COURSE : SC202 (CHEMISTRY)

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LECTURE-5

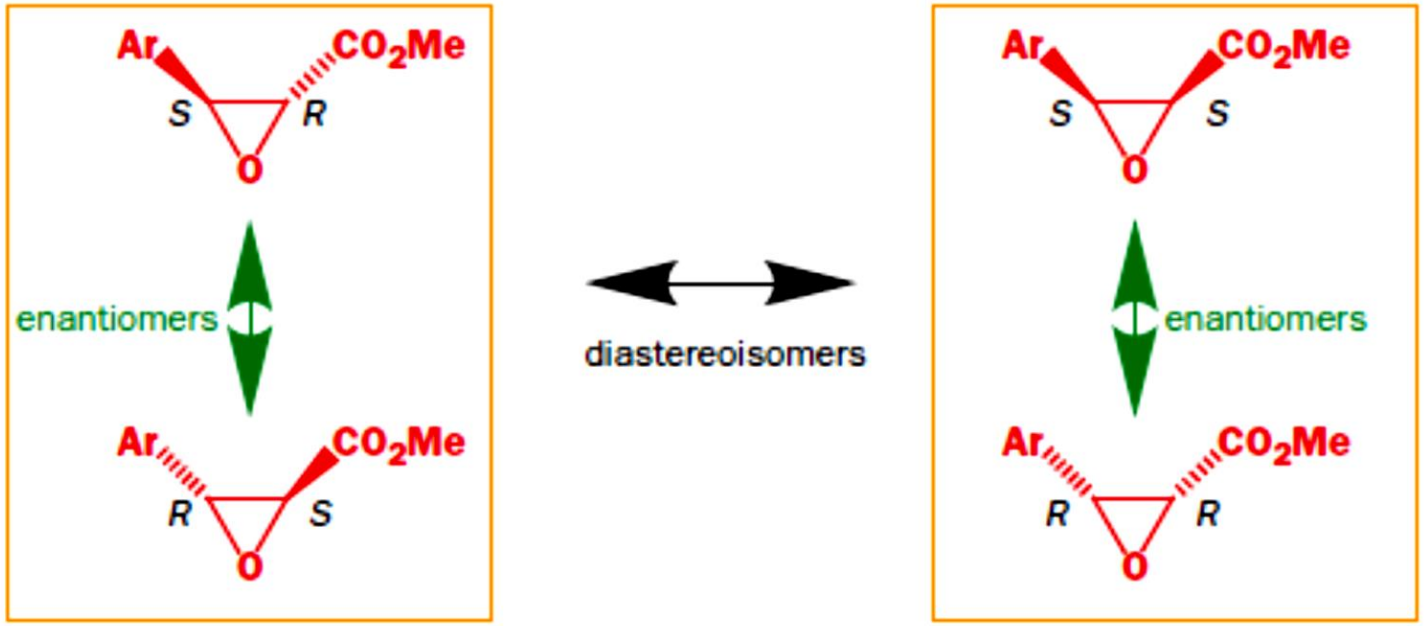
DATE: 18.1.2021

Stereochemistry

- Enantiomers are stereoisomers that are mirror images. A pair of enantiomers are mirror-image forms of the same compound and have opposite absolute stereochemistry.
- Diastereoisomers are stereoisomers that are not mirror images. Two diastereoisomers are different compounds, and have different relative stereochemistry.

Converting enantiometers and diastereoisomers

- **To go from one *enantiomer* to another, *both* stereogenic centres are inverted**
- **To go from one *diastereoisomer* to another, only *one* of the two is inverted**

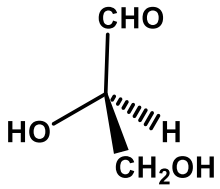


Enantiomers can be described as (+) or (–)

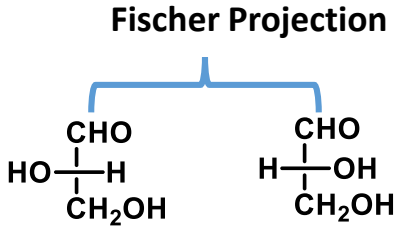
The enantiomer that rotates plane-polarized light to the right (gives a positive rotation) the **(+)-enantiomer** (or the *dextrorotatory* enantiomer) and the enantiomer that rotates plane-polarized light to the left (gives a negative rotation) the **(–)-enantiomer** (or the *laevorotatory* enantiomer). The direction in which light is rotated is not dependent on whether a stereogenic centre is *R* or *S*.

Enantiomers can be described as D or L

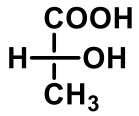
Glyceraldehyde is one of the simplest chiral compounds in nature. Because of this, chemists took it as a standard against which the configurations of other compounds could be compared.



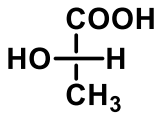
Wedge and Dash model



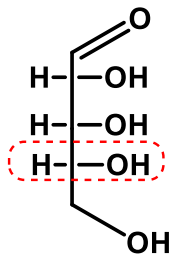
L- Glyceraldehyde D- Glyceraldehyde



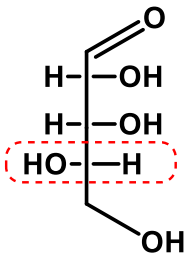
D-Lactic acid



L-Lactic acid



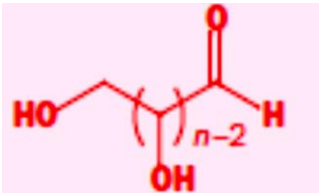
D-ribose



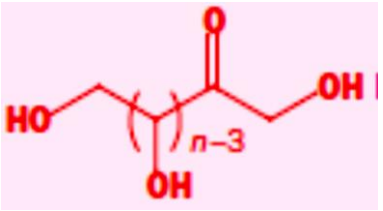
L-ribose

The two enantiomers of glyceraldehyde were given the labels D (for dextro—because it was the (+)-enantiomer) and L (for laevo—because it was the (–)-enantiomer).

- A sugar has the empirical formula $C_nH_{2n}O_n$, and consists of a chain of carbon atoms, one being a carbonyl group and the rest carrying OH groups. If the number of carbon atoms is n, aldoses have (n – 2) stereogenic centres and ketoses (n – 3) stereogenic centres.



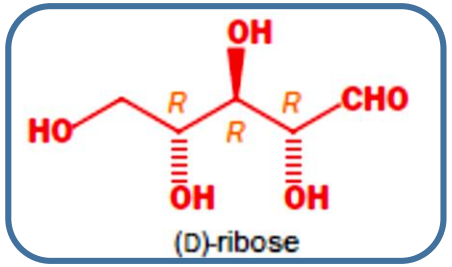
An aldose



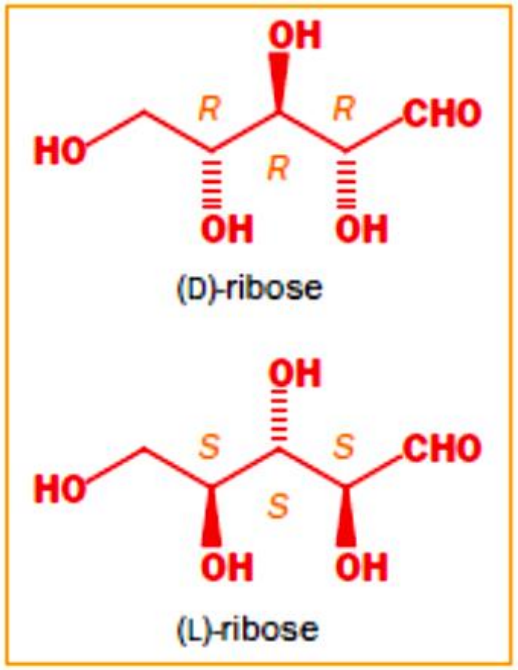
a ketose

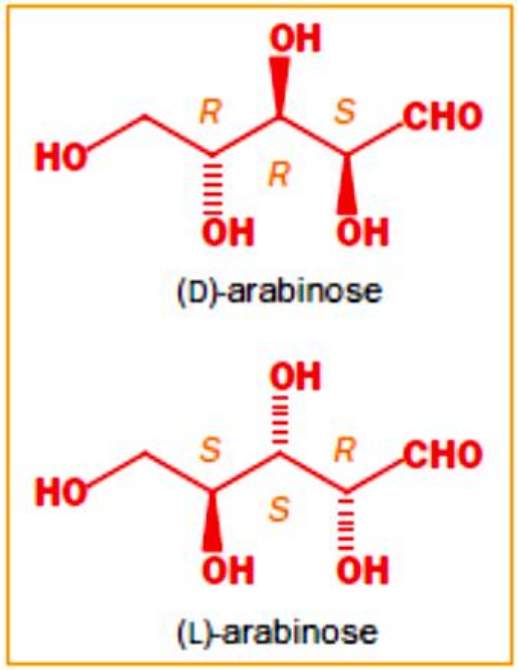
- A structure with *n* stereogenic centres can exist as 2^n stereoisomers

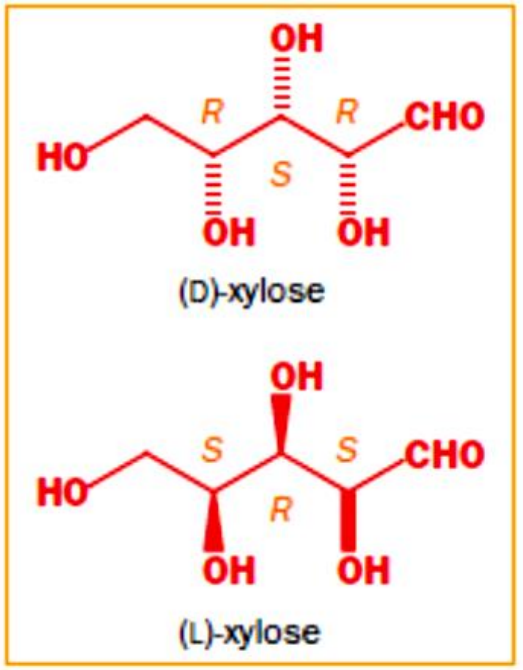
For a molecule with 1 chiral center, $2^1 = 2$ stereoisomers are possible
For a molecule with 2 chiral centers, a maximum of $2^2 = 4$ stereoisomers are possible
These stereoisomers consist of $2^{(n-1)}$ diastereoisomers, each of which has a pair of enantiomers.

