Enantiomeric excess

- **Optical purity** - an outdated measurement of the enantiomeric excess (amount of two enantiomers) in a solution / mixture
- If a solution contains only one enantiomer, the maximum rotation is observed...

\[
\left[\alpha\right]_D = +14 \quad \text{100% (+) enantiomer} \\
\left[\alpha\right]_D = -14 \quad \text{100% (-) enantiomer}
\]

The observed rotation is proportional to the amount of each enantiomer present...
Enantiomeric excess II

90% (+) enantiomer + 10% anti-clockwise = 100% (+) enantiomer

90% of maximum rotation observed

60% (+) enantiomer + 40% anti-clockwise = 100% (+) enantiomer

40% of major enantiomer is ‘cancelled out’

20% of maximum rotation observed

50% (+) enantiomer + 50% anti-clockwise = 100% (+) enantiomer

50% of major enantiomer is ‘cancelled out’

0% of maximum rotation observed
Enantiomeric excess III

- Previous slide indicates that a polarimeter measures difference in the amount of each enantiomer
- **Racemate (racemic mixture)** - 1 to 1 mixture of enantiomers (50% of each)
- **Racemisation** - converting 1 enantiomer to a 1:1 mixture of enantiomers

- Optical rotation very unreliable so use new methods to measure amounts and use the value **enantiomeric excess**

\[
\text{Enantiomeric excess (\% ee) = } \frac{[R] - [S]}{[R] + [S]} = %R - %S
\]

- How do we measure enantiomeric excess?
- **Problem** - all the physical properties of enantiomers are identical (in an achiral environment) except rotation of plane polarised light
- **Solution** - the interaction of a chiral molecule with other chiral compounds is different depending on the enantiomer used...
- Imagine you have a mixture of left and right-handed gloves and you are asked to separate them...suddenly there is a power cut, and you are left in a darkened room. How would you do it? Use just one hand and try the gloves on...
Resolution of enantiomers: chiral chromatography

- **Resolution** - the separation of enantiomers from either a racemic mixture or enantiomerically enriched mixture
- **Chiral chromatography** - Normally HPLC or GC
- A racemic solution is passed over a chiral stationary phase
- Compound has rapid and reversible diastereotopic interaction with stationary phase
- Hopefully, each complex has a different stability allowing separation

[racemic mixture in solution] → [chiral stationary phase] → [‘matched’ enantiomer - more stable (3 interactions)] → [‘matched’ enantiomer travels slowly]  
[‘mis-matched’ enantiomer - less stable (1 interaction)] → [‘mis-matched’ enantiomer readily eluted]
Chiral chromatography

- Measurements of ee by HPLC or GC are quick and accurate (±0.05%)
- Chiral stationary phase may only work for limited types of compounds
- Columns are expensive (>£1000)
- Need **both enantiomers** to set-up an accurate method
NMR spectroscopy: chiral shift reagents

- Chiral **paramagnetic lanthanide** complexes can bind reversibly to certain chiral molecules via the metal centre
- Process faster than nmr timescale and normally observe a **downfield shift** (higher ppm)
- Two diastereomeric complexes are formed on coordination; these may have different nmr signals

![Chemical structure](image)

- **Problems** - as complexes are paramagnetic, line broadening is observed (especially on high field machines)
- Compound must contain **Lewis basic lone pair** (OH, NH₂, C=O, CO₂H etc)
- Accuracy is only ±2%
Chiral shift reagents II

- New reagents are being developed all that time that can overcome many of these problems
- $^1$H NMR spectra (400 MHz) of valine (0.06 M, $[D]/[L] = 1/2.85$) in D$_2$O at pH 9.4
Chiral derivatising agents

- A racemic mixture of enantiomers can be converted to a mixture of diastereoisomers by covalently attaching a second, enantiomerically pure unit.
- The advantage of this over the previous methods is there is normally larger signal separation in nmr.
- There is no reversibility.
- Diastereoisomers can often be separated by normal, achiral chromatography.

\[
\text{HOH} + \text{MeO} \quad \text{MeO} \quad \text{CO}_2\text{H} \quad \text{DCC, DMAP, DCM, rt, 24h} \rightarrow \begin{cases} \text{MeO} \quad \text{Me} \quad \text{O} \quad \text{Me} \\ \text{MeO} \quad \text{Me} \quad \text{O} \quad \text{Me} \end{cases} + \begin{cases} \text{MeO} \quad \text{Me} \quad \text{O} \quad \text{Me} \\ \text{MeO} \quad \text{Me} \quad \text{O} \quad \text{Me} \end{cases}
\]

- (±) racemate = mixture of enantiomers + enantiomerically pure

- To understand why diastereoisomers are useful we need to do some more revision...
Two chiral centres

- A molecule with **one** stereogenic centre exists as **two** stereoisomers or **enantiomers**
- The two enantiomers differ by their **absolute configuration**
- A molecule with **two** stereogenic centres **can** exist as **four** stereoisomers

- A molecule can have **one enantiomer** but any number of **diastereoisomers**
Diastereoisomers

- Diastereoisomers can have the **same relative** stereochemistry
- The stereoisomers above differ only by their **absolute** stereochemistry
- Or they can have **different relative** stereochemistry

**Relative stereochemistry** - defines configuration with respect to any other stereogenic element within the molecule but does NOT differentiate between enantiomers

- In simple systems the two different relative stereochemistries are defined as below

- Occasionally you will see the terms *erthyro* & *threo* - depending on the convention used, these can mean two either relative stereochemistry so I will not use them!
• If a molecule has 3 stereogenic centres then it has potentially 8 stereoisomers (4 diastereoisomers & 4 enantiomers)
• If a molecule has \( n \) stereogenic centres then it has potentially \( 2^n \) stereoisomers
• Problem is, the molecule will never have more than \( 2^n \) stereoisomers but it might have less...
Tartaric acid has 2 stereogenic centres. But does it have 4 diastereoisomers?

