Anglo-Chinese Junior College
Department of Chemistry

Molecular Stereochemistry

Prepared by: Mr Marcus Yip

Learning Outcomes
At the end of the lectures, you should be able to:

(a) (i) use stereochemical projections including Newman projections, to represent molecules
(ii) interpret stereochemical projections of molecules
[knowledge of Fischer projection is **not** required]

(b) apply their understanding of the following types of isomerism to explain the stereochemistry of molecules, including saturated ring systems:
(i) conformational isomerism, including energy barriers to rotation and interconversion
(ii) *cis-trans* isomerism, including *E*, *Z* nomenclature
(iii) enantiomerism and diastereomerism:
– *R*, *S* configuration
– optical activity
– optical purity as the excess of one enantiomer, including calculation of optical purity by the equation:

$$\text{optical purity} = \frac{[\alpha]_{\text{obs}}}{[\alpha]_{\text{pure material}}} \times 100\%$$

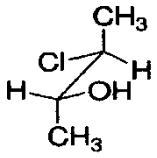
(c) recognise that transition element complexes can also exhibit stereoisomerism:
(i) cis-trans isomerism, e.g. square planar complexes such as $[Pt(NH_3)_2Cl_2]$ and octahedral complexes such as $[Co(NH_3)_4(H_2O)_2]^{2+}$
(ii) enantiomerism, e.g. $[Ni(H_2NCH_2CH_2NH_2)_3]^{2+}$ and $[Ni(H_2NCH_2CH_2NH_2)_2(H_2O)_2]^{2+}$ [identification of fac-mer isomerism is **not** required]

No. References

1 Clayden, Greeves, Warren and Wothers; Organic Chemistry
2 L. G. Wade, Jr; Organic Chemistry International Edition; 6th Edition; USA; 2006
3 David R. Klein; Organic Chemistry as a Second Language (I and II)
4 John E. McMurry; Organic Chemistry
5 Solomons and Fryhle: Organic Chemistry (8th edition)
6 Pharmaceutical Chemistry Notes by MOE
7 K. C. Nicolaou, E. J. Sorensen; Classics in Total Synthesis (547.70459)

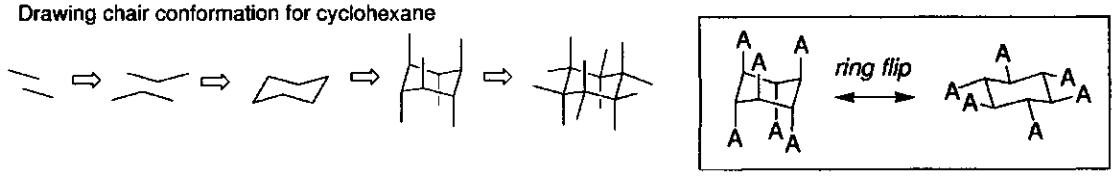
A) Representing molecules in 3D manner

- **Straight chain compounds**
  a) Wedge-dash diagram (learnt in H2 chemistry)
  b) Sawhorse diagrams



  c) Newman projection
  d) Fischer projection (non-examinable additional reading at the back)

- **6-membered ring compounds**



B) Conformational Isomerism

Conformational isomerism is a form of stereoisomerism in which the isomers can be interconverted exclusively by rotations about σ bonds (as they are cylindrically symmetrical). Such isomers are generally referred to as conformational isomers or conformers.

Conformational isomers are thus distinct from the other classes of stereoisomers where interconversion necessarily involves breaking and reforming of chemical bonds.

Strain in molecules

A molecule experiences **strain** when its chemical structure undergoes some stress which raises its internal energy in comparison to a strain-free reference compound.

Naturally, molecules will contort and rotate about σ bonds to minimise such strain in order to make itself as stable as possible.

A study of the Newman projections and chair-boat conformations is essentially a study in the avoidance of such strain.

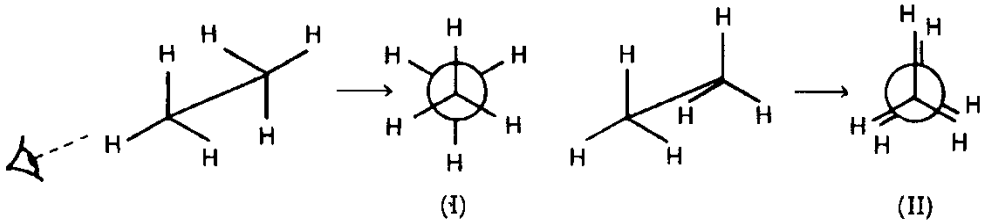
Three types of strain

- Angle strain – also known as 'ring' strain. Caused by abnormal bond angles.
- Steric strain - the electron-electron repulsion of atoms (or groups of atoms) that are too close together
- Torsional strain – a type of steric strain that occurs when bonds are stacked on each other.

Torsional strain can be relieved by bond rotation whereas steric strain cannot.
http://www.chem.illinois.edu/clcwebsite/CLCtutorials_HTML5/104/Newman%20projections_2017/index.html
Online ball-and-stick models!

Newman projections – using ethane as illustration

Newman projections of two conformations of ethane: fully eclipsed (II) and staggered or anti (I)



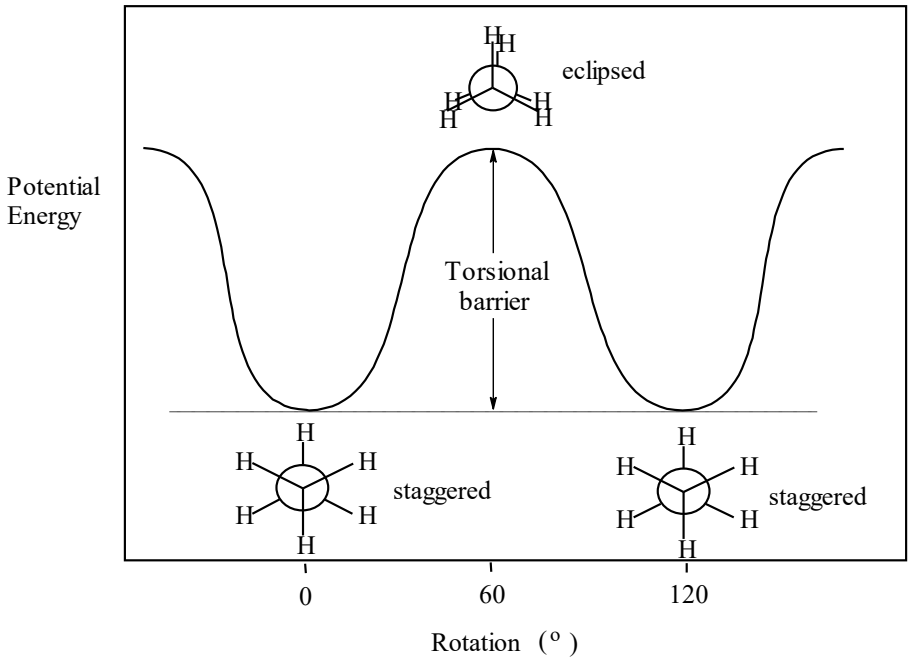
In the staggered conformation, the H atoms are as far apart as possible, and the electrostatic repulsion between the C-H bonding electron pairs is at a minimum.

In the least stable eclipsed conformation, electron pair repulsion is maximised.

* **Torsional barrier** - energy barrier to the rotation from one staggered conformation to another. The difference in energy between the eclipsed and the staggered conformations is only about 12 kJ mol^{-1}. This is comparable to the thermal energy that molecules have at room temperature, and so molecules experience little hindrance to free rotation around the C-C bond.

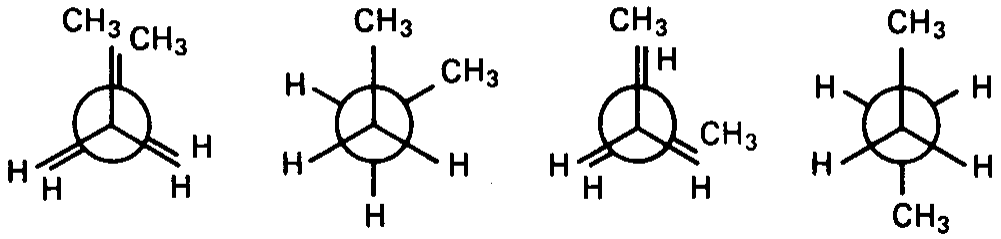
* **Torsional strain** - present in the eclipsed conformation due to the electron repulsion between the eclipsed C-H bonding electron pairs

The changes in internal (potential) energy which accompany rotation about the C–C bond in ethane are shown.



Newman projections – using butane as illustration

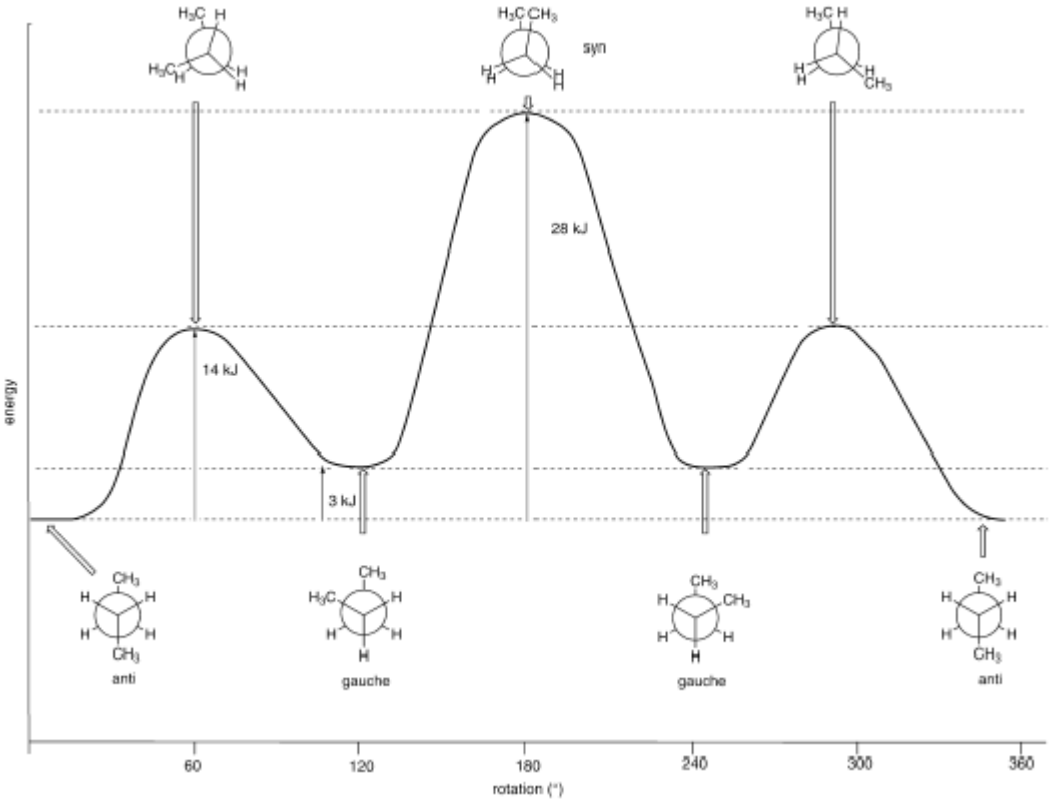
* Newman projections for the principal conformations of butane are shown:



I (syn) II (gauche) III IV (anti)

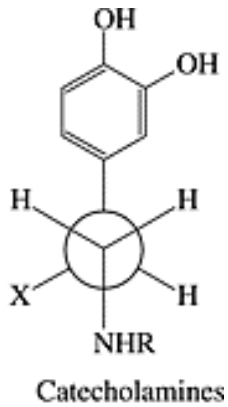
* I, III-- eclipsed conformation
  -- I is least stable because of additional steric strain due to the close proximity of the 2 bulky methyl groups.
* II, IV-- staggered conformations
  --IV is more stable than II since some steric strain is present in II.

* Energy differences for the various conformations are shown below. At room temperature about 70% of butane molecules are anti, which is said to be the preferred conformation.



The classic example of conformations being important to the pharmacological action of a drug is the nerve transmitter acetylcholine.

