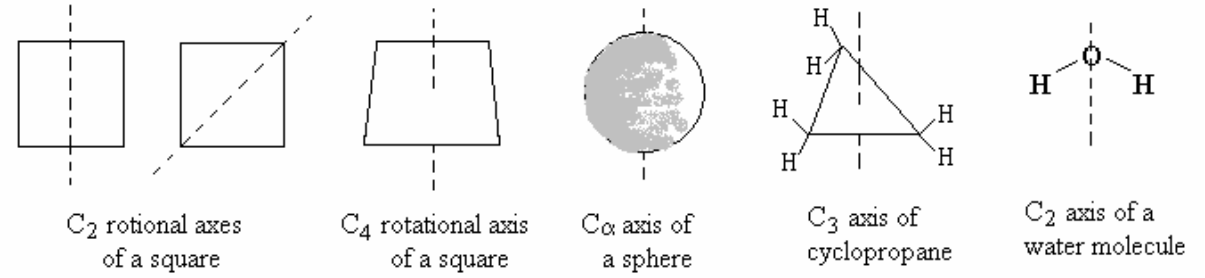
Stereochemical properties depend on the '*symmetry*' of the **shape of a molecule**, so it is useful to understand the mathematical description of **symmetry**.

Symmetry operations: The mathematical classification of symmetry properties is based on symmetry operations. *"Symmetry operations" means those transformations or movements of an object, after which the object is indistinguishable from the original*; comparison of the object before and after performing a symmetry operation provides no way of determining whether such an operation has been performed or not. A few examples are (1) rotating a square by 90°, (2) rotating a line segment through 180° and (3) looking at the reflection of a square in a mirror placed along a diagonal. *The combination of any operations leaving the object unchanged is called an* ***identity operation***.

Elements of symmetry: *The geometrical elements in relation to which symmetry operations are performed are called elements of symmetry*. There are mainly four elements of symmetry, namely (1) **axis of symmetry**, (2) **plane of symmetry**, (3) **improper axis of symmetry** and (4) **centre of symmetry**.

Axis of symmetry, C_n: *If an object* (in our discussions, the object is a molecule) *looks identical to the original after rotating around an imaginary axis through (360/n)° , it is said to have an* ***n-fold*** *axis of symmetry,* C_n. For example:

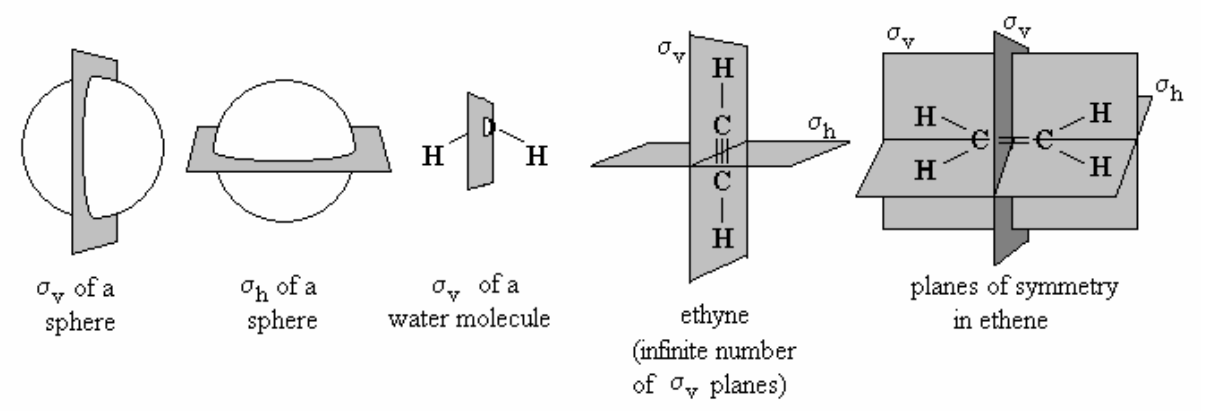


C_2 rotional axes of a square | C_4 rotational axis of a square | C_∞ axis of a sphere | C_3 axis of cyclopropane | C_2 axis of a water molecule

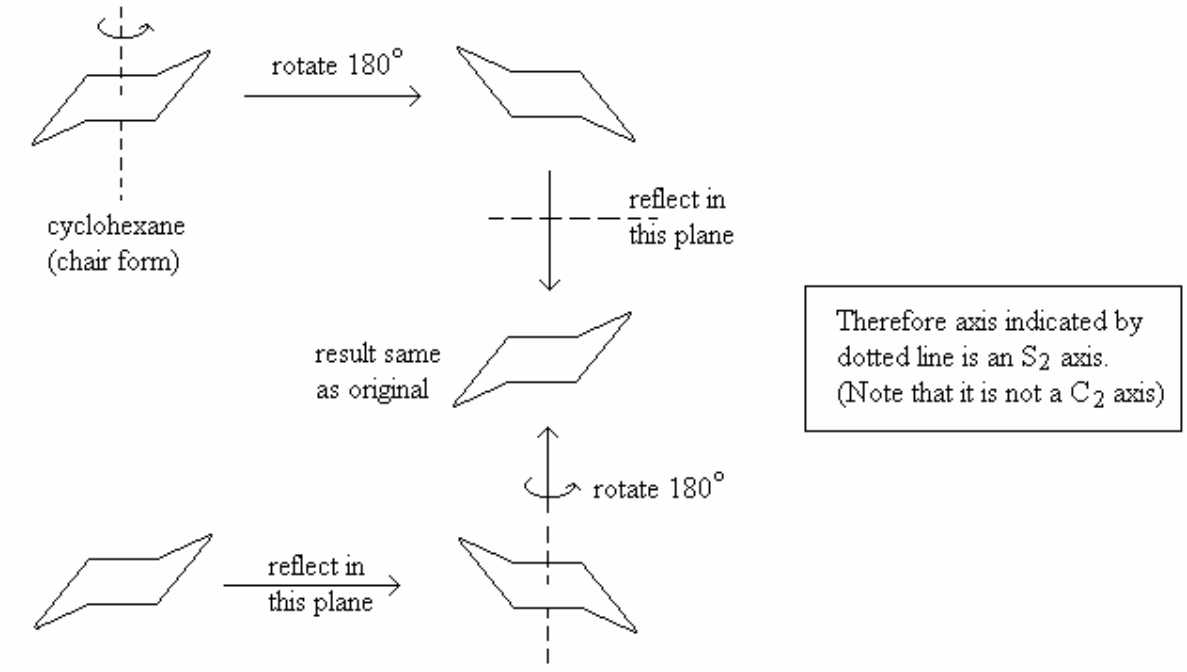
The square has four C_2 axes and one C_4 axis of symmetry. The sphere has an infinite number of C_∞ axes. An equilateral triangle (or a cyclopropane molecule) has a C_3 axis and three C_2 axes perpendicular to it. The water molecule has a C_2 axis. (Note: *All objects, symmetric or not, has a* C_1 *axis of symmetry*).

The rotational axis of symmetry having the highest order (highest value of n) is called the ***principal axis***. By convention, the object or molecule is viewed with the principal axis held vertically.

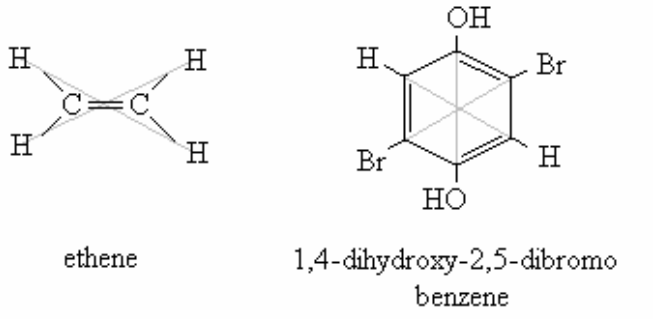
Plane of symmetry, σ: *If the molecule possesses an imaginary plane such that reflection of the molecule in a double-sided mirror placed along this plane produces a configuration indistinguishable from the original, it is said to have a plane of symmetry,* **σ**. *The vertical plane of symmetry containing the principal axis is designated as* σ_v*, and the horizontal planes of symmetry (perpendicular to the principal axis) are designated as* σ_h.



Improper axis of symmetry, S_n (rotation – reflection): *If a rotation followed by reflection in a plane makes an identity operation, then the molecule is said to have an improper axis of symmetry* S_n, where 'n' is the order of the rotational axis. It can be shown that in such cases the order in which the operations are performed (rotation after reflection or reflection after rotation) does not matter. ie. $S_n = C_n \times \sigma_h = \sigma_h \times C_n$. Cyclohexane illustrates this point.