- 2 diastereoisomers with different relative stereochemistry
- 2 mirror images with different relative stereochemistry
- 1 is an enantiomer
- The other is identical / same compound
- Simple rotation shows that the two mirror images are superimposable.
Meso compounds II

- **Meso compounds** - an *achiral* member of a set of diastereoisomers that also includes at least one chiral member
- Simplistically - a molecule that contains at least one *stereogenic* centre but has a *plane of symmetry* and is thus *achiral*
- Meso compounds have a plane of symmetry with \((R)\) configuration on one side and \((S)\) on the other

• Another example...

[Diagram showing a molecule with a plane of symmetry and its mirror image, labeled as chiral and achiral, respectively.]

- **Chiral**
  - No plane of symmetry
  - Non-superimposable on mirror image
  - (but it is symmetric!)

- **Achiral**
  - Plane of symmetry
  - Superimposable on mirror image
  - (meso)
Meso compounds III

- One compound displays two CH₃ peaks in ¹H nmr; the other just one peak. Which one is which?
- The meso compound shows two peaks for the cis and anti CH₃ (wrt to CO₂Et) This compound is achiral
- The chiral ester shows only one peak because it is symmetrical
  It has a C₄ axis of symmetry
  This molecule is chiral but symmetrical
Enantiomers vs. diastereoisomers

- Two enantiomers have **identical** physical properties in an achiral environment.
- Two **diastereoisomers** have **different** physical properties.

- Different physical properties, such as crystallinity or polarity allow diastereoisomers to be separated.

![Chemical structures and properties](image)
Chiral derivatising agents II

- This difference allows **chiral derivatising agents** to **resolve** enantiomers

- **Remember a good chiral derivatising agent should:**
  - Be enantiomerically pure (or it is pointless)
  - Coupling reaction of both enantiomers must reach 100% (if you are measuring ee)
  - Coupling conditions should not racemise stereogenic centre
  - Enantiomers must contain point of attachment
  - Above list probably influenced depending whether you are measuring %ee or preparatively separating enantiomers
Chiral derivatising agents: Mosher’s acid

- Popular derivatising agent for alcohols and amines is α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or Mosher’s acid
- Difference in nmr signals between diastereoisomers (above): $^{1}H$ nmr $\Delta\delta = 0.08$ (Me) $^{19}F$ nmr $\Delta\delta = 0.17$ (CF$_3$)
- Typical difference in chemical shifts in $^{1}H$ nmr 0.15 ppm
- $^{19}F$ nmr gives one signal for each diastereoisomer
- No α-hydrogen so configurationally stable
- Diastereoisomers can frequently be separated

- In many cases use of both enantiomers of MTPA can be used to determine the absolute configuration of a stereocentre (73JACS512, 73JOC2143 & 91JACS4092)
Chiral derivatising agents: salts

- No need to covalently attach chiral derivatising group can use **diastereoisomeric ionic salts**
- **Benefit** - normally easier to **recover** and **reuse** reagent
Enzymatic resolution

- **Enzymes** are very useful for the resolution of certain compounds
- Frequently they display very high selectivity
- There can be limitations due to solubility, normally only one enantiomer exists and can be too substrate specific
- Below is the rationale for the selectivity observed above...

![Diagram of enzymatic resolution process]

- **Diastereomeric interaction of enzyme lone pair with \( \sigma^* \) orbital of C–F of (S)-enantiomer** favoured over interaction with (R)-enantiomer
Stereoselective synthesis

- The term ‘asymmetric synthesis’ should be used with caution. As we shall see, a number of important chiral compounds are symmetric!!
- As such this course will primarily focus on \textit{diastereoselective} or \textit{enantioselective} synthesis or the \textit{synthesis of chiral} molecules
- Chiral compounds can be prepared in a number of ways:
  
  \textbf{Enantiospecific synthesis}; ‘the chiral pool’

- Use \textit{enantiomerically pure} starting material and \textit{stereospecific} reactions
- \textbf{Good} - if a cheap, readily available source of chirality exists
- \textbf{Problems} - often results in long, tortuous syntheses, suitable material not always available
**Stereoselective synthesis**

**Chiral auxiliaries**

- **Chiral auxiliary** - allows enantioselective synthesis via diastereoselective reaction
- Add chiral unit to substrate to control stereoselective reaction
- Can act as a built in resolving agent (if reaction not diastereoselective)
- **Problems** - need point of attachment
  adds additional steps
  cleavage conditions must not damage product!
Chiral reagents

- **Chiral reagent** - stereochemistry initially resides on the reagent
- **Advantages** - No coupling / cleavage steps required
  - Often override substrate control
  - Can be far milder than chiral auxiliaries
- **Disadvantages** - Need a stoichiometric quantity (not atom economic)
  - Frequently expensive
  - Problematic work-ups

Substrate (achiral) + chiral reagent → chiral complex → reaction → product (chiral) + dead reagent
• **Chiral catalysis** - ideally a reagent that accelerates a reaction (without being destroyed) in a chiral environment thus permitting one chiral molecule to generate millions of new chiral molecules...