Prof Ben Davis

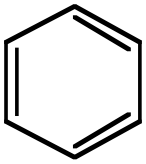
THIRD YEAR ORGANIC CHEMISTRY - REVISION COURSE Lecture 1

MOLECULAR STRUCTURE 1: STEREOCHEMISTRY

Good books and reading: **Carey and Sundberg, Part A, Ch 2.**
Stereochemistry of Organic Compounds, Eliel, Wilen & Mander
This book is a masterpiece & the best on this stuff – great glossary.

1. Compounds without Stereochemistry.

Some planar and all linear molecules cannot exist as stereoisomers.

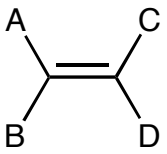


(sp^2)

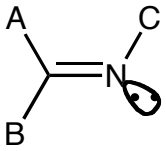
(sp)

2. Compounds which can exist as Geometrical Isomers.

This can occur for planar systems with sp^2 hybridised atoms, giving *E* (*trans-, anti-*) or Z (*cis-*, *syn-*) stereoisomers.



If A, C of highest priority, then *Z-*
If A, D of highest priority, then *E-*



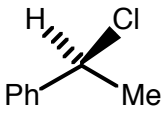
If A, C of highest priority, then *syn-*
If B, C of highest priority, then *anti-*

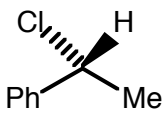
N.B. Assign priority with C-I-P rules (see below)

3. Compounds which can exist as Stereoisomers.

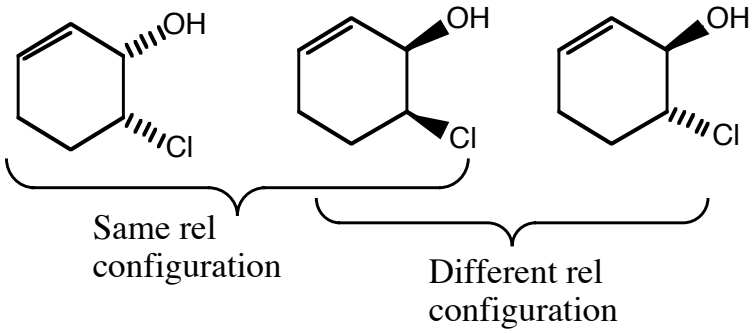
RECALL some important definitions:

Absolute Configuration is the actual 3D structure of a molecule.
Relative Configuration describes the relative disposition of all of the substituents but does not differentiate between the two enantiomeric forms.





Different absolute configuration



Absolute stereochemistry can be determined by X-ray analysis, chemical conversion to a substance of known chirality (glyceraldehyde has historically been chosen as the reference compound), or by optical rotatory dispersion (ORD) using the octant rule for ketones, or the Cotton effect.

A **chiral** molecule is one which cannot be superimposed on its mirror image. These two non-superimposable mirror images are called **enantiomers**. Stereoisomers which are not enantiomers are called **diastereomers**.

Chirality usually arises from the presence of **stereogenic** centres (i.e. a tetrahedral centre bearing 4 different substituents), but there are exceptions, e.g. biaryls, helicenes. When a compound consists of only one of a pair of enantiomers, it is called **homochiral** or **enantiopure**.

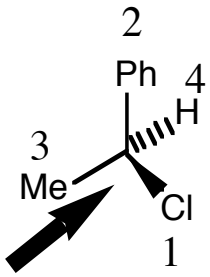
Note that enantiomers have *identical* chemical and physical properties (in an achiral environment) but diastereomers have *different* chemical and physical properties. Enantiomers can react with chiral reagents, but usually do so with different rates, giving rise to **kinetic resolution**.

Experimentally, we distinguish between 2 enantiomers by the way they rotate the plane of plane polarised light; if it is rotated to the right, it is designated (+); to the left, (-). This technique can be used to determine the **Optical Purity** of a compound.

Description of Chirality

(i) One Chiral Centre

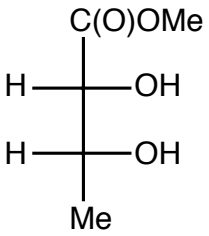
Use Cahn-Ingold-Prelog Rules: assign priority on the basis of atomic number, and with lowest priority group away from the viewer, assign as *R* (clockwise) or *S* (anticlockwise) using the priority of the 3 remaining substituents.



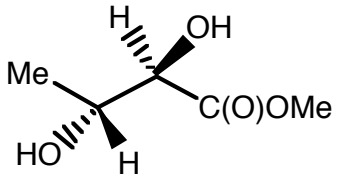
(S)-

(ii) More than one chiral centre

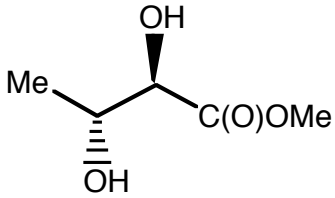
We use various representations: traditionally, the Fischer projection was used to assign *erythro-* and *threo-* to acyclic structures. More recently, the same descriptors were applied to the more widely used zig-zag line representations, so that there is now a situation in which these two terms can mean exactly the opposite, depending on the convention which has been followed (and this is not always made clear!). The only reliable descriptor in use now is *syn-/anti-*. This is outlined below.