Centre of symmetry: In some molecules, there may be *a point such that when a line drawn from an atom or group through this point is extended, it meets a similar atom or group on the other side at the same distance.* In other words, if the origin is placed at this point, for every atom or group with coordinates (x, y, z) there is a similar atom or group at (-x, -y, -z). Such a point is called centre of symmetry. *Reflection*

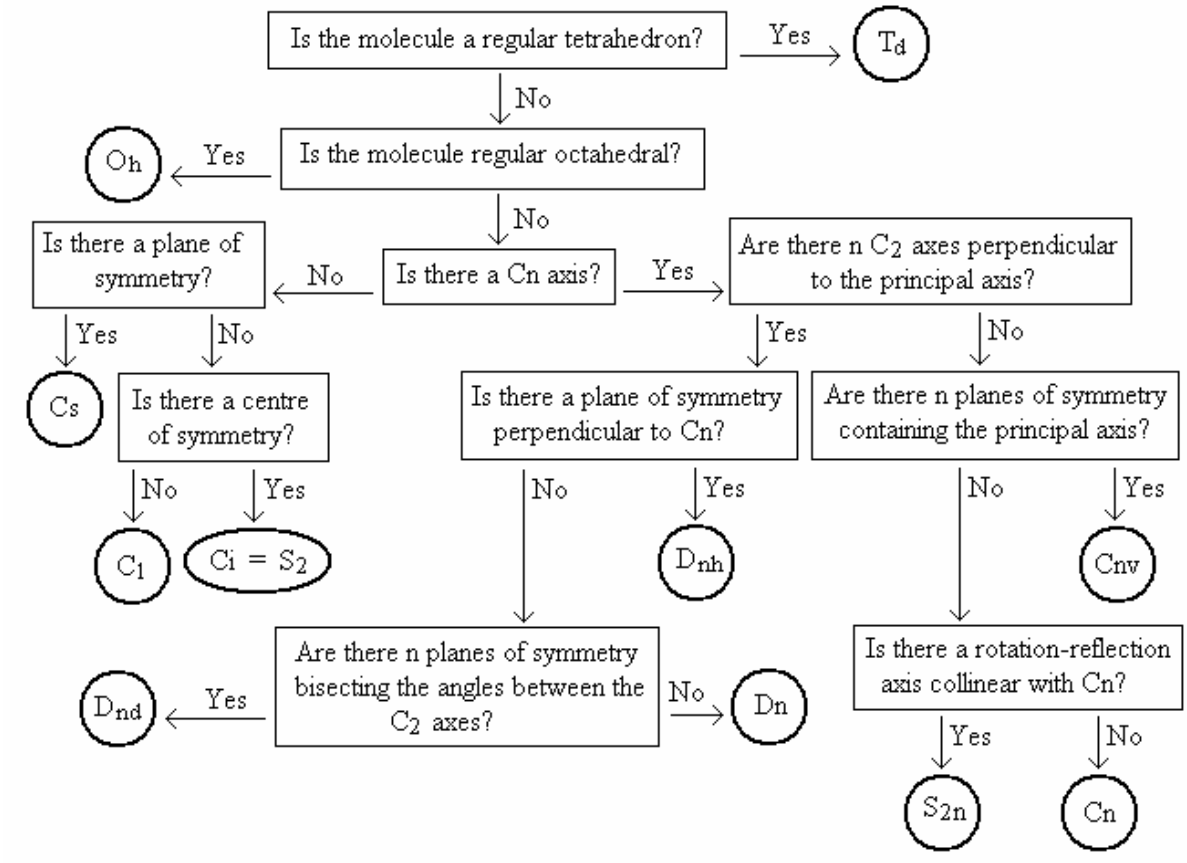


of all atoms through that point gives a molecule identical to the original. This operation is called ***inversion***, represented by 'i'. **The presence of a centre of symmetry is identical to the presence of an S_2 axis**. (Verify using cyclohexane given in the previous page).

Point groups: Analysis of symmetry elements have shown that the presence of some symmetry elements necessarily implies the presence of other symmetry elements. For example, $i \equiv S_2$, $S_3 \equiv C_3 \times \sigma_h$, $C_2 \equiv \sigma_h \times \sigma_v$. Mathematicians have been able to deduce what combinations of symmetry operations are possible, and which operations are consequences of other symmetry operations. *All molecules having the same symmetry elements constitute a group called the* ***symmetry point group***.

Molecules belonging to the same point group need not all have the same appearance. For example, the water molecule belongs to the point group C_{2v}. C_2 tells us that the highest order axis is C_2 and 'v' tells us that the planes of symmetry also contain the axis of highest symmetry. CH_2Cl_2 also belongs to the same point group C_{2v}. A regular tetrahedral molecule such as CH_4 or CCl_4 belongs to the T_d point group. These have four C_3 axes, three C_2 axes and six σ planes. But this point group can normally be assigned by simple inspection of the molecule. A regular octahedral molecule such as SF_6 belongs to the O_h point group. It contains three C_4 axes, four C_3 axes, six C_2 axes and nine σ planes! The highest symmetry point group is K_h, which applies to objects containing all symmetry elements. Only a sphere possesses such a high symmetry and it is not found in molecules. Only atoms belong to this group.

The simplest way to determine the point group of a molecule is to work logically through a set of questions concerning the number and type of symmetry elements contained in it. The flow chart is given below:



Chirality: A molecule is "chiral" when its mirror image is not superimposable on it. Thus a chiral molecule should not have any plane of symmetry. Therefore, inspection of the point groups show that only C_1, C_n and D_n groups can have chiral molecules (all having no planes of symmetry). Molecules with plane of symmetry are called "achiral". ["Chiral" in Greek means "hand"].

Asymmetry: Chiral molecules having no symmetry elements whatsoever are called "asymmetric". Thus only molecules belonging to the C1 point group are asymmetric. Eg., CHClFBr.

Dissymmetry: Chiral molecules which contain at least one symmetry element (an axis of symmetry) are called dissymmetric. Thus molecules belonging to C_n and D_n point groups are dissymmetric.

Chiral (no reflection symmetry)

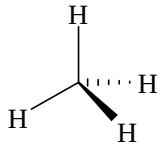
Asymmetric (no symmetry elements) **Dissymmetric** (having axis of symmetry)

Enantiomers: The two mirror images of a chiral molecule are called "enantiomers". Whether a molecule is capable of enantiomerism can be checked in two ways, (1) by constructing molecular models of the mirror images and checking whether they are superimposable or not (2) by looking for symmetry properties in the molecule and determining its point group.

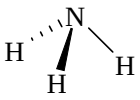
Flying wedge, sawhorse, Newman and Fischer projections of molecular architecture.

In the study of stereochemistry, it is necessary to understand the orientation of atoms and groups in a molecule in 3-dimensional space. This causes difficulties when the molecule is to be drawn on the 2-dimensional plane of paper. Therefore various methods of "projecting" a 3-dimensional molecule on a 2-dimensional plane surface have been developed to visualize the spatial distribution of atoms or groups without the use of actual molecular models.

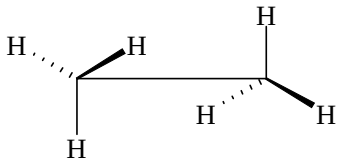
Flying wedge representation: In this representation, a molecular model is viewed from a convenient angle so that all atoms and groups being examined can be seen. Atoms or groups that appear in a vertical plane are drawn on the paper with normal lines indicating bonds between atoms. Bonds with atoms projecting towards the observer are indicated using a thick wedge with the flat or thick end pointing towards the observer. Bonds pointing away from the observer, which are behind the plane of the paper, are indicated by dotted lines (or sometimes outline wedges or hatched wedges with the pointed end further behind the observer). This gives a 3-dimensional appearance to the picture. Examples:



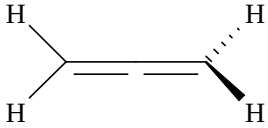
methane



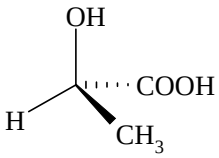
ammonia



ethane



allene



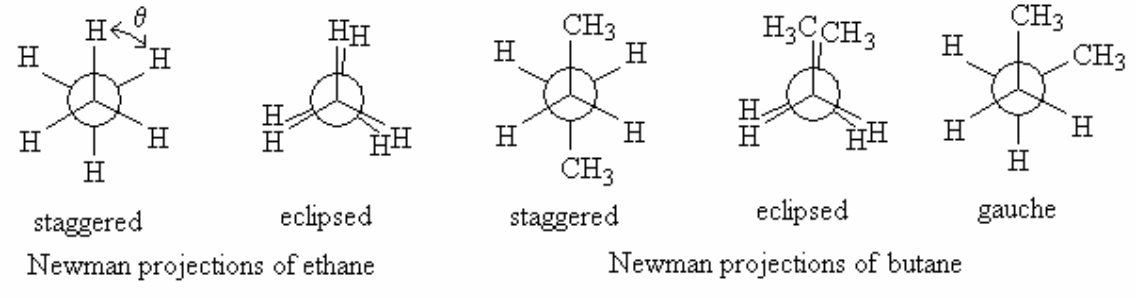
lactic acid

The carbon atoms from which the bonds are shown are not usually indicated for clarity (it is the stereochemistry around this C atom which is being studied). But hetero atoms like N, P, O etc. must be explicitly shown.

Sawhorse representation: This is a model of limited application in **conformational analysis** (*study of different orientations arising by free rotation on a single bond*). The bond under consideration is held at an angle pointing away from the observer such that the atoms in front as well as those behind can be seen. The remaining three bonds on each of the two carbon atoms are indicated by lines 120° apart in the form of a sawhorse.

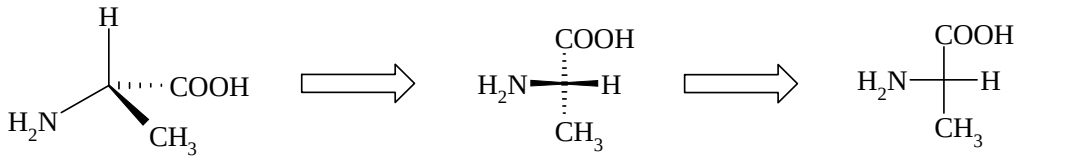
Sawhorse representation of two
different conformations of ethane

Newman projection: This is an extremely useful representation for conformational analysis. It shows the geometry of a molecule when looking along a particular C-C bond. The C atom near the observer is shown as a point and the three atoms or groups attached to it are joined by solid lines meeting at that point. The configuration about this forward atom is fixed, and defined by the clockwise or anticlockwise disposition of the groups according to sequence rules. The atom immediately behind the near atom is represented by a circle centered on the internuclear axis. The atoms or groups connected to it are attached to the circle. The angle marked as θ is called the **dihedral angle**. Varying the dihedral angle by rotating the rear atom on the bond changes the molecular geometry.



Newman projections of ethane Newman projections of butane

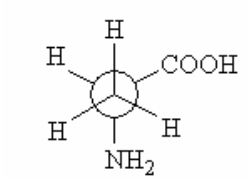
Fischer projection: This is of great help in understanding the absolute configuration around an asymmetric carbon atom when drawn on the plane of paper by following certain rules. It is used mostly in the study of the structure of sugars. In Fischer projection, one observes the asymmetric carbon atom in such a way as to see the *longest carbon chain vertically and bending backward, with the most oxygenated carbon atom placed at the top*. The four atoms or groups on the asymmetric carbon atom are placed at right angles in the form of a cross. By agreement, the groups above and below are considered to lie below the plane of the paper. The groups placed horizontally on the left and right lie above the plane pointing towards the observer. For example, the steps in the conversion of the flying wedge representation of (+)alanine to its equivalent Fischer projection and Newman projection is indicated below.



