Enantioselective synthesis

Why is enantioselective synthesis important?

- Nature yields an enormous variety of chiral compounds
- A change in stereochemistry can have profound effects

Azadiractin
anti-feedant

(S)-3-(1-methylpyrrolidin-2-yl)pyridine
nicotine
toxin / stimulant

MeCO₂H
NH₂
(S)-2-aminopropanoic acid
L-alanine
mammalian amino acid

MeCO₂H
NH₂
(R)-2-aminopropanoic acid
D-alanine
bacterial cell wall

(1R,2R,3S,5S)-2-acetyl-8-methyl-8-aza-bicyclo[3.2.1]octan-3-yl benzoate
cocaine
stimulant

(S)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione
(S)-thalidomide
teratogen (birth defects)
Chirality and biology

- Enzymes & receptors are invariably chiral
- Chiral drugs can interact with these to give two diastereomeric complexes
- Imagine the hand below is the enzyme, it can form two very different complexes depending on the chirality or “handness” of the drug it interacts with...
Chirality and biology II

- As you can imagine, these two complexes can have very different effects.
- The three drugs above highlight the possible effects of using the “wrong” compound.
- As a result, we must have methods to prepare the correct enantiomers.
Revision: terminology

- **Stereoisomers** - Isomers that differ only by the arrangement of substituents in space
- **Stereogenic element** - the focus of stereoisomerism, be it a stereogenic centre, axis or plane, within the molecule such that the change of two substituents about this element leads to different stereoisomers

- The easiest to identify are the *cis-trans isomers* found with sp² systems
- Alkenes should be assigned *E* or *Z* using Cahn-Ingold-Prelog rules
- We are not going to look at these BUT will see their effects in enolate chemistry

![Diagrams showing alkene and imine configurations]

- Imines are treated in a similar manner
One stereogenic centre: chirality on an atom

- **Chiral compounds** - simply a molecule (or object) that cannot be superimposed upon its mirror image
- Most obvious example is our hands...

![Mirror image](image1)
![Left & right hands](image2)
![Non-superimposable](image3)

- **Chiral centre** - In a tetrahedral \((\text{X}abcd)\) or trigonal pyramidal \((\text{X}abc)\) structure, the atom \(\text{X}\) to which the four (or three, respectively) substituents \(\text{abc(d)}\) are attached
One stereogenic centre: chirality on an atom

**Chiral**
- Mirror images are non-superimposable
- Each mirror image is an enantiomer
- Only differ by their absolute configuration or actual 3D shape
- Simplistically - 4 different groups
- Do not have a plane of symmetry

**Achiral**
- Mirror images are superimposable
- Compound has a plane of symmetry

Diagram:
- Mirror plane
- Chiral
- Achiral
- Plane of symmetry running through central carbon, hydrogen and OH

Advanced organic
Enantiomers & optical rotation

- Each enantiomer has identical physical & chemical properties (in an achiral environment)
- Only differ by how they rotate plane polarised light (rotate in opposite directions)
- Enantiomers are said to be **optically active**
- Not very useful as value is very unreliable (dependent on solvent & all factors below)
- Even sign (+/-) can change depending on concentration!!

![Diagram of optical rotation process]

**Optical rotation** $[\alpha]_D^t = \frac{\alpha}{l \times c}$

$\alpha = \text{observed rotation}; \ l = \text{cell path} \ (\text{dm}); \ c = \text{concentration} \ g/\text{ml} \ (\text{or} \ g/100\text{ml}); \ t = \text{temperature}$
Defining absolute configuration

- Need to be able to define the absolute configuration of a chiral centre
- First assign priorities according to Cahn-Ingold-Prelog rules (highest atomic number)
  
  - Next rotate molecule until lowest priority (4) is pointing away from viewer
  - Draw a line connecting 1 to 3
  - If line clockwise (right) the (R)
  - If line anti-clockwise (left) the (S)
Defining absolute configuration II

- Define priorities according to CIP
- Point lowest priority (4) away from viewer
- Draw line from 1 to 3
- Line is anti-clockwise so (S)

- Define priorities according to CIP
- Point lowest priority (4) away from viewer
- Draw line from 1 to 3
- Line is anti-clockwise so (R)
Central chirality at elements other than carbon

Chiral Nitrogen compounds

- As last two examples indicated it is not just carbon that can have central chirality
- Any tetrahedral or pyramidal atom with four (three) different substituents can be chiral
- Nitrogen / amines have the potential to be chiral...

But rapid pyramidal inversion normally prevents isolation of either enantiomer
- If substituents are constrained in a ring then rigid structure prevents inversion
- Quaternary ammonium salts (below) can be isolated enantiomerically pure
- Racemisation has been observed, presumably via dissociation...

Advanced organic
Central chirality at phosphorus

- Trigonal pyramidal phosphorus (III) is configurationally stable below 200°C
- P-chiral phosphines have a rich history as chiral ligands

- Tetrahedral phosphorus (V) is configurationally stable
Central chirality at sulfur

- Sulfoxides are tetrahedral; remember they have a lone pair!
- Configurationally stable at room temperature
- Certain anions (Cl\(\Theta\)) can cause racemisation (interconversion of the enantiomers)

\[
\text{(R)-1-methyl-4-} \\
\text{(methylsulfinyl)benzene}
\]

\[
\text{(R)-S-tert-butyl 2-}
\text{methylpropane-2-}
\text{sulfinothioate}
\]

\[
\text{(S)-N-benzylidene-2-}
\text{methylpropane-2-sulfinamide}
\]

- It should be stressed that the definition of a chiral compound is that it **cannot be superimposed upon its mirror image**
- A stereogenic centre (central chirality) is sufficient for the existence of chirality **it is not a requirement**
- Furthermore, as we shall see, not all compounds with a stereogenic centre are chiral!!
Axial chirality

- Nonplanar arrangement of four groups about an axis

**Spiro-compounds**

- D-Fecht acid: \((S)\)-spiro[3.3]heptane-2,6-dicarboxylic acid
- L-Fecht acid: \((R)\)-spiro[3.3]heptane-2,6-dicarboxylic acid

**Axial chirality**

- Mirror view of the axis of chirality

**Olean compounds**

- \((R)\)-1,7-dioxaspiro[5.5]undecane attracts male olive flies
- \((S)\)-1,7-dioxaspiro[5.5]undecane attracts female olive flies

Viewed along axis
Axial chirality II

**Axial chirality and atropisomerism**

**Atropisomers** - stereoisomers resulting from restricted rotation about a single bond. Mostly commonly found in hindered biaryls.
Axial chirality III

- Atropisomerism is not just found in biaryl compounds
- Any molecule in which rotation is restricted sufficiently to allow isolation of each isomer can be chiral...

- Atropisomerism is found in nature
- Vancomycin is an anti-bacterial
- Kotanin is from rice mold
Helicity

- Molecules that twist like a helix, propeller or screw
- Right-handed helix is denoted $P$ (clockwise as you travel away from viewer)
- Interestingly, [8]helicene racemises (1:1 mixture of enantiomers) readily at 293°C!
Planar chirality

- **Planar chirality** - chirality resulting from the arrangement of out-of-plane groups with respect to a plane, called the chiral plane.

- In [2.2]paracyclophane the more substituted benzene ring is considered the chiral plane.

[Diagram showing two mirror images of the amino[2.2]paracyclophane molecule, illustrating planar chirality.]
Planar chirality II

- Probably the most important planar chiral compounds are ferrocene derivatives
- These have found considerable use in enantioselective catalysis

An interesting example of planar chirality is found in some (E)-cycloalkenes