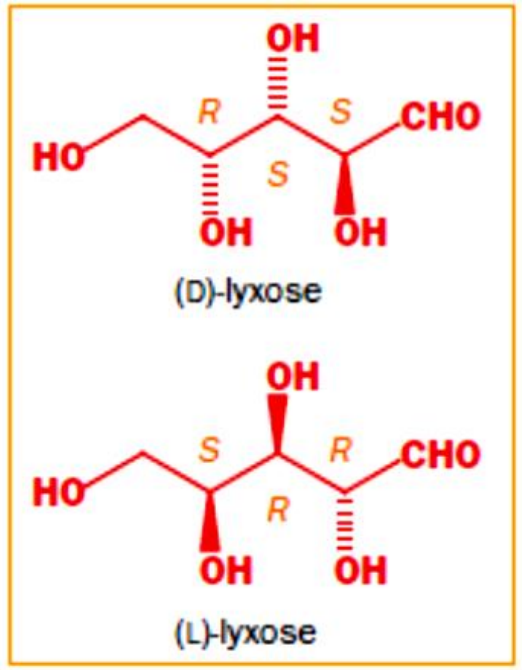


(D)-ribose

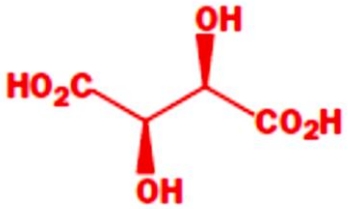






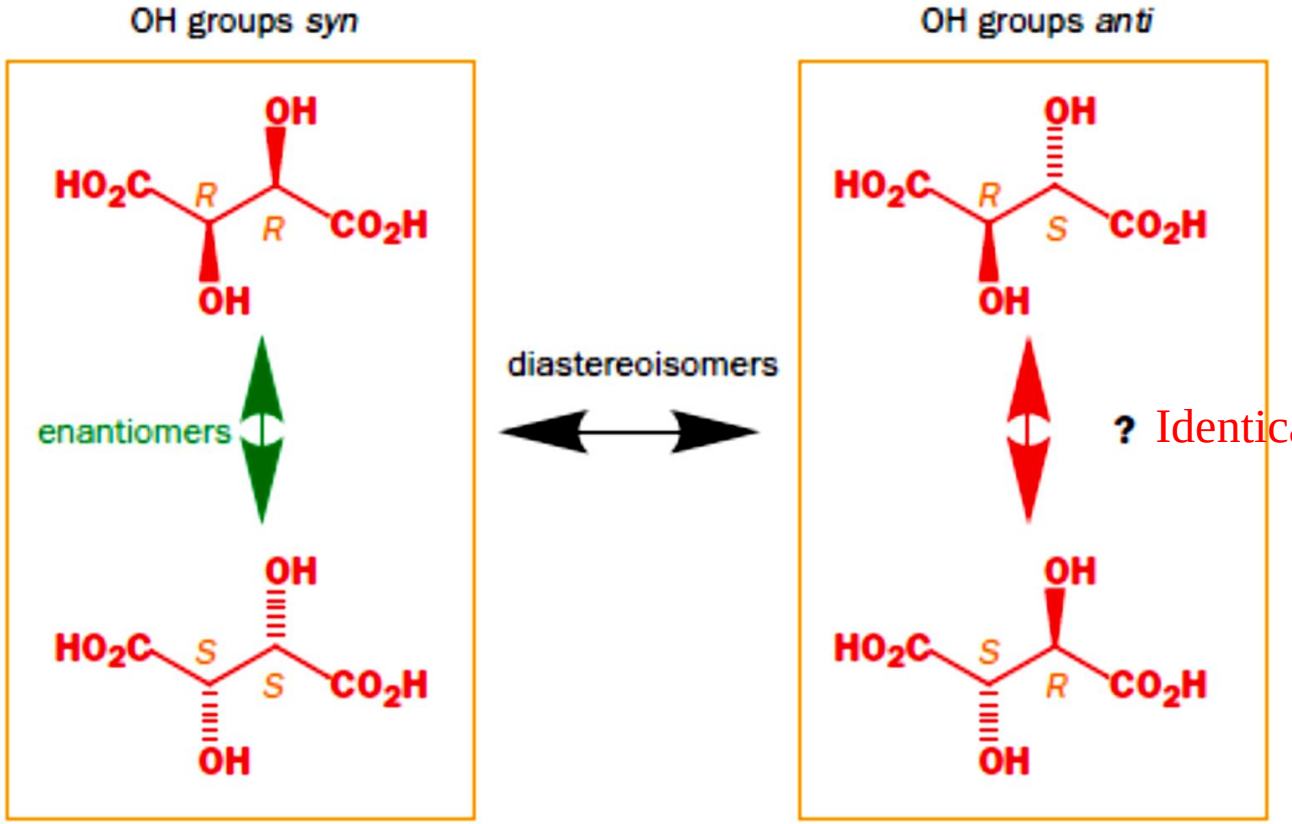


Exceptions

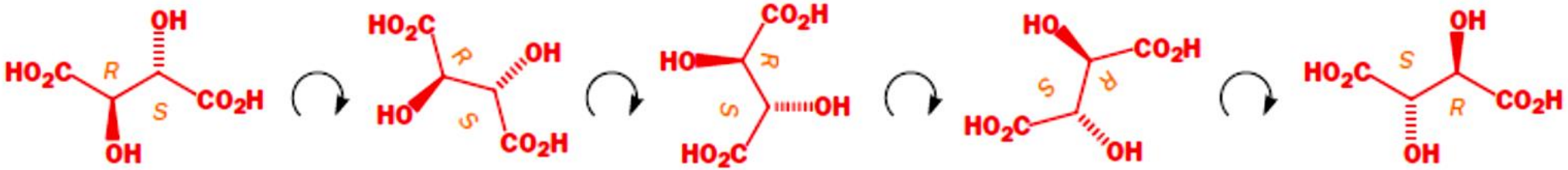


(+)-tartaric acid

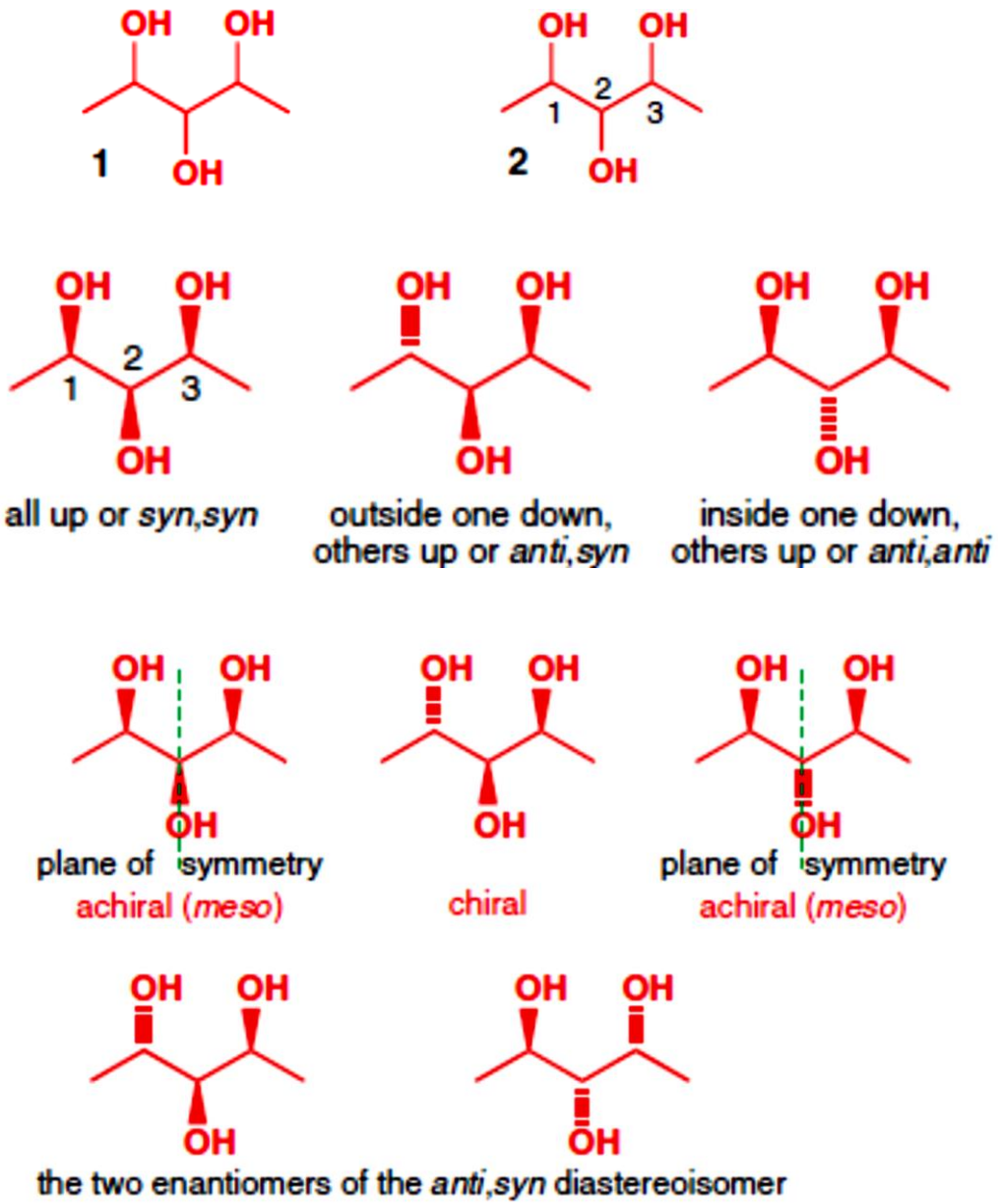
It has two stereogenic centres, so you'd expect $2^2 = 4$ stereoisomers; two diastereoisomers, each a pair of enantiomers.



just rotate the top one through 180° in the plane of the paper.



Stereochemistry of linear triol 2,3,4-trihydroxypentane or pentane-2,3,4-triol



1. Identify the stereogenic centres.

2. Decide how many diastereoisomers there are by putting the substituents at those centres up or down. We can call the first *syn,syn* because the two pairs of chiral centres (1 & 2, and 2 & 3) groups are both arranged with the OHs on the same side of the molecule (*syn*).

3. By checking on possible planes of symmetry, see which diastereoisomers are chiral. In this case only the plane down the centre can be a plane of symmetry.

4. Draw the enantiomers of any chiral diastereoisomer by inverting *all* the stereogenic centres.

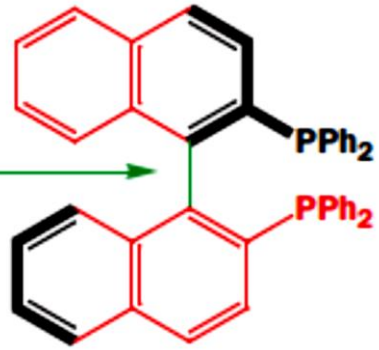
5. There are three diastereoisomers, the *syn,syn*, the *syn,anti*, and the *anti,anti*. The *syn,syn* and the *anti,anti* are achiral (*meso*) compounds but the *syn,anti* is chiral and has two enantiomers.