For example, experimental data suggest that catecholamines such as norepinephrine and dopamine interact with their receptors in the antiperiplanar conformation.

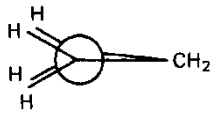


Catecholamines

Pharmacophoric conformation of catecholamines (norepinephrine).

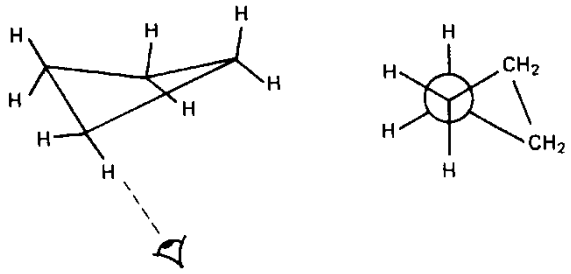
Conformations of cycloalkanes

* Cyclopropane is relatively unstable because it has both ring strain from shortening of the C-C-C bond angle (109.5° down to 60°) and torsional strain due to eclipsing of the hydrogen atoms.

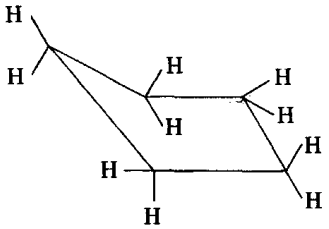


A Newman projection of cyclopropane

* The folded shape of cyclobutane is a compromise in which a slight increase in ring strain (88° rather than 90°) allows relief from torsional strain by non-eclipsing of the hydrogen atoms.

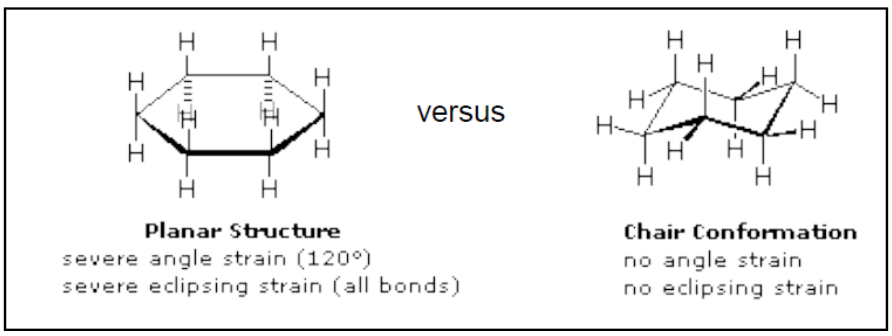


* Cyclopentane is a flexible molecule with rapidly interchanging conformations. The most stable of these is the 'envelope' in which torsional strain is minimised by having one carbon atom above the plane of the other four.



Chair/boat conformations

The cyclic compounds that are most commonly found in nature contain 6-membered rings because such rings can exist in a conformation that is almost completely free from strain. This conformation is called the chair conformation.

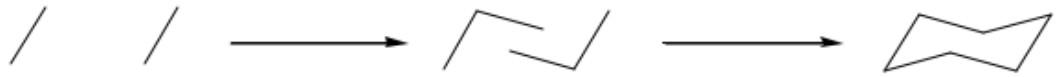


In the chair conformation of cyclohexane, all the bond angles are 111^0, which is very close to the ideal tetrahedral bond angle of 109.45^0 (hence there is little angle strain) and all the adjacent bonds are staggered (hence there is little torsional strain).

Chair conformations – steps to draw them

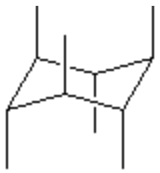
I. The chair conformation consists of three sets of parallel lines of the same length, slanted upward, drawn in one set at a time. It is important to draw the structure clearly so that the substituents can be placed correctly on the ring.

Connect the tops of the lines with a V; the left hand side of the V should be slightly longer than the right hand side. Connect the bottoms of the lines with an inverted V; the lines of the V and the inverted V should be parallel.

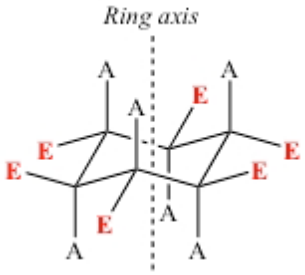


II. Axial bonds are parallel to the axis of the ring, while equatorial bonds are perpendicular to the axis of the ring and lie along the equator of the chair. Notice that each carbon has one axial and one equatorial bond.

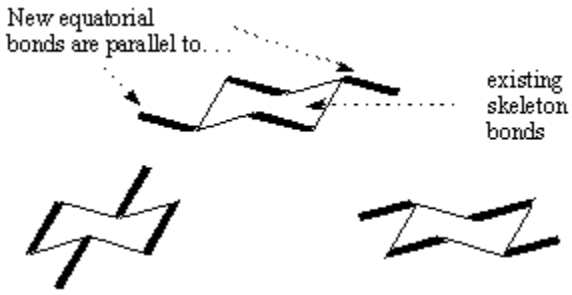
equatorial bonds



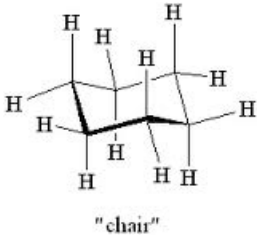
axial bonds



III. When drawing the bonds, it is important to clearly distinguish between axial and equatorial. The equatorial bonds should be drawn parallel to the lines representing the carbon-carbon bonds in the ring. After the equatorial bonds are drawn, fill in the axial bonds by drawing lines up or down.



Without any other substituents i.e. just cyclohexane itself, the final chair conformation would have hydrogen atoms at the ends of all the axial and equatorial bonds. The structure would look like this:



Now let's number the structure and place substituents on the ring.

The carbons can be numbered any way, as long as you are consistent in counting either clockwise or counterclockwise.

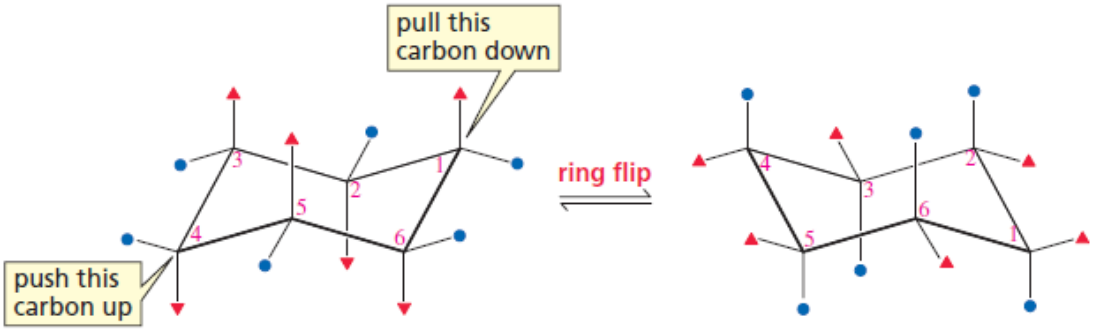
Now for the substituents. Solid wedges indicate that the bond projects outward towards the viewer, and broken (dashed) wedges indicate that the bond recedes away from the viewer. For simplicity in drawing, we will label atoms on solid wedges as being "up" on the ring and atoms on dashed wedges as being "down" on the ring. This makes sense, because in the chair conformation, each attachment to a carbon will have either an up or down orientation. It is important to note, however, that there is no correlation between up/down and axial/equatorial. Let's take a look at an example.

First we number the carbons on the structure to the left. The OH group is on carbon 1. We see that it is on a solid wedge, so we place it "up" on carbon 1 on the chair. For the methyl group on carbon 3, we see that it is on dashed wedge, so we place it on "down" on carbon 3 on the chair. In this case, the OH group happens to be axial up and the methyl group happens to be equatorial down. But there is no relation between our naming of up/down and axial/equatorial. For example, if the OH was on carbon 2, then it would be "up" on the equatorial position instead. It just depends which carbon the substituent is on.

<u>Chair/boat conformations – how to flip one to another</u>

When the chair is flipped, all the axial positions become equatorial, and all the equatorial positions become axial.

It is also important to note that even after the chair flips, all the "up" substituents remain "up" and all the "down" substituents remain "down."



In the above example, the "triangle" switches from axial to equatorial, but it is still in the "up" position. The "circle" on carbon 3 switches from equatorial to axial, but it is still in the "down" position.

To draw the flipped conformation, follow the same steps as before, but take note of the difference in drawing the parallel lines. Also use the same method to number the carbons as before. This time, however, the more common way to number the carbons is starting with carbon 1 on the bottom right corner.

1 2

Also take note of the arrow between the conformations that indicate equilibrium. The cyclohexane structure continuously flips from one chair conformation to the other.

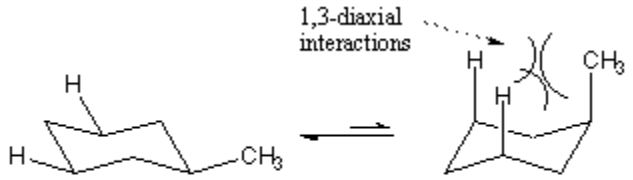
Without any substituents, both forms are equal in energy and are equivalent to each other. However, once substituents are placed on the ring, the two forms may not be equal in energy, and the molecule may spend more time in one conformation compared to the other. The next section will address this difference in stability.

Stability between two chair conformations

Substituents on the chair conformation prefer to be in the equatorial position.

The reason is that when substituents are in the axial position, there tends to be more unfavourable interactions with other axial atoms on the same side. These unfavourable interactions are called 1,3-diaxial interactions. When substituents are in the equatorial position, they are farther away from each other. This increases the stability of the conformation.

In the picture below, the methyl in the equatorial position is more stable because it avoids interaction with the hydrogen atoms.



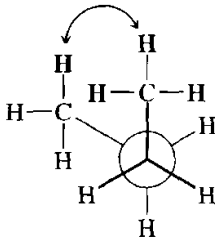
equatorial methyl **axial methyl**

The larger the group is, the more it will tend to remain in the equatorial position, to minimise the steric strain.

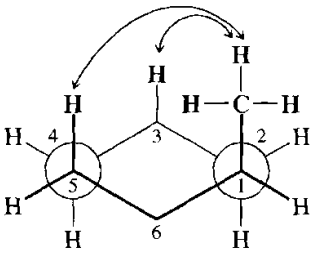
Table 2.10 Equilibrium Constants for Several Monosubstituted Cyclohexanes at 25 °C

Substituent	Axial $\rightleftharpoons^{K_{eq}}$ Equatorial	Substituent	Axial $\rightleftharpoons^{K_{eq}}$ Equatorial
H	1	CN	1.4
CH_3	18	F	1.5
CH_3CH_2	21	Cl	2.4
$CH_3CH(CH_3)$	35	Br	2.2
$CH_3C(CH_3)_2$	4800	I	2.2
		HO	5.4

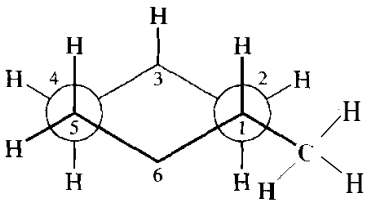
Understanding the stability of chair conformations using Newman projections



***gauche*-Butane**
(3.8 kJ mol^{-1} steric strain)



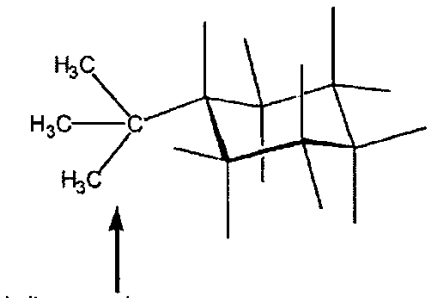
Axial methylcyclohexane
(two gauche interactions = 7.6 kJ mol^{-1} steric strain)



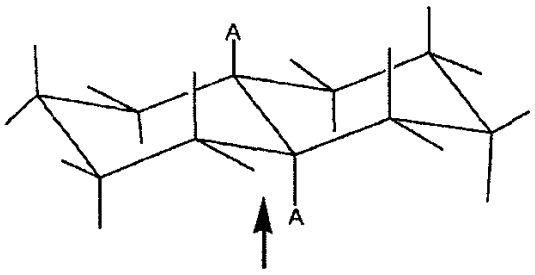
Equatorial methylcyclohexane

Therefore, when trying to determine which chair is more stable, place the larger group(s) in the equatorial position.