(+) alanine

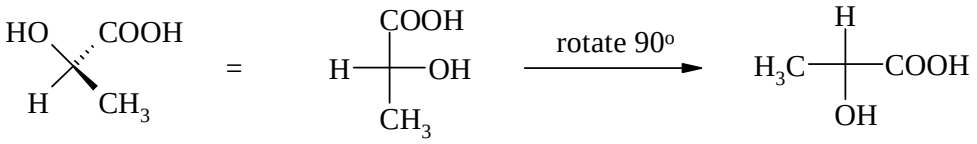
Fischer projection of (+) alanine

look along the CH_3-C bond

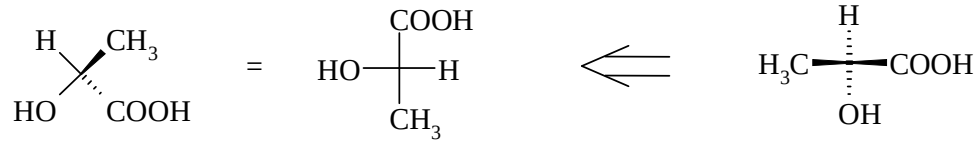


Newman projection of (+) alanine

The Fischer projection is very useful when more than one asymmetric carbon atoms are present in the molecule, eg., sugars. It should be noted that rotation of the Fischer projection by 90° on the plane of the paper changes the configuration to the mirror image.



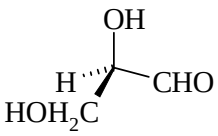
lactic acid



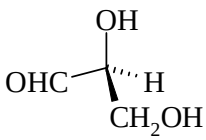
mirror image

Configuration = spatial arrangements that are independent of the rotational motion of the molecule. Mirror images cannot be interconverted by rotation about a single bond (conformation).

Absolute and relative configurations: We know that there are two enantiomers of glyceraldehyde, A and B shown below: One of them rotates the plane of polarized light to the left and the other to the right. But which is which?

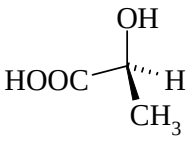


A

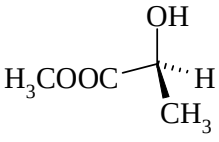


B

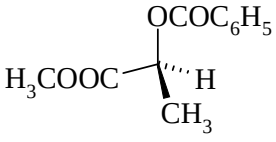
Relating the rotation to the correct structure gives the **absolute configuration** of the isomers. One may at first have the impression that if the correct configuration and sign of rotation are identified for one compound, it will hold true for all related compounds. But actually no such relation exists, as illustrated by the following compounds with structures related to lactic acid.



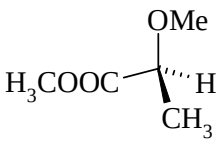
+3.8°



-8.6°



+40.3°

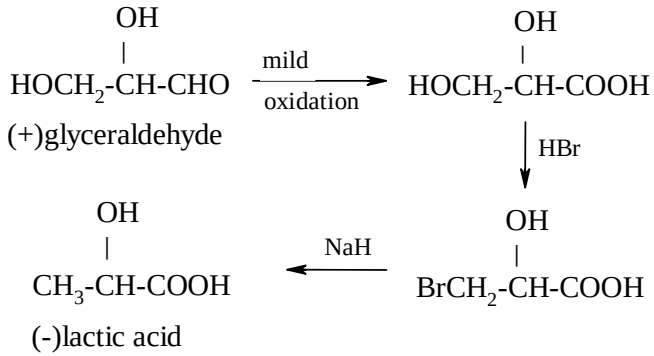


-112.7°

Direct determination of absolute configuration: Calculation of the optical rotation of a compound of known configuration can be carried out, in principle, by using a quantity called **bond polarisability**. *It is a measure of the response of the electrons in bonds to electric field gradients*. But the calculations are very complex and is of not much use at present.

The only practical method now available for the determination of absolute configuration directly is **anomalous X-ray diffraction**. Normal X-ray diffraction is a scalar method since right and left cannot be distinguished. Anomalous X-ray diffraction depends on the presence of a heavy atom that can absorb X-rays as well as diffract them. The pattern obtained from this technique depends on the chirality of the molecule and allows unambiguous assignment of absolute configurations.

Relative determination of absolute configuration: For many years, it was arbitrarily assumed that (+)glyceraldehyde had structure A shown above. This molecule was then used as a configurational standard and many other molecules were related to it configurationally. *This is done by synthesizing the molecules starting from glyceraldehyde of known rotation, without breaking any of the bonds connected to the asymmetric carbon atom*. Later studies showed that (+)glyceraldehyde *does indeed have the assigned configuration* (what luck for chemists!). The technique can be illustrated by the following transformation:



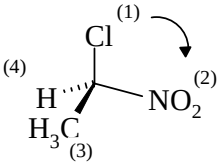
Since no bond attached to the asymmetric carbon atom was broken in this synthetic sequence, (-)lactic acid can be assumed to have the same absolute configuration as (+)glyceraldehyde. Similarly, (+)tartaric acid was also configurationally related to (+)glyceraldehyde.

Cahn-Ingold-Prelog convention (CIP rules): The statement that "(+)glyceraldehyde has structure A" (on the previous page) is useful only for those who can see the figure. The following description must be substituted: "(+)glyceraldehyde is that stereoisomer which, when viewed along the C-H bond from the asymmetric carbon towards the hydrogen, the OH, CHO and CH_2OH groups are arranged in a clockwise direction." Rules for producing a short form of the stereochemical information of the above type were developed by Cahn, Ingold and Prelog.

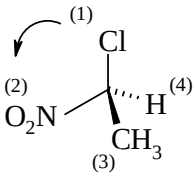
The CIP convention does two things: (1) *it outlines a system by which the four groups attached to the chiral centre can be assigned a priority order* and (2) *it prescribes a label that relates to the arrangement of groups around the chiral atom.*

The priority sequence is determined by the atomic mass – higher the mass number, higher the priority. Thus: Cl > O > N > C > H. One then looks along the bond axis from the chiral atom

toward the group of lowest priority. Then if the remaining atoms or groups, in their decreasing order of priority, appear in a clockwise direction, it is said to have ***R*** configuration (latin, *rectus* = right). If they appear in an anticlockwise direction, it is said to have an ***S*** configuration (*sinister* = left).



For example, in the molecule $CH_3CH(Cl)NO_2$ the atomic masses are Cl = 35.5, N = 14, C = 12 and H = 1. Thus Cl, N, C and H get priority 1 (highest), 2, 3 and 4 (lowest) in that order. Since H has the lowest priority, the molecule is viewed along the C-H bond. Then priority order 1 → 2 → 3 appears in the clockwise direction in the molecule shown on the left.

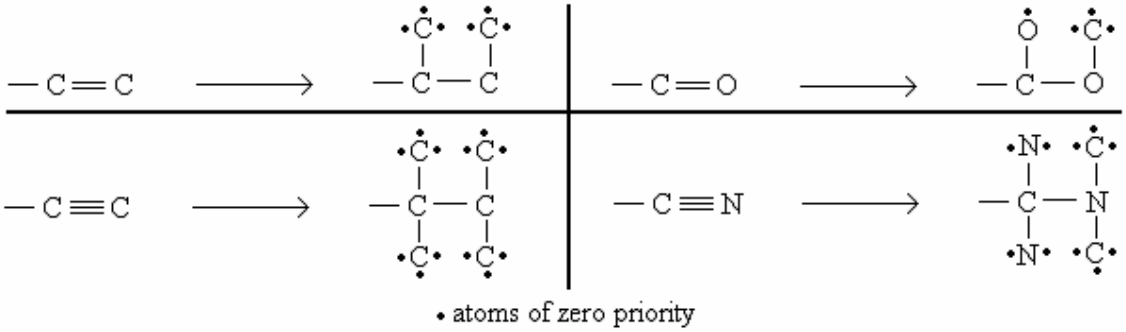


Therefore the molecule has ***R*** configuration at the asymmetric carbon atom. In the mirror image shown on the right, the priority order 1 → 2 → 3 appears in the anticlockwise direction and hence it has the ***S*** configuration.

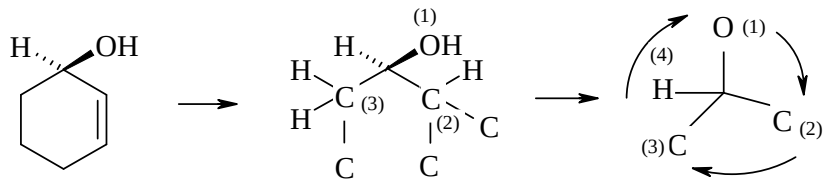
If two atoms connected to the chiral atom happens to be the same, then the next atoms of highest priority attached to them are examined. This process of examining priority in pairs is continued till a proper priority order can be established. Examples:

$CH_3CH_2– > CH_3–$	(compare C with H)
$HOCH_2– > CH_3CH_2–$	(compare O with C)
$ClCH_2– > HOCH_2–$	(compare Cl with O)

If double bonds or triple bonds are present, the carbon atoms will not have a full complement of four attached atoms. This problem is solved by artificially supplying the missing atom (a double bond is assumed to be two separate bonds to similar atoms). The atoms which are thus supplied are sometimes called *phantom atoms*. The remaining three valencies of the phantom atoms are considered as connected to atoms with priority zero (least priority). Thus:



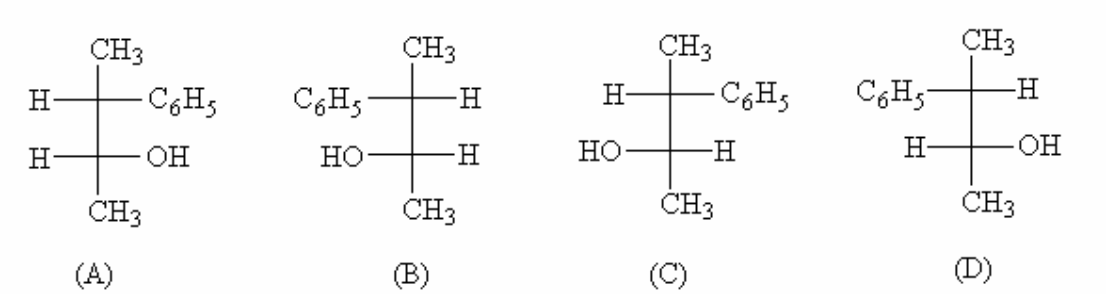
Example: Assign CIP notation to the following 2-cyclohexenol isomer.



