatory isomer of glyceraldehyde is, in fact, the D- isomer. Nine of the nineteen L-amino acids commonly found in proteins are dextrorotatory (at a wavelength of 589 nm), and D-fructose is also referred to as levulose because it is levorotatory. A rule of thumb for determining the D/L isomeric form of an amino acid is the "CORN" rule. The groups COOH, **R**, NH₂ and H (where R is the side-chain) are arranged around the chiral center carbon atom. With the hydrogen atom away from the viewer, if the arrangement of the CO→**R**→N groups around the carbon atom as center is counter-clockwise, then it is the L form. If the arrangement is clockwise, it is the D form. As usual, if the molecule itself is oriented differently, for example, with H towards the viewer, the pattern may be reversed. The L form is the usual one found in natural proteins. For most amino acids, the L form corresponds to an *S* absolute stereochemistry, but is *R* instead for certain side-chains.

Stackexchange at

<https://chemistry.stackexchange.com/questions/44260/what-is-the-difference-between-d-and-l-configuration-and-and-%E2%88%92>

has this to say:

- The D-L system corresponds to the **configuration** of the molecule: spatial arrangement of its atoms around the chiral center.
- While (+) and (-) notation corresponds to the **optical activity** of the substance, whether it rotates the plane of polarized light clockwise (+) or counterclockwise (-).
- D-L system tells us about the *relative configuration* of the molecule, compared to the enantiomers of glyceraldehyde as the standard compound. Compounds with the same relative configuration as (+)-glyceraldehyde are assigned the D prefix, and those with the relative configuration of (-)-glyceraldehyde are given the L prefix.
- It's kind of another way to tell the configuration of molecules beside the Cahn–Ingold–Prelog convention (R/S system), with little difference. (D-L system labels the *whole* molecule, while R/S system labels the *absolute configuration* of *each* chirality center.)
- In short, the D-L system doesn't have direct connection to (+)/(-) notation. It only relates the stereochemistry of the compound with that of glyceraldehyde, but says nothing about its optical activity. We may have compound with same relative configuration as (+)-glyceraldehyde (thus, it's given the D prefix), yet it rotates the polarized light counterclockwise (-), such as D-(-)-ribose.
- And also, don't confuse the D-L system with d- and l- naming. d- and l- is the exact same with (+) and (-) notation.

Additional explanation

- D-L system (also called Fischer–Rosanoff convention) is mainly used for naming α -amino acids and sugars. It compares the relative configurations of molecules to the enantiomers of glyceraldehyde. This convention is still in common use today.
- Rosanoff in 1906 selected the enantiomeric glyceraldehydes as the point of reference^[1]; any sugar derivable by chain lengthening from what is now known as (+)-glyceraldehyde (or named D-glyceraldehyde) belongs to the D series. In other words, we used a D to designate the sugars that degrade to (+)-glyceraldehyde and an L for those that degrade to (-)-glyceraldehyde.
- In assigning the D and L configurations of sugars, we could directly look for the OH group of the bottom asymmetric carbon in the Fischer projection. If it's located on the right, we designate it with D, and vice versa, since they would have the same relative configurations with glyceraldehyde for the bottom asymmetric carbon.

Reference

[1]: IUPAC and IUBMB. Joint Commission On Biochemical Nomenclature. *Nomenclature of Carbohydrates*. **1996**, 7.