Chiral compounds with no stereogenic centres

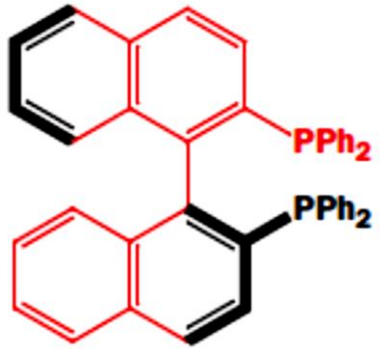
No plane of symmetry

A chiral allene

steric hindrance means rotation about this bond is restricted

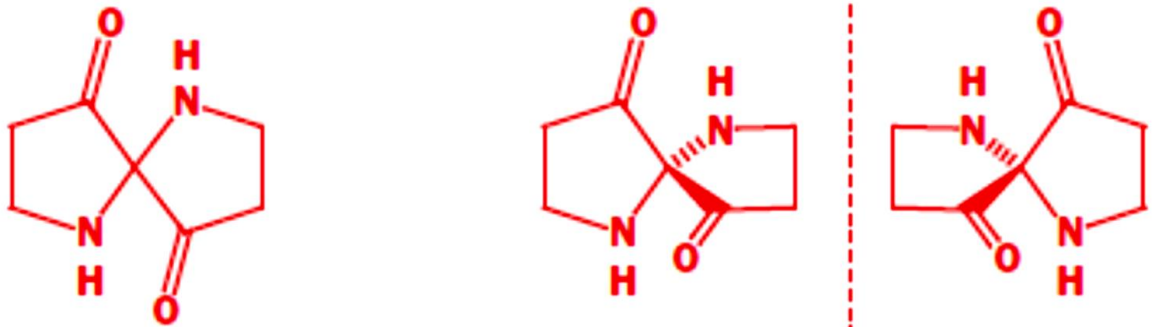


(R)-BINAP



(S)-BINAP

Compounds that are chiral because of restricted rotation about a single bond are called ***atropisomers*** (from the Greek for 'won't turn')



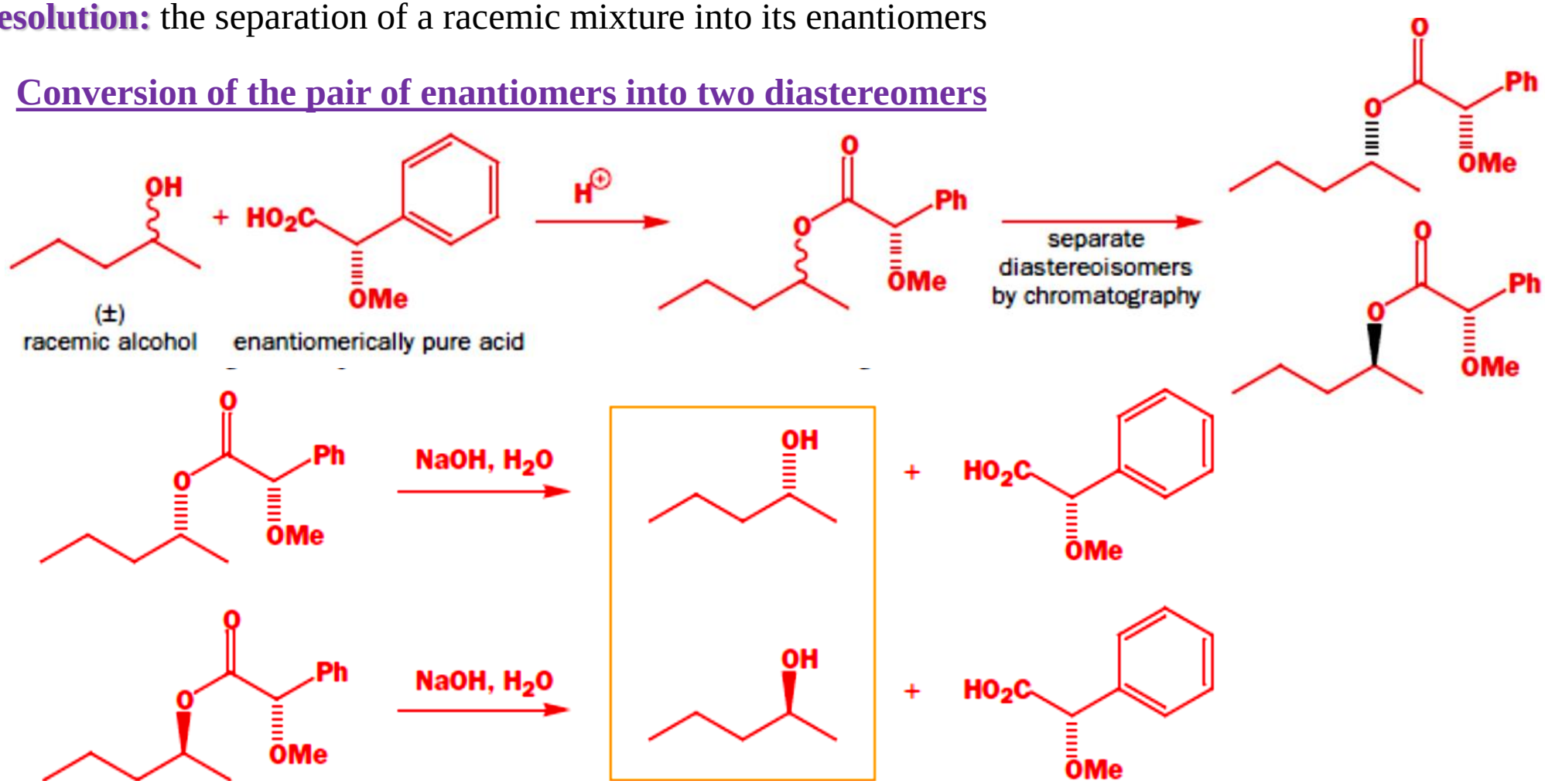
Separation of enantiomers

Racemic mixture: an equimolar mixture of two enantiomers

because a racemic mixture contains equal numbers of dextrorotatory and levorotatory molecules, its specific rotation is zero

Resolution: the separation of a racemic mixture into its enantiomers

1. **Conversion of the pair of enantiomers into two diastereomers**



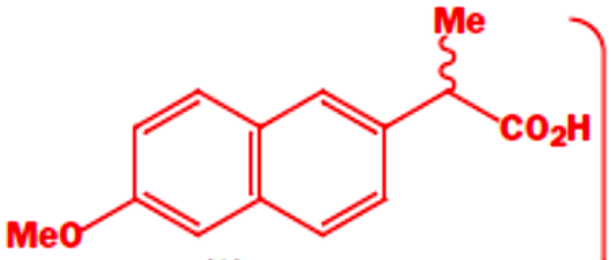
two enantiomers obtained separately:a resolution has been accomplished

2. Resolutions using diastereoisomeric salts

RCOOH + :B ⇌ RCOO⁻ HB⁺

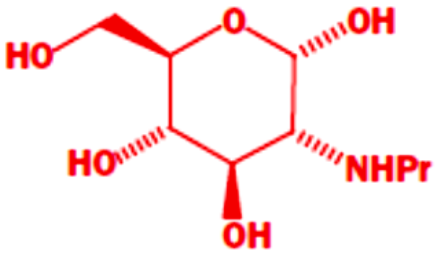
(*R*,*S*)-Carboxylic acid + (*R*)-Base → (*R*,*R*)-Salt + (*S*,*R*)-Salt)