Since the priority order 1 → 2 → 3 appears in the clockwise direction, the asymmetric carbon has ***R*** configuration.

Molecules with more than one asymmetric centres – Diastereoisomers and Meso forms

Fischer projections of the various possible configurations of 3-phenyl-2-butanol are given below:

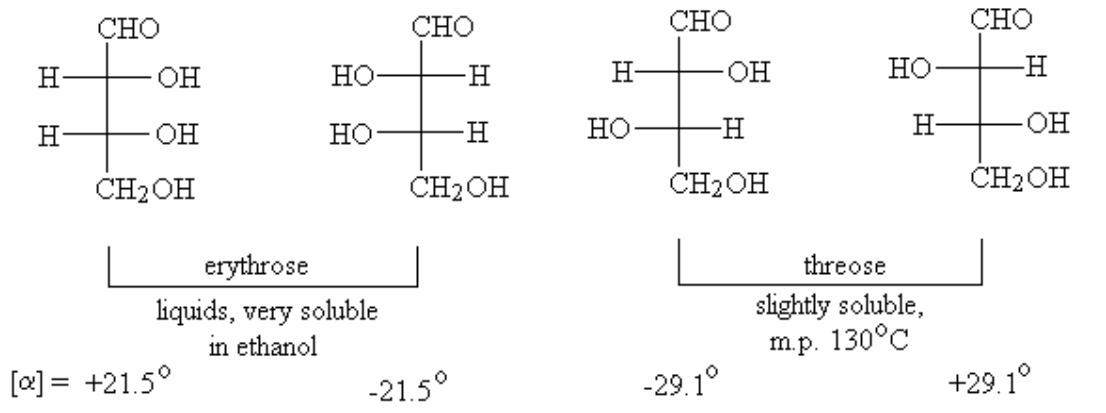


Since there are two asymmetric carbon atoms, each capable of having two configurations, there are $2 \times 2 = 4$ possible configurations. These are shown as A, B, C and D in the figure above.

The number of configurations double for each additional asymmetric carbon atom. In general, for 'n' asymmetric carbon atoms, there are 2^n configurational isomers.

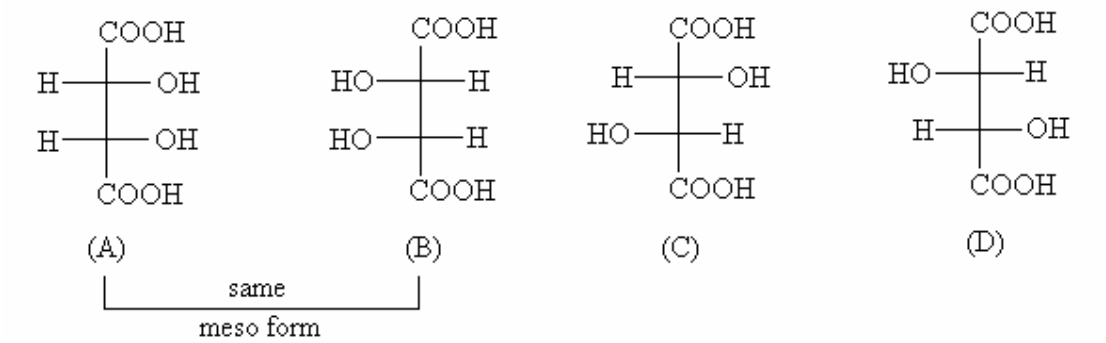
In the figure, it is easily understood that A and B are mirror images (**enantiomers**). Similarly C and D are enantiomers. But A & C or A & D or B & C or B & D are not enantiomers.Such configurational isomers which are not enantiomers are called **diastereoisomers**.

Physical and chemical properties of enantiomers are very similar, except for the opposite signs of rotation. But *properties of diastereoisomers are different*, permitting easy separation. For example:



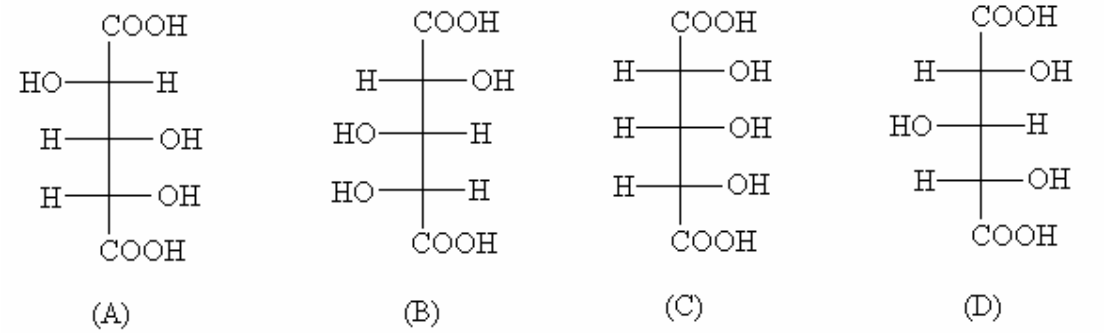
Epimers: Diastereoisomers differing in the configuration of one asymmetric centre only are called epimers. For example, A & D or B & C are epimers.

If the two asymmetric C atoms are *similarly substituted* such that there is a plane of reflection symmetry in the molecule, then the number of isomers may be less than 2^n. For example, tartaric acid with two asymmetric C-atoms show only three isomers instead of four.



C & D are enantiomers. But A (or B) contains a plane of symmetry. C or D and the meso form are diastereomers. The meso form is optically inactive since both asymmetric C-atoms rotate the plane of polarization to the same extent, but in opposite directions (internal compensation). The meso form in the above example is sometimes called the *erythro*-form (both OH on the same side as in erythrose). C and D are *threo*-forms (OH on different sides as in threose).

The same principle can be extended to compounds with three or more chiral centres. Trihydroxy glutaric acid with two asymmetric C-atoms gives all four isomers (the middle C-atom is not asymmetric).

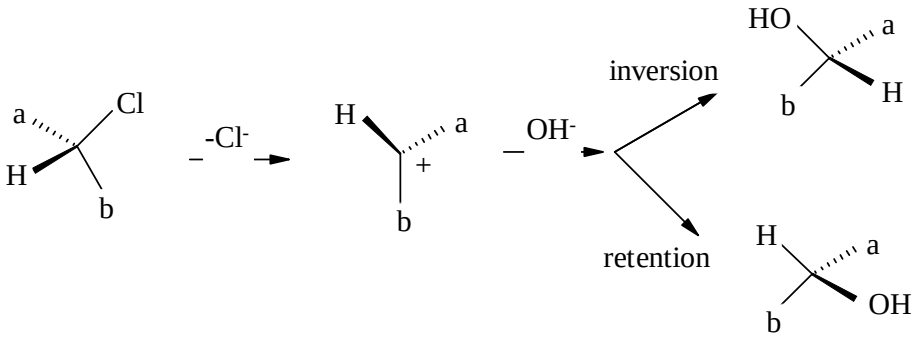


A and B are enantiomers. C and D are meso forms (horizontal plane of symmetry passing through the middle OH). These two meso forms are diastereomers.

Racemic mixtures: Since enantiomers rotate the plane of polarization in opposite directions but in equal amounts, an equimolar mixture of the two enantiomers will be optically inactive (external compensation). Such a mixture is called a racemic mixture.

Racemisation: When any one of the atoms or groups on an asymmetric centre is substituted by another atom or group through an S_N1 mechanism, there is equal probability for the original configuration to be retained or to become inverted. This is because it passes through an sp^2-hybridised flat carbonium ion intermediate, which can then be attacked by the reagent from any of the two sides. This results in the formation of a racemic mixture, and is therefore known as racemisation.

If the reaction proceeds through an S_N2 mechanism, inversion of configuration takes place. This is similar to an umbrella back-folding and is known as **Walden inversion**. Inversion may or may not change the R/S notation assigned to the chiral centre because this depends on the preference sequence assigned to the reactant and the product.



Substitution through S_N1 mechanism.
The flat carbonium ion can be attacked by the OH group either from the left or from the right, giving a racemic mixture.

Asymmetric synthesis: Any synthetic step which produces one of the enantiomers predominantly is called asymmetric synthesis. Such a reaction is usually brought about by using chiral reagents and is kinetically controlled. Reactions which are thermodynamically controlled usually give rise to racemic mixtures. In asymmetric syntheses, the yield as well as optical purity is specified.