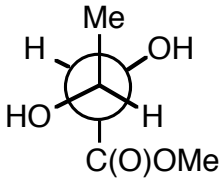
Fischer
erythro-



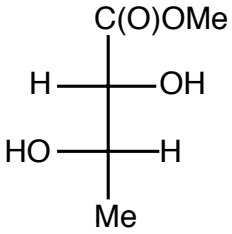
Heathcock
threo-
(2R,3R)



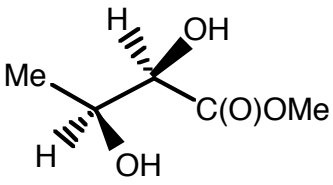
anti-



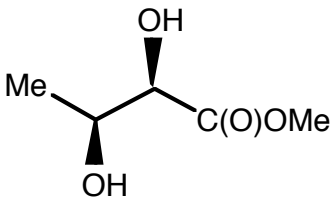
Newman



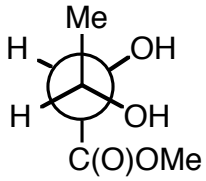
Fischer
threo-



Heathcock
erythro-
(2R,3S)

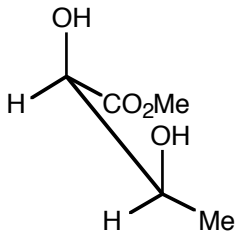


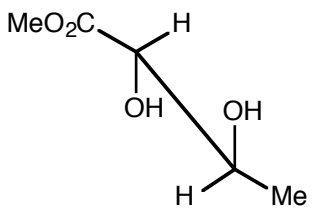
syn-



Newman

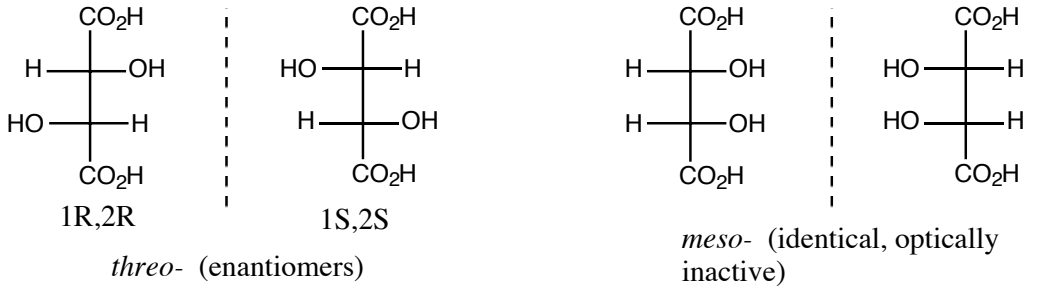
Sawhorse projections are often a simple way of describing stereochemistry for 2 chiral centres:



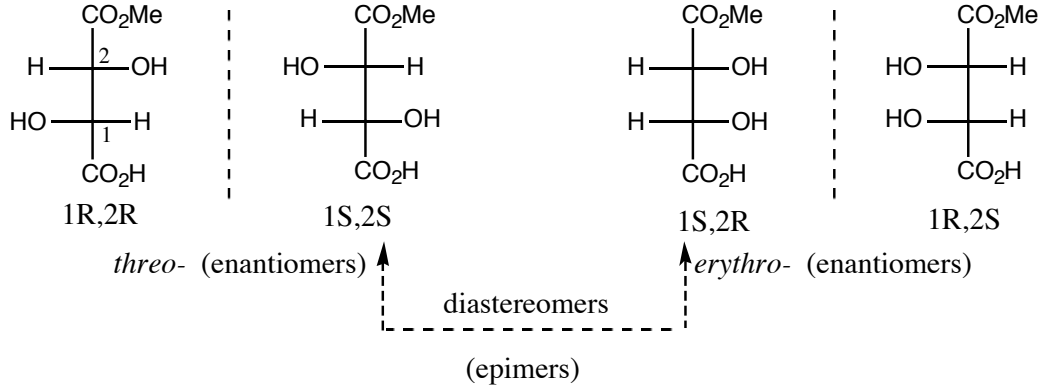


Case study: tartaric acid.

2,3-Dihydroxybutanedioic acid



but if there is no internal symmetry:

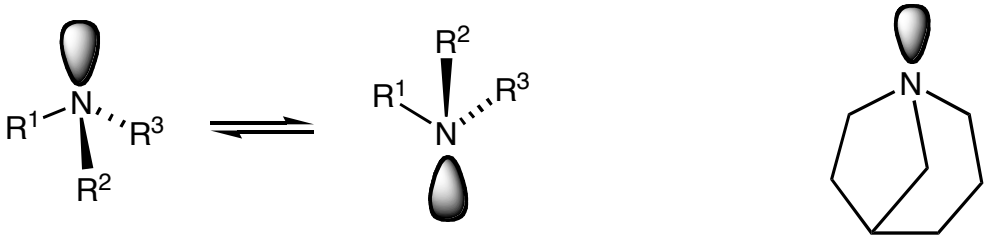


Notes:
* Any chiral compound can be converted to its enantiomer by inverting every asymmetric centre which is present; this is most simply done by drawing out its mirror image;
* A compound with n different chiral centres has a maximum of 2^n stereoisomers; molecular symmetry, however, will reduce this number;

Asymmetric Heteroatoms

Nitrogen

Most amines are unresolvable at RT, due to rapid Walden inversion; however, if the substituents are constrained, then enantiomers are in principle resolvable.



Phosphorus

Chiral phosphines are resolvable, as the inversion occurs only slowly even at 200°C.

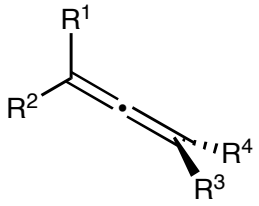
Sulfur Sulfoxides are configurationally stable at room temperature.

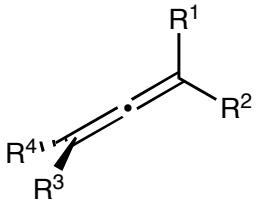
Molecular Asymmetry

Optically active molecules which do not possess an asymmetric atom.

1. Molecules with structural orthogonality:

(a) Allenes

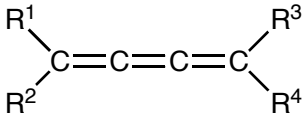




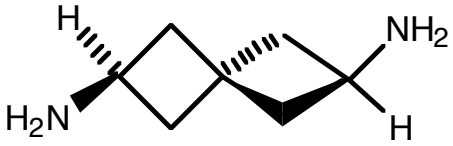
enantiomers if $R^1=R^2$ and $R^3=R^4$

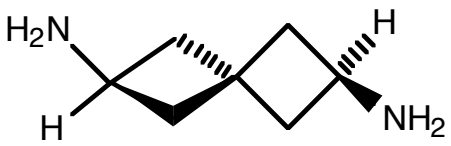
(also true for cumulenes with even numbers of p systems)

but for odd numbers of p systems, there is only *E*- and *Z*-

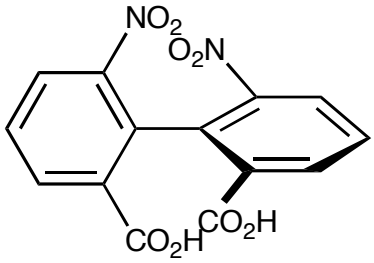


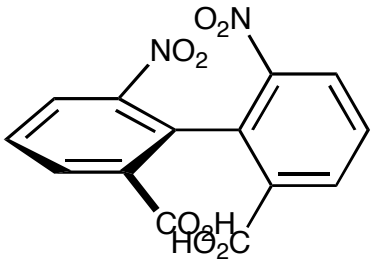
(b) Spiranes



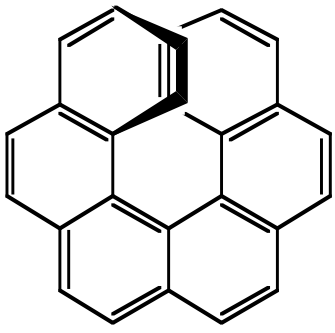


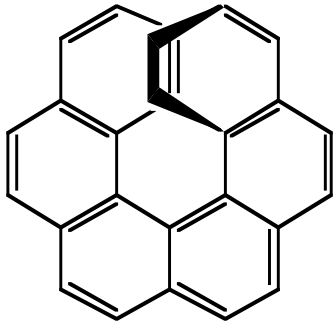
(c) Hindered Biphenyls



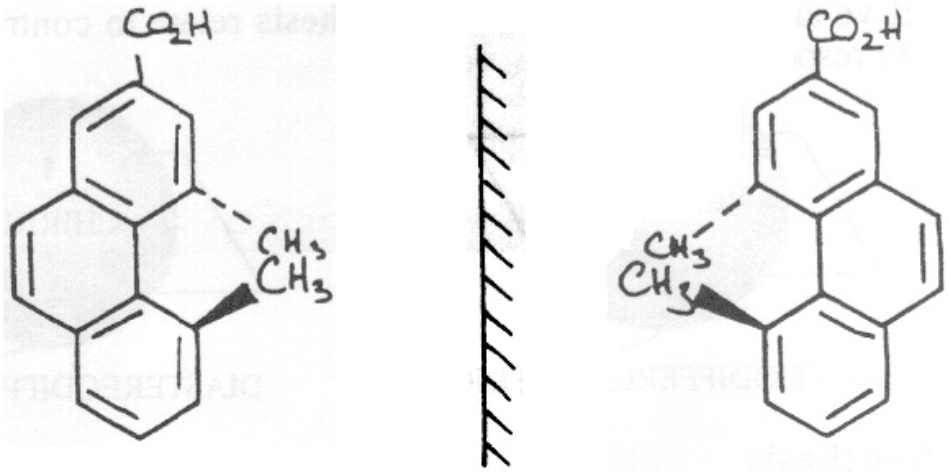


2. Molecules with structural helicity:



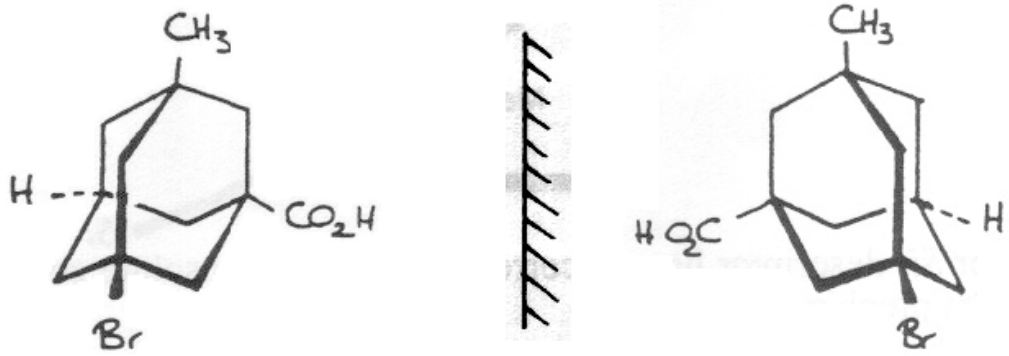


b. 4,5-disubstituted Phenanthrenes



c. **E-Cycloalkenes**

3. Bridgehead functionalised Adamantanes

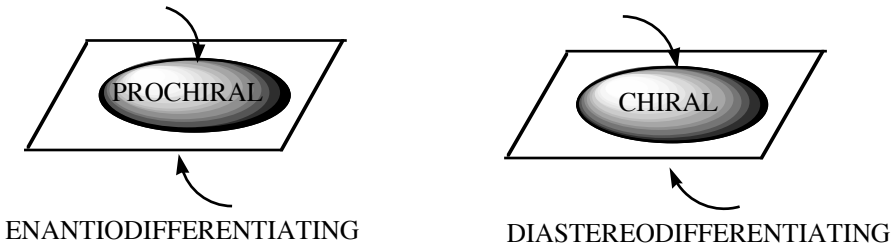


- effectively an extended tetrahedron.

