Topic 5 – Stereochemistry and optical isomers

Recap Classification of isomers

- **Isomers**
  - same molecular formula

- **Constitutional Isomers**
  - Different nature/sequence of bonds

- **Stereoisomers**
  - Different arrangement of groups in space

- **Conformational Isomers**
  - Differ by rotation about a single bond

- **Configurational Isomers**
  - Interconversion requires breaking bonds

- **Enantiomers**
  - Non-superposable mirror images

- **Diastereoisomers**
  - Not mirror images

Stereoisomers - enantiomers

**Chiral molecules (optical isomers)**
- A molecule is *chiral* if it is not superimposable upon its mirror image.
- A pair of molecules which are not identical but are mirror images of each other are called *enantiomers*.
- Almost all of the physical and chemical properties of a pair of enantiomers are identical (melting point, boiling point, solubility *etc*).
- A chiral molecule contains a *stereogenic centre* (also known as a stereocentre or chiral centre).
- A stereogenic centre may be recognised as it is a carbon atom with *four different groups* attached to it.
- In these molecules there is no plane of symmetry.
1. Look at your hands. Are they mirror images of each other (overlooking any warts, freckles, unevenly chewed fingernails etc)?

Are they superimposable? (i.e. can you lay one hand directly on top of the other, both facing the same way, with the thumb on the thumb, the little finger on the little finger, everything mapping directly from one hand to the other?)

Now ask the same questions of two blank sheets of paper: are they mirror images of each other? Are they superimposable?

Why the difference between the hands and the sheets of paper?

2. Mark with a "*" the stereocentres in each of these chiral molecules

Our smell and taste receptors are chiral and so may differentiate between these enantiomers. This is also true of other proteins in our bodies.

The stereochemical labels (L) and (D) are often used in biology for sugars and amino acids. In this course we will use the more general (and therefore more useful) labels (R) and (S).

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1 superimpose: to impose, place, or set over, above, or on something else (dictionary.com)
Chirality in nature

We live in an asymmetric world!

- The enantiomers of a chiral molecule behave in an identical way when reacting with an achiral reagent (ie one that does not contain a stereogenic centre, eg $\text{H}^+$, $\text{Br}_2$, benzene).
- But they may react quite differently to one another towards another chiral compound.

Pharmaceuticals are often sold as a mixture of the two enantiomers.

3. Now how about these ones … where are the stereocentres in these well known drug molecules?

![Chemical structures of ibuprofen, fluoxetine (Prozac), and penicillin G.]

4. So far we have seen two sorts of configurational stereoisomers. Two pairs of configurational isomers are shown below. What type of isomers are A & B? What type of isomers are C & D?
**Optical activity**

How may we distinguish enantiomers in the lab?
- The physical properties of a pair of enantiomers are identical with the exception of their interaction with plane polarised light.
- Plane polarised light consists of waves oscillating in only one plane.

Polarimeter: when plane polarised light is passed through a solution of one pure enantiomer of a compound, *the plane of polarisation is rotated*.
- The enantiomer is said to be optically active.
- The amount of rotation (α) is a characteristic of the enantiomer.
- Rotation in a clockwise direction is labelled (+) and rotation in a counter-clockwise direction (-).
- One enantiomer rotates plane polarised light in a clockwise direction, the other enantiomer rotates the light by an equal amount in the opposite direction.
- It is not (yet) possible to predict which enantiomer is (+) and which (-) without performing the experiment.
- A mixture of equal amounts of the two enantiomers will give no net rotation and is called a racemic mixture.

**Nomenclature**

The *absolute configuration* of a stereogenic centre refers to the exact three dimensional arrangement of the groups
- Identify the stereogenic centre
- Rank the atoms attached to the stereogenic carbon in order of atomic number; highest atomic number = highest priority

If two atoms have the same atomic number, compare the atoms to which they are attached. Continue along carbon chains until a difference is reached.
- Multiple bonds are expanded to the same number of single bonds to that atom.
- Orientate the molecule with the lowest priority group at the back.
- Examine remaining three groups as if they are the spokes of a wheel and trace a curve from priority a to b to c.
- A clockwise curve indicates the \( R \) configuration; a counter-clockwise curve indicates the \( S \) configuration

**Note: Absolute configuration cannot be correlated to direction of optical rotation**
- Enantiomers rotate plane polarised light in opposite directions and have opposite absolute configurations.
- But...the direction of rotation is not directly related to configuration.

\[
\text{R-Lactic acid has an optical rotation of } -2.6^\circ \\
\text{S-Glyceraldehyde has an optical rotation of } -8.7^\circ
\]

5. Identify the configuration (\( R \) or \( S \)) of the stereogenic centre in each of the following compounds:

6. Give the structure of:

   (S)-2-methyl-3-pentanol

   (S)-1-phenylethylamine

7. Lactic acid (\( \text{CH}_3\text{CH(OH)CO}_2\text{H} \)) can accumulate in muscle tissue where there is a deficiency of oxygen and cause cramp. Only the (S) enantiomer is formed. Draw the structure of (S)-lactic acid.
8. The compound ‘fluoxetine’, shown below, is sold as a racemic mixture under the trade name *prozac*. It is a very effective anti-depressant but has no activity against migraine. The pure S-enantiomer however works well in preventing migraine. Identify the stereogenic centre in fluoxetine and draw the S-enantiomer.

![Fluoxetine structure](image)

9. Penicillin V has the absolute configuration shown. How many stereogenic centres are present in penicillin V?

![Penicillin V structure](image)

10. Consider a molecule like this one, which has two stereogenic centres. Identify the stereocentres.

![Example structure](image)

How many different stereoisomers are possible?

What if there were three stereogenic centres? Or four … or n stereocentres? How many stereoisomers are possible?

11. Using wedges and dashes, draw three more stereoisomers of 2-bromo-butano-1-ol alongside the one shown below.

![2-Bromo-butano-1-ol structure with R,R configuration](image)

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
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<td>(R,R)</td>
<td>(S,S)</td>
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