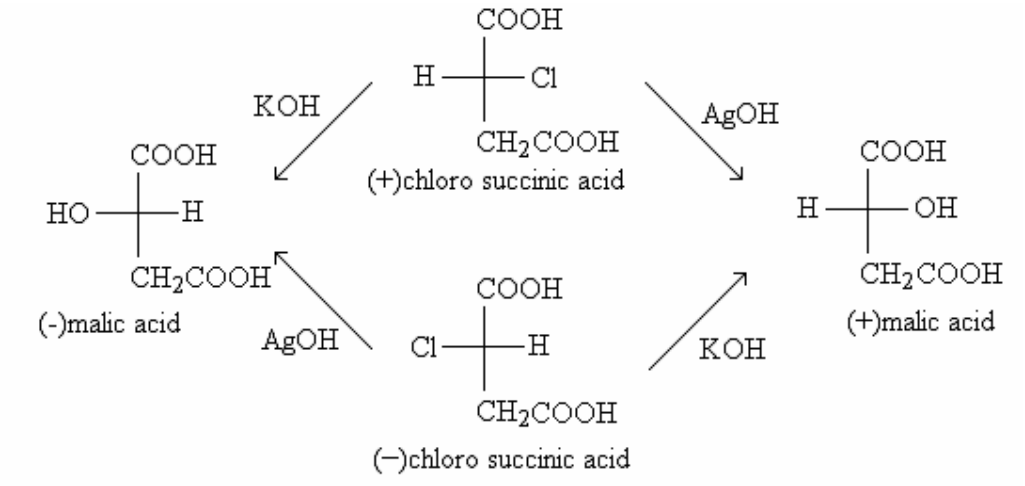
Optical purity: If $[\alpha]_{max}$ is the specific rotation of one enantiomer and $[\alpha]$ is the measured specific rotation of the product, the optical purity P is defined as:

$$P = \frac{[\alpha]}{[\alpha]_{max}}$$

Enantiomeric purity: In a solution, if 'd' is the concentration of the (+) isomer and 'l' is the concentration of the (-) isomer, then the enantiomeric purity P is defined as:

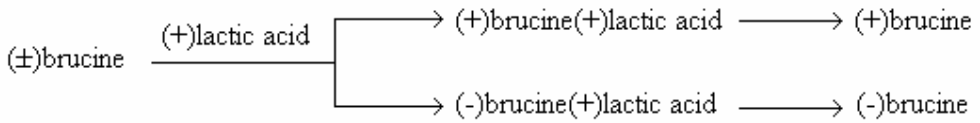
$$P = \frac{d - l}{d + l}$$

An example for asymmetric synthesis:



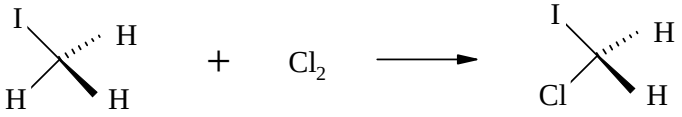
AgOH reacts with retention of configuration while KOH reacts with inversion of configuration.

Resolution: Resolution means the separation of a racemic mixture into the (+) and (-) optically active forms. Since there are no differences in the physical or chemical properties of enantiomers, there is no easy physical method of separation. But diastereomers differ considerably in their properties. This offers a chemical method of separation. Suppose we want to separate the enantiomers (±) of a basic substance, we can react it with the pure (+) form of an asymmetric organic acid. Then the salt formed with the (+) form of the base will be the (+ +) diastereomer and that with the (-) form of the base will be the (- +) diastereomer. The (+ +) and (- +) diastereomers differ very much in their solubilities and may be separated by fractional crystallization of the salt. The separated diastereomers can then be hydrolysed separately to get the free (+) and (-) forms of the base. Separation of a racemic mixture of an acid may similarly be achieved using an optically active base. Example:

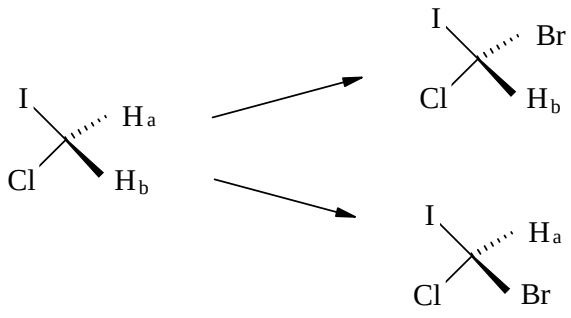


Prostereoisomerism: In asymmetric synthesis, it becomes necessary to know whether isomeric compounds can be produced from symmetric molecules. In prostereoisomerism, we examine whether a symmetric molecule is prone to exhibit isomerism if it undergoes addition or substitution reactions.

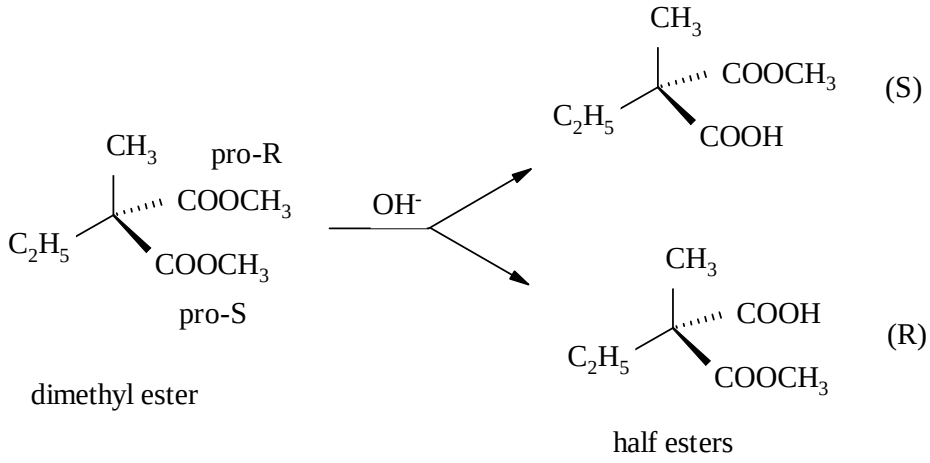
Topocity is the name given to the stereo relationships of atoms or groups within a molecule. Consider the molecule ICH_3. The three H atoms in the molecule are in identical environment. Therefore they are indistinguishable from each other chemically or using NMR. Replacement of any one H atom with another atom or group will give the same result and produce only a single product. Such atoms or groups which are indistinguishable from one another are called **homotopic ligands**.



The topocity of ligands is studied by the substitution rule. In this rule, we examine the consequence of substituting each ligand by a test-group which is different from all other groups already present and having the highest priority. For example, in the case of $IClCH_2$, substitution using a bromine atom may be examined. There are two H atoms in $IClCH_2$, which have the same environment and are indistinguishable using NMR. We shall label them H_a and H_b. They give a single NMR signal. If H_a is substituted by a Br atom, the S-stereo isomer will be produced. But when H_b is substituted by the Br atom, the R-isomer is obtained. Ligands that produce enantiomers on applying the substitution rule are called **enantiotopic ligands**. H_a and H_b in this case are enantiotopic ligands.

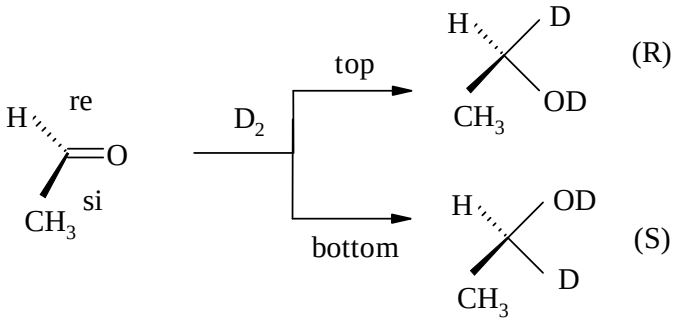


In the above case, H_a is called the pro-S ligand and H_b is called the pro-R ligand, since their substitution gives the S and R isomers respectively. The C-atom bearing enantiotopic groups is said to be prochiral. Another example is given below:



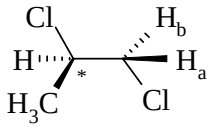
In the dimethyl ester of ethyl methyl malonic acid, the two $–COOCH_3$ groups are enantiotopic ligands. The central C-atom is prochiral. The proximal $–COOCH_3$ is pro-S and the distant $–COOCH_3$ is pro-R for this partial hydrolysis reaction.

The analysis of prochirality can be applied to the two faces of a flat molecule such as ketones. For example, if acetaldehyde is reduced using deuterium, enantiomeric alcohols are produced. Adition from the top face gives the R-isomer and addition from the bottom face gives the S-isomer.



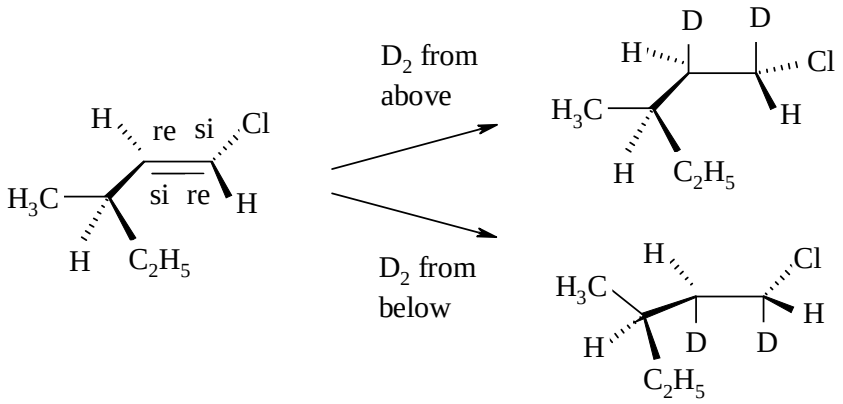
When addition to opposite faces of a π-system produces enantiomers, they are said to be **enantiotopic faces**. If on looking down on one face, the eye travels clockwise on moving from ligands with higher priority to lower, that face is defined as **re** (rectus). The other face is called **si** (sinister).

If the prochiral C-atom is already connected to another asymmetric centre in the same molecule, then testing for prochirality produces diastereo isomers. Here, H_a and H_b are **diastereotopic ligands**. H_a is pro-R and H_b is Pro-S. The carbon atom bearing H_a and H_b is prochiral.



Similarly, if a π-bond system is attached to an asymmetric centre, it can have **diastereotopic faces**. There must be an sp^2 system and a chiral centre in the same molecule. In this case, each sp^2 prochiral centre is labeled separately as shown.