Asymmetric Synthesis

Asymmetric or **Stereoselective Synthesis** is the synthesis of chiral compounds enriched in one enantiomer. It can be defined as the conversion of an achiral unit of a substrate molecule into a chiral unit, in such a way that the possible stereoisomeric products are formed in unequal amounts. Such stereocontrol can be achieved using either chiral starting materials or chiral reagents (or both). If the synthesis arrives at a single enantiomer of a chiral compound, the synthesis is called a **homochiral synthesis**. However, these terms are used very loosely, and are often interchanged.

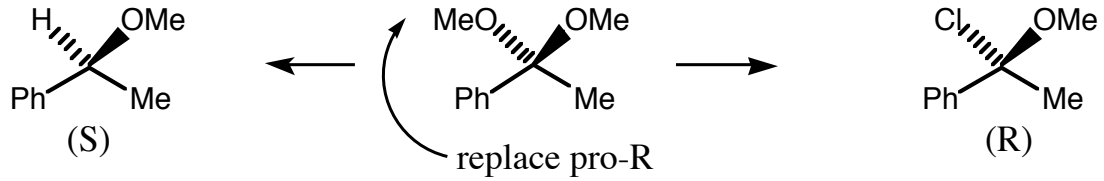
Enantioselective and **diastereoselective synthesis** relate to control of absolute stereochemistry and relative stereochemistry respectively.



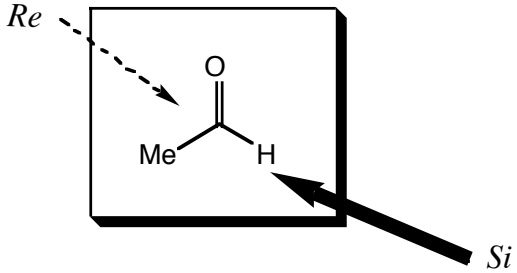
Enantioselective Synthesis

A carbon atom which can be converted to a chiral carbon in one chemical step is **prochiral**; this allows the possibility for the synthesis of a single enantiomer. Such a carbon can be:

(i) *tetrahedral*: and bears one pair of identical substituents; replacement of one of these substituents will give a chiral carbon. Each of the substituents are labelled *pro-R* or *pro-S*. Note that this does not necessarily correspond to the configuration assignments on the products.



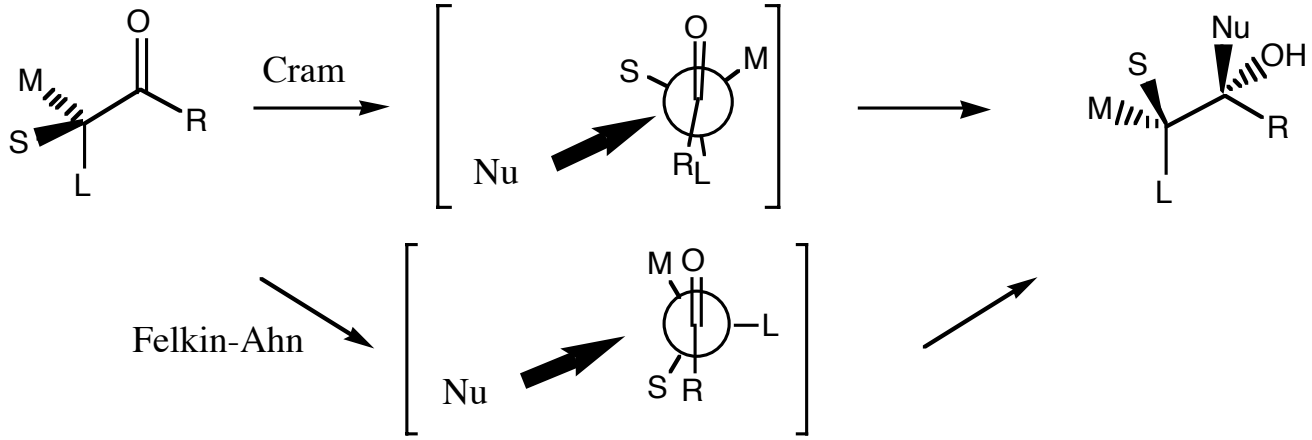
(ii) *planar*: in this case, prochirality is described as *Re* or *Si* : assign substituents using the normal priority rules, and then classify as *Re* or *Si* depending on whether the substituents appear clockwise (*Re*) or anticlockwise (*Si*) respectively in decreasing order of priority.



NB. the *Re* or *Si* descriptor has **no** correlation with the absolute configuration of the product formed from substitution of the prochiral atom.

Diastereoselective Synthesis

An example of a diastereoselective reaction: Cram's Rule predicts the stereochemistry of the nucleophilic addition to carbonyl groups with an adjacent chiral centre.



Prof Ben Davis

MOLECULAR STRUCTURE 2: CONFORMATIONAL ANALYSIS

Books: **Carey and Sundberg, Part A, Ch 3.**

Conformations are different spatial arrangements of a molecule that are generated by rotation around single bonds. There are in principle an infinite number of conformations, but a molecule will adopt a geometry that minimises total energy; this minimum energy is given by

$$E_{steric} = E(r) + E(q + E(f) + E(d)$$

where E(r) = stretching energy, E(q = strain energy, E(f) = torsion energy, E(d) = non-bonding interactions

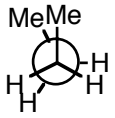
Generally speaking, the activation energy for rotation around bonds in simple alkanes is very small (12kJmol^{-1}) and can be easily surmounted at ambient temperature.

Different conformations of the same molecule are called **conformers** or **rotamers**.