resolution of naproxen via an amine salt

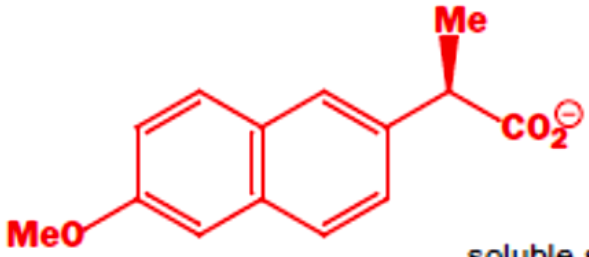


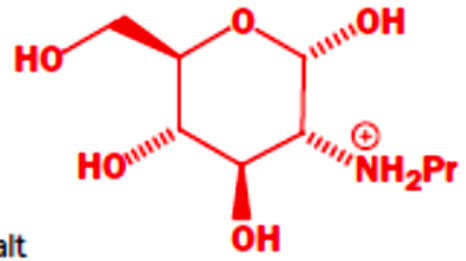
(±)-naproxen

mixed to give

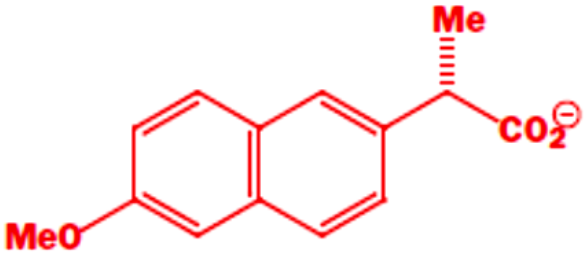


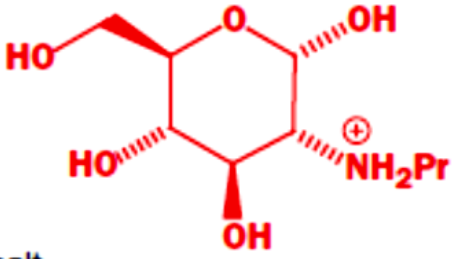
N-propylglucosamine





soluble salt



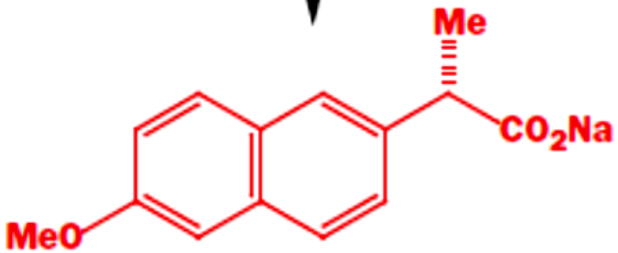


crystalline salt

filtered off and basified with NaOH

reusable

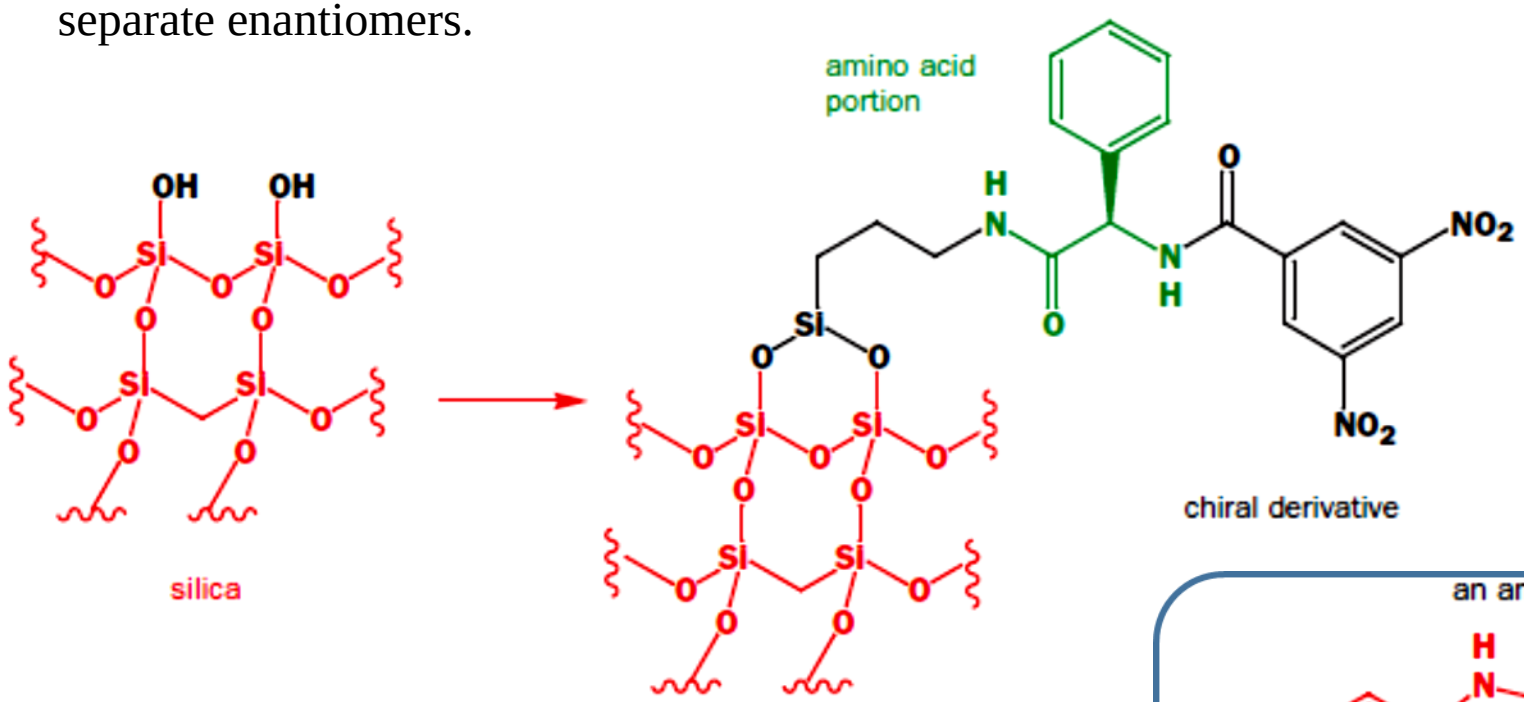
N-propylglucosamine plus



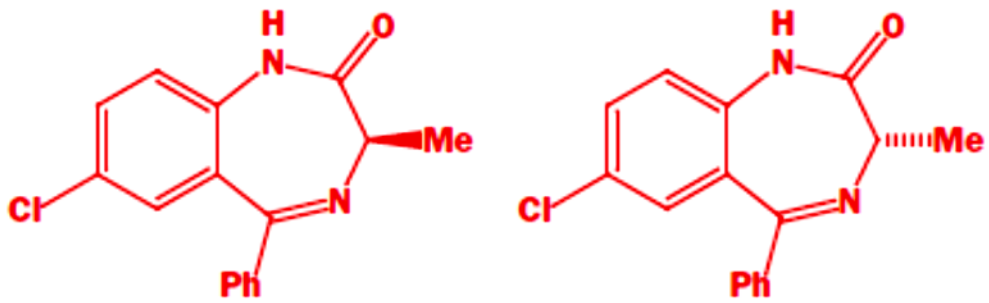
sodium salt of (*S*)-naproxen

3. Resolutions can be carried out by chromatography on chiral materials

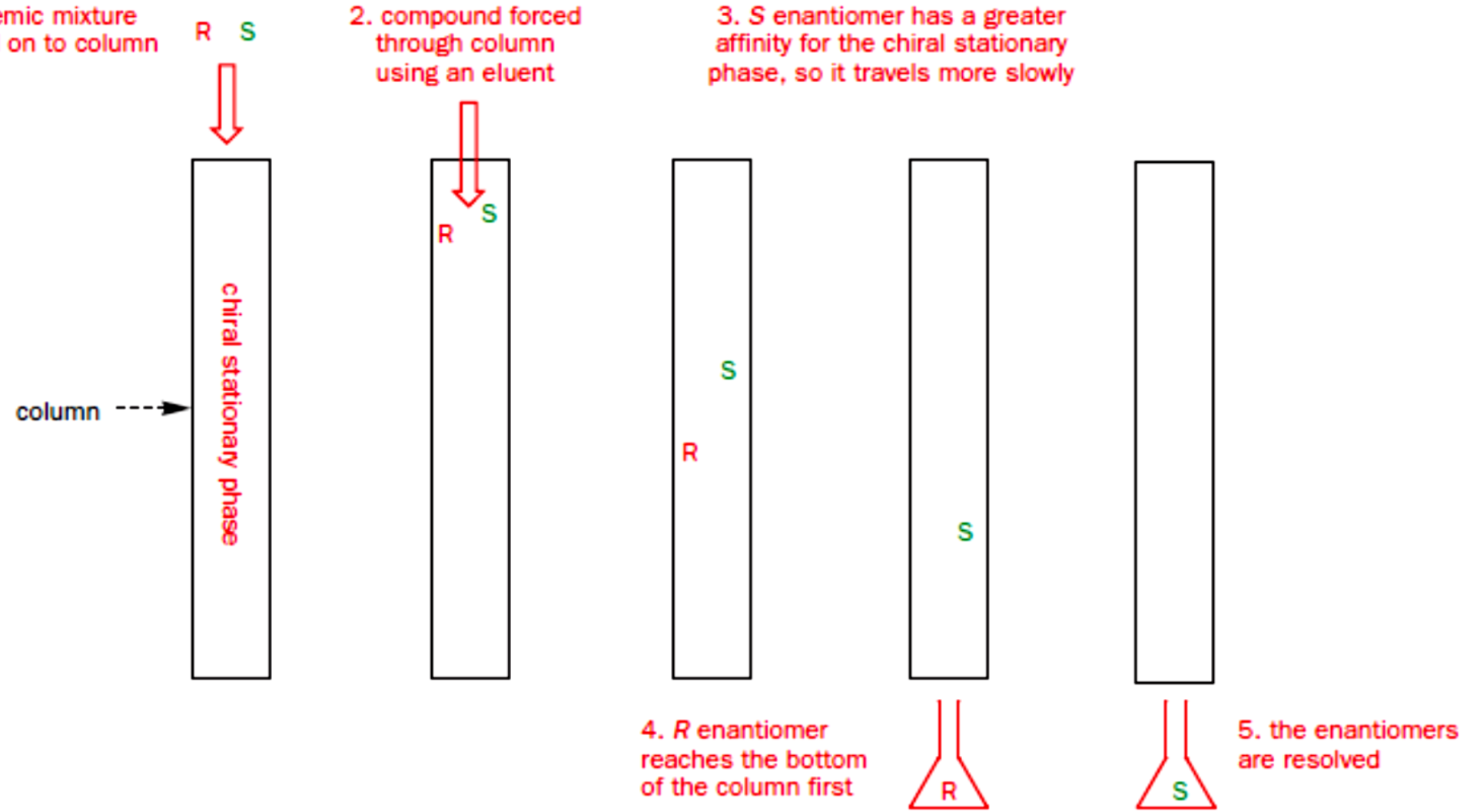
Chromatographic separation relies on a difference in affinity between a stationary phase (often silica) and a mobile phase (the solvent travelling through the stationary phase, known as the eluent) mediated by, for example, hydrogen bonds or van der Waals interactions. If the stationary phase is made chiral by bonding it with an enantiomerically pure compound (often a derivative of an amino acid), chromatography can be used to separate enantiomers.



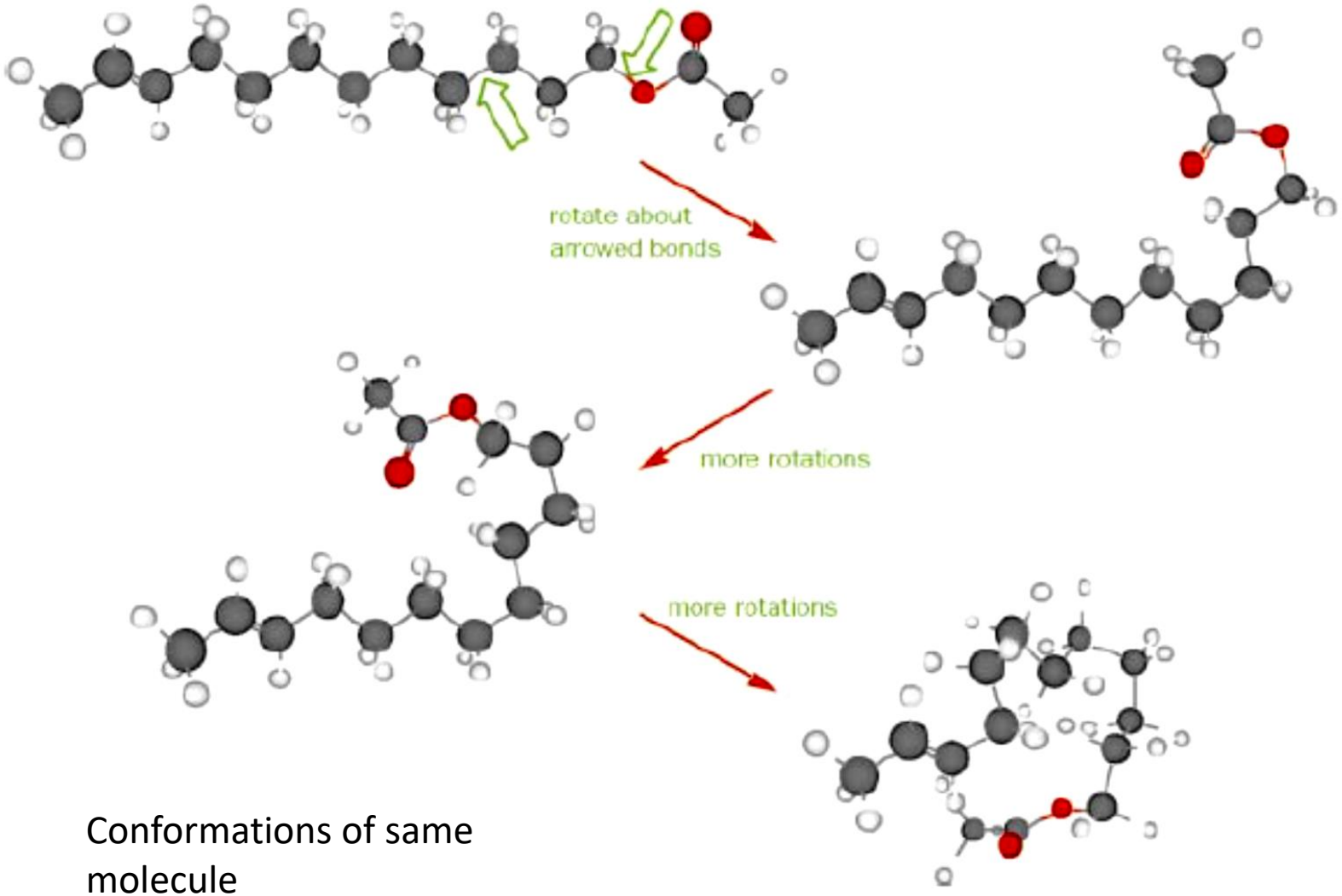
an analogue of the tranquillizer Valium



In order to study these compounds further, it was necessary to obtain them enantiomerically pure. This was done by passing a solution of the racemic compound through a column of silica bonded to an amino-acid-derived chiral stationary phase. The (*R*)-(–)- enantiomer showed a lower affinity for the stationary phase, and therefore was eluted from the column first, followed by the (*S*)-(+)-enantiomer.

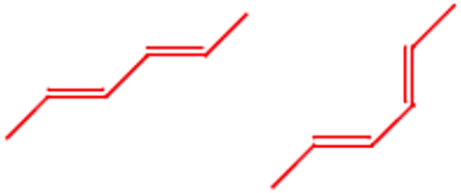


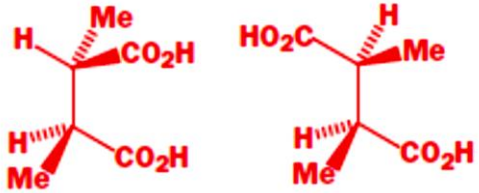
Conformational Analysis

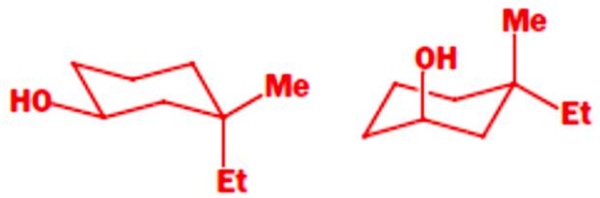


Conformations of same molecule

Three compounds,
each shown in two conformations

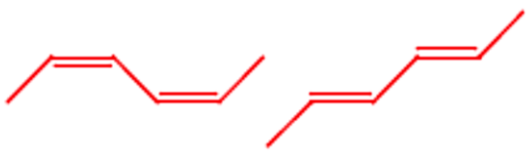


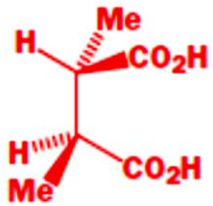


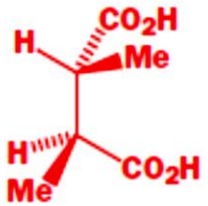


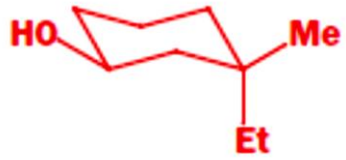
Conformation: Structures that can be interconverted simply by rotation about single bonds are conformations of the same molecule.

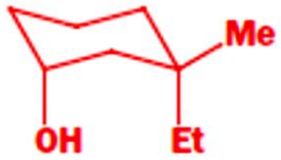
Configuration: Structures that can be interconverted only by breaking one or more bonds have different configurations, and are stereoisomers.



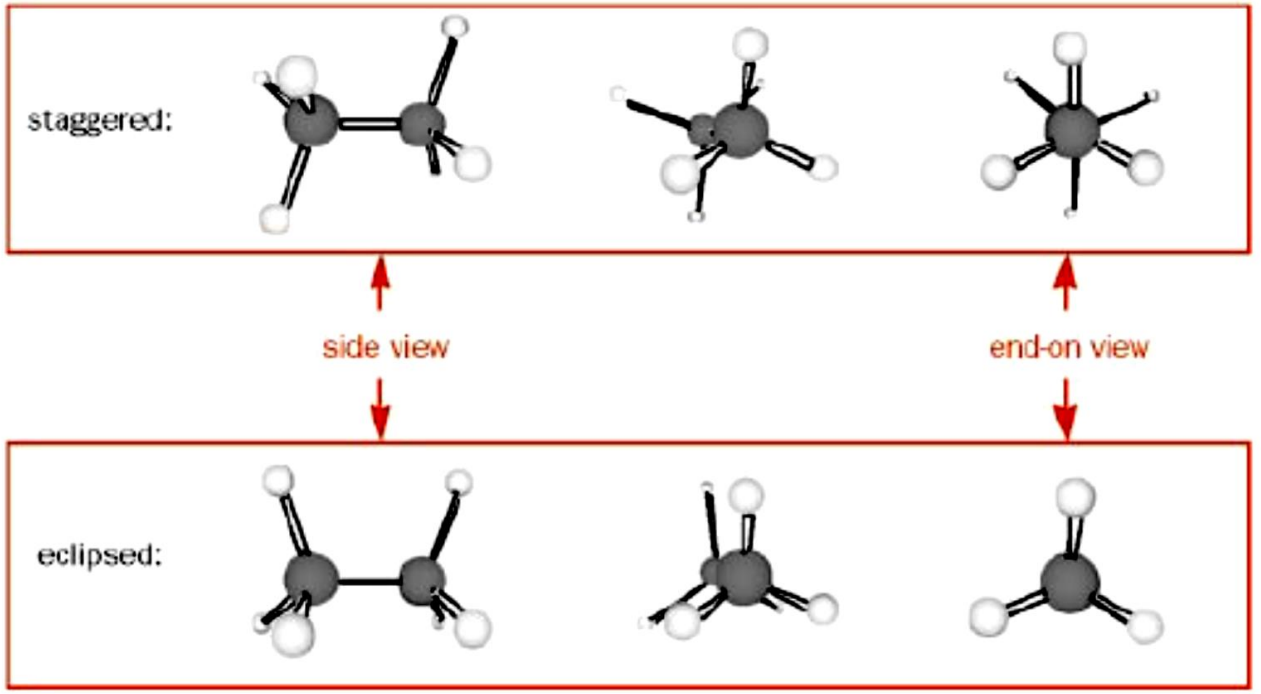




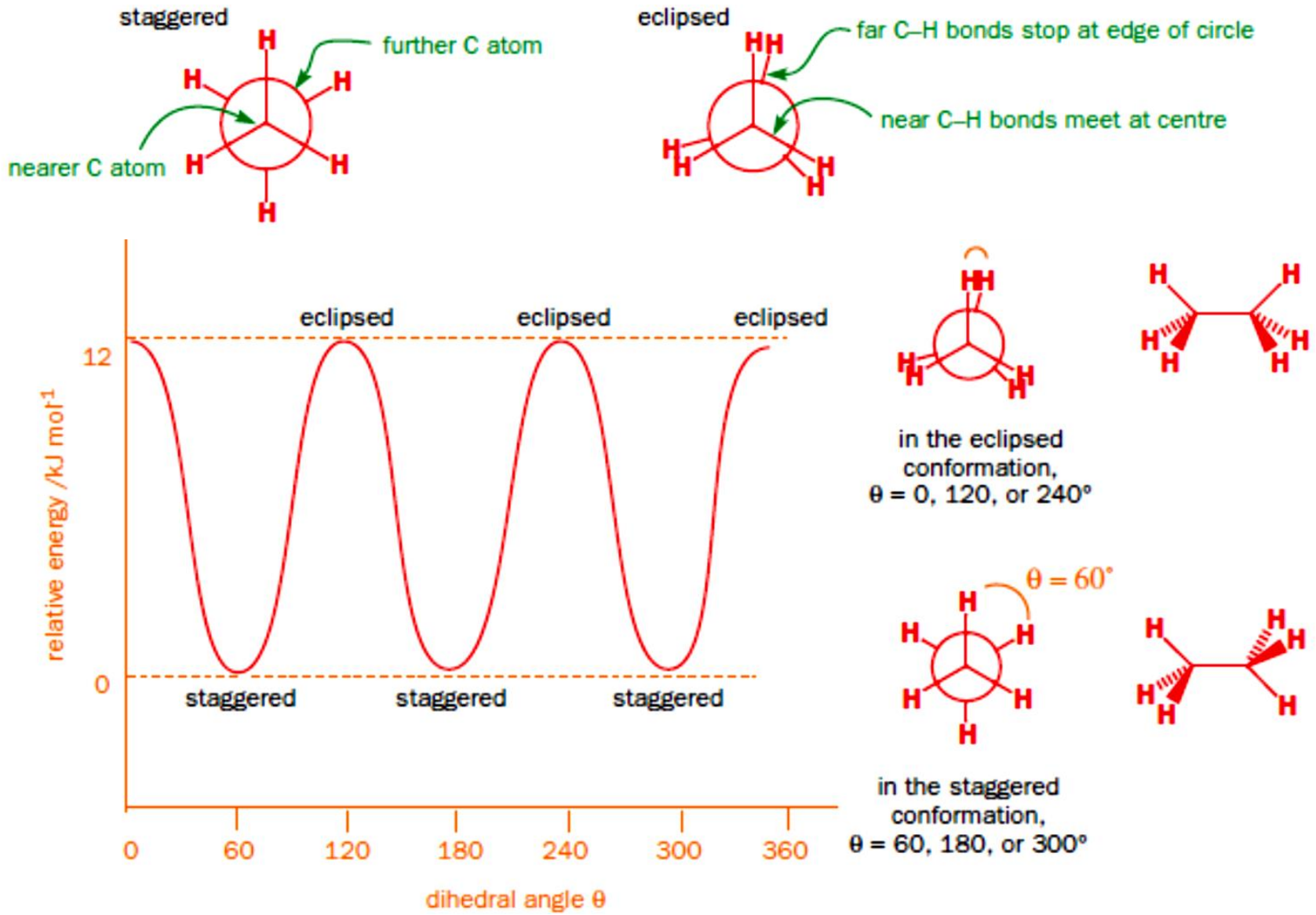




Conformations of ethane

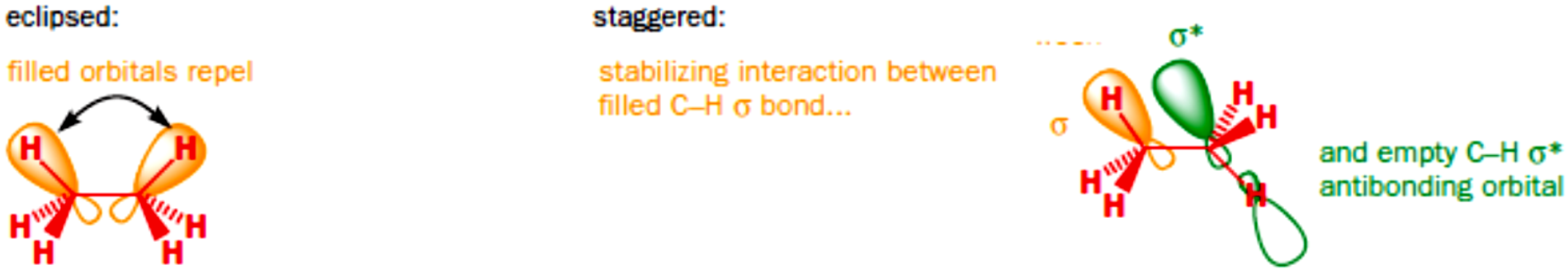


In the second method we draw the end-on view, looking along the C–C bond. This view is known as a **Newman projection**



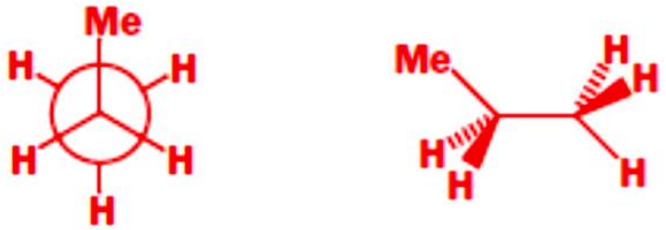
There are two more important reasons why the staggered conformation of ethane is lower in energy than the eclipsed conformation.

1. the electrons in the bonds repel each other and this repulsion is at a maximum in the eclipsed conformation.
2. there may be some stabilizing interaction between the C–H σ bonding orbital on one carbon and the C–H σ* antibonding orbital on the other carbon, which is greatest when the two orbitals are exactly parallel: this only happens in the staggered conformation.



Conformations of propane

two extreme conformations of propane are possible—in one the C–H and C–C bonds are staggered; in the other they are eclipsed.

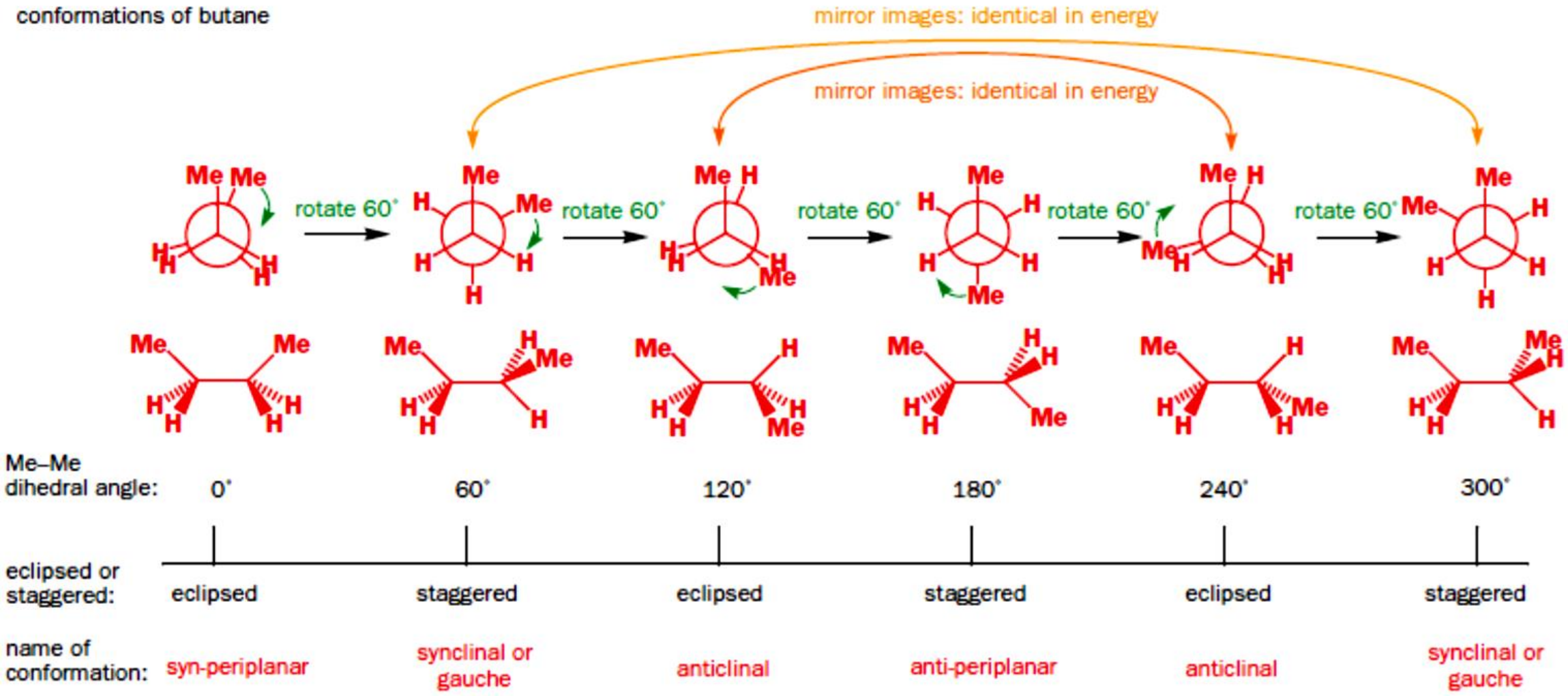


the staggered conformation of propane

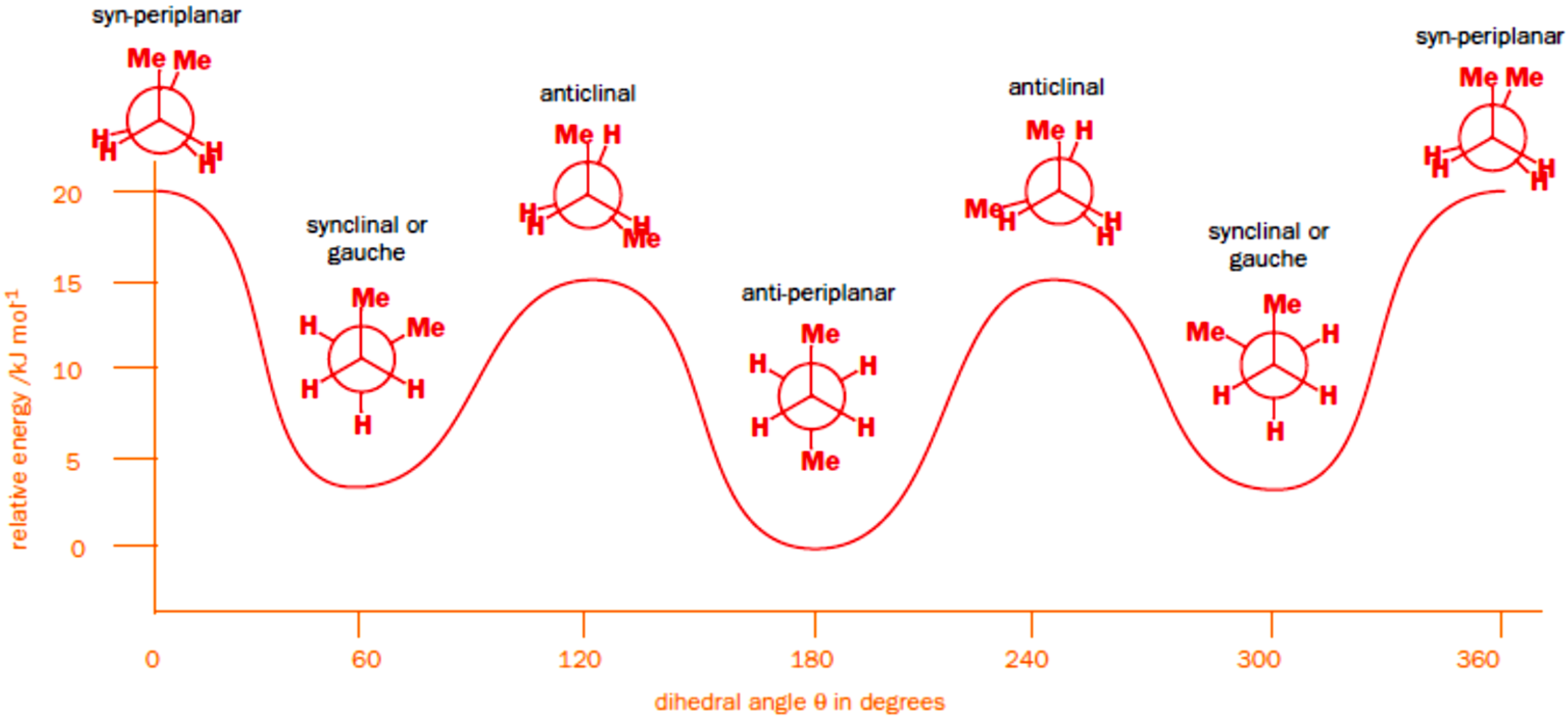
the eclipsed conformation of propane

The rotational barrier is now slightly higher than for ethane: 14 kJ mol–1

Conformations of butane



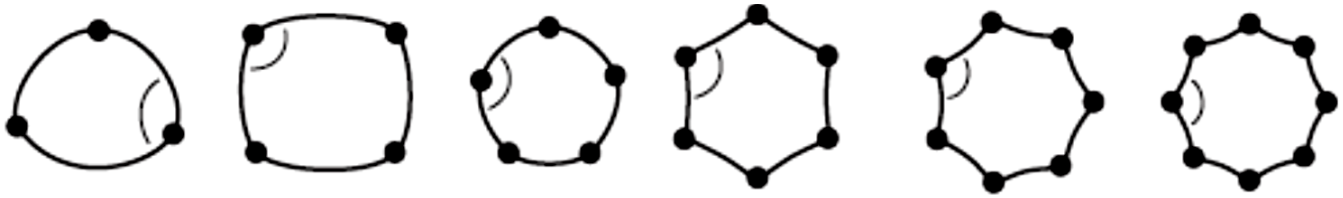
The rotation is very rapid indeed: the barrier of 20 kJ mol^{-1} corresponds to a rate at room temperature of 2 x 10^9 s^{-1}. This is far too fast for the different conformers to be detected by NMR. The NMR spectrum of butane shows only one set of signals.

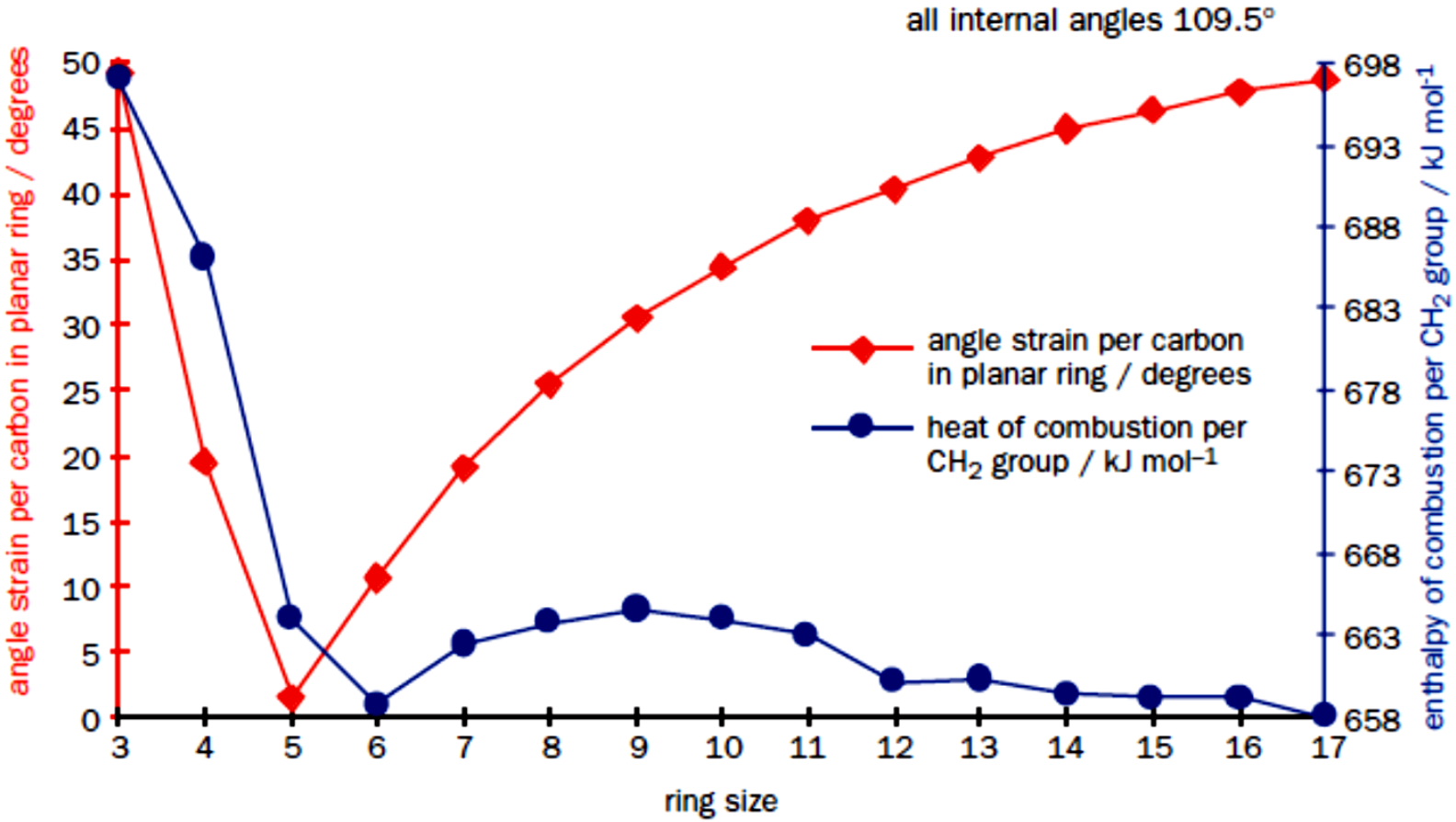


Butane can exist in an infinite number of ***conformations*** (we have chosen to show only the six most significant) but has only three ***conformers*** (potential energy minima)—the two synclinal (gauche) conformations and the anti-periplanar

Chemists class rings as small, normal, medium, and large depending on their size.

- small, n = 3 or 4
- normal, n = 5, 6, or 7
- medium, n = 8–about 14
- large, n > about 14

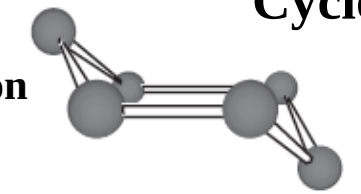


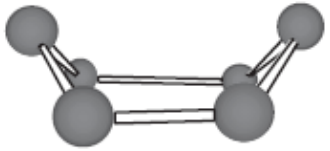


Cyclohexane (n = 6) and the larger cycloalkanes (n > 14) all have heats of combustion per $–CH_2–$ group of around 658 kJ mol^{-1}, the same value as that of a –CH2– group in a straight-chain alkane, that is, *they are essentially strain-free*

Cyclohexane

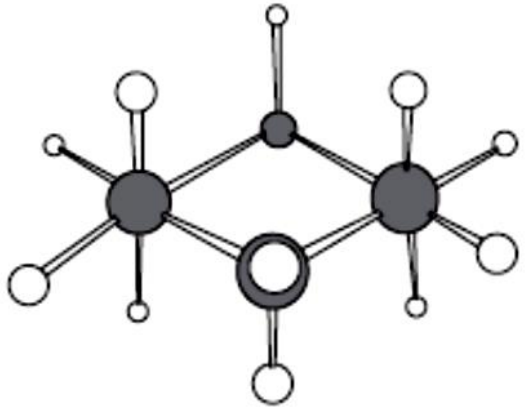
Chair conformation

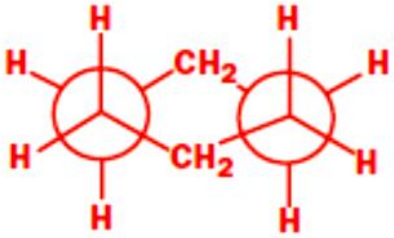




Boat conformation

view along C–C

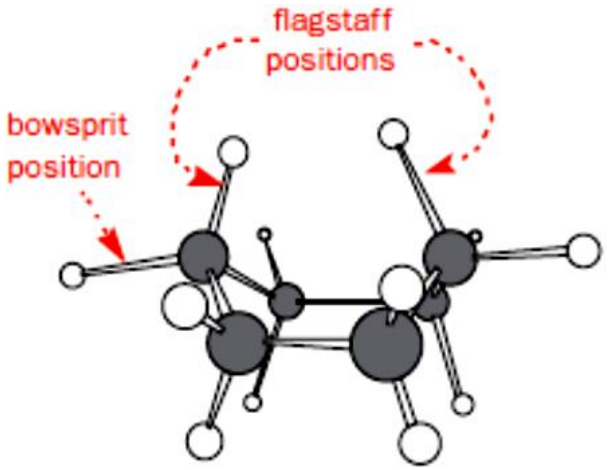




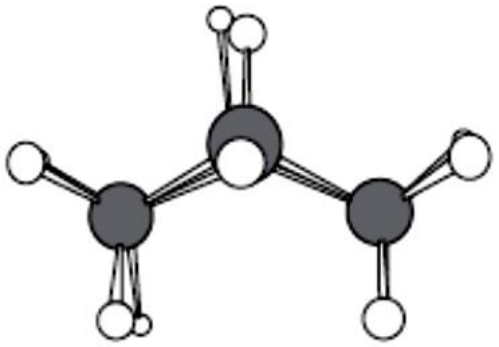
A side-on view of the chair conformation of cyclohexane

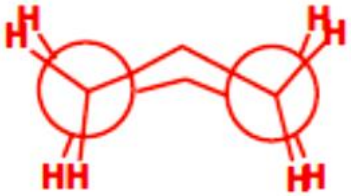
A view of cyclohexane looking along two of the C–C bonds.

A Newman projection of the same view



view along C–C

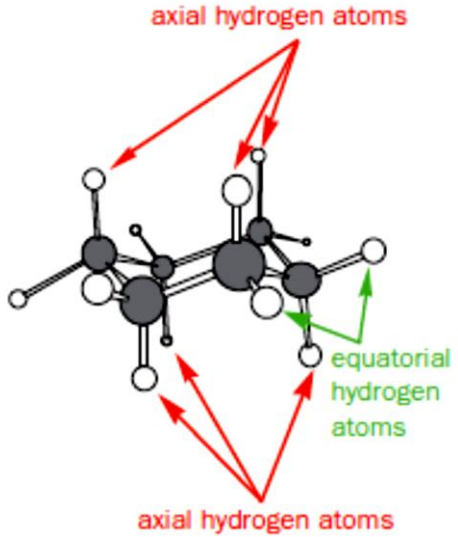




a side-on view of the boat conformation of cyclohexane

a view of the boat conformation looking along two of the C–C bonds

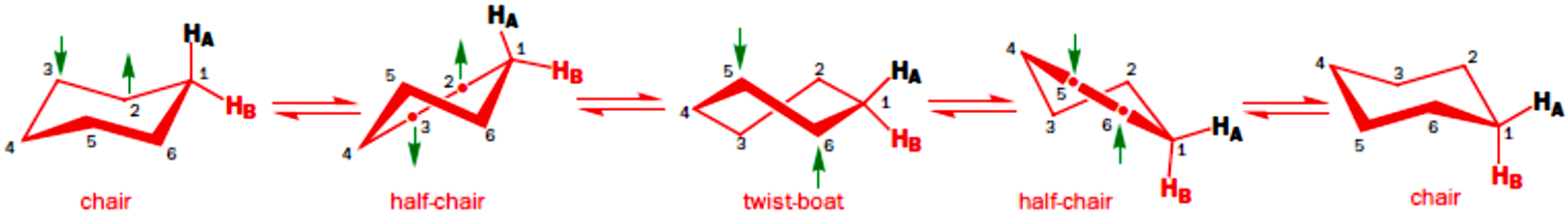
Newman projection of the same view

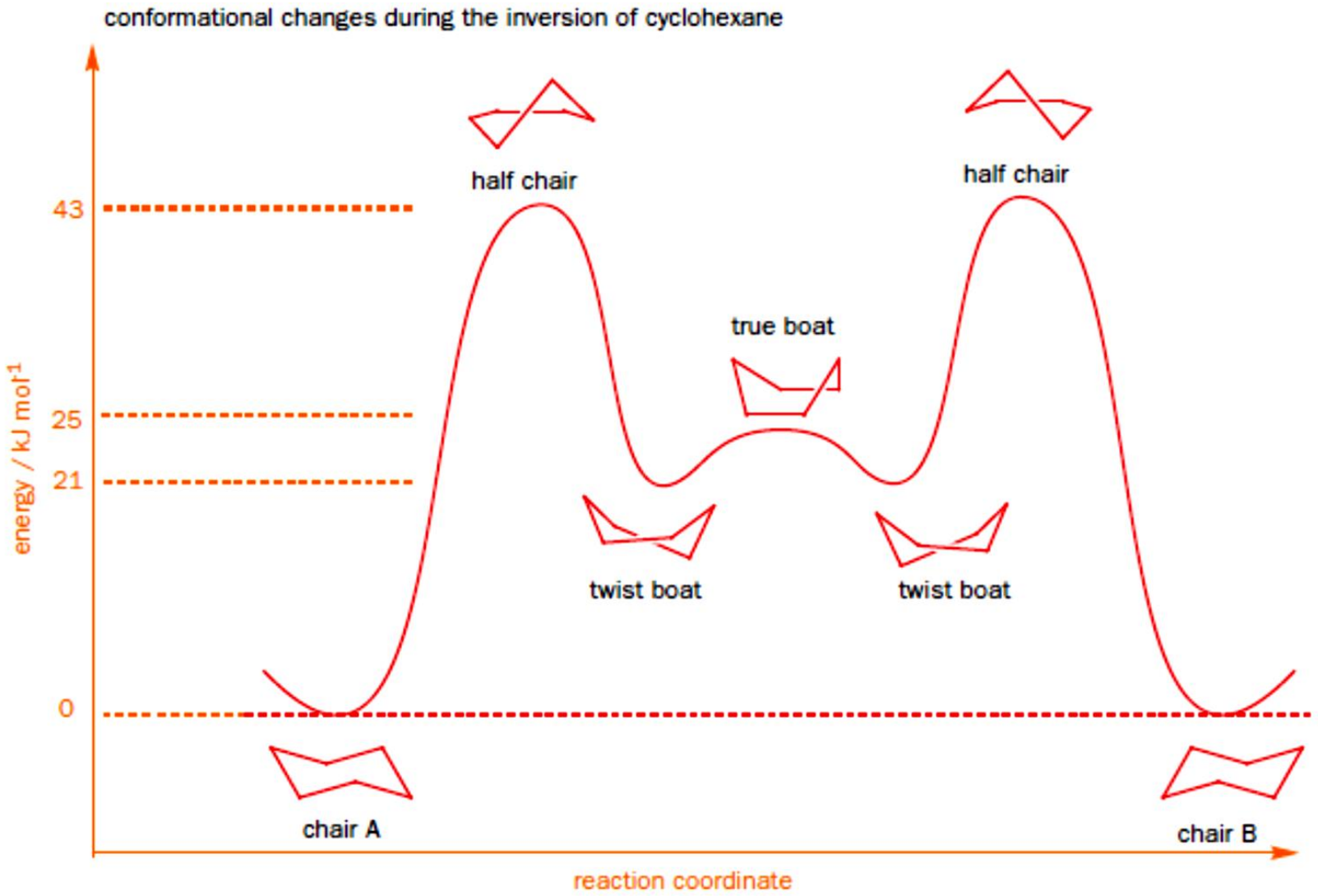


The two different sorts of protons (axial and equatorial) ought to resonate at different frequencies, so two signals should be seen (each with coupling to neighbouring protons). In fact, there is only *one* resonance in the proton spectrum, at 1.40 p.p.m.

After ring inversion has taken place, all the bonds that were axial are now equatorial and vice versa.

The whole inversion process of cyclohexane can be broken down into the conformations shown below.



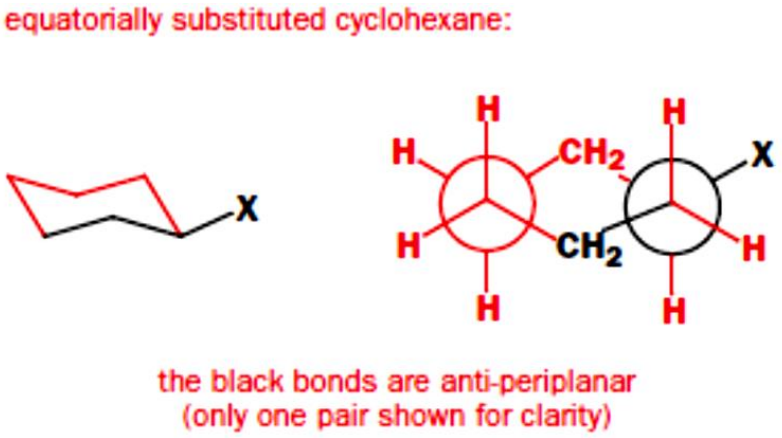


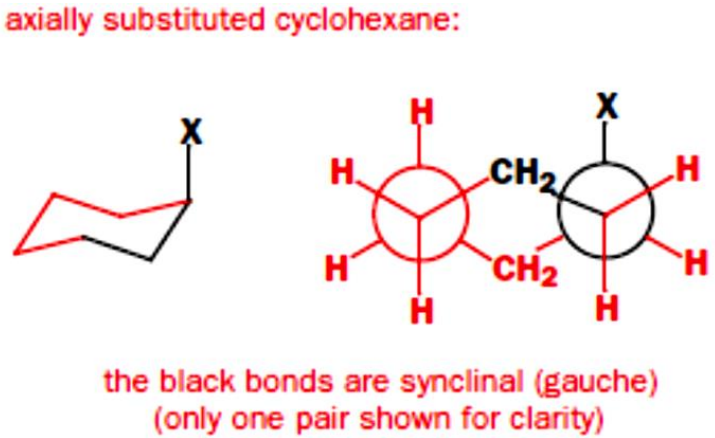
Ring inversion also interconverts the axial and equatorial protons, so these are also exchanging at a rate of 2 x 10^5 s^{-1} at 25 °C—too fast for them to be detected individually by NMR, which is why they appear as an averaged signal.

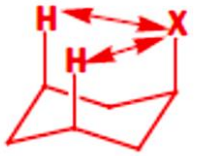
Substituted cyclohexanes

The conformer with the substituent axial is higher in energy, which means there will be less of this form present at equilibrium.

The first is that the axial conformer is destabilized by the repulsion between the axial group X and the two axial hydrogen atoms on the same side of the ring. This interaction is known as the **1,3-diaxial interaction**. As the group X gets larger, this interaction becomes more severe and there is less of the conformer with the group axial.







1,3-diaxial interaction

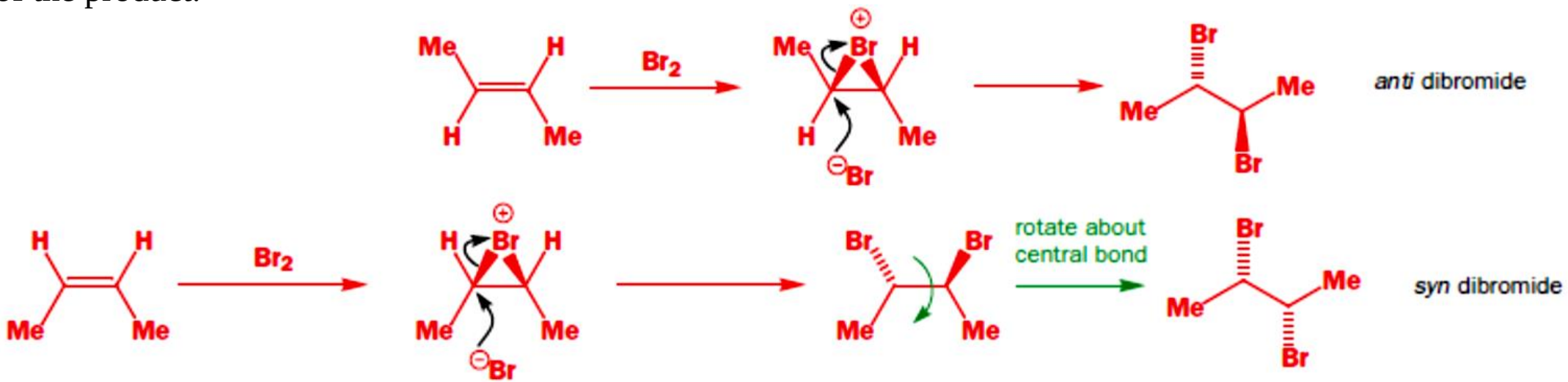
The second reason is that in the equatorial conformer the C–X bond is anti-periplanar to two C–C bonds, while, for the axial conformer, the C–X bond is synclinal (gauche) to two C–C bonds.

- **Stereospecific reactions**: reactions where the mechanism means that the stereochemistry of the starting material determines the stereochemistry of the product and there is no choice involved.
- **Stereoselective reactions:** reactions where one stereoisomer of product is formed predominantly because the reaction has a choice of pathways, and one pathway is more favourable than the other.
- **Regiospecific reactions:** By analogy with stereospecific, we can define regiospecific to mean a reaction where the regiochemistry (that is, the location of the functional groups) of the product is determined by the regiochemistry of the starting material.

Examples of Stereospecific reactions

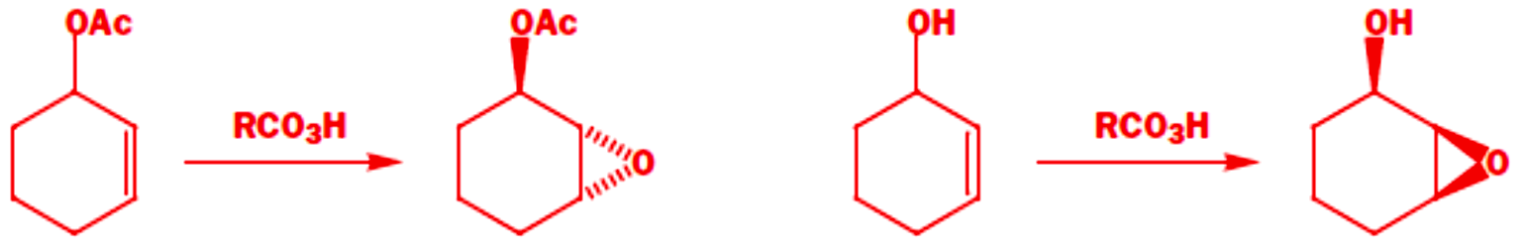
1. S_N2 reactions are stereospecific: they proceed with inversion so that the absolute stereochemistry of the starting material determines the absolute stereochemistry of the product

2. Electrophilic addition of bromine to alkenes is stereospecific and leads to *anti* addition across a double bond. So if we want the *anti* dibromide we choose to start with the *trans* double bond; if we want the *syn* dibromide we start with the *cis* double bond. The geometry of the starting material determines the relative stereochemistry of the product.

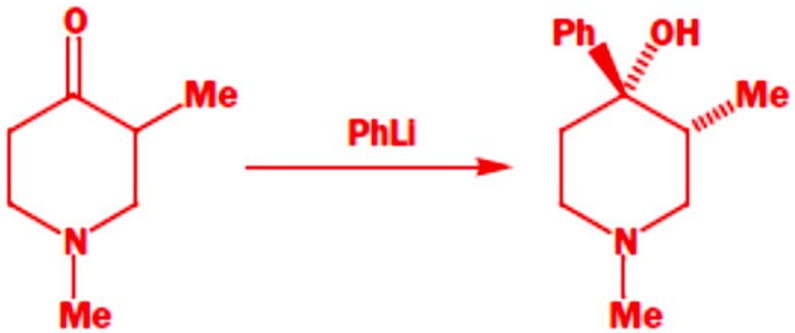


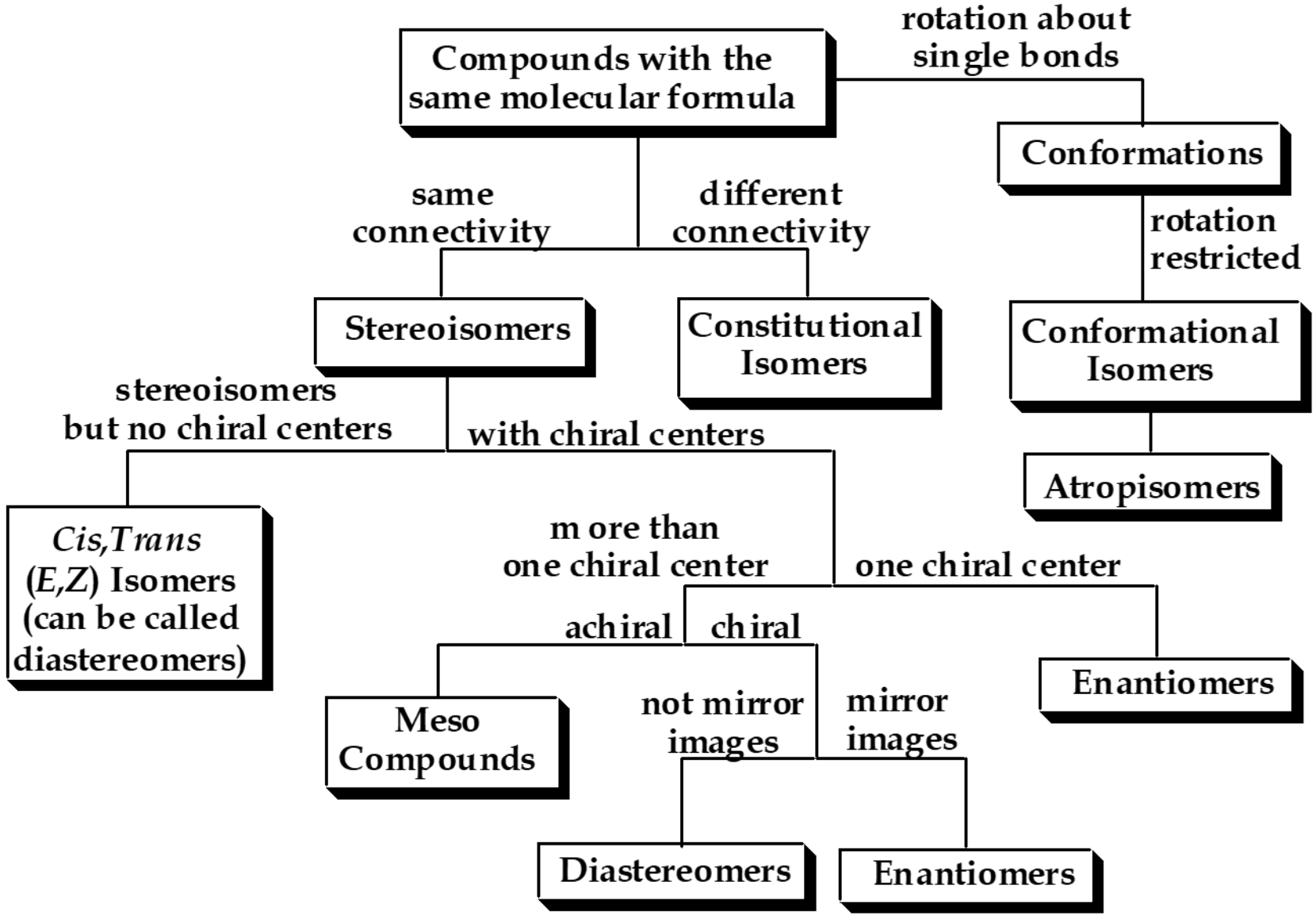
Examples of Stereoselective reactions

1. Epoxidation of cyclic alkenes is stereoselective, with reaction taking place on the less hindered face, or directed by hydrogen bonding to a hydroxyl group



2. Nucleophilic attack on six-membered ring ketones is stereoselective: small nucleophiles attack axially and large ones equatorially




Compounds with the same molecular formula
rotation about single bonds
Conformations
same connectivity
different connectivity
rotation restricted
Stereoisomers
Constitutional Isomers
Conformational Isomers
stereoisomers but no chiral centers
with chiral centers
Atropisomers
Cis,Trans (E,Z) Isomers (can be called diastereomers)
more than one chiral center
one chiral center
achiral
chiral
Enantiomers
Meso Compounds
not mirror images
mirror images
Diastereomers
Enantiomers