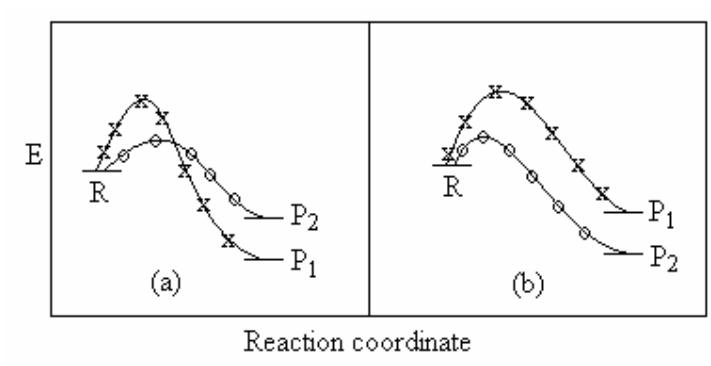
NMR cannot distinguish between prochiral groups, but chiral reagents and catalysts can. They react preferentially with either the pro-R or Pro-S group resulting in a higher yield of one of the isomers (asymmetric synthesis). A circularly polarized light is also able to induce asymmetric synthesis.



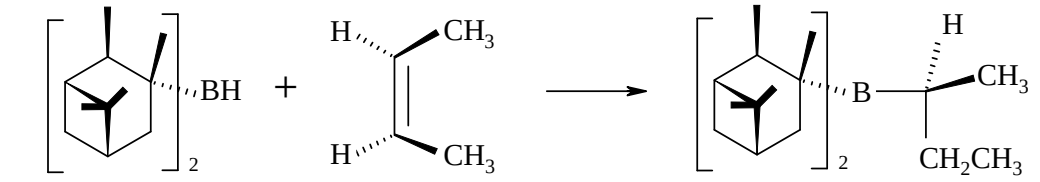
Principles of asymmetric synthesis:

A synthesis in which one of the isomers is predominantly formed is called asymmetric synthesis. All such reactions must be under kinetic control. The competing reactions with diastereoisomeric transition states take place at different rates. Thermodynamic control can only lead to racemic mixtures Thermodynamically controlled reactions favour product with lowest final energy. This refers to the product favoured under equilibrium conditions. But asymmetric syntheses are not equilibrium reactions. Kinetically controlled reactions favour products produced faster ie. with a lower energy for the transition state.

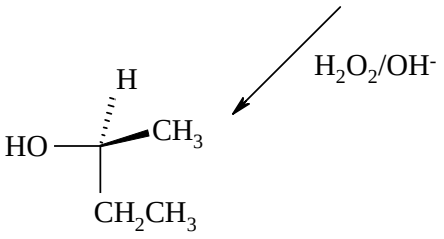
In the diagram, a reactant 'R' gives two products P_1 and P_2 through two different routes. P_1 is the product requiring high activation energy and P_2 requires low activation energy. But the final energy content of P_1 is lower in case (a) but higher in case (b). A thermodynamically controlled reaction will always favour the product with lower final energy content ie. P_1 in (a) and P_2 in (b). But a kinetically controlled reaction will favour the product with low activation energy ie. P_2 in both cases.



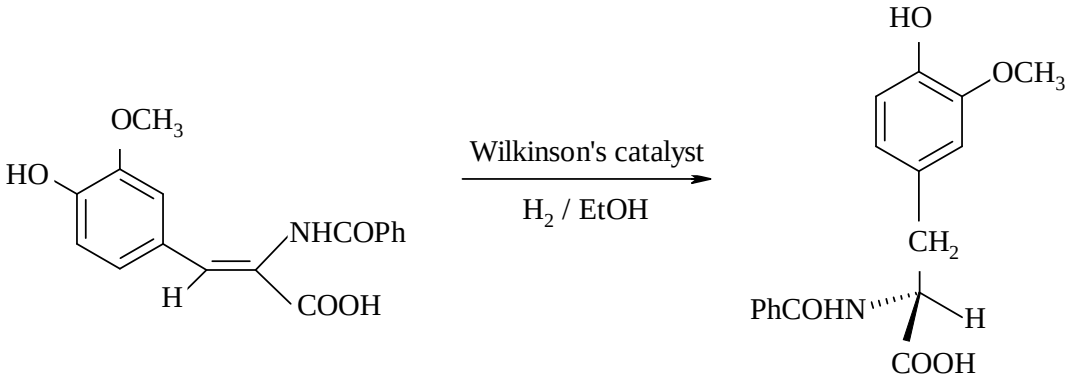
An example of enantioface differentiation using dipinnanyl borane is given below. The addition product formed between the borane and *cis* 2-butene is the one obtained in 81% optical yield, which can be stereoselectively converted to the alcohol. Thus chiral dipinnanyl borane is a stereoselective reagent.



(-)dipinnanyl borane



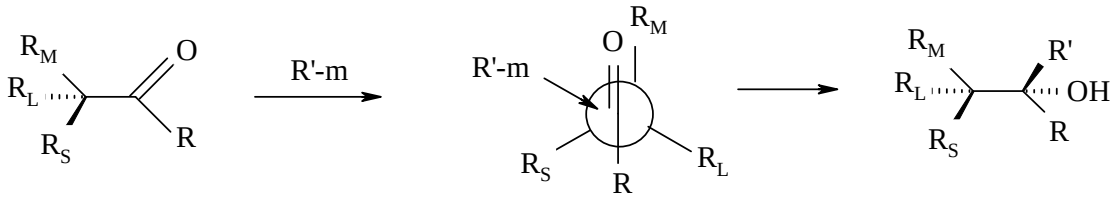
An example of a stereoselective catalyst is **Wilkinson's catalyst, $(Ph_3P)_3RhCl$** (Nobel Prize in 1973). The anti-Parkinson's desease drug L-dopa has been synthesized with 95% optical yield using this catalyst.



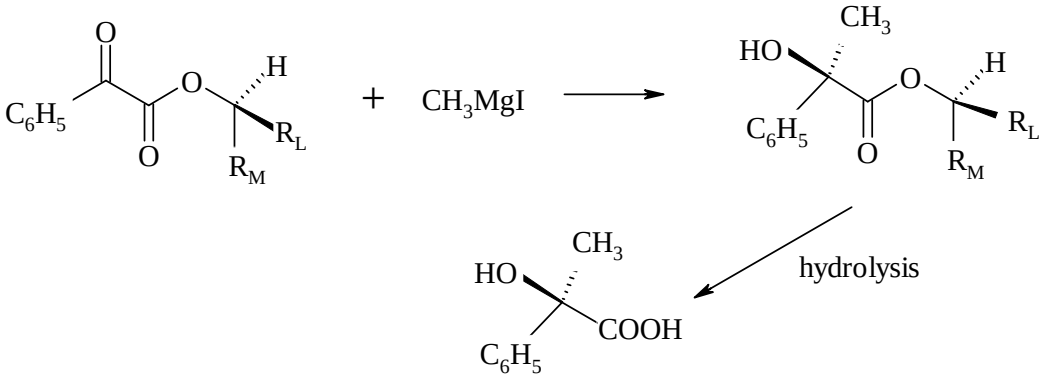
L-dopa

The exact mechanism with which stereoselectivity is obtained is not clearly understood. However, attack of the reagent from a less-hindered side has been proposed as an explanation, which is of use in rigid ring systems such as steroids. Some empirical rules have been proposed.

Cram's rule: In 1950, D.J.Cram formulated a rule to account for the preferential formation of one diastereo isomer in the reaction of chiral ketones with organometallic or anionic reagents. The statement of the rule is that "*in a kinetically controlled addition to a carbonyl C-atom that is adjacent to a chiral centre, the anion will attack from the side containing the smallest ligand, when the chiral group is oriented so that the medium ligand is eclipsing the carbonyl group*."



Prelog's rule: (Nobel Prize, 1975) At about the same time as Cram, Prelog proposed a similar rule to account for the predominant formation of *R*(+)atrolactic acid by reaction of CH_3MgI with the diketoester:



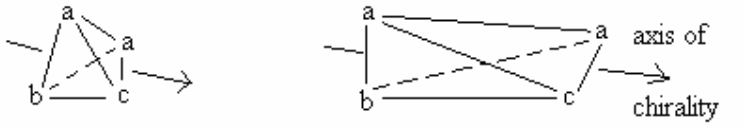
R(+)atropo lactic acid

The statement of Prelog's rule is "*When the medium-sized group R_M is in a plane with both carbonyl groups, the reagent attacks from the least hindered side (of H) to give the product*."

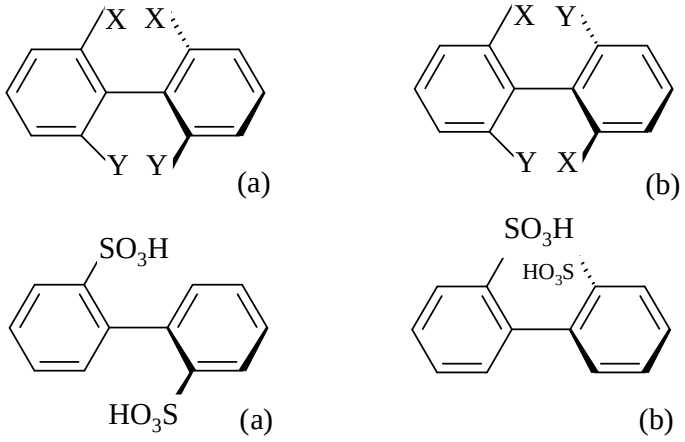
CHIRALITY IN THE ABSENCE OF ASYMMETRIC CARBON ATOMS

Even when there are no asymmetric carbon atoms in a molecule, the molecule as a whole may not have symmetry and may therefore exhibit enantiomerism. There can be two main reasons for such isomerism and are classified into (1) axial chirality and (2) planar chirality. Axial chirality and is exhibited by substituted biphenyls, allenes and spirans. Planar chirality is exhibited by hexahelicene.

Axial chirality: This is a consequence of a chiral distribution of substituents around an axis. The tetrahedral molecule C(aabc) has a plane of reflection symmetry. But if the tetrahedron is deformed by stretching along an axis, this imaginary extension will reduce the molecular symmetry and so the plane of reflection symmetry will disappear. The imaginary axis along which the stretching was carried out is called the axis of chirality. Allenes, alkylidine cycloalkanes, biphenyl etc. are said to possess a ***chiral axis*** (Cahn, Ingold & Prelog, 1956).