Hence if there is/are large substituent(s) on the ring, this tends to 'fix' into a particular conformation in which the largest substituent is in an equatorial position. Another way in which the conformation can be fixed is by joining another ring to the first.



bulky group is
always equatorial

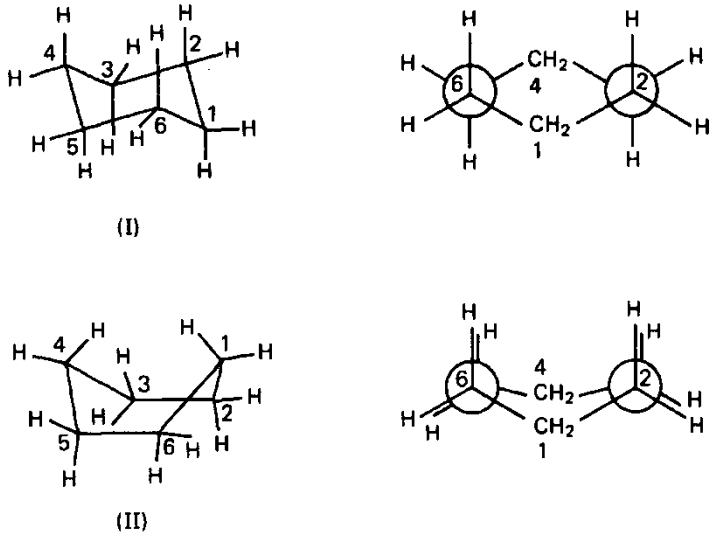


each ring fixes the conformation of the other ring
(the bonds marked A must always be axial)

Chair/boat conformations – using cyclohexane as illustration

Two important conformations of cyclohexane are

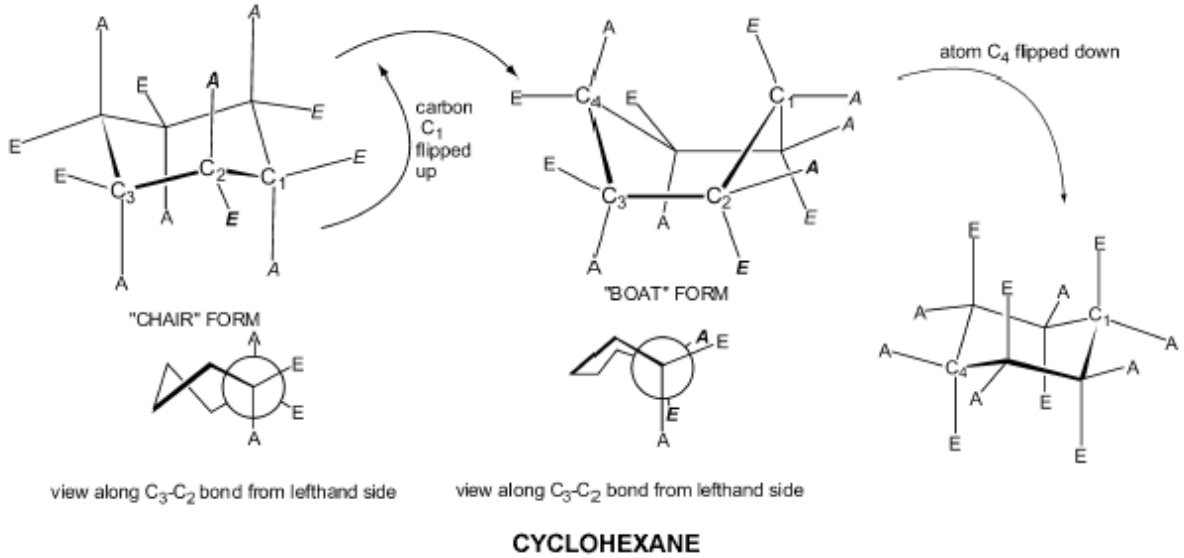
- the 'chair form' which is free of both ring strain and torsional strain (all the groups on all C-C bonds are in the staggered conformation) (figure I)
- the 'boat form' which, although free of ring strain, has both torsional strain and van der Waals' repulsion ('flagpole interaction') between H atoms on carbons 1 and 4 (figure II).



Chair (I) and boat (II) conformations of cyclohexane

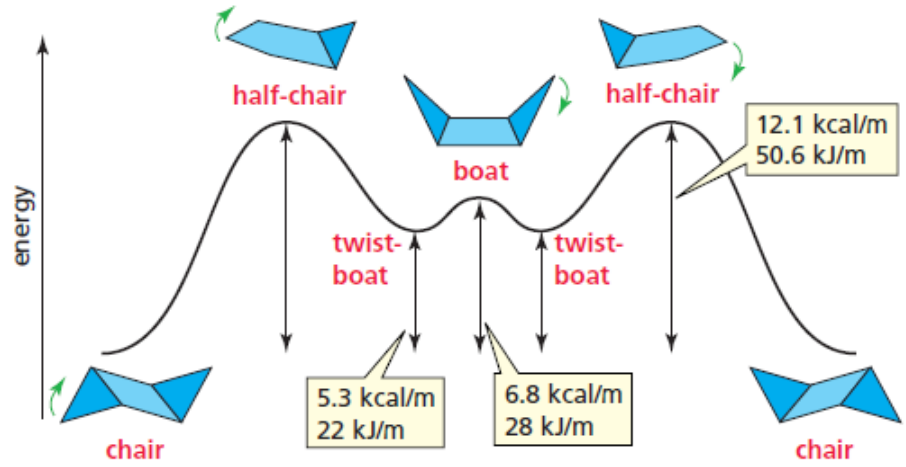
The barrier to "flipping' from the chair to the boat and then to the alternative chair is small enough for the non-substituted cyclohexane to move from one conformation to the other with ease at room temperature.

- C1 flipped up-- chair form to boat form
- C4 flipped down--boat form to another chair form where all the bonds in the original chair that were axial become equatorial and vice versa.

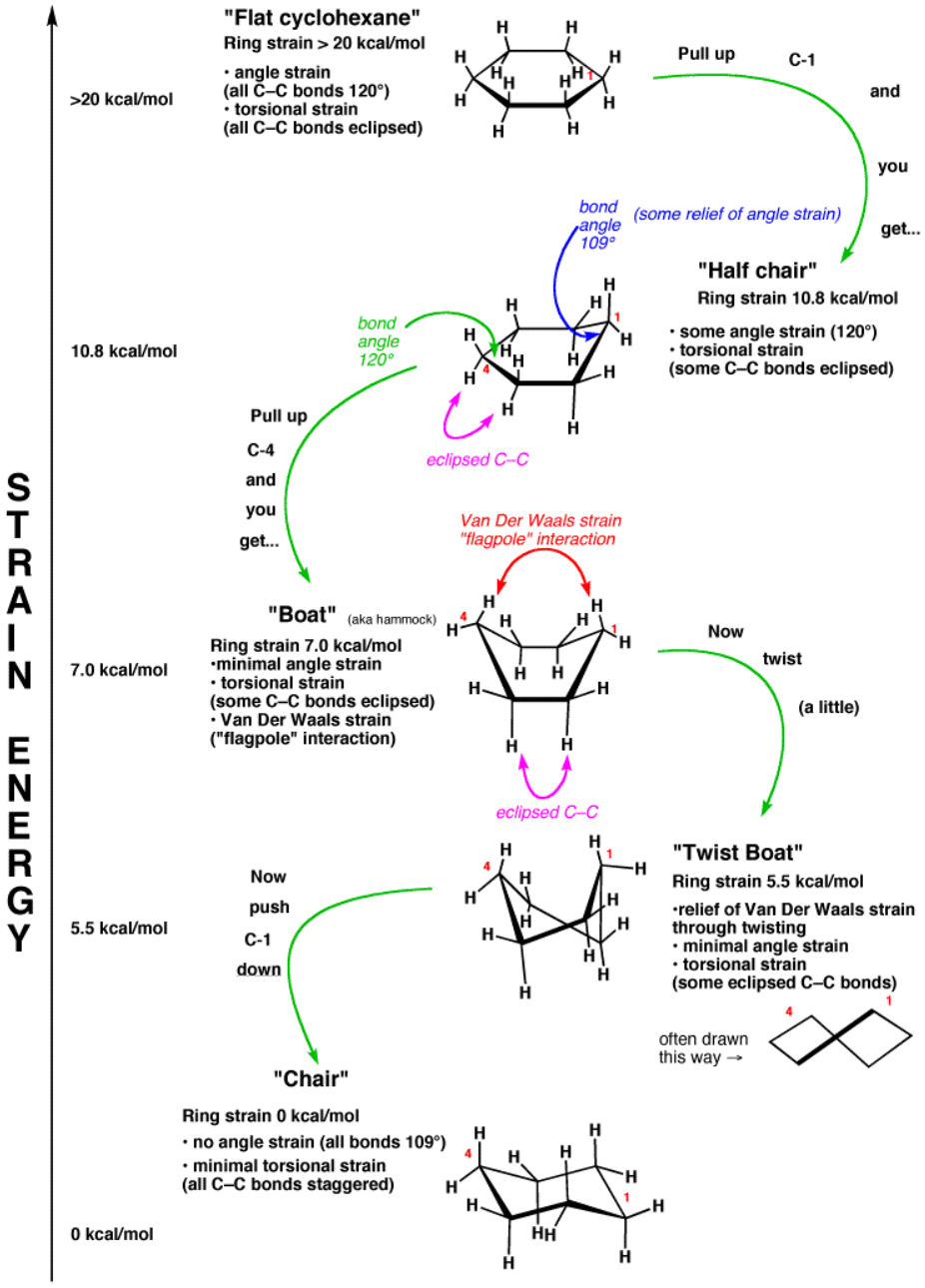


CYCLOHEXANE

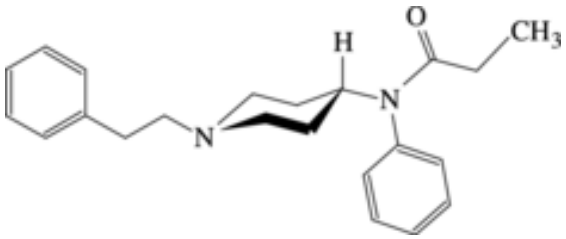
Due to the greater stability of the chair, more than 99% of the molecules are estimated to be in a chair conformation at any given moment.



The Many Shapes Of Cyclohexane



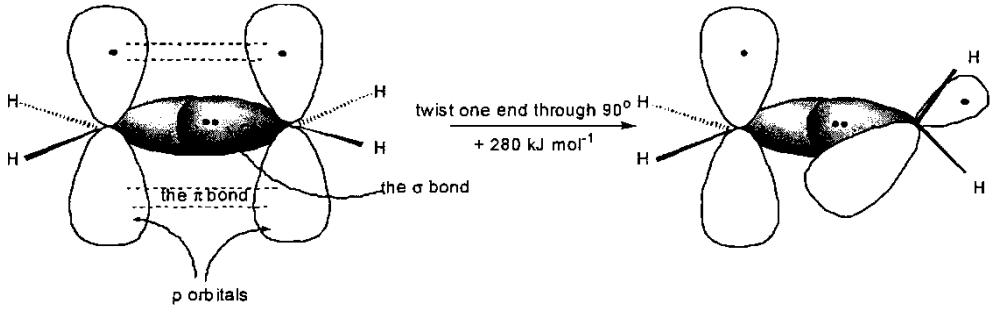
Ring conformations are believed to be important in drug activity. For example, experimental evidence suggests that the analgesic fentanyl binds to opiate receptors preferentially in the conformation shown below, where the bulky substituents are positioned equatorially to maximise conformational stability.



C) *cis-trans* isomerism

Caused by **restricted rotation** about a certain bond.

