Lecture 12 – Stereochemistry

A/Prof Sebastien Perrier, Room 351, kcpc
s.perrier@chem.usyd.edu.au
Chirality

This Lecture
- Stereoisomers: enantiomers \((R/S)\)
- Optical activity
- Enantiomers and nature

Next Lecture
- Diastereoisomers & Fischer projections
Isomerism Recap

**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
Diastereoisomerism in Alkenes

Higher priority groups on the **same side** of double bond $\rightarrow$ alkene is denoted \((Z)\)

Higher priority groups on **opposite sides** of double bond $\rightarrow$ alkene is denoted \((E)\)

\[
\begin{align*}
\text{H} & \quad \text{C} = \text{C} & \quad \text{H} \\
\text{H}_3\text{C} & \quad \text{CH}_3 & \quad \text{H}_3\text{C} & \quad \text{H} \\
\text{H} & \quad \text{C} = \text{C} & \quad \text{H} & \quad \text{Cl} \\
\text{Br} & \quad \text{C} = \text{C} & \quad \text{CH}_3
\end{align*}
\]

\((Z)\)-2-butene

\((E)\)-2-butene

\((E)\)-1-bromo-2-chloropropene

higher priority groups on **same side**

higher priority groups on **opposite sides**

higher priority groups on **opposite sides**
**Chirality**

**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 often 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.

Greek: *cheir* – hand; *enantio* – opposite
Mirror Images

All molecules have mirror images

- If a molecule contains a carbon atom with *four different groups* attached to it are the mirror images not superimposable

- In these molecules there is *no plane of symmetry*
Mirror Images

We live in an asymmetric world!

- The enantiomers of a chiral molecule behave in an identical way when reacting with an achiral reagent (i.e., one that does not contain a stereogenic centre).
- But they may react quite differently to one another towards another chiral compound.
Our smell and taste receptors are chiral and so may differentiate between enantiomers.

- **Limonene**: odor in oranges, odor in lemons
- **Asparagine**: bitter, sweet
Pharmaceuticals are often sold as a 1:1 mixture of the two enantiomers (a “racemate” or “racemic mixture”).

There have been cases in which the two enantiomers have very different effects in the body.

-thalidomide

mild sedative

extreme teratogen
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.
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 ($\alpha$) is a characteristic of the enantiomer
Optical Rotation

- 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.
- Racemates give an overall rotation of zero.

**Limonene**

<table>
<thead>
<tr>
<th>(+)-limonene</th>
<th>(-)-limonene</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>odor in oranges</em></td>
<td><em>odor in lemons</em></td>
</tr>
</tbody>
</table>
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

Hydrogen has an atomic number of 1
Fluorine has an atomic number of 9
Chlorine has an atomic number of 17
Bromine has an atomic number of 35
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.

The carbon of the methyl group is attached to three hydrogen atoms.

The carbon of the other group is attached to two hydrogens and one bromine atom.

Bromine has higher priority than hydrogen.
Multiple bonds are expanded to the same number of single bonds to that atom

The carbon of the ethyl group is attached to one carbon and two hydrogen atoms

Assume the carbon of the other group is attached to two carbons and one hydrogen atom

Carbon has higher priority than hydrogen
Nomenclature IV

- 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 1 to 2 to 3
- A clockwise curve indicates the $R$ configuration; a counter-clockwise curve indicates the $S$ configuration
Nomenclature V !
Example Questions

– 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.

– Penicillin V has the absolute configuration shown. Assign the stereogenic centres as R or S.
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

R-Lactic acid has an optical rotation of -2.6°  
S-Glyceraldehyde has an optical rotation of -8.7°
Summary

You should now be able to

- Recognise the structural features in a molecule that result in diastereoisomers and enantiomers
- Draw and correctly label ($E/Z$) the diastereoisomers of an alkene
- Identify the stereogenic centre(s) in a molecule and use the priority rules to assign absolute configuration (R/S)
- Draw a molecule indicating its stereochemistry from the systematic name of the compound

Next

- But don’t most natural molecules contain more than one stereogenic centre?