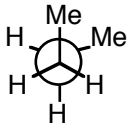
Note that where rotation around bonds is not possible, then conformational effects cannot be observed, e.g. alkenes.

Description of Conformations

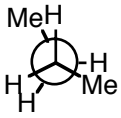
Use wedge-dash, sawhorse and Newman projections as before.



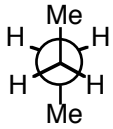
synperiplanar
eclipsed
torsion angle = 0^o



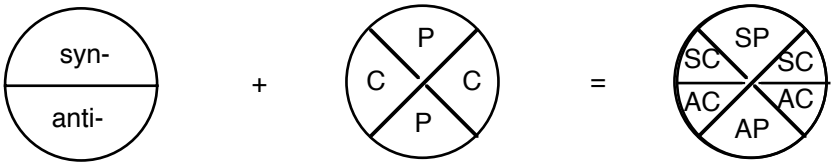
synclinal
gauche
torsion angle = 60^o



anticlinal
eclipsed
torsion angle = 120^o

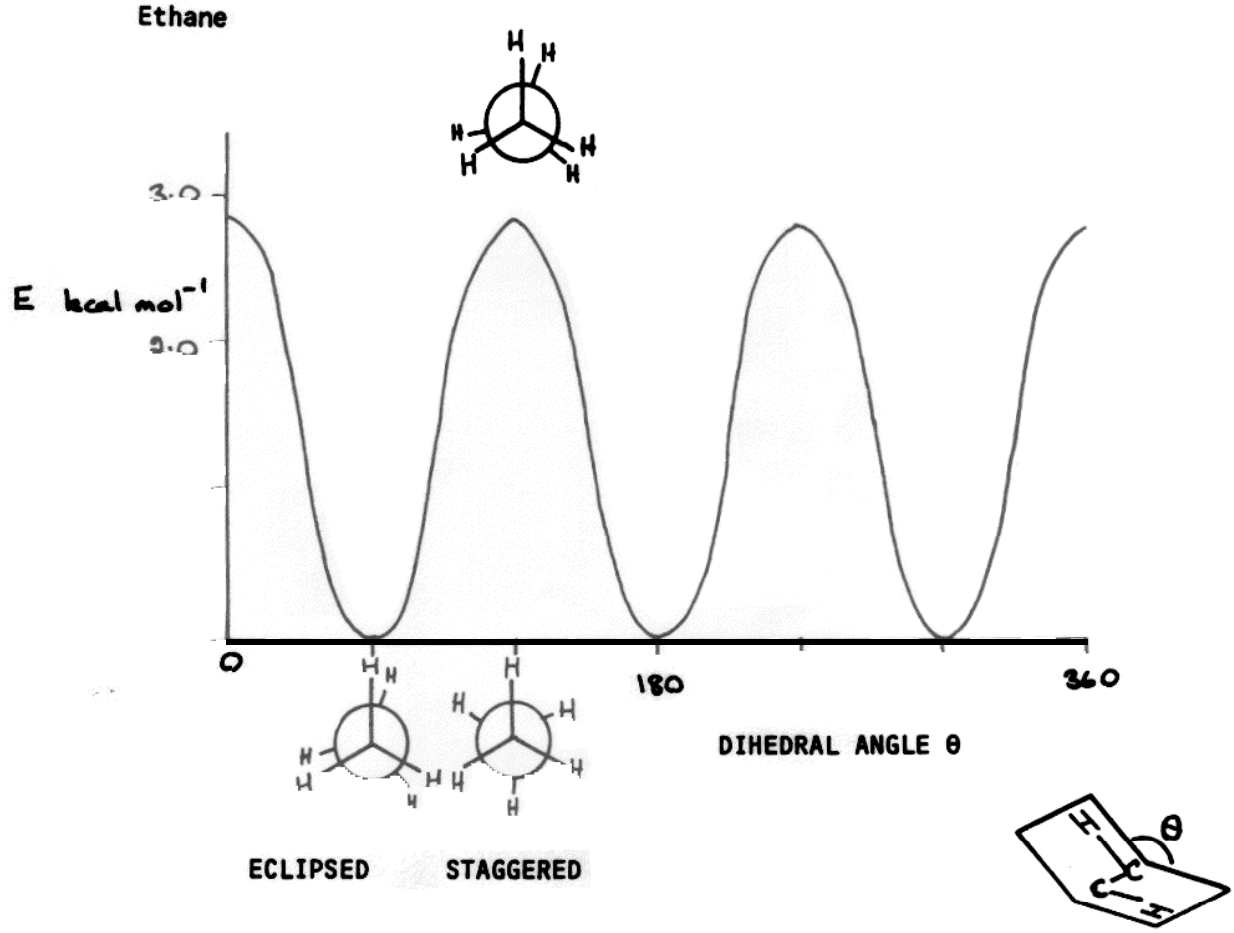


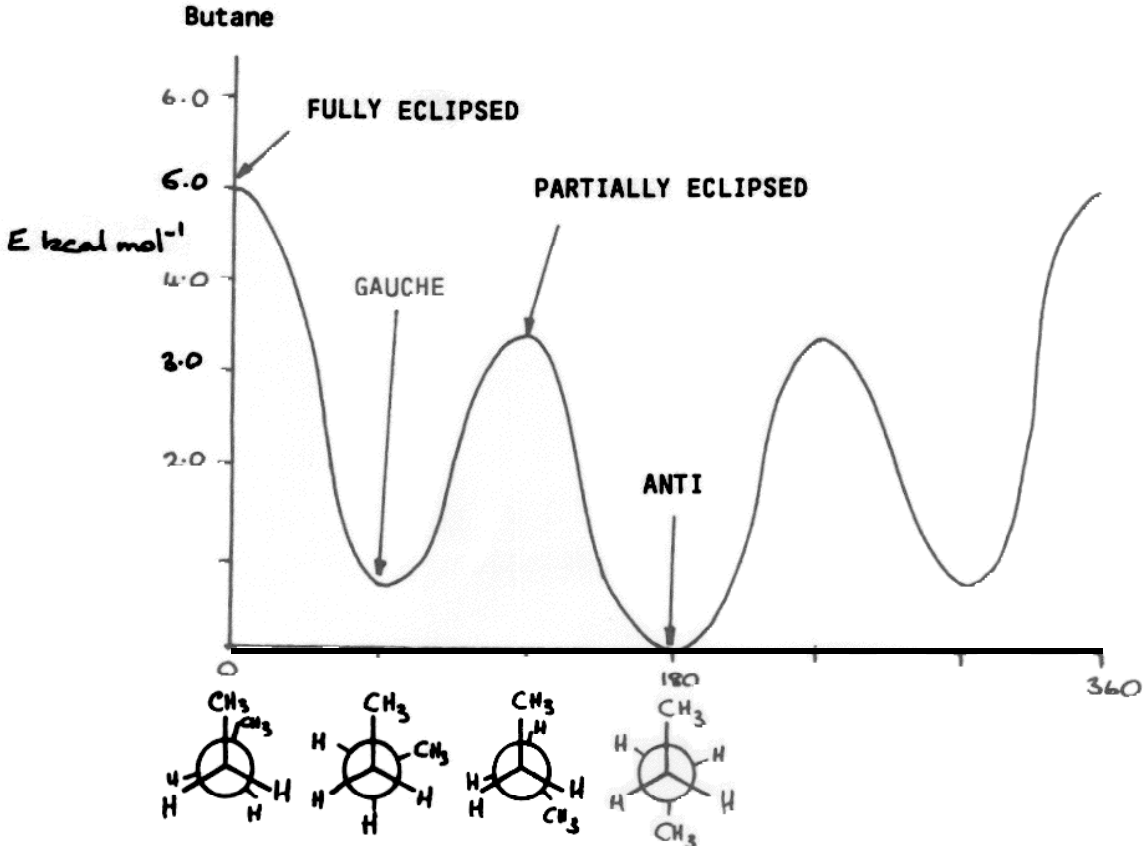
antiperiplanar
anti
torsion angle = 180^o



P =periplanar
C = clinal

Consider the typical potential energy diagrams for rotations in some alkanes:

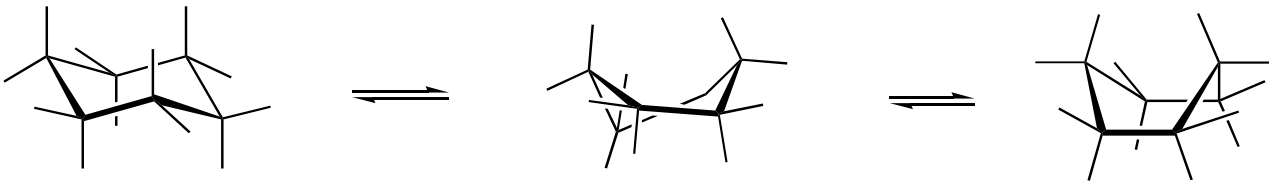




Factors Controlling Ring Conformations

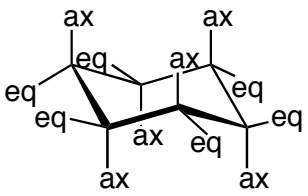
1. Angle Strain - the strain resulting from the deviation of bond angles from the ideal; for alkanes, this is of course 109º28'. For a cyclohexane, a planar ring would have angles of 120º, but puckering allows the more normal sp^3 angle to be achieved.

2. Torsional Strain - rotation around single bonds gives rise to conformers in which eclipsing interactions may or may not be present; this can give rise to torsional strain.

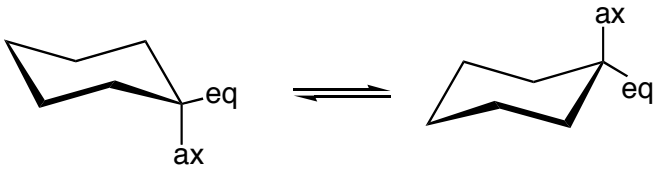


chair twist-boat boat

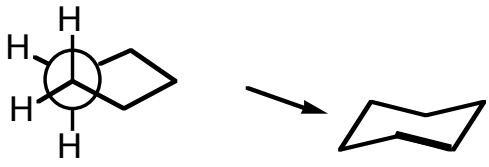
Two distinct stereochemical environments:



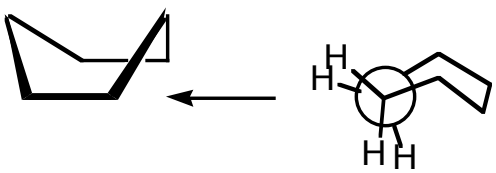
Ring flipping results in interchange of ax/eq substituents:



In cyclohexane, there are several forms with minimum angle strain, but which possess different torsional strains; the lowest energy conformer is the chair form.



gauche

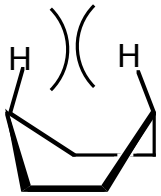


eclipsed

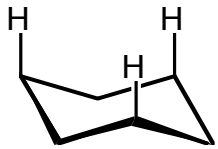
3. Non-bonded interactions

Steric constraints arise when ring substituents are close in space, i.e. their separation approaches the sum of their van der Waal's radius. Such interactions can be minimised by conformational modification:

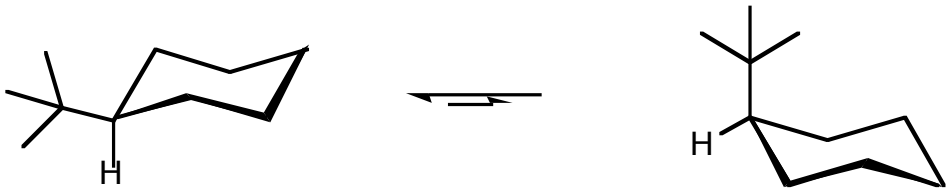
1,4- or Bowsprit interaction



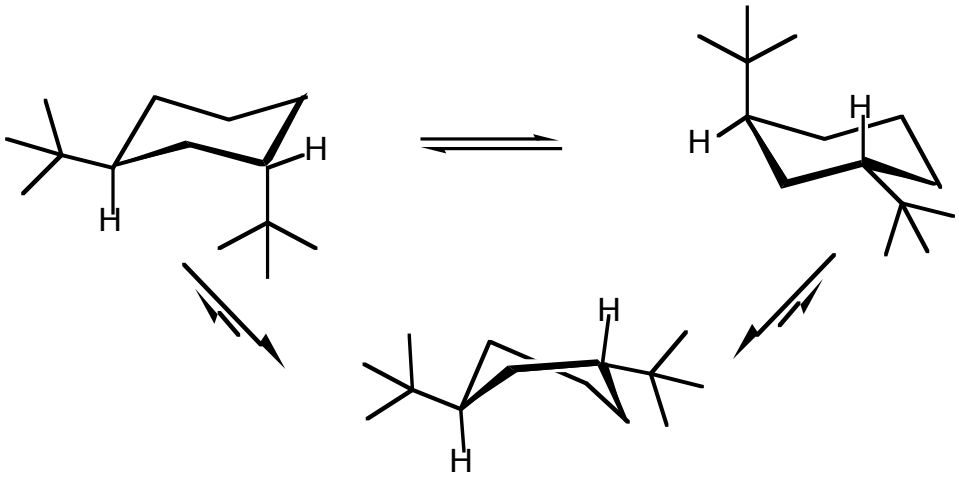
1,3-Diaxial interaction



For this reason, bulky substituents prefer to be equatorial, which can be achieved by ring flipping:, e.g.

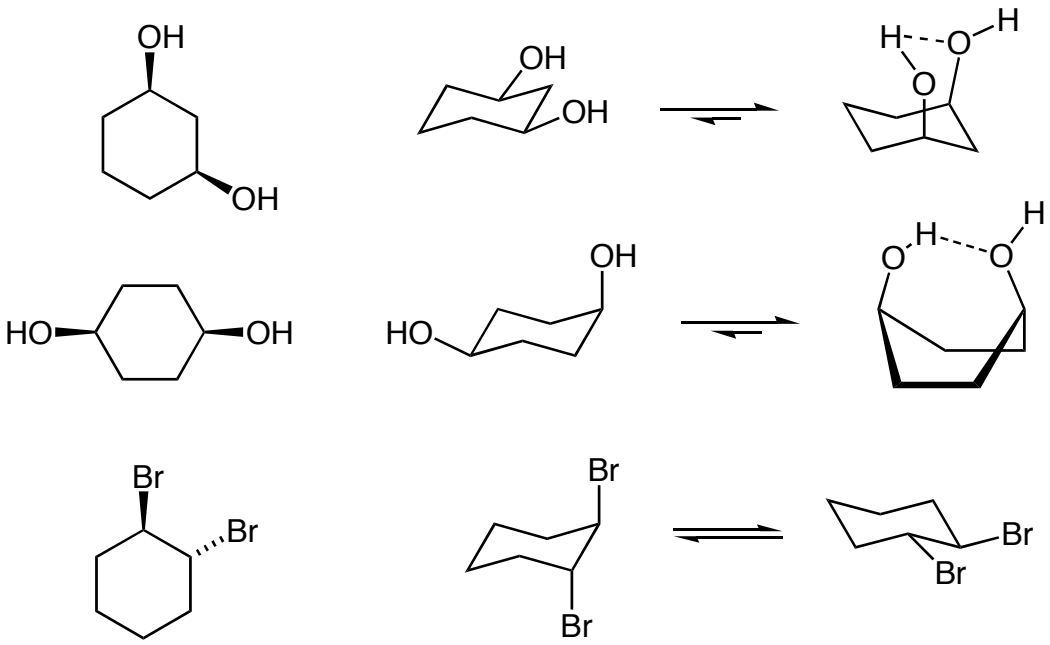


In the case of two bulky groups, a twist boat conformation may be adopted allowing both substituents to adopt a pseudo-equatorial position, e.g. trans-1,3-ditertbutylcyclohexane



twist-boat

4. Hydrogen bonding and Dipole effects - these can override the previous steric considerations



dipoles cancel
favoured in apolar solvents

dipoles add
favoured in polar solvents

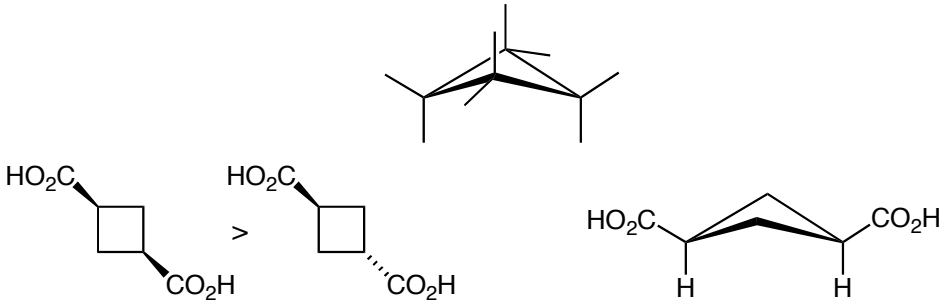
But note that conformations are not fixed, and the position of the equilibrium can be altered by other factors; thus the disfavoured conformers may still play important roles in reactions.

5. Stereoelectronic effects - these can override the previous steric considerations

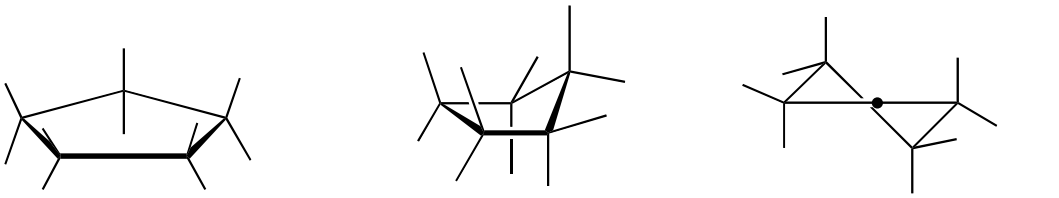
Conformation and Ring Size

(i) Cyclopropane - necessarily planar. The resulting angle and torsional strain makes the ring susceptible to ring opening

(ii) Cyclobutane - not planar but puckered. *syn*-1,3-Disubstituted cyclobutanes are more stable than their *anti*- isomers, since the substituents can adopt pseudo-diequatorial arrangement:



(iii) Cyclopentane - not planar (although angle strain is small - angle of 108º - torsional strain can be substantial as a result of eclipsing interactions) but can be envelope or half-chair.

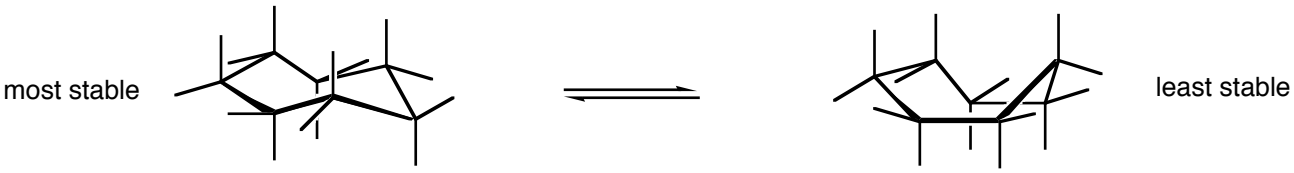


planar envelope (4 atoms planar) half-chair (3 atoms planar)

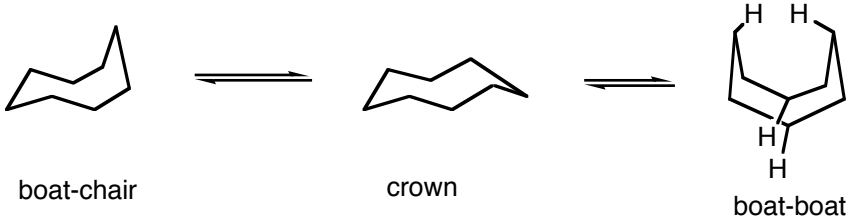
However, energy differences between conformers are small. Pseudorotation, in which each carbon is alternatively out of the plane of the ring, is especially facile and leads to an averaging of stereochemical environments. Thus, cyclopentanes do not have conformationally well-defined structures.

(iii) Cyclohexane - see earlier
- ring flipping can have important consequences for optical activity in disubstituted cyclohexanes

(iv) Cycloheptane - more flexible than cyclohexane



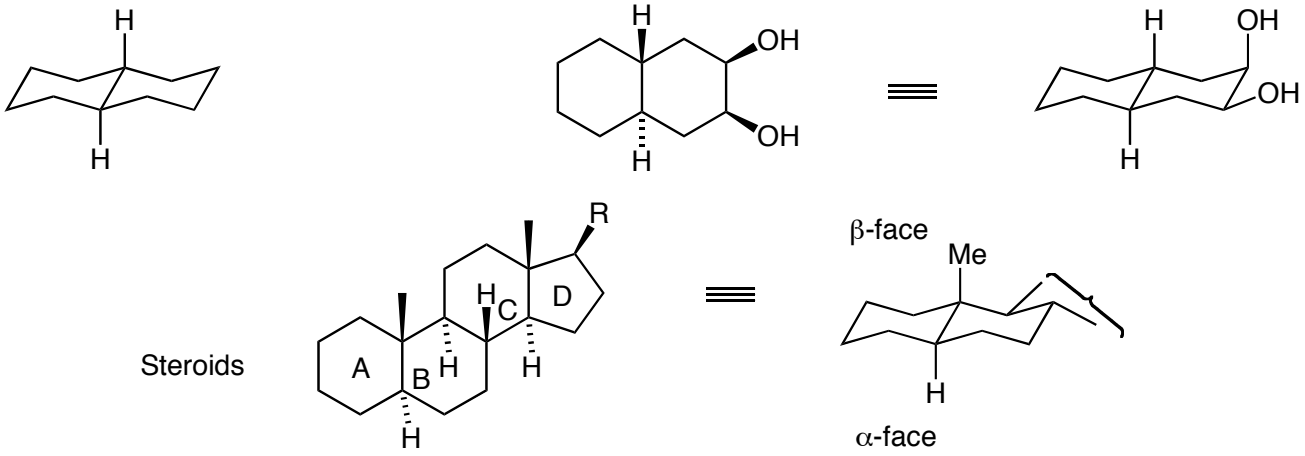
(v) Cyclooctane - even more flexible, giving rise to many more energetically accessible conformations



boat-chair crown boat-boat

Fused Ring Systems

(i) <u>trans-Decalins</u> - conformationally rigid - no ring flipping



(ii) <u>cis-Decalins</u> - conformationally flexible - ring flipping possible