I) Involving C=C



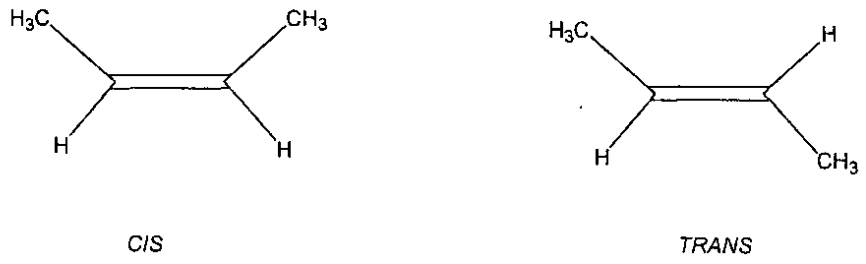
the double bond in ethene

A C=C bond consists of

- σ bond - cylindrically symmetrical (formed by head on overlap of 2 sp^2 orbitals) and allows free rotation about C-C bond

- π bond - sideway overlap of two p orbitals
  --maximum overlap if both orbitals are parallel
  --when 2 p orbitals are aligned 90° to each other, π bond is broken (280 kJ mol^{-1} is needed to break bond)
  --Hence no free rotation about C=C

Due to this restricted rotation, *cis-trans* isomerism arises when there are two different groups attached to each carbon at C=C. Example:



CIS *TRANS*

the two isomers of but-2-ene

--similar chemical properties but slightly different physical properties

Food for thought

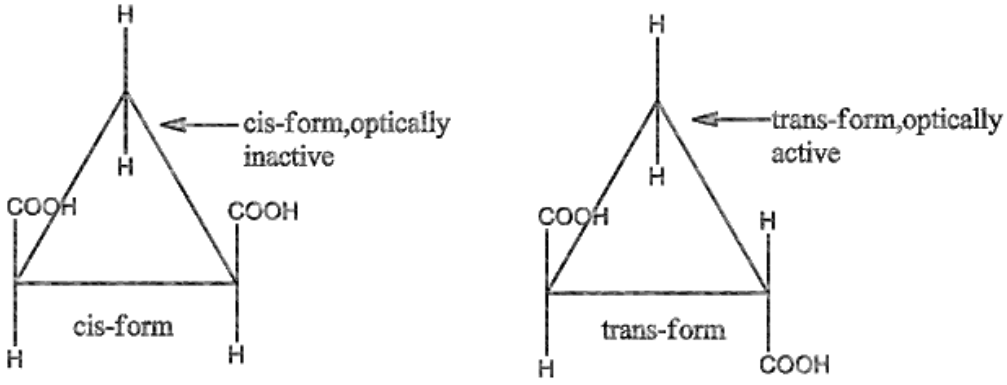
- How are *cis-trans* isomers considered as diastereomers?

- Are all diastereomers *cis-trans* isomers?
  On the other hand, are all *cis-trans* isomers diastereomers?

II) Involving the ring system

C–C single <u>bond rotation is constrained</u> within a ring, hence *cis-trans* isomers exists.

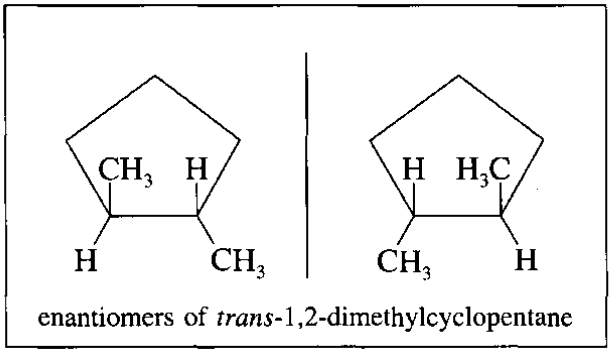
Example 1



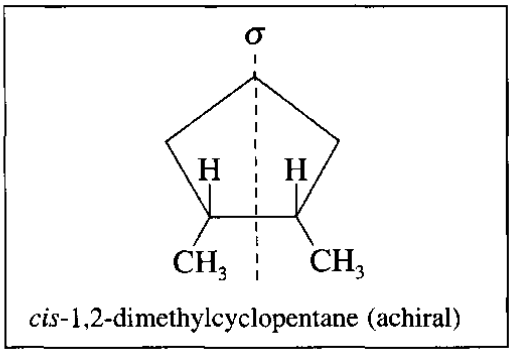
cyclopropane-1,2-dioic acid

Try drawing the third isomer of cyclopropane-1,2-dioic acid

Example 2



enantiomers of *trans*-1,2-dimethylcyclopentane



cis-1,2-dimethylcyclopentane (achiral)

D) CIP rules in identifying stereoisomers

Three chemists, Cahn, Ingold, Prelog devised the "C.I.P. method" to name two stereoisomers based on atomic number.

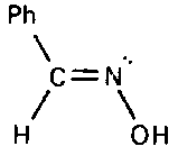
1. The higher the atomic number of the atom bonded directly to the chiral centre, the higher the priority.
2. If the atom bonded directly to the chiral centre is the same, look at the next atom with the highest atomic number.
3. Atoms in double or triple bond is considered to bond to an equivalent number of the atom bonded by single bond.

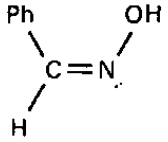
E) Designating *E*/*Z* isomers

I. Apply the sequence rules to assign priorities to the two ligands attached to each of the doubly bonded atoms.

II. If the two ligands of higher priority are on diagonally opposite sides of the double bond, the isomer is ***E*** (*entgegen*, across).
If the higher priority ligands are on the same side of the double bond, the isomer is ***Z*** (*zusammen*, together) "***Ze Z****ame* ***Z****ide*"

Example 1

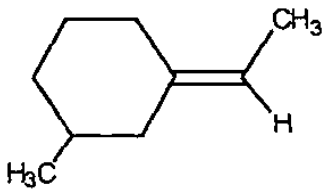




Top priority ligands on diagonally opposite sides of the double bond (*E*)

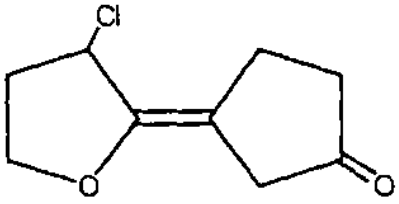
Z

Example 2



The lower half of the ring has a higher priority than the upper half, so the compound is *E* isomer.

Example 3

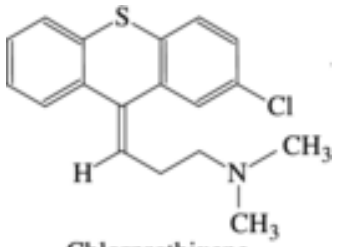


The lower half of each ring has a higher priority than the upper half, so the compound is the *Z* isomer.

Food for thought

- Is it possible to designate the pairs of isomers in the three examples above as *cis* and *trans*?

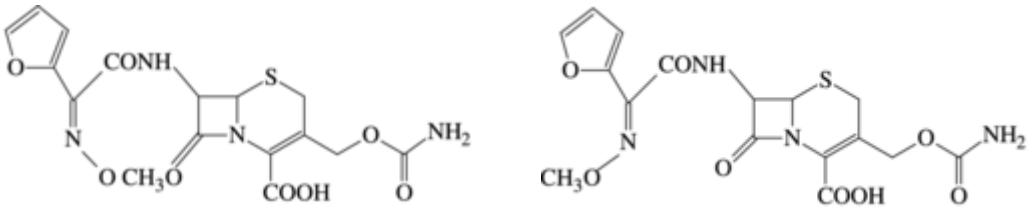
Example 4
A number of drugs contain dissymmetrically substituted carbon-carbon double bonds and therefore can exist as two distinct *E/Z* isomers.



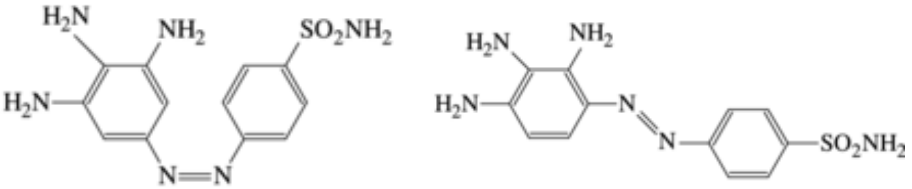
Chlorprothixene

Example 5
E/Z isomerism is also possible in double-bonded carbon-heteroatom systems such as imines (C=N) and oximes (C=N–O), and in azo (N=N) systems.

For example, several cephalosporin derivatives contain an alkoxyimino side chain that may exist in *E* or *Z* isomeric forms.

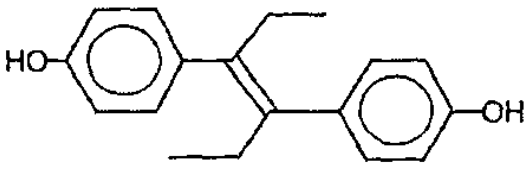


(Above) *E/Z* isomerism about C-heteroatom double bonds.
Which is *E* and which is *Z*?



(Above) The azo compound prontosil may display similar isomerism.
Which is E and which is Z?

E/Z isomers show very different pharmacological activity from each other. For instance, the *E* isomer of diethylstibesterol, a synthetic oestrogen, is only one fifteenth as active as the *Z* isomer.

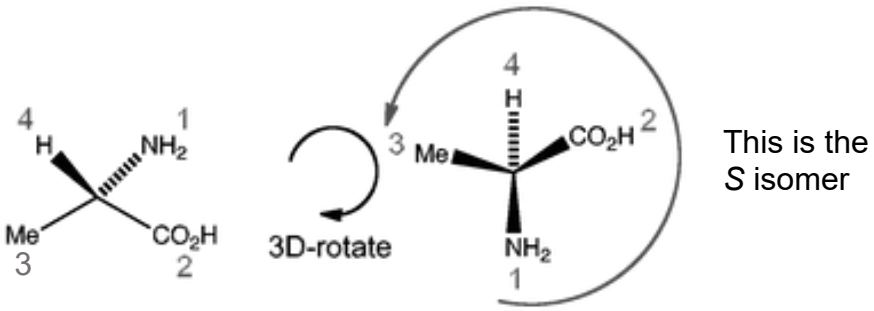


diethylstilbesterol

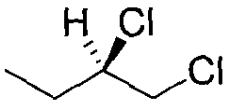
F) Designating *R/S* configurations for chiral centres

Note: There is no relationship between configuration of a molecule and the direction and extent of rotation of plane-polarised light

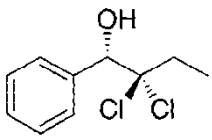
I. Assign an order of priority to each ligand on the chiral carbon by the CIP Sequence Rules.
II. Orient the drawing of the molecules so that the ligand of lowest priority faces away from the viewer.
III. Observe the order of decreasing priority of the other three ligands:
IV. **If it is clockwise, the configuration is *R* (*rectus*-right)**
If it is anticlockwise, the configuration is *S* (*sinister*-left)



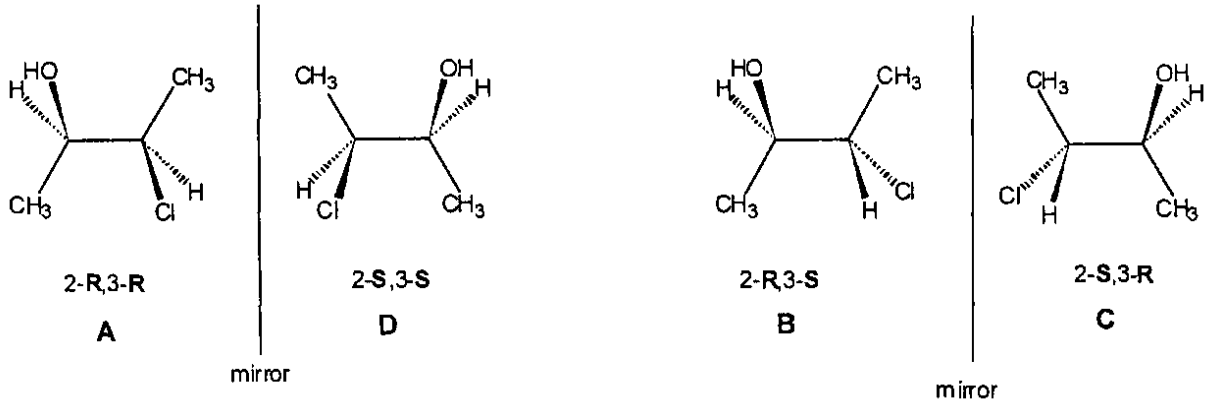
Example 1



Example 2



Example 3 (3-chlorobutan-2-ol)



a) **Verify the *R/S* configurations.**
b) **What are the stereochemical relationships?**
c) **Are you able to discern a pattern in the *R/S* designations between (i) enantiomers and between (ii) diastereomers?**

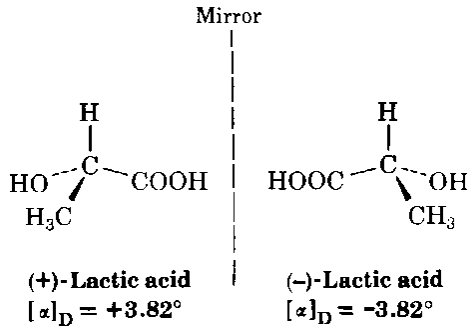
G) Enantiomers or optical isomers

Non-superimposable mirror images which exist due to the absence of an internal mirror plane of symmetry

Misconception alert!

Do not get the wrong impression from H2 chemistry – having chiral atoms does not necessarily mean that the molecule is chiral. Neither does the absence of chiral atoms guarantee non-chirality. More examples to follow.

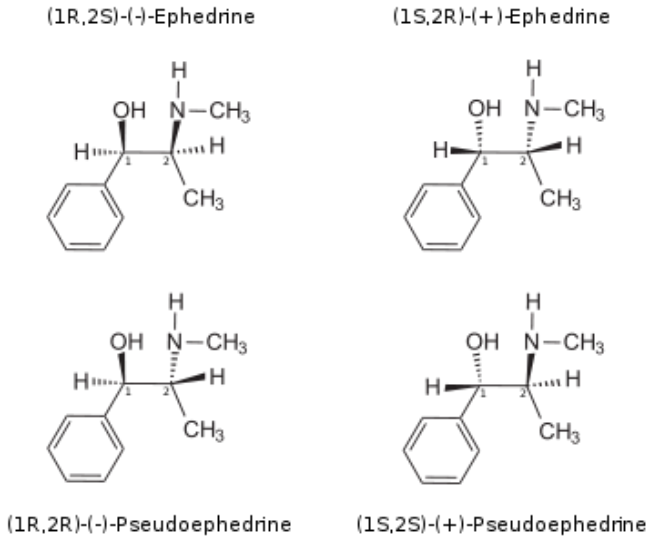
Example 1 (one chiral carbon) – enantiomers of lactic acid



Example 2

Many stereoisomeric drugs contain more than one asymmetrically substituted atom. For example, ephedrine has two chiral centres.

In this case, a greater number of configurational isomers is possible; the maximum number possible is 2^n, where n is the number of chiral atoms. Hence, the maximum number of possible configurational isomers for ephedrine is four, which we shall learn how to designate later.



The *RS* and *SR* isomers are non-superimposable mirror images and hence are enantiomers. The same relationship exists for the *RR* and *SS* isomers.

Pertinent question

What about the relationship between RS and RR / RS and SS etc?

H) Diastereomers

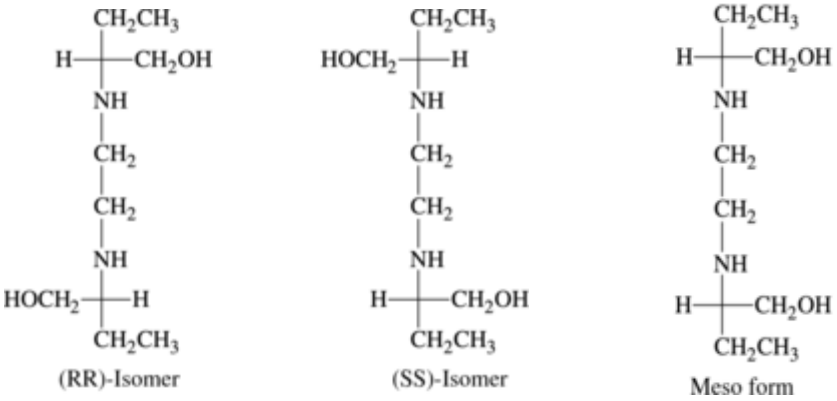
Non-superimposable non-mirror images
Similar chemical properties but different physical properties

It is important to note that the 2^n rule predicts *only* the **maximum** number of stereoisomers possible in compounds with more than one centre of chirality.

For example, some compounds with two asymmetrically substituted carbon atoms may have only three stereoisomeric forms. This occurs when three of the substituents on one asymmetric carbon are the same as those on the other asymmetric carbon, as shown for the antitubercular drug – ethambutol.

In this case, one stereoisomer has a plane of symmetry even though two asymmetric atoms are present. Such an isomer is referred to as a *meso* compound and is optically inactive.

In general, when a plane of symmetry is present in a compound with two chiral centres, three stereoisomeric forms are possible.



Ethambutol stereoisomers

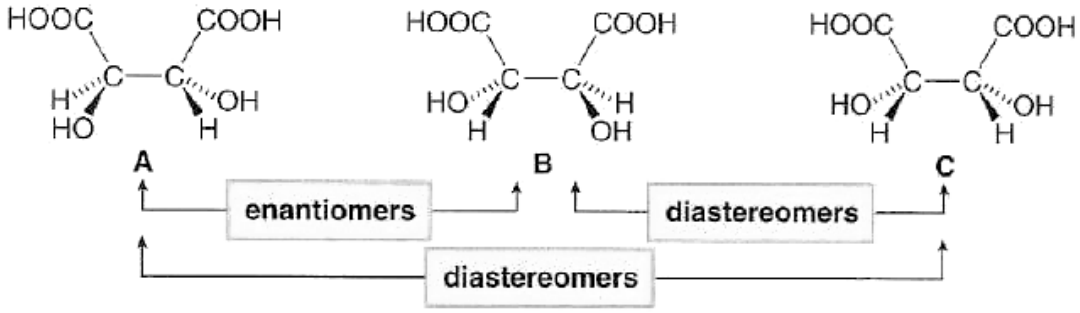
The relationship between each member of an enantiomeric pair and each member of the other enantiomeric pair is diastereomeric; they are non-superimposable non-mirror images. Thus, the *RS* isomer is a diastereomer of the *RR* and *SS* isomers, and the *SS* isomer is a diastereomer of the *RS* and *SR* isomers.

For compounds with more than two chiral centres, there may be more than one meso compound.

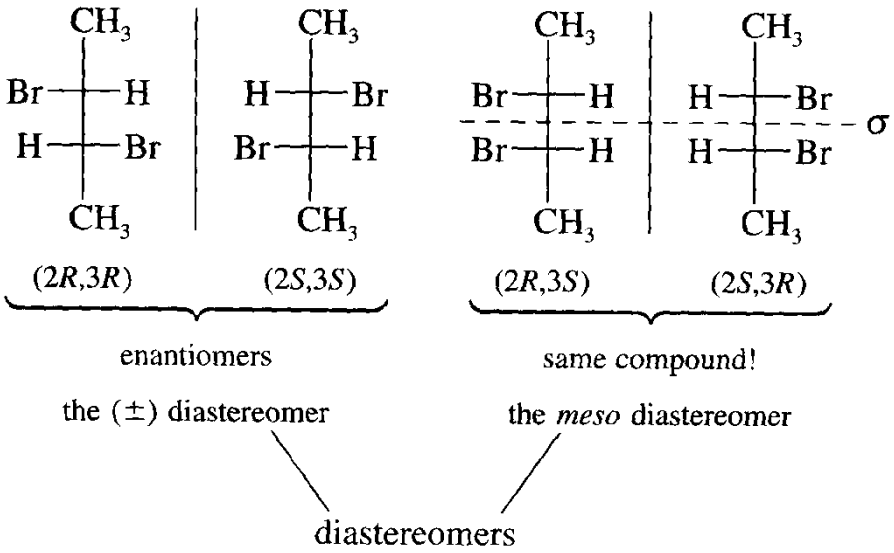
Food for thought

- Why can't meso compounds occur in molecules with only one chiral centre?

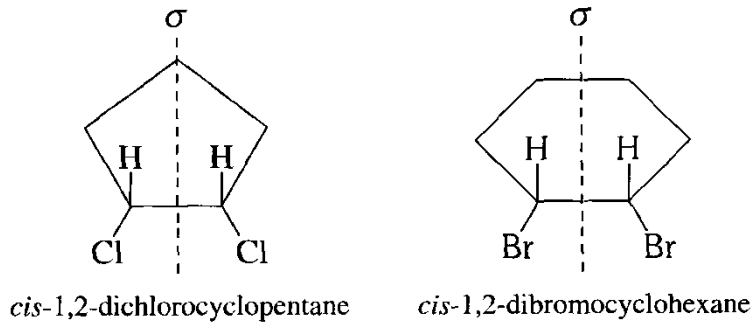
Example 1 (two chiral carbons-tartaric acid)



Example 2 (two chiral carbons)



Examples (two cyclic compounds that are meso)



cis-1,2-dichlorocyclopentane *cis*-1,2-dibromocyclohexane

Food for thought
Critically evaluate the following statement:
"Diastereomers are stereoisomers with two or more chiral centres."

I) Chirality in non-carbon compounds and those which have no chiral centres

Most optically active drugs are chiral as a result of the presence of chiral atom(s).

However, chirality can result from the presence of other asymmetrically substituted atoms within molecules as illustrated below including phosphorus (Fig. 1), nitrogen (Fig. 2), and sulfur (Fig. 3).

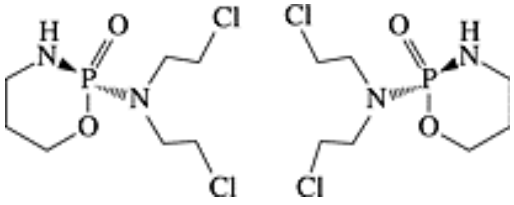


Fig. 1 Optical isomers of cyclophosphamide

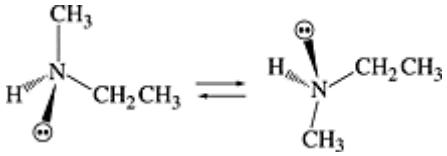


Fig. 2 Pyramidal inversion of chiral nitrogen.

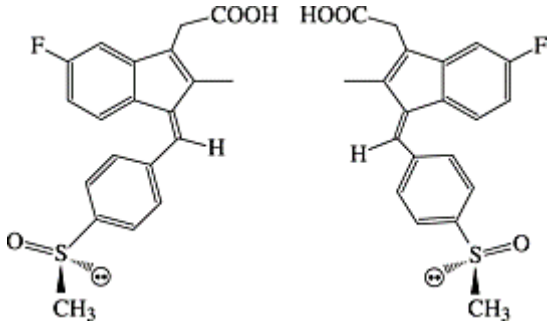
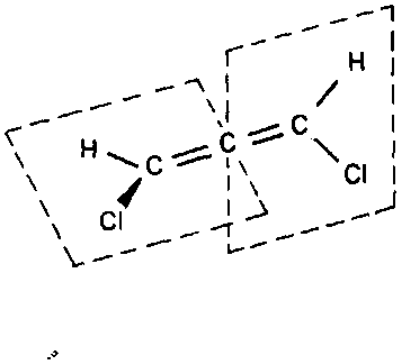


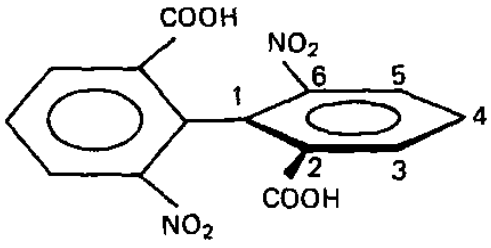
Fig. 3 The chiral sulfoxide – sulindac

Chirality can also arise without chiral centres.

Examples:



1,3-dichloropropadiene
(an allene)



6,6′-dinitrobiphenyl-2,2′-dicarboxylic acid

J) Optical activity of chiral molecules

Each enantiomer rotates the plane of polarised light to the same degree, but in opposite directions.

The enantiomer rotating the plane to right (clockwise) is designated as the dextrorotatory (D) or (+)-enantiomer. The other enantiomer rotates the plane to the left (counter clockwise) and is designated as the levorotatory (L) or (–)-enantiomer.
Note again that the D/L and +/– designations are determined experimentally and have no links to the R/S designations.

