

Stereochemical Considerations



What are stereoisomers?



How are stereoisomers experimentally characterized?



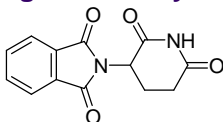
Why consider stereochemistry?



Example of Stereochemical Influence on Biological Activity

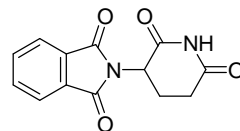


- Thalidomide



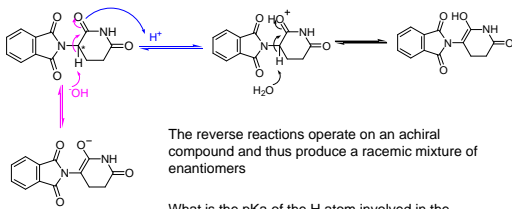
- Sold outside the US in the 1950's as a sleep aid and to treat morning sickness
- Teratogenic side effects occurred
- (R) enantiomer possesses sedative property
- (S) enantiomer is teratogenic
- Recently approved by FDA to treat leprosy
- Racemizes under physiological conditions

Thalidomide



- Where is the stereogenic center?
- Propose a mechanism for racemization of thalidomide

Thalidomide Racemization

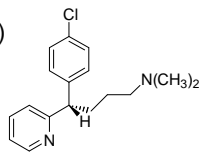


Quantitating Stereochemical Effect

- Terminology
 - More active enantiomer = eutomer
 - Less active enantiomer = distomer
 - Eudismic Ratio (ER) = $\text{activity}_{\text{eutomer}} / \text{activity}_{\text{distomer}}$
- Possible distomer effects
 - Inactive (ER is high)
 - Independent therapeutic effect
 - Harmful side effect (thalidomide, for example)
 - Opposes eutomer

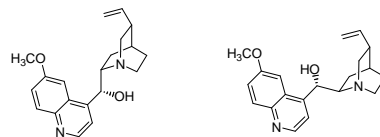
High ER Example

- Antihistamines antagonize the effects of histamine and are commonly used to treat the symptoms of allergies and the common cold
- Dexchlorpheniramine (right) is an antihistamine
 - ER=200
 - The eutomer is shown
 - What configuration does the eutomer have?



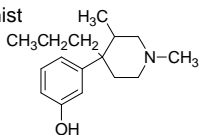
Independent Therapeutic Action

- Quinine (left) is used to treat malaria
- Quinidine (right) is used to treat arrhythmia
- What is the stereochemical relationship between quinine and quinidine?



Enantiomeric Antagonism

- Opiate receptors are targets for morphine and other therapeutic compounds
- Picecadol isomers act at the opiate receptors
 - *d*-picecadol is a narcotic analgetic
 - *l*-picecadol is a narcotic antagonist
 - *d*-picecadol is a partial agonist
- What do *d* and *l* mean?



Obtaining Pure Stereoisomers

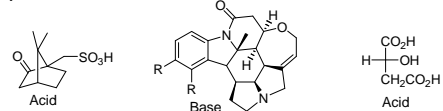
- Chiral resolution (separate a mixture)
- Use natural chiral compounds (chiral pool)
- Stereoselective synthesis
 - Laboratory methods/reagents
 - Enzymes as chiral catalysts

Chiral Resolution

- Chiral resolution is based on the principle that enantiomers differ in their interactions with chiral materials
- Methods
 - Crystallization of diastereomers
 - Chiral chromatography

Crystallization of Diastereomers

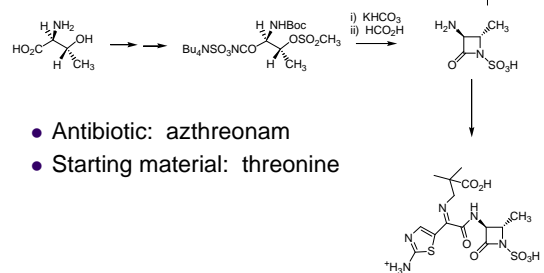
- React a chiral acid (base) with a racemic base (acid) to produce diastereomeric salts
- Diastereomers have different physical properties (such as solubility) and can be separated
- Structures below are available from the chiral pool – which are acids and which are bases?



The Chiral Pool

- Many natural products are chiral
 - amino acids
 - carbohydrates
 - alkaloids
 - terpenes
 - steroids

Example Synthesis

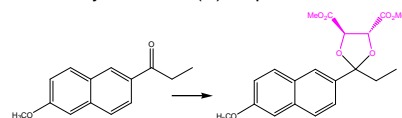


Stereoselective synthesis

- Chiral auxiliary
- Chiral reagents and catalysts
- Enzymes
- Whole organisms
- Generation of catalytic antibodies (1986)

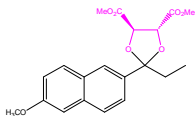
Chiral Auxiliary

- Required features
 - Like a protecting group, an auxiliary must be easily appended and removed
 - The auxiliary must affect the ratio of diastereomers produced in the desired reaction
 - Tartaric acid (magenta) converts ketone to acetal in the synthesis of (S)-Naproxen



Chiral auxiliary

- Build the intermediate below in MOE
- Consider how the auxiliary might influence reactions at the carbons α , β and γ to the aromatic ring



Reading

- Chapter 3.2E
- 3.4 Problem 6