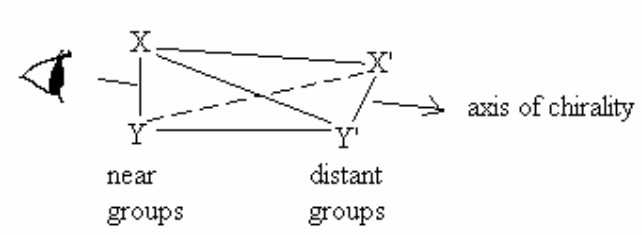


Isomerism in biphenyls: The bond between the two rings in biphenyl is a single bond. However, when there are bulky substituents in the ortho positions, there are numerous examples where enantiomeric compounds have been isolated in the pure form. This is possible because of restricted rotation on the single bond due to the steric interaction between the bulky groups in the ortho positions. Strictly speaking, rotation about a single bond is only a conformational change. Therefore a new term has been introduced – **atropoisomerism**. *Atropoisomers are species that are isolable, but can be interchanged by rotation around single bonds*. They can be isolated if the Gibb's energy barrier is greater than 100 kJ mol^{-1}. Larger the substituents, more stable the isomers.



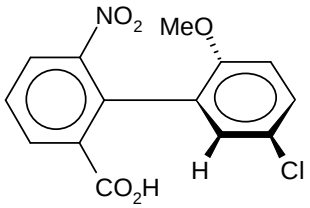
Enantiomeric forms of biphenyl-2,2'-disulphonic acid

Assignment of absolute configuration in axial chirality: The molecule is viewed along the axis of chirality. The nearer groups are given priority over the distant groups, and the CIP rules are followed. For example, if 'X' has priority over 'Y', then the priority order in the above figure is X > X' > Y > Y'.



Thus in the disulphonic acid molecules shown above, (a) is the R-isomer and (b) is the S-isomer.

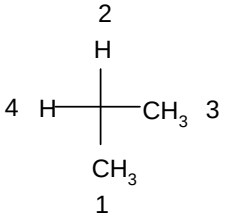
To specify chirality in molecules possessing a chiral axis, an additional sequence rule is needed – near groups precede far groups [Eliel EL andWilen SH, Stereochemistry of Organic Compounds, John Wiley (2003); p. 1120]. --- The same configurational descriptor results when viewed from left or right, so no specification in this regard is needed. --- In case of biphenyl it is important to note that the ring substituents are to be explored from the centre on outward, regardless of the rule given above. Thus in A, in the right ring the sequence is OMe > H; the Cl atom is too farout to matter, a decision being made before it is reached in the outward exploration.



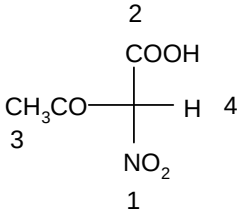
A

The descriptors **aR** and **aS** are sometimes used to distinguish axial chirality from other types, but the use of the prefix is optional.

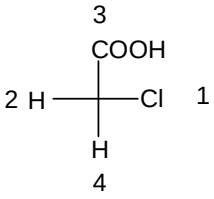
Molecules with chiral axes may alternately be viewed as helices (see hexahelicene) and their configuration may be denoted as **P** or **M**, in a manner similar to conformational isomers. For this designation, only the ligands of highest priority in front and in the back of the framework are considered. If the turn from the priority front ligand 1 to priority rear ligand 3 is clockwise, the configuration is P; if counterclockwise, it is M. For example:



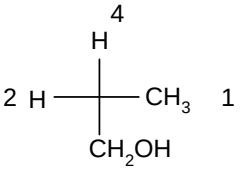
aR or M



aS or P

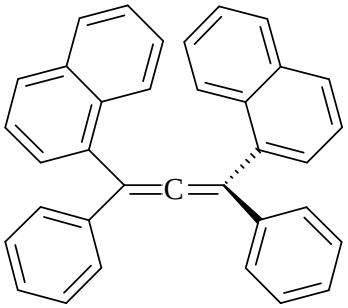


aR or M



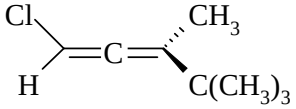
aS or P

Allenes: Since the two double bonds are perpendicular to each other, allenes also show axial chirality. The two atoms or groups attached to any one C-atom must be different for the molecule to be optically active. The assignment of absolute configuration is the same as in biphenyls.



(1)

Allene which was first resolved



(2)

The maximum possible symmetry for allene is C_2. If all the four groups are different as in (2), the symmetry is reduced to C_1.

Optically active allenes occurring in nature:
[Eliel EL andWilen SH, Stereochemistry of Organic Compounds, John Wiley (2003); p. 1123]

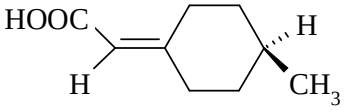
(1) Antibiotic ***mycomycin***, a fungal metabolite:

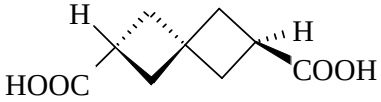
$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2COOH$$

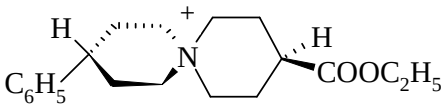
(2) Sex pheromone produced by male dried-bean beetle:

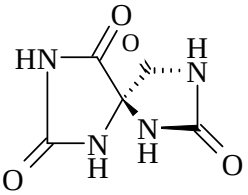
$$CH_3{-}(CH_2)_7{-}CH{-}CH{=}C{=}CH{-}CH{=}CH{-}COOCH_3$$

One or both of the double bonds in allenes may be replaced by rings. When both are rings, the compounds are known as **spirans**. Such compounds are also axially asymmetric. For example,





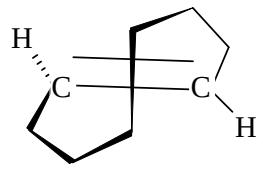




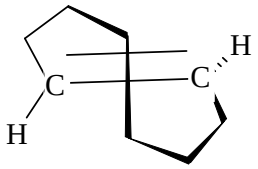
The sequence rules for all these compounds are the same as discussed earlier.

Planar chirality: This is shown by extremely strained molecules. Some examples are given below:

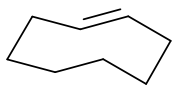
(1) **Cyclo alkenes**: *Trans* cyclo octane. (a) and (b) are enantiomers. (c) is another way of drawing the same molecule.



(a)

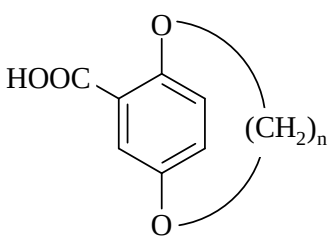


(b)



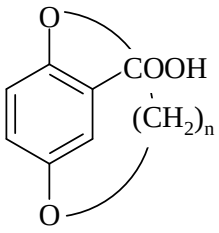
(c)

(2) **Ansa derivatives**: Cyclic para-diethers of benzene where the ring contains 8, 9 or 10 C-atoms. (a) and (b) shown below are enantiomers because the tight ring of methylene groups prevents the benzene ring from rotating.



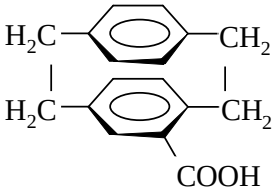
(a)

n = 8, 9 or 10

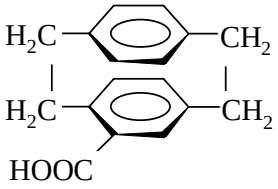


(b)

(3) **Para cyclophanes**: (a) and (b) shown below are enantiomers because of restricted rotation.

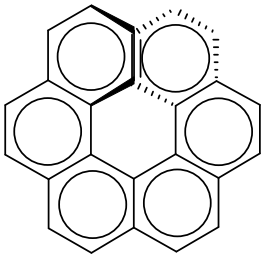


(a)

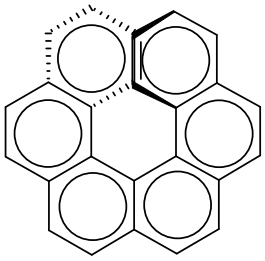


(b)

(4) **Hexahelicene**: Hexahelicene cannot be planar because of steric hindrance between the terminal rings. Note that the terminal rings are not fused. Therefore the ring system is deformed and takes up a helical conformation. It has a remarkable rotatory power. Molar rotation [α] = ± 3600°.



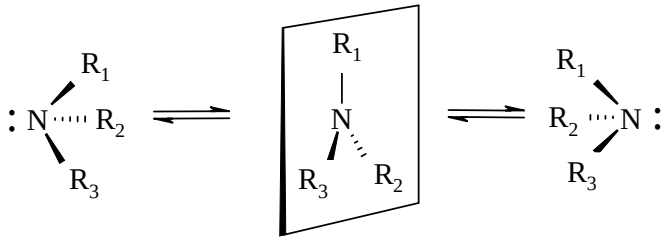
(a)



(b)

OPTICAL ISOMERISM IN NITROGEN AND SULPHUR COMPOUNDS

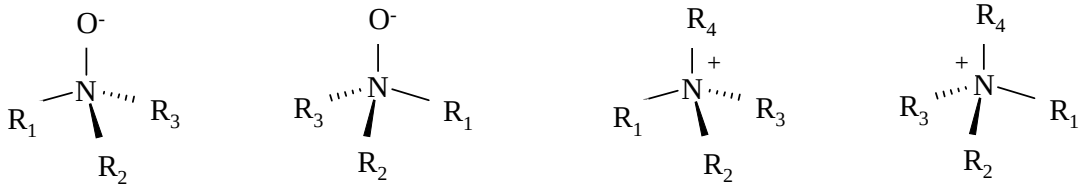
The N-atom is pyramidal in amines, but enantiomeric forms cannot be separated because the molecule undergoes rapid inversion through the planar intermediate. For example, for dibenzyl methyl amine, the frequency of inversion is 76 s^{-1} at -146°C.