- The optical activity of a given enantiomer is expressed in terms of its **specific rotation.**
- The specific rotation, [α], of an enantiomer at a given temperature (usually 25°C) and specified wavelength of light (usually that of the sodium D-line, 598 nm) is constant, and is given by

$$[\alpha]_{D}^{25} = \frac{\alpha}{c\ell}$$

- where
  - α is the observed rotation in degrees (negative if the rotation is levorotatory and positive if it is dextrorotatory)
  - *c* is the concentration of the solution in g cm^{-3} or density of the pure liquid in g cm^{-3}
  - *l* is the length of the sample the light passes through, in dm.
- Units are, strictly speaking, deg cm^2 g^{-1}, but usually [α] is given simply in degrees
- A mixture of equimolar amounts of (*R*)- and (*S*)-enantiomers is known as a **racemic mixture** (or a **racemate). A racemic mixture is optically inactive, i.e. [α] = 0°.**
- A racemic mixture is indicated by the prefix (±), *e.g.* a racemic mixture of (*R*)-(–)-2-butanol and *S*-(+)-2-butanol is indicated as (±)-2-butanol.

Optical Purity

$$\text{optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{pure\ material}} \times 100\%$$

- Describes the excess of one enantiomer in a solution containing two enantiomers in unequal amount – also known as enantiomeric excess (e.e.).
- It can be calculated by subtracting the percentage of minor enantiomer from the major enantiomer.
  100:0 ratio of (*R*):(*S*) isomer ⟹ (R) optically pure
  60:40 ratio of (*R*):(*S*) isomer ⟹ (R) 20% optical purity

Example 1: What is the optical rotation of a sample of (+)-2-bromobutane that is 75% optically pure? What percentage of (+) and (–) enantiomers are present in this sample? ($[\alpha]^{25}$ = +23.1°)

$$\text{optical purity} = \text{e.e.} = \frac{[\alpha]_{obs}}{[\alpha]_{pure\ material}} \times 100\% = 75\%$$

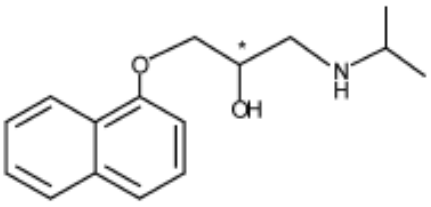
$$[\alpha]_{obs} = 75\% \times +23.1^{\circ} = \underline{+17.3^{\circ}}$$

75% e.e. ⟹ 87.5% (+)-2-bromobutane and 12.5% (–)-2-bromobutane

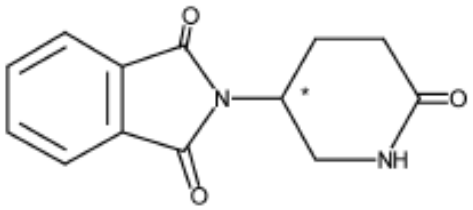
Stereochemical Purity

- Usually only one isomer is pharmacologically active. The other stereoisomers represent a waste of valuable chemicals that may have been the product of a long and expensive synthesis.
- Other isomers could have a deleterious, or even lethal, side effect on the metabolism of the patient.
- Hence it is paramount to try to ensure optical purity in the final product.

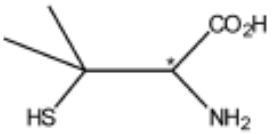
Some examples of pharmaceuticals whose enantiomers have different physiological effects are as follows:



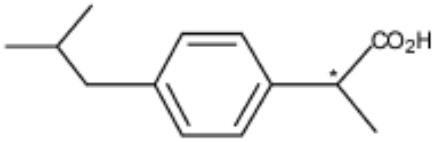
propranolol
R is a beta-blocker for the heart
S is a contraceptive



thalidomide
R is mutagenic
S is anti-emetic

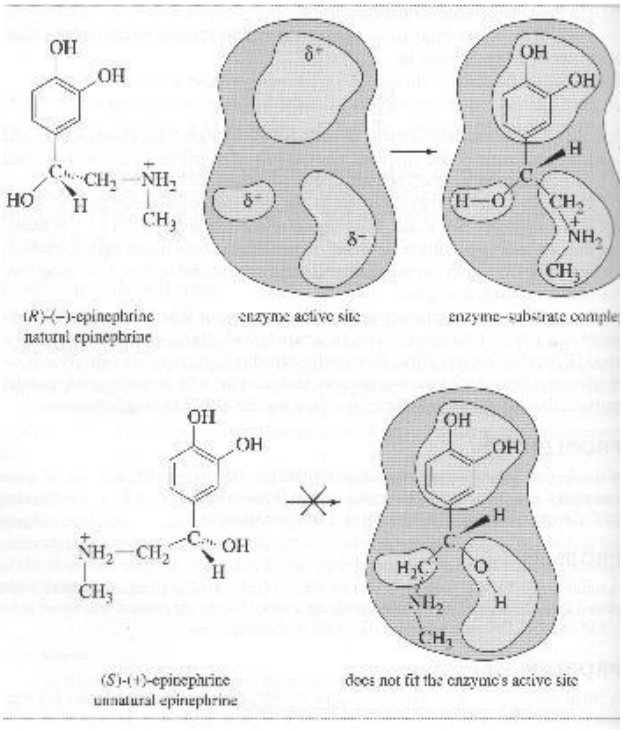


penicillamine
R is anti-arthritic
S is highly toxic



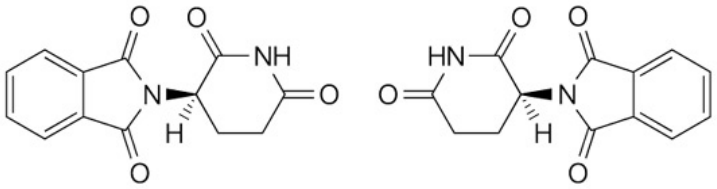
ibuprofen
R is anti-inflammatory
S is inactive

For example, the L-form of epinephrine is one of the natural hormones secreted by the glands. Synthetic epinephrine of the D-form has no stimulating effect and is also mildly toxic.



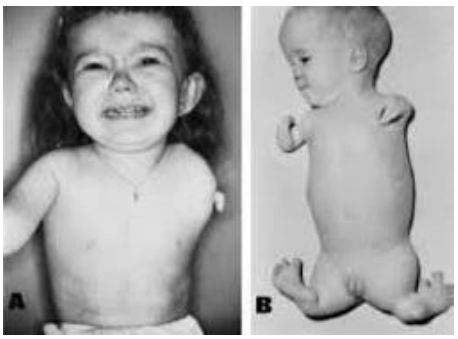
A case study in the importance of stereochemical purity in drugs

The thalidomide disaster is one of the darkest episodes in pharmaceutical research history.



***R*-(+)-Thalidomide** **S-(–)-Thalidomide**

The drug was marketed in Germany in 1957 as a mild sleeping pill safe even for pregnant women. Tragically, thalidomide was found to have serious side-effects; thousands of babies were born with missing or abnormal arms, hands, legs, or feet.



More photos of malformations caused by thalidomide are available at http://www.chm.bris.ac.uk/motm/thalidomide/first.html
Warning: Not for the faint of heart!

It was banned by many countries in 1961.

The action of drugs is usually explained using the receptor theory. Receptors are protein molecules in our body. Because protein molecules are chiral, they have different reaction with the two enantiomers of a chiral drug.

Sadly, in the 1950s, pharmacists and doctors did not know that the (+)(*R*)-thalidomide is an effective sedative, whereas the (–)(*S*)-thalidomide is a teratogen (a substance affecting the development of the foetus and causing structural or functional disability).

Therefore, the enantiomeric composition of a chiral drug is a critically important issue in drug development. The thalidomide tragedy forced drug companies to reconsider enantiomers as separate molecules rather than just different forms of the same drug.

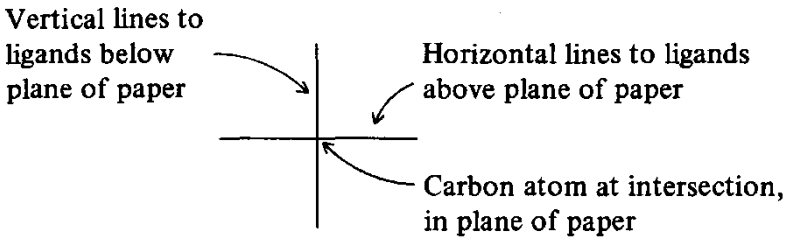
Not all drug molecules are chiral. Chiral drugs that are produced by chemical synthesis are usually a racemic mixture. Currently, regulatory guidelines do not prohibit the development of racemates of chiral drugs. However, drug companies should investigate the properties of each enantiomer of a new chiral drug before they introduce it to the market.

K) Fischer projection (non-examinable additional reading)

Named after Emil Fischer, the pioneer of carbohydrate chemistry, this type of projections are indispensable in carbohydrate chemistry.

A two-dimensional representation that shows the configuration of a tetrahedral stereocentre without using wedge and dashes.

- The carbon atoms in a sugar are arranged vertically with carbon 1 (the carbonyl carbon) at the top.
- Horizontal lines represent bonds projecting forward (wedges).
- Vertical lines represent bonds projecting to the rear (dashes).
- The first and last carbons in the chain are written with a "C"; others are indicated by the crossing of bonds.



To designate R/S configurations on Fischer projections, the structure has to be mentally manipulated such that the ligand of lowest priority is at the top or bottom of the projection.

The following operations result in an alternative projection of the *same* molecule:

1. Rotation of the whole molecule through 180°.
2. Rotation of any three ligands by one or two places clockwise or anti-clockwise, whilst the fourth ligand remains in the same position (Fig. 2.1).

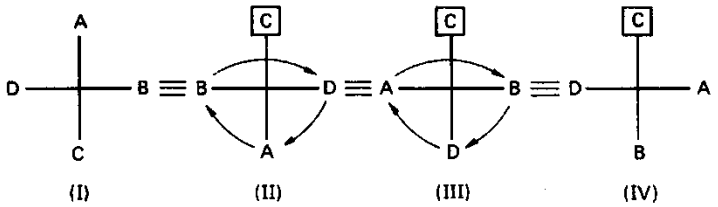


Fig. 2.1 Manipulation of Fischer projection formulae. I–IV are different projections of the same molecule

The following operations lead to mirror image projections;

1. Rotation of the whole formula through 90°;
2. Interchange of any two ligands (Fig. 2.2).

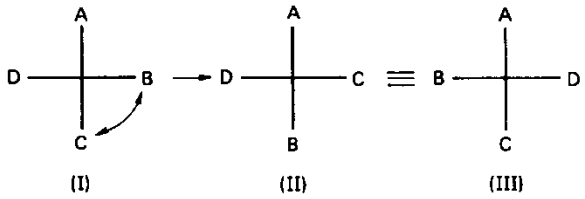
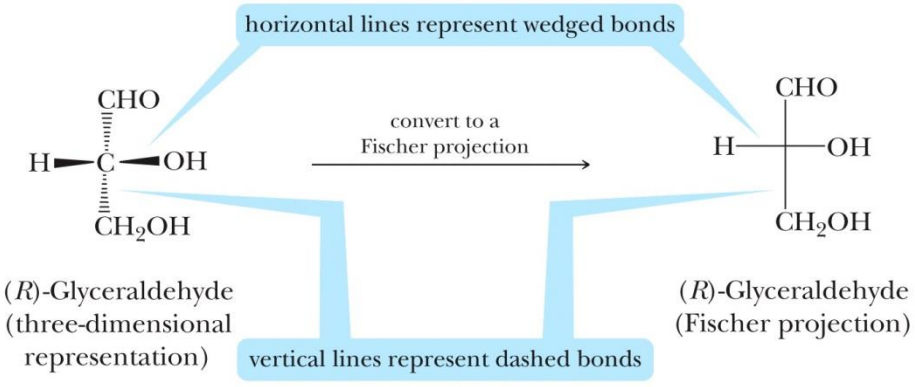
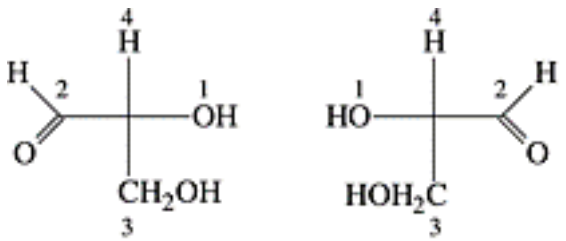


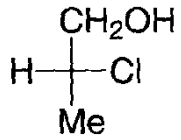
Fig. 2.2 Interconversion of Fischer projection formulae. Projections I and III are mirror images and represent an enantiomeric pair of molecules





S-Glyceraldehyde *R*-Glyceraldehyde

Example 1



(*R*)-2-chloropropan-1-ol

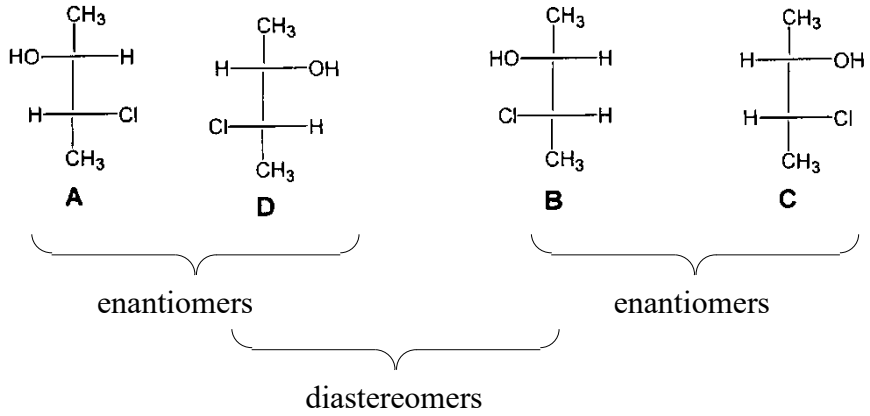
---

http://orgchem.chem.uconn.edu/courses/243f97-rs-practice.html more exercises on R/S designations.

http://www.bluffton.edu/~bergerd/models/homez.html#index models for you to manipulate in three dimensions!

http://orgchem.chem.uconn.edu/courses/243f97-rs-practice.html more exercises on interpreting Fischer projections.

Example 2

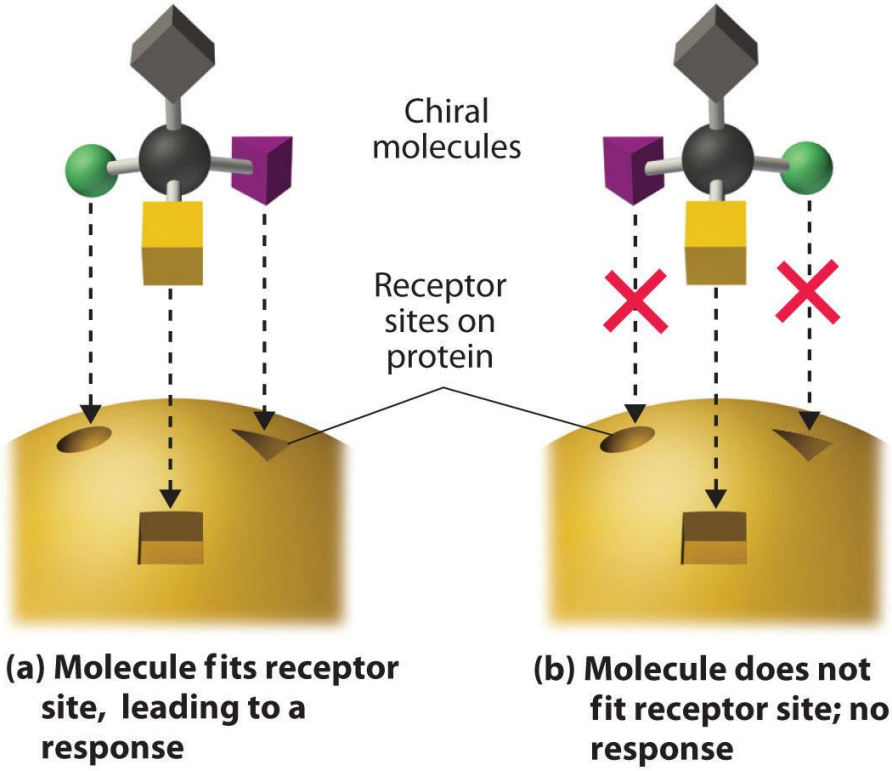


Note: Fischer projections can be converted into Newman projections by viewing along the central C–C bond, either from top or bottom.

L) Separating enantiomers (non-examinable additional reading)

Most optically active molecules are found as only one enantiomer in living organisms e.g. pure (+)-tartaric acid can be isolated from the precipitate formed by yeast during the fermentation of wine.

Nature designs enzymes and receptor sites in such a way that they selectively make one stereoisomer over the other. They are chiral and are capable of distinguishing between different stereoisomers. Usually, only one isomer fits properly into the active site of an enzyme.



Without the help of enzymes, we always obtain the racemic mixture of enantiomers when synthesising a chiral compound from non-chiral starting materials.

How then can we ensure that our target compound, if chiral, is just the one enantiomer that we want?

Generally, optical isomers or enantiomers have identical physical and chemical properties. This makes it extremely difficult to separate them.

The separation of one or both pure enantiomers from a racemic modification is called **resolution**.

One major difference between enantiomers is their interactions with other chiral substances. For example, enantiomers may have different solubility in chiral solvents, they may react at different rates in the presence of an optically active reagent or enzyme, and many have different affinities for chiral surfaces and receptors.

There are two main methods for resolving a mixture of enantiomers.

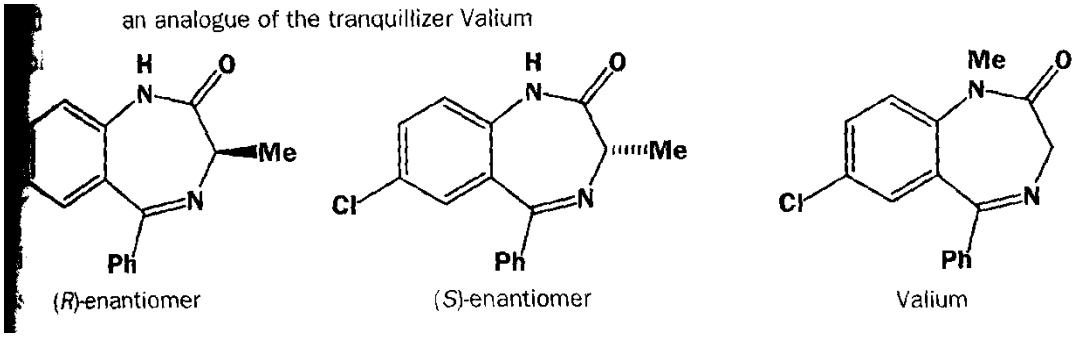
The **first method** involves passing the racemate through a column of a chiral solid support (chiral stationary phase (CSP).

The process is called **enantioselective chromatography**, and works because the column will preferentially absorb one of the isomers, letting the other through at a quicker rate. They can thus be separated, and both can be recovered in good yield.

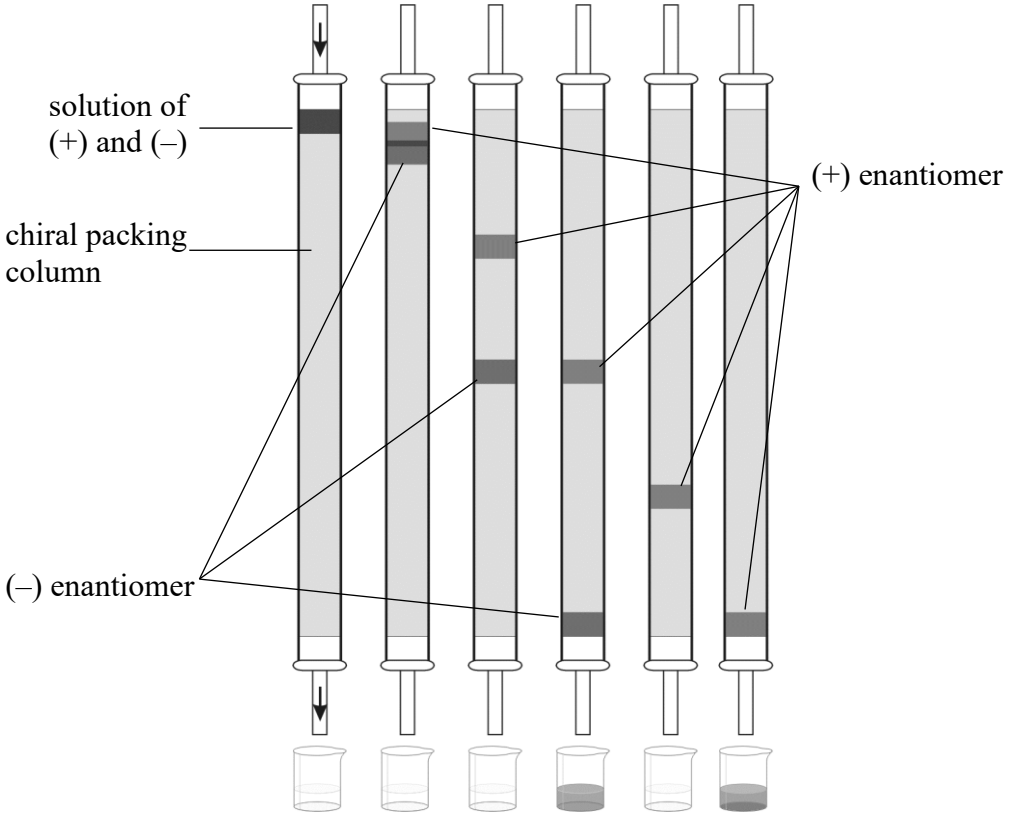
Chromatographic separation relies on a difference in affinity between a stationary phase (often silica) and a mobile phase (the solvent travelling through the stationary phase, known as the eluent) mediated by, for example, hydrogen bonds or Van der Waals' interactions.

Chromatography on a chiral stationary phase is especially important when the compounds being resolved have no functional groups suitable for making the derivatives (usually esters or salts) needed for the more classical resolution.

Example:
The enantiomers of an analogue of the tranquilliser Valium were found to have quite different biological activities.



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.

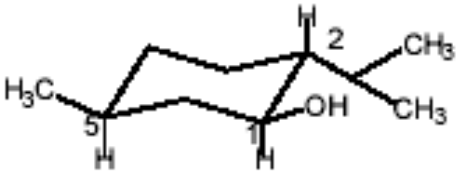


The **second method** is to use an optically active compound to form an adduct with the racemic mixture, and rely on the different physical properties of the two adducts, which are no longer enantiomers, but diastereomers, to allow a physical separation to be done.

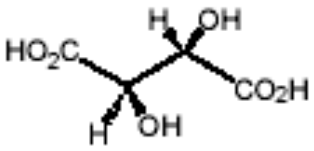
Example: if the racemic mixture is a carboxylic acid, forming a salt with an optically active natural base, such as strychnine, it will produce the following:

R-acid + S-acid + 2 R-base → (R-acid-R-base) + (S-acid-R-base)
enantiomers diastereomers

The diastereomers will often have different solubility, and so can be separated by fractional crystallisation. The free carboxylic acids can then be liberated from the salts by reaction with dilute HC*l* (aq). Other adducts that have been used include carboxylic esters with an optically active alcohol such as menthol, or, if it is the alcohol that required resolution, with an optically active acid such as tartaric acid.

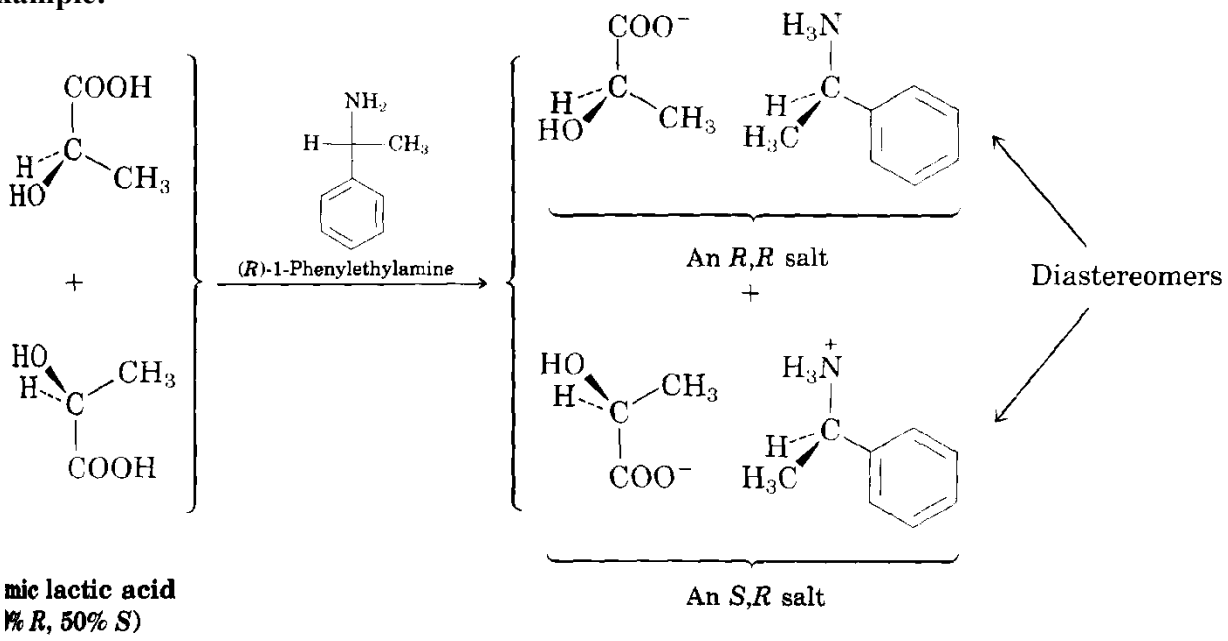


1-(S)-menthol
(-)-menthol

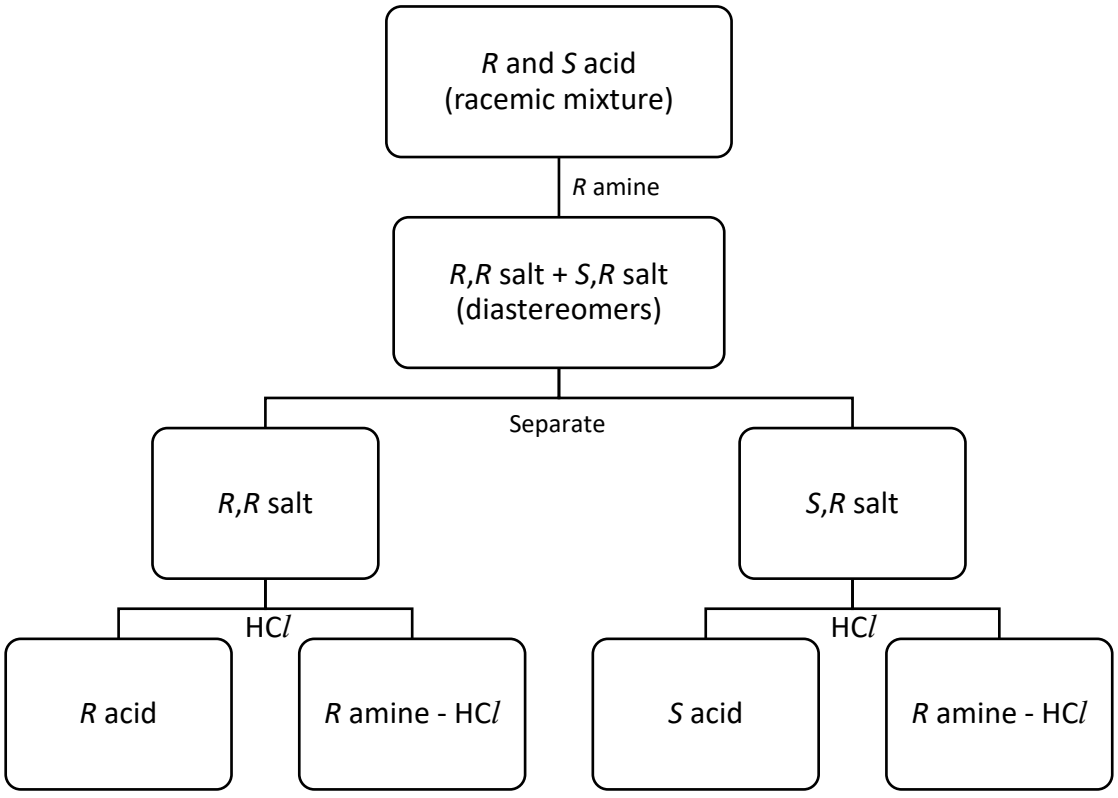


(R,R)-tartaric acid
(+)-tartaric acid

Example:



mic lactic acid
% *R*, 50% *S*)



M) Stereoisomerism of Transition Element Complexes

* Cis-Trans Isomerism

- Cis-trans isomerism occur in TE complexes when atoms or groups of atoms are arranged differently in space relative to the central metal atom (or ion).
    - Cis isomer – pair of identical ligands are adjacent to each other
    - Trans isomer – pair of identical ligands are opposite to each other

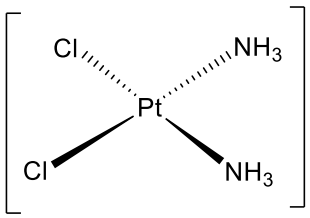
- Cis-trans isomers have distinct physical properties

- Possible for complexes with coordination number ≥ 4
- **Square planar** (not tetrahedral) and **octahedral** complexes

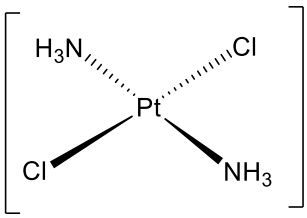
Examples:

Square planar complex, e.g. $[Pt(NH_3)_2Cl_2]$

- Cis-$[Pt(NH_3)_2Cl_2]$ (also known as cisplatin) is an anti-tumour agent discovered in the 1960s by Rosenberg. It is predicted that cisplatin works by lying within the cancer cell's DNA double helix, such that each DNA strand substitutes the Cl- ligand. By binding strongly to the Pt(II) ion, DNA replication is prevented.
- Trans-$[Pt(NH_3)_2Cl_2]$ does not have anti-tumour effect.

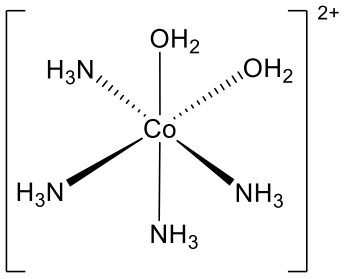


cis

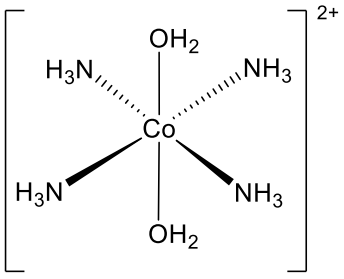


trans

Octahedral complex, e.g. $[Co(NH_3)_4(H_2O)_2]^{2+}$



cis



trans

*** Enantiomerism**

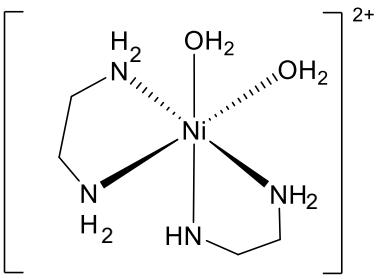
- Enantiomers occur when a molecule has no internal plane of symmetry
    - Enantiomers cannot be superimposed on its mirror image.

- Enantiomers are identical in all physical properties except the direction in which they rotate the plane of polarised light.

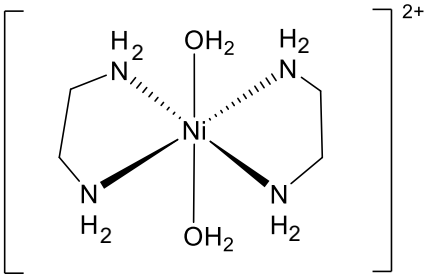
- Observed in **octahedral complexes** which involve **at least 2 bidentate ligands**

Examples:

Octahedral complex with 2 bidentate ligands
e.g. $[Ni(H_2NCH_2CH_2NH_2)_2(H_2O)_2]^{2+}$
only the cis isomer shows enantiomerism

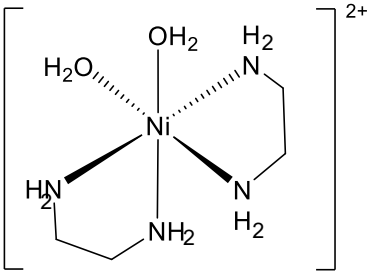


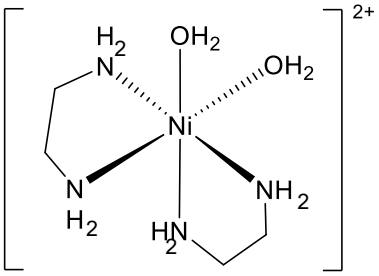
cis



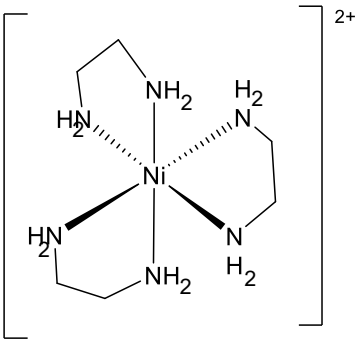
trans

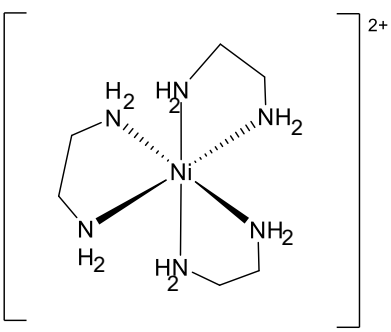
Enantiomers of the cis isomers





Octahedral complex with 3 bidentate ligands
e.g. $[Ni(H_2NCH_2CH_2NH_2)_3]^{2+}$





N) Overview of the types of isomerism

Tree of Isomers

(*adapted from http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch07/ch7-1.html)*

Isomers
Compounds with the same molecular formulae but are structurally different in some way.

Do the compounds have the same connectivity?

No →

Constitutional isomers
Isomers that differ in the order in which the atoms are connected
- Chain isomerism
- Positional isomerism
- Functional group isomerism

Yes →

Stereoisomers
Isomers with the same functional groups and connectivity but differ only in the arrangement of atoms and bonds in space.

Can the compounds be interconverted by rotation about single bonds?

Yes →

Conformational isomers
(***or conformers/rotational isomers/rotamers***)
Stereoisomers produced by the rotation about σ bond, and are often rapidly interconverting at room temperature

No →

Configurational isomers
Stereoisomers that do not readily interconvert at room temperature and can (in principle at least) be separated. Interconversion requires bond breaking and forming

Do the compounds exist as mirror images?

Yes →

Enantiomers
(**Optical** isomers – R/S configuration)
- Enantiomers are **CHIRAL** and do not possess an element of symmetry. They exist as a pair of non-superimposable mirror images.
- Enantiomers have the same chemical and physical properties (melting and boiling points, heat of combustion, etc.), ***except*** for their interaction with plane polarised light or with other chiral molecules (reagents, solvents, catalysts, etc.) and bonds in space.

No →

Diastereomers
Stereoisomers that are not enantiomers.
Diastereomers have similar, but not identical chemical properties, such as melting and boiling point, solubility, etc.
- **Stereoisomers with 2 chiral centres** where one is the same configuration but differ at the other. (i.e. not mirror images, ***see below***)
- **Meso compounds** contain chiral centres but are optically inactive due to the presence of an internal plane of symmetry

cis-trans isomers (*E*, *Z* configuration)
Configurational isomers that differ in the spatial position around a bond with restricted rotation (e.g. a double bond or ring)
cis-trans isomerism is a type of diastereomerism

- A **racemic mixture** is a 50:50 mixture of a pair of enantiomers that is optically inactive since the rotation produced by each of the enantiomers will cancel out.
- **Stereoisomer with two chiral centres**