But when the N-atom is part of a small ring system as in the case of N-halogenated **aziridines**, the inversion is restricted and enantiomers have been isolated. Thus (a) and (b) are enantiomers.

(a) (b)

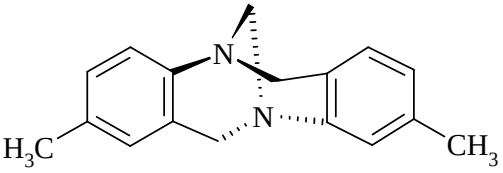
Other nitrogen compounds which can be resolved are **tertiary amine oxides** and **quaternary ammonium salts** in which inversion is restricted.



(a) (b) (a) (b)

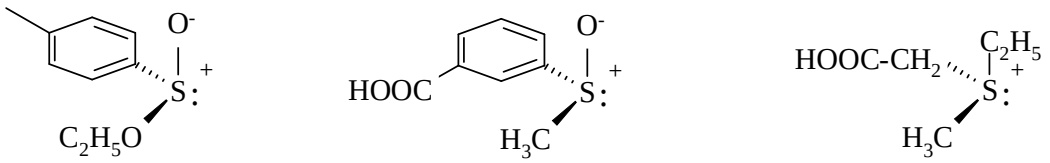
Tertiary amine oxides Quaternary ammonium salts

The first amine to be resolved due to restricted inversion was Troger's base, by Prelog in 1956.



Troger's base

Sulphinates, **sulphonium salts** and **sulphoxides** also show enantiomerism due to the tetrahedral nature of the sulphur atom.

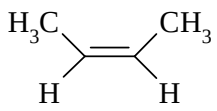


A chiral sulphinate A chiral sulphoxide A chiral sulphonium ion

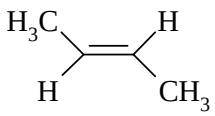
GEOMETRICAL ISOMERISM

In compounds with double-bonds, if the two groups on each C-atom connected by the double-bond are different, then geometrical isomerism becomes possible, due to restricted rotation on the double-bond. Two isomers are possible for each double-bond. If there are 'n' double-bonds, the total number of geometrical isomers possible is 2^n.

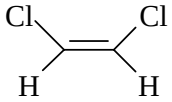
Nomenclature: The isomer with similar groups on the same side is called *cis* or *Z* [zusammen (German) = together]. If they are on opposite sides, it is called *trans* or *E* [entgegend (German) = opposite].



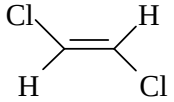
cis-2-butene
Z-2-butene



trans-2-butene
E-2-butene

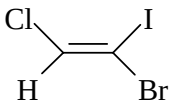


cis-1,2-dichloro ethene
Z-1,2-dichloro ethene

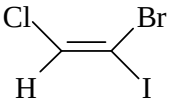


trans-1,2-dichloro ethene
E-1,2-dichloro ethene

If all the four groups are different, the groups are assigned priority as in the CIP rule. The isomer in which the high-priority groups on both C-atoms are on the same side is called the *Z*-isomer. The isomer in which the high-priority groups on both C-atoms are on opposite sides is called the *E*-isomer.

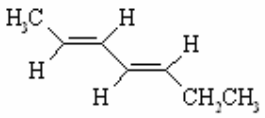


Z-1-bromo-2-chloro-1-iodo ethene

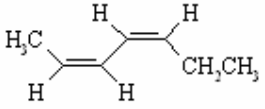


E-1-bromo-2-chloro-1-iodo ethene

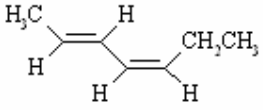
When more than one double-bonds are present, each double-bond is classified in this fashion. For example, there are four geometrical isomers for 2,4-heptadiene.



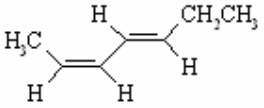
2(*E*),4(*E*)-heptadiene



2(*Z*),4(*Z*)-heptadiene

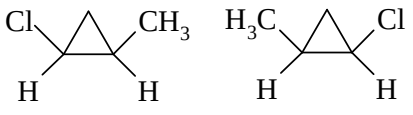


2(*E*),4(*Z*)-heptadiene

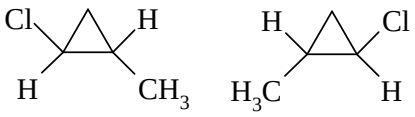


2(*Z*),4(*E*)-heptadiene

Restricted rotation in ring compounds: The double-bond may be replaced by small rings with the same result. Optical isomerism is also possible in addition to geometrical isomerism. For example, 1-chloro-2-methyl cyclopropane has four isomers, which are enantiomers of the *cis*- and *trans*-forms.

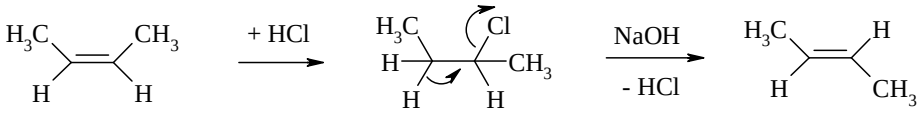


Z-1-chloro-2-methyl cyclopropane enantiomers

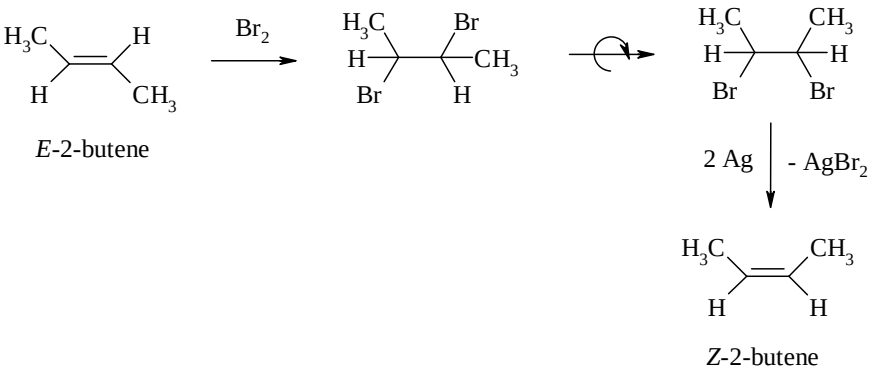


E-1-chloro-2-methyl cyclopropane enantiomers

Interconversion of geometrical isomers: Interconversion (*Z* to *E* and *E* to *Z*) is possible only through reactions in which the double-bond is broken and reformed. After breaking the bond, reactions of known stereochemistry have to be used in reforming the bond. For example,



Z-2-butene — *trans*-elimination — *E*-2-butene



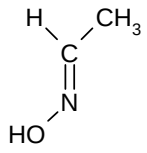
E-2-butene — *Z*-2-butene

Methods of determining configuration in geometrical isomers: Since the environments of protons in cis and trans isomers are different, their NMR spectrum will be different.

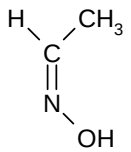
Stereochemistry of aldoximes and ketoximes

[Eliel EL andWilen SH, Stereochemistry of Organic Compounds, John Wiley (2003); p. 540]

Oximes can also exhibit geometrical isomerism about the C-N double bond. Before 1968, the prefixes *cis*- and *trans*- were used for alkenes and the prefixes *syn*- and *anti*- for oximes and other aldehyde or ketone derivatives. In the case of aldoximes, the molecule with the H and OH on the same side of the double bond was called *syn*- and the one with H and OH on opposite sides of the double bond was called *anti*- (Ref: Nasipuri). For example,

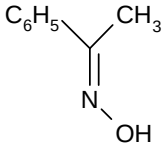


syn-acetaldoxime



anti-acetaldoxime

But in the case of ketones, the group to which the OH is *syn*- or *anti*- has to be specified:

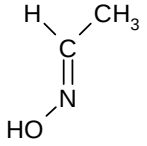


syn-methyl acetophenone oxime

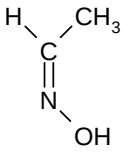
or

anti-phenyl acetophenone oxime

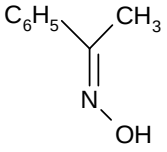
This gives rise to much confusion. But the *E-Z* nomenclature can be applied without any problem. The molecule in which the OH group is on the same side as the highest priority group is termed *Z* and the one in which they are on opposite sides is termed *E*. For example:



(*E*)-acetaldoxime



(*Z*)-acetaldoxime

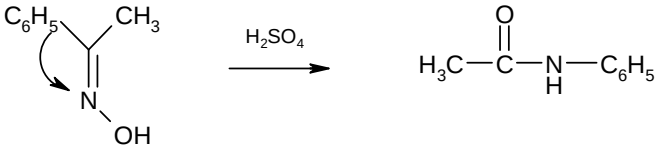


(*E*)-acetophenone oxime

It should be noted that *Z* does not always correspond to *cis* or *syn* and *E* does not necessarily correspond to *trans* or *anti*. The acetaldoxime given on the left above is *syn* by convension, but it is *E*.

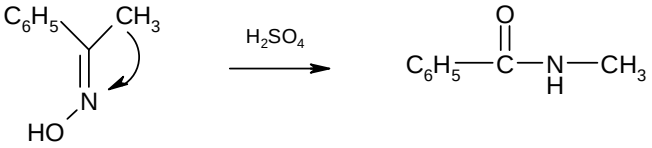
Determination of the stereochemistry of oximes – The Beckmann rearrangement:
[Eliel EL andWilen SH, Stereochemistry of Organic Compounds, John Wiley (2003); p. 561]

There is an important stereochemical aspect to the migrating group in Beckmann rearrangement – the group that migrates is the group ***trans*** to the OH moiety in the oxime. This fact allows one to infer the stereochemistry of the oxime from the nature of the amide formed from it.



(E)-acetophenone oxime

acetanilide



(Z)-acetophenone oxime

N-methyl benzamide

Thus acid treatment of (E)-acetophenone oxime will lead to acetanilide through phenyl migration, whereas (Z)-acetophenone oxime will give N-methyl benzamide through methyl migration.

Mechanism: