Stereoisomerism

Introduction:

When two compounds have same structure (hence same name) but still they are not identical and some of their properties are different then it means they are stereoisomers. They are not superimposable with each other. They differ in the spatial relationship between their atoms or groups. See this example.

\[
\begin{align*}
\text{cis(Z)-but-2-ene} & : & \text{CH}_3 & \text{C} & \text{C} & \text{H} & \text{CH}_3 \\
\text{trans(E)-but-2-ene} & : & \text{CH}_3 & \text{C} & \text{C} & \text{H} & \text{CH}_3
\end{align*}
\]

Both are but-2-ene, but they are not identical. Their melting points and boiling points are different. They evolve different heat energy when hydrogenated. So what is the difference between them? Is it structure-wise? The answer is NO, as their structures are same i.e but-2-ene. They differ with respect the relationship between some atoms or groups in space. In cis-but-2-ene, the –CH$_3$ groups are on the same side of the double bond and so also the H atoms. However, in trans-but-2-ene, the –CH$_3$ groups lie on opposite sides of the double bond and so also the H atoms. For that reason, the two are not superimposable with each other. If you carry the model of cis-but-2-ene and try to overlap with trans-but-2-ene for the purpose of matching of groups and atoms, what do you find? Are the two superimposable? When one –CH$_3$ group matches, the other not. When one –H atom matches, the other not. Thus the structures are non-superimposable. This kind of stereoisomerism is called Geometrical Isomerism (now-a-days called E-Z isomerism), because the geometrical relationship between groups are different.

But can you tell, how can you convert cis-but-1-ene to trans-but-2-ene or vice versa, if you are given a ball and stick model of any one of them. Since C=C bond is rigid and you cannot rotate it like a single bond, you have to exchange between CH$_3$– and H– groups bonded to any of the two carbon (sp$^3$ hybrid) atoms by way of bond breaking and making. Then you can convert one to the other. See another case.

\[
\begin{align*}
\text{I} & : & \text{Cl} & \text{C} & \text{H} & \text{HO} & \text{CH}_3 \\
\text{II} & : & \text{H}_3 & \text{C} & \text{C} & \text{Cl} & \text{HO}
\end{align*}
\]

The above two compounds have the same structure and and hence same name i.e 1-chloroethanol. Cl– and CH$_3$– are lying above the plane while H– and OH– are lying below the plane. But can you superimpose the two forms. The answer is NO. If you rotate the model (I) by 180$^\circ$ about a vertical axis, then Cl– and CH$_3$– will go below the plane and H– and OH– will come above the plane. In the model (II), CH$_3$– and Cl– are lying above the plane while H– and OH– are lying below the plane. Then how can the rotated model of I be superimposable with II? Make sure that you can never superimpose the two forms I and II. Hence they are stereoisomers. Interestingly they are non-superimposable mirror image forms of each other. They are called optical isomers or more precisely enantiomers because, as they have a special quality to respond to a type of...
Organic : Stereoisomerism

light called plane polarized light differently. Can you tell, how can you convert one enantioomer to the other? Like you did for the geometrical isomers, here also you have to exchange between any two groups (atoms) by bond breaking and making process at that particular carbon atom bonded to the four different groups (stereocentre). This is another type of stereoisomerism like E-Z isomerism discussed before. We shall discuss in details about each case later. This is mere introduction.

Note that in the above two cases of geometrical and optical isomerism, the stereoisomers are interconvertible by bond breaking and making at a particular atom, which is called stereogenic centre or stereocentre. Hence these two belong to a general type of stereoisomerism called Configurational isomerism. The stereoisomers are said to have different configurations. They can have separate existence.

See another case.

Both are butane molecule. But are the two forms look superimposable? NO. But you can rotate one form by 120° about the C₂–C₃ bond, you will find the superimposition with the other. But the forms shown above are stereoisomers. Here bond breaking and making processes are not required to convert one form to the other. Simply rotation of single bond will do the job. Unlike C=C, in which rotation is prohibited, the rotation of a single bond is allowed, though there might be some hindrance for converting a more stable conformation to a less stable conformation. Such stereoisomerism is called Conformation isomerism. First one is called Gauche-butane and the second one is Anti-butane, which always coexist in equilibrium. There can be infinite number of different conformations obtained by rotating the single bond. But some of them are stable and that is why the molecules remain in that conformation. We shall stop now further discussion on conformational isomerism.

So let us classify stereoisomerism.

(A) Configuration Isomerism:

When one stereoisomer is converted to the other by bond breaking and making at the stereocentre, it is a case of configurational isomerism. This manifests in two varieties, namely

(i) Geometrical (E-Z) isomerism
(ii) Optical isomerism

(B) Conformational Isomerism:

When stereoisomers are interconvertible by merely rotation of single bonds, then it is case of conformational isomerism. The stable forms among them are called conformational isomers or conformers.

OPTICAL ISOMERISM

Molecules which are disymmetric are called chiral molecules. Such molecules do not superimpose with their mirror image forms. Just like your left hand does not superimpose with your right hand when you keep the palm tops of the two hands either both upwards or both downwards.

Chirality or handedness is due to the absence of the following elements of symmetry.

(a) Plane of symmetry (σ)
(b) Centre of Symmetry (i)
(c) Alternating axis of symmetry/Improper rotation axis (Sₙ)

Conversely, presence of any of these three elements of symmetry makes a molecule achiral. An achiral molecule superimposes with its mirror image form.

Dr. S. S. Tripathy
Chiral molecule can have only a
(d) n-fold axis of symmetry (C\textsubscript{n})

To know more about this let us study molecular symmetry in little greater details.

**Molecular Symmetry and Chirality:**

Any operation (reflection/rotation) done onto the molecule so that the form obtained after the operation is indistinguishable or superimposable with the original molecule, then the operation is called a symmetry operation and the molecule possesses an element of symmetry defined by that operation.

There are four elements of symmetry.

(a) **Plane of symmetry (PS)** (\(\sigma\) plane)

Any imaginary mirror plane (reflecting surface on both the sides) passing somewhere in between the molecule which divides one half as the mirror image of the other half is called a PS. To be more precise, the reflection of the molecule by this mirror plane will give a form which is superimposable with the original form. In the following example (I) you find that the groups -OH are on the same side (in line), so also H atoms and Cl atoms. So such a molecule has a \(\sigma\) plane. Here reflection through the plane of symmetry is the symmetry operation.

If we compare the original form (I) with the reflected form through the PS, the two will be superimposable or indistinguishable. To be more simple, one half is exactly the mirror image of the other half. Hence molecule (I) is achiral, i.e not disymmetric. Hence its mirror image form is superimposable with the original form. However, such a \(\sigma\)-plane is absent in molecule (II), hence it is disymmetric or chiral. Note that only chiral molecules show optical activity. We shall come to optical isomerism little later.

In molecule (III), the \(\sigma\)-plane passes through C atom and also contains Br and Cl atoms. On either side of the plane there are H atoms. Hence one half is the mirror image of the other half. So such a molecule is achiral and does not show optical isomerism. But molecule (IV), there is no plane of symmetry. On either side of the mirror plane, the groups are different. Hence it is not a \(\sigma\)-plane for the molecule, and so the molecule is disymmetric and chiral. We shall come back to further discussion on PS a little later.
**Organic : Stereoisomerism**

**(b) Centre of Symmetry/Inversion Centre/Point of Symmetry (i):**

It is an imaginary point at the centre of a molecule and straight lines drawn through this point will touch identical groups/atoms at equal distances on either side of the point on that line.

In other words, if you consider this point to be a point mirror, then reflection of the molecule through this point mirror will get the reflected form indistinguishable from the original form.

![Diagram](image)

In this molecule(V), there is a centre of symmetry(i) as identical groups lie on the opposite side at equal distances w.r.t the centre of symmetry. If the molecule is reflected through this point mirror, then it will generate the same indistinguishable form. So this molecule is achiral. If you rotate molecule (I) (which has a PS) by 180°, you will get (V) which has a centre of symmetry (i). Though the molecules I and V have same structure and same configuration(called meso form), they have different conformations. (I) is called eclipsed conformation while (V) is called anti-conformation. By changing the conformation, we do not change the configuration or the identity of the molecule. But in any case, they are different stereoisomers to be dealt with separately when dealing with chirality.

Note that eclipsed conformation is unstable and does not exist. But students are trained to bring the conformation to eclipsed form to find for a possible PS. Actually the molecule exists in staggered forms, one of which is (V), which is also achiral due to presence of ‘i’. Note that in another stable conformation of the same meso compound(another staggered form), the three elements of symmetry are absent and hence will be chiral. But the compound is optically inactive. This riddle will be solved a little later. Let it remain as a suspense for a while.

If σ and i are absent, one looks for the presence of another element of symmetry called improper axis of rotation or alternating axis of symmetry(Sn) which can also make the molecule achiral. Before knowing what is an improper axis let us know first what is a proper axis of rotation.

**(3) n-fold Axis of Symmetry(C_n)/ Proper axis of rotation:**

Rotation of the molecule by \( \frac{360°}{n} \) about an imaginary axis(line) passing through the molecule, makes the form indistinguishable from the original form.

![Diagram](image)

In H₂O, the all the three atoms are lying on the same plane(i.e plane of paper), the axis also lies on the same plane passing through O atom. If you rotate the molecule by 180° \( \left( \frac{360°}{2} \right) \), then the new form becomes indistinguishable from the original form. So it is called a 2-fold axis of symmetry or a C₂ axis.

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Similarly in BF₃, the axis passes perpendicular to the plane carrying the four atoms. Every 120° rotation generates the same form. Hence it is a C₃ axis. In NH₃ too, there is a C₃ axis. NH₃ is pyramidal in shape and the axis passes through the N atom sitting at the apex of the pyramid and through the mid point of the equilateral triangle formed by the H atoms on the base.

In XeF₄, there is a C₄ axis, which means every 90° rotation generates the same form.

Benzene has one C₆ axis and six C₂ axes as shown below. C₆ axis passes perpendicular to the benzene plane, while all the C₂ axes lie on the benzene plane as shown below. Trans-1,2-dichloroethene (two Cl- atoms lie on the opposite side) has one C₂ axis lying perpendicular to the plane carrying all the atoms.

C₁ axis is trivial because, by rotating any molecule about any axis (C₁ axis) by 360°, regenerates the original form. If higher order of Cₙ (C₂ onwards) are not available in a molecule, then C₁ axis is definitely present. But a molecule having only C₁ is disymmetric. It may possess an asymmetric carbon atom which is bonded to four different groups. Such molecule is always CHIRAL.

C₁ axis is equivalent to another symmetry operation called **IDENTITY** operation (E), means doing nothing on to the molecule (sounds funny !!!!). This operation is purely mathematical in nature which is required in group theory for matrix operations (not to be discussed here). So the term ‘E’ is used in preference to C₁ axis.

In symmetrical linear molecule like acetylene (C₂H₂), there is one C₆ axis coinciding with internuclear axis (rotating by any angle about this axis regenerates the original form) and infinite number of C₂ axes lying on a plane perpendicular to the C₆ axis. Unsymmetrical molecule like HCN, HCl, ICl etc. has only C₆ axis.

Dr. S. S. Tripathy
Principal Axis:
If a molecule has more than one \(C_n\) axes, then the highest order axis is called the principal axis. For example in benzene, \(C_6\) is the principal axis. If more than one axis of highest order are available in a molecule, then the one carrying maximum number of atoms is the principal axis. In ethylene, the vertical \(C_2\) axis as shown in the figure carrying the two C-atoms becomes the principal axis, while the horizontal \(C_2\) axis is not. Principal axis is usually taken as \(z\)-axis and conventionally (not necessarily always) kept in vertical position in diagrams.

Chirality and \(C_n\):
We already know that a molecule having only \(C_1\) or \(E\) is asymmetric and is chiral. Molecules having \(C_n\) axis \((n>1)\) and having no other elements of symmetry, are also chiral. We shall see this a little later.

Let us return to PS again to know little more about their types.

Types of Planes of Symmetry(\(\sigma\))
(i) Vertical plane of symmetry\((\sigma_v)\): Plane of symmetry containing principal axis\((C_n)\)
(ii) Horizontal plane of symmetry\((\sigma_h)\): Plane of symmetry perpendicular to principal axis\((C_n)\)
(iii) Dihedral plane of symmetry\((\sigma_d)\): Vertical plane of symmetry that bisects the angle between two \(C_2\) axes. Note that \(\sigma_d\) is a special case of \(\sigma_v\). When both are present in a molecule, it is customary to designate \(\sigma_d\) to those which do not pass through atoms rather pass through bonds ((or pass through less atoms) and \(\sigma_v\) to those pass through atoms (or more atoms).

In ethene, the plane carrying the principal axis (vertical) is the vertical mirror plane\((\sigma_v)\), while the plane perpendicular to it is the horizontal mirror plane\((\sigma_h)\).

In XeF\(_4\), the principal axis is \(C_4\) passing perpendicular to the molecular plane (here shown as a horizontal axis passing perpendicular to the plane of the paper). There are four \(C_2\) axes as shown (two passing through atoms and the other two passing in between atoms). There are four vertical mirror planes all of which bisect \(C_2\) axes and hence satisfy the definition of \(\sigma_d\), hence can be called \(\sigma_d\). But customarily those two passing in between atoms are to be called dihedral mirror \((\sigma_d)\) planes. The other two passing through atoms are to be called vertical mirror plane\((\sigma_v)\).

Every planar molecule has a horizontal plane of symmetry\((\sigma_h)\) passing through the nuclei of all the atoms. So XeF\(_4\) has also one \(\sigma_h\) as it is perpendicular to the principal axis. The plane of the paper is the \(\sigma_h\) (not shown).

Note that if a \(\sigma_d\) is present in a molecule along with one or more \(\sigma_v\)s, then \(\sigma_v\)s are to be treated as \(\sigma_v\) for the purpose of making point groups (discussed later). We shall count any mirror plane under \(\sigma_v\) category as \(\sigma_v\). Note that distinguishing between \(\sigma_d\) and \(\sigma_v\) is really tricky. Hence in XeF\(_4\), we have to consider the four \(\sigma\) planes as \(\sigma_v\) when there is \(\sigma_h\), when we study about point groups. This we shall see this a little later.

Note that BF\(_3\) has a \(\sigma_h\) while H\(_2\)O has none. Because in H\(_2\)O, the principal \(C_2\) axis is contained in the molecular plane. So it cannot be \(\sigma_h\).

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SAQ: How many symmetry elements the following molecules have?
(a) BF₃  (b) NH₃  (c) H₂O  (d) XeF₄  (e) CH₃*C°H(OH)Cl

Answer:
(a) BF₃: One C₃ perpendicular to molecular plane, three C₂ perpendicular to C₃ and lying on the molecular plane passing through each B–F bond, three σᵥ passing through each B–F bond and carrying the C₃ axis and one σᵥ (molecular plane) and E (note that identity element E is present in all molecules)
(b) one C₃, three σᵥ passing through each N–H bond and bisecting the molecule and E
(c) one C₂; two σᵥ (molecular plane and its perpendicular plane carry C₂) and E
(d) one C₄, four C₂ perpendicular to C₄, four σᵥ (out of which 2 can be called σᵥ) one σᵥ and E
(e) only E(C₁) as all the groups attached to the carbon with asterisk are different. This carbon is a chiral centre (asymmetric carbon atom).

The presence of only a Cₙ axis in a molecule (no other element of symmetry) makes a molecule chiral. About C₁, we have already discussed. Earlier, we knew that the presence of σ and i make a molecule achiral. But the presence of a Cₙ axis, including C₂ (E) (no other element of symmetry) makes molecule chiral. See the example below.

This molecule does not have σ, i or Sₜ (we shall know about Sₜ later), hence it is chiral. But now we know that it has a C₂ axis of symmetry, hence it is chiral. Rotating by 180° about the C₂ axis as shown regenerates the original form. We have shown in both eclipsed conformation (which really does not exist) as well as in staggered (anti) form (which really exist), a C₂ axis exists. No other element of symmetry is present in it. Note that if we draw other staggered conformations by rotating 120° w.r.t the staggered form shown, we will have only C₁ (E) in it. Hence in all conformations it is chiral.

(d) Alternating axis of symmetry/Improper Axis of rotation/Rotary Reflection axis(Sₜ):

First rotation by \( \frac{360°}{n} \) about the axis then reflection through a mirror plane perpendicular to this axis(σᵥ).

In CH₄, there is a S₄ axis. First the molecule is rotated by a C₄ axis (90°) and then reflected through a perpendicular plane to generate the original form. This is shown in the subsequent diagram.
In above molecule A, B, C and D are all H atoms. First a $C_4$ operation (90° rotation) about the axis followed by reflection through a perpendicular plane regenerates the original form. Hence that axis becomes a $S_4$ axis. I would be interested to write an extensive article on group theory in future here in this e-book for interested readers to study. Let me see, how far I can stretch the topic here before I finally come to optical isomerism.

$S_2$ axis = ‘i’

This is the same molecular form shown before to indicate the presence of centre of symmetry (i). Here we prove that symmetry element ‘i’ is same as ‘$S_2$’. Now this form also has a $S_2$ axis. First rotate the molecule by 180° ($C_2$ operation) passing through the mid-point as shown and then reflect by a horizontal plane perpendicular to the axis regenerates the original form. Can you visualise this? Note that $C_2$ here is the operation. The molecule does not have a $C_2$ axis. It has $S_2$ axis which is same as ‘i’.

$S_1$ axis = $\sigma$

Similarly we can prove that $S_1$ is same as $\sigma$. Rotating the molecule by 360° about $C_1$ axis (E) and then reflecting through a perpendicular plane regenerates the original form. This is $S_1$ axis which is same as $PS(\sigma)$

Conclusion:

© The sufficient condition for a molecule to be achiral is the presence of $S_n$ ($S_1$, $S_2$, $S_3$, .......) and to be chiral is its absence. Now we know that $S_1$ is $\sigma$ and $S_2$ is ‘i’. Earlier we were saying that if a molecule has a plane of symmetry ($\sigma$), centre of symmetry (i) or alternating axis of symmetry ($S_n$) it is achiral and absence of all these make it chiral. The example we have cited here ($V$) = (I) is the meso-form of 1,2-dichloroethane 1,2-diol which is achiral and optically inactive. We shall know about ‘meso’ a little later. We have taken the eclipsed conformation (I) to show the presence of plane of symmetry ($\sigma$ = $S_1$), and anti conformation (V) to show ‘i’ = ‘$S_2$’. The presence of one of the three elements of symmetry (in fact any $S_n$) makes the molecule achiral. There are examples, where the presence of a higher order ‘$S_n$’ makes a molecule achiral (2nd example below).

Molecule (VI) is an example in which there is ‘i’ = $S_2$. Hence it is achiral. But molecule (VII) has a $S_4$ element of symmetry. Hence it is also achiral. If you concentrate on the diagram, you can visualising by rotating 90° about the $S_4$ axis (perpendicular to the paper) so that Br atoms and $CH_3$-group exchange their sides (below the

Dr. S. S. Tripathy
plane/above the plane). However, a reflection about a horizontal axis (plane of paper) again reverses the sides and the form becomes superimposable with the original form. Sometimes it will be too hard for you to conceive the rotation-reflection operations through different elements of symmetry without manipulating the ball-stick model of the molecule. In such case, never bother until you play with a model.

If a molecule has only a $C_n$ axis ($C_1, C_2, C_3, ...$) and NO OTHER ELEMENT OF SYMMETRY, it is chiral. The example given is compound (II) which is the active form of 1,2-dichloroethane-1,2-diol and is chiral. Do not worry, you shall know the details of optical activity very soon. Note that if it has only a $C_n$ axis, and no other elements of symmetry i.e $S_n$ (which includes $\sigma$ and $i$), it is chiral. We shall be back to this point little more rigorously a bit later, when we study about POINT GROUPS.

Note that when we say $S_n$, literally it includes three elements of symmetry i.e $\sigma$, $i$ and $S_n$ (of higher order than 2).

(Do not read the following portion on POINT GROUPS now. Later, after finishing stereoisomerism, or at a later time, you can read this portion, which I have written merely out of my excitement. You may not also read it, as it is not included in your syllabus).

POINT GROUPS:

I feel tempted here to initiate discussion on point groups. Knowledge of POINT Groups will be highly essential in all branches of science and even engineering. The rigorous mathematics of group theory cannot be advanced until you have a thorough knowledge of point groups. I promise, I shall not discuss about Group theory here. I shall surely do it in future for you, of course, in a rudimentary level, as my present knowledge of mathematics is too limited to dive deep into group theory. However, I shall discuss on this to the extent that first time learners can get the feel of it.

Molecules/ions possessing same symmetry elements (both quality and quantity) belong to the same group (like a periodic group). They have many similar properties due to that. We can predict the Infrared spectra produced by molecules, the type of orbitals used by the atoms in bonding, optical activity shown, electronic spectra (UV/Visible) produced and so many other properties can be predicted from the symmetry properties of the molecules. The term POINT is due to the fact that there is at least one point within the molecule which remain unmoved (unchanged) during any kind of symmetry operation. Here we shall apply Schoenflies notation to put forth a few point groups. Here we give only two major series of point groups beginning with the letters C and D. We won’t discuss about the ‘T’ (tetrahedron), ‘O’ (octahedron) and ‘I’ (icosahedron) series of point groups. Only I shall give a few examples of such groups in this edition.

**Under C series we have**
- (a) $C_1$ point group
- (b) $C_i$ point group
- (c) $C_n$ point group
- (d) $C_{3v}$ point group
- (e) $C_{nv}$ point group
- (f) $C_{nh}$ point group

**Under D series we have**
- (a) $D_n$ point group
- (b) $D_{nh}$ point group
- (c) $D_{nd}$ point group

C-Series:

In C-series of groups, there is no $C_2$ axis perpendicular to the principal axis of higher order i.e $C_n$. In D series, however, there are $C_2$ axes perpendicular to the principal axis of higher order ($C_n$). That is the big difference between the two series.

(a) $C_1$ Point group:
It has only $C_1 = E$ and nothing else. In a common sense, we say the molecule has no element of symmetry.

Example $C(P)(Q)(R)(S)$

Dr. S. S. Tripathy
The central carbon atom bonded to four different groups is called an \textit{ASYMMETRIC} carbon atom (hence the molecule is disymmetric) or a chiral centre. Molecule belonging to such point group is chiral.

\textbf{(b) C\textsubscript{1} Point Group:}
Contains E and ‘i’ and nothing else

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {A}
ode at (1,1) {B}
ode at (1,-1) {D}
ode at (-1,1) {A}
ode at (-1,-1) {D};
\end{tikzpicture}
\end{center}

Examples: Staggered form Cl–CH\textsubscript{2}–CH\textsubscript{2}–Cl or the type C(A)(B)(D)–C(A)(B)(D)
Note that i = S\textsubscript{2}.

\textbf{(c) C\textsubscript{5} point group:}
Contains E and one plane of symmetry(σ) and nothing else
CH\textsubscript{2}XY type, all alkenes (molecular plane) containing different groups, SOCl\textsubscript{2} (pyramidal), any planar molecule having differently substituted at the sp\textsuperscript{2} carbon.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {Cl}
ode at (1,1) {H}
ode at (1,-1) {F}
ode at (-1,1) {F}
ode at (-1,-1) {Cl};
\end{tikzpicture}
\end{center}

\textbf{(d) C\textsubscript{n} Point Group:}
Contains only E and one C\textsubscript{n} (n \textgreater 1) and nothing else.
\textbf{C\textsubscript{2} Group:}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {Cl}
ode at (0,1) {OH}
ode at (1,0) {HO}
ode at (0,-1) {HO}
ode at (1,0) {Cl};
\end{tikzpicture}
\end{center}

The first one is eclipsed conformation and second one is staggered (anti) conformation of same compound called active-1,2-dichloroethane-1,2-diol. Each of these forms has a C\textsubscript{2} axis.

Other examples of C\textsubscript{2} Point Group:
H\textsubscript{2}O\textsubscript{2} which has a open book structure, 1,3-dichloroallene (or similar unsymmetrical allene),
\textbf{Unsymmetrical Allene:} The two CHCl planes (CAB) planes are perpendicular to each other as the central carbon is sp-hybridised while the terminal carbon atoms are sp\textsuperscript{2} hybridised.

\textbf{Dr. S. S. Tripathy}
It has only one $C_2$ axis passing through the middle carbon atom and perpendicular to molecular axis. It also makes 45° inclination w.r.t both CHCl perpendicular planes. This is not really easy to conceive until you have a model at your hand to manipulate. (See later for more on this)

While viewing the molecule from the internuclear axes of three carbon atoms, it appears like a tetrahedral geometry w.r.t the four groups (ABAB). By switch between between A and B at any terminal carbon atom produces its mirror image. If A has higher priority than B, then R/S notation is given by looking the higher priority group of front carbon and then to the lower priority group of the rear carbon. Thus in the above case, the first one is R- and second one is S-. We shall be back to this again later.

Substituted allene (A, B different) is chiral and show optical activity. It does not contain a chiral centre. In stead it has a chiral axis. I am sure, you have not understood R- and S- as well as chiral centre/chiral axis. Do not worry, we shall come back to all these a bit later.

H$_2$O$_2$: Open book structure ($C_2$ axis passing at the midpoint of the bond and lie in the plane carrying the carbon atoms perpendicular to the internuclear axis.

C$_3$ Point Group: Triphenyl phosphine
Note that molecule belonging to $C_2$ group are chiral.

(e) C$_{nv}$ Point Group:
Contains E, one $C_n$, and n - vertical mirror plane ($\sigma_v$)

(i) C$_2v$ Point Group: E, one $C_2$-axis, and 2 $\sigma_v$.

H$_2$O (V-shaped), COCl$_2$ (Trigonal planar), ClF$_3$ (T-shaped), SF$_4$ (See-saw shaped), PF$_4$I (trigonal bipyramidal with I on the triangular base), cis-1,2-dichloroethene, boat form cyclohexane

Dr. S. S. Tripathy
(ii) **C₃ᵥ** Point Group: E, one C₃, 3 σᵥ.
Examples: NH₃, PCl₃, CHCl₃, NF₃, all such pyramidal molecule

(iii) **C₄ᵥ** Point Group: E, C₄ and 4 σᵥ.
Example: ClF₅ (square pyramidal type), VOF₄, SF₅Cl

(iv) **Cₙᵣ** Point Group: E, Cₙ axis and infinite number σᵥ.
Examples: linear but unsymmetrical molecule like HCN, HCl or ICl, CO, HF belong to this category

(f) **Cₙh** Point Group:
Contains Cₙ, and one σₕ (obviously ‘i’ if n- is even).

(i) **C₂h** point Group: E, C₂ and one σₕ. (also one S₂ coincident with C₂)
Example: Trans but-2-ene type. Note that presence of C₂ and σₕ indicates the presence of ‘i’ (which is equivalent to S₂)

(ii) **C₃h** Group: example B(OH)₃ : orthoboric acid : C₃ and one σₕ. No ‘i’ as n = odd.
(g) \(S_{2n}\) Point Group:
Contains \(C_n\) and \(S_{2n}\) along with \(E\). In \(C_n\) group the latter is absent.
1,3,5,7-tetrafluorocyclooctatetraene belongs to \(S_4\) group. Each of them have a \(C_2\) and a \(S_4\) axis.

\[ \text{C}_2, \text{S}_4 \]

D-Series of Groups:
(a) \(D_n\) Point Group:
Contains \(E\), \(C_n\), \(n\)-\(C_2\) axis perpendicular to \(C_n\). This is very rare group having small number of examples.
Examples: \([\text{Co(en)}_3]^{3+}\) : (\(D_3\) group); \([\text{Cu(en)}_2]^{2+}\) : \(D_2\) group

\(\text{D}_{2h}\) group:
\(\text{(CN)}_2\text{C}^=\text{C(CN)}_2\), colplanar biphenyl, diborane

Twist Boat form of cyclohexane also belongs to \(D_2\) group.

All the molecules belonging to \(D_{2h}\) point group are chiral.

(b) \(D_{nh}\) Point Group:
Contains \(E\), \(C_n\), \(n\)-\(C_2\) axes perpendicular to \(C_n\), \(n\)-\(\sigma_v\), and one \(\sigma_h\) (obviously ‘i’ and also \(S_2\) coinciding with \(C_2\).

\(\text{D}_{2h}\) group:
\(\text{(CN)}_2\text{C}^=\text{C(CN)}_2\), colplanar biphenyl, diborane

\((\sigma_v)\) \(C_2\) \((\sigma_v)\) \(C_2\) \((\sigma_h)\) \(C_2\)

(molecular plane = \(\sigma_h\), not shown)
**Organic : Stereoisomerism**

**D_{3h} group:**
- BF<sub>3</sub>, Cyclopropane, 1,3,5-trimethylbenzene (mesitylene), PCl<sub>5</sub>, Eclipsed conformation of ethane

- ![Image of D_{3h} group](image)

**D_{4h} Group:**
- XeF<sub>4</sub>, [PtCl<sub>4</sub>]<sup>2−</sup>, SF<sub>4</sub>Cl<sub>2</sub>; cyclobutane

No σ plane is considered under σ<sub>v</sub> category even though some qualify for it, as there is σ<sub>h</sub>.

**D_{6h} group:**
- Benzene: Benzene has a C<sub>6</sub> six C<sub>2</sub> perpendicular to C<sub>6</sub>. It has also six σ<sub>v</sub> each containing one C<sub>2</sub> axis and the C<sub>6</sub>. All the six qualify to be called as σ<sub>d</sub> as they bisect C<sub>2</sub> axes. But customarily, three of them can be called σ<sub>v</sub> which pass through atoms and the other three can be called σ<sub>d</sub> which pass between bonds. But since there is a σ<sub>h</sub>, all the six are counted under σ<sub>v</sub>. We do not include any plane under σ<sub>d</sub> category. Hence it belongs to D<sub>6h</sub>.

**D<sub>5h</sub> Group:**
- Example IF<sub>7</sub>, pentagonal bipyramidal

**D<sub>oh</sub> Point Group:**
- Linear symmetrical molecules like C<sub>2</sub>H<sub>2</sub>, CO<sub>2</sub>, O<sub>2</sub>, H<sub>2</sub> etc. have C<sub>∞v</sub>, infinite number C<sub>2</sub> perpendicular to C<sub>∞v</sub>, infinite σ<sub>v</sub> and one σ<sub>h</sub>.

(c) **D<sub>nd</sub> Group:**
- Contains E, C<sub>n</sub>, n- C<sub>2</sub> perpendicular to C<sub>n</sub> and n- σ<sub>d</sub> (no σ<sub>h</sub>) , (also S<sub>2n</sub>)

**D<sub>2d</sub> Group:**
- Example: Allene, biphenyl with rings perpendicular to each other.

**MIRROR PLANES - DIHEDRAL PLANE**
- The vertical planes, σ<sub>v</sub>, go through the carbon atoms, and include the C<sub>6</sub> axis.
- The planes that bisect the bonds are called dihedral planes, σ<sub>d</sub>.

- ![Image of mirror planes](image)

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Dr. S. S. Tripathy
Allene: You know that central C- is sp hybridised and the terminal carbons are sp^2 hybridised. Hence the terminal CH_2 groups lie in two different planes perpendicular to each other. The principal C_2 is passing through the three C-atoms the internuclear axis (shown only by a cross mark at the centre). The two other C_2 axes are perpendicular to principal axis and also perpendicular to each other pass through the middle carbon atom, making 45^0 inclination with the two CH_2 perpendicular planes. The \( \sigma_d \) planes coincide with each CH_2 plane which are perpendicular to each other. Hence it belongs to D_{2d} point group. If you view the model in front of the principal axis, four H atoms (two on each terminal C-atoms) will appear to form a tetrahedron. It has a \( S_4 \) axis coinciding with principal C_2.

**D_{3d} Group:**
- \( C_3 \), 3- C_2 perpendicular to \( C_3 \), 3 \( \sigma_d \).
- Example: Staggered form of ethane, chair form cyclohexane

Eclipsed ethane is shown for comparison. While eclipsed ethane belong to D_{3h} group, staggered ethane belong to D_{3d} group.

**D_{4d} Group:**
- Example: \([\text{ZrF}_8]\)+. square antiprism shaped

Other Symmetry Groups:
- **N.B:** CH_4, CCl_4, NH_4^+ etc belong to a higher symmetry point group called Td Group which contains large number of symmetry elements for a regular tetrahedron (not given here)
- SF_6, [Mo(CO)_6], [Fe(CN)_6]^4-, etc belongs to another higher symmetry group called Oh point group which contains all the symmetry elements of a regular octahedron. (not given here)
- C_{60} (Bucky ball/fullerene): belongs to Ih point group having the highest number of symmetry elements (not given here). It has all the symmetry elements of a regular icosahedron.

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Dr. S. S. Tripathy
OPTICAL ISOMERISM (contd)

Already you know that disymmetric molecules do not superimpose with their mirror image forms. These are
called chiral molecules which respond differently to plane polarized light. The actual cause of chirality is the
absence of $S_n$ symmetry element ($\sigma$, $i$, higher orders of $S_n$). Chiral molecules must belong to $C_1$, $C_n$ or $D_n$ point
groups as explained before. That means it might have no real elements of symmetry (i.e. presence of only $C_1$ or
$E$) or it might have only one $C_n$ ($n > 1$), or it might have a $C_n$ axis with $n-C_2$ axis perpendicular to $C_n$ ($D_n$ point
group). To simplify the study of optical isomerism, we divide the molecules into two types.

Types:
(A) Molecules having Chiral Centre or Asymmetric Centre:
(B) Molecules without having Chiral centre or Asymmetric Centre:

Chiral Centre/Asymmetric Centre:

Tetrahedral central atom (sp$^3$ hybridised) bonded to four different groups. You know that such a
molecule belongs to $C_1$ point group. Note the difference between a chiral centre and chiral molecule. A molecule
having one or more chiral centres (asymmetric centres) is chiral, but the vice versa is not true, i.e ‘all chiral
molecules possess one or more chiral centres’ is not true. In the case (B), we shall see disymmetric molecules
having a chiral axis also shows optical isomerism

(i) Asymmetric Carbon atom: C- atom bonded to four different groups/atoms.
(ii) Asymmetric Nitrogen atom/ Phosphorous/ Sulfur atoms: X-atom bonded to different groups/atoms.

Chiral trialkyl amine, though chiral does not show optical activity due to rapid flipping (pyramidal inversion) at
the rate of $2 \times 10^{11}$ Hz. However, introducing cyclic structure in it, produces detectable enantiomerism (resolvable).

But chiral trialky phosphines are resolvable without cyclization. Please do not bother about this example now.
You read it after finishing the chapter.
Optical Isomerism with One Asymmetric Carbon atom:
The chiral centres are also called STEROGENIC Centre or Sterocentre.

A molecule having one asymmetric carbon atom, like lactic acid (2-hydroxypropanoic acid) exists in two non-superimposable forms. Form (I) and (II) are interconvertible by one exchange between any two groups by bond breaking and making processes at the chiral centre (called one SWITCH). In the above diagram, the groups lying at the Left and Right have been exchanged for simplicity in visualizing the mirror images in a vertical mirror plane shown. But in principle, exchange between any two groups (any single switch) will convert one form to its mirror image form. These mirror image stereoisomers are called Enantiomers/optical antipodes.

Optical Activity: If plane polarized light i.e PPL (we will discussed about it later) is passed through one of the two forms, it will rotate the PPL to the right and then that is to be named as dextrorotatory or d- or (+) and the other form will definitely rotate the PPL to the left and will be called laevorotatory or l- or (–). To know to which direction the PPL rotates, we have to put the compound dissolved in a achiral (optically inactive solvent) in an instrument called POLARIMETER and then detect which is d- and which is l-.

Since the two enantiomers respond differently to PPL, they are called optical isomers and hence the this configurational stereoisomerism is called Optical isomerism.

Inversion and Retention of Configuration:
If we make one or any odd number of switches (exchange between any two groups is called one switch), the configuration will be inverted. d- will change to l- and vice versa. This is called Inversion of configuration.

\[
\begin{align*}
\text{d} & \quad \rightarrow \quad \text{l} \\
\text{l} & \quad \rightarrow \quad \text{d}
\end{align*}
\]

If we make two or any even number of switches, then the same configuration is revived. This is called retention of configuration.

\[
\begin{align*}
\text{d} & \quad \rightarrow \quad \text{d} \\
\text{l} & \quad \rightarrow \quad \text{l}
\end{align*}
\]

Enantiomers are identical with each other in all properties except their response to PPL.

In the above example of lactic acid, we have two different lactic acids i.e d-lactic acid and l-lactic acid. Both are produced in the fermented milk products like curd/yogurt and are present in many food and beverages. The two have different biological response.

Sometimes, one form a chiral molecule is biologically active while the other is not. For example glucose that our body requires should be in ‘d’ or ‘+’ form. ‘l’ or – glucose has no action. Sometimes one enantiomer act as poison to the body while the other is useful.

Racemic Mixture(d/l mixture/recemate):
A physical mixture containing 50% of d- and 50% of l- form of a particular chiral molecule is called racemic mixture or d/l mixture. Such a mixture is optically inactive due to external compensation. The individual components can be separated from the mixture by adopting special techniques. This is called Resolution of a racemic mixture. We shall discuss about it later.

Dr. S. S. Tripathy
Organic : Stereoisomerism

**PPL:** When monochromatic light (say D line of Sodium i.e 589 nm) is passed through a NICOL prism (made up of pure CaCO₃ crystal), then it becomes PPL. In ordinary monochromatic light, the light waves travel in all possible directions, while in PPL, the light waves travel along one particular plane. Hence it is called polarized. Now we shall not discuss the reason behind the conversion of normal light to PPL by passing through Nicol prism. Also we won’t discuss the reason why one enantiomer rotates PPL to the right and its mirror image rotates to left. The hard-core physics behind it, we choose to ignore it now.

**Optical Rotation:**

Light from a monochromatic light source passes through a polarizer (Nicol prism) and becomes PPL. PPL is then allowed to pass through the a cylindrical tube having length ‘l’ containing a solution of the chiral substance in an achiral solvent like EtOH, acetone etc. having concentration ‘c’. On the other side of the tube, when the PPL emerges out, it is deviated by an angle ‘\( \alpha \)’. From these data, the specific rotation of the sample is determined. See below.

Every chiral molecule has a standard value of optical rotation called **Specific Rotation** which is defined as follows.

\[
\left[ \alpha \right]_D^{20} = \frac{\alpha}{c \times l}
\]

Where  
- \( c \) = concentration of the chiral substance in an achiral solvent in g/mL  
- \( l \) = length of the polarimeter tube in ‘dm’.  
- \( \alpha \) = actual angle of rotation of the substance  
- \( D = D_1 \) line of sodium is used to prepare the PPL.  
- 20 stands for the temperature i.e 20°C.

If the solution contains a racemic mixture, \( \alpha = 0 \). But for pure (+) or (–) compound \( \left[ \alpha \right]_D^{20} \) is fixed and is available in the literature. Often, during synthesis of a chiral compound, pure enantiomer is not obtained. Either a racemic mixture is obtained (\( \alpha = 0 \)), or an unequal mixture of d- and l- forms are present with one of the two remaining in excess. This can be determined by measuring \( \left[ \alpha \right]_D^{20} \) for the mixture and comparing it with that of a pure enantiomer.

\[
\text{Enantiomeric Excess(EE)/Optical Purity(OP)} = \frac{\left[ \alpha \right]_{\text{sample}}}{\left[ \alpha \right]_{\text{pure}}} \times 100
\]

**SAQ:** During synthesis of a (+) compound(product) from a pure (–) compound(reactant), the \( \left[ \alpha \right]_D^{20} \) of the product was found to be +6°. But from literature the same enantiomer in pure form has \( \left[ \alpha \right]_D^{20} = 20° \). Then what is percentage of d- and l- form in the mixture. What is the % of racemization and % of inversion during the synthetic reaction step?

Dr. S. S. Tripathy
Solution:

\[ \text{EE} = \frac{6}{20} \times 100 = 30 \text{, Hence 30% is in d-form has remained in excess and the rest 70% is racemic mixture, out of which 35% d- and 35% l-}.

So total % of d- form = 30 + 35 = 65 %;  Total % of l- form = 35 %

So % of racemization = 70%, % of inversion of configuration(same as total d-form) = 65%(because it has been synthesised from a pure l- reactant).

**Wedge Formula and Fisher Formula for a molecule having chiral centre:**

When 3-D molecule is represented in 2D(paper) with the help of wedges(having thick or bold faced lines) along with normal and broken lines, it is called a wedge formula. The two wedges in formula I and II represent bonds(or groups, here q and s) lying above the plane. The broken line represent the bond(or group, here r ) lying below the plane. However a normal line represent a bond(a group, here p in I and both p and s in III and none in III) lying on the plane.

Formula (I) and (II) are similar. Just by tilting the model little backwards, group p which was lying on the plane in (I) will go below the plane in (II). Now both p and r lie below the plane in (II). Though q and s will be pushed a little up, they still remain above the plane.

Wedge formula (III) is sometimes called “FLYING WEDGE FORMULA”. In this, two groups(here p and s) lie on the plane while the third lie above(here r) and fourth below the plane(here q).

**Fischer Projection Formula:**

To represent a 3-D molecule without using wedges and broken lines as shown in the three wedge formulae, Fischer put forth a simple way of writing it with normal lines.

*Fischer formula is a projection of the wedge formula on a vertical plane.

**Wedge formula (I) and (II) converted to Fischer Formula:**

The groups which are lying above the plane( q and s ) give horizontal projections and the groups which lie below the plane or lie on the plane ( p and r ) give vertical projection.

Note that the vertical projections(line UP and DOWN of the central C) actually lie below the plane and the horizontal projections(line to LHS and RHS of the central C) line above the plane.

Dr. S. S. Tripathy
Organic : Stereoisomerism

**Flying Wedge Formula Conveted to Fischer Formula:**
First, the group lying below the plane (connected by broken line) is to be put in any of the two vertical positions (up or down) which really lie below the plane. Then the other three groups are placed in the same sequence in the other three positions of the Fischer formula. You can look for clockwise sequence or anticlockwise sequence and start with any group at any position, you like. The configuration will remain the same but it will look differently in the Fischer formula. Such formula which have same configuration but look differently are called **HOMOMERS**.

![Flying Wedge Formula](image)

First group q is place in any vertical position (in the 1st Fischer formula it is placed in UP position and in the 2nd F.F it is placed in DOWN position) and then start from any of the remaining three groups from any position you like. I have shown clockwise sequence. You can, as well, show anticlockwise sequence. p → s → r follow in clockwise sequence, in my case. You could have shown that p → r → s follow anticlockwise sequence. Once you put the group 'q' in any vertical position, you forget that group. Concentrate on the other three. Start from any group and place the other two groups in the same sequence as present in the flying wedge formula.

Now the question arises, how can you know that the homomers which appear differently have the same configuration. The two are one and the same (superimposable) or they are enantiomers (optical isomers)? For that let us know two types of configurations namely relative and absolute configurations.

**Relative and Absolute Configurations:**

**Relative Configuration:** (d/l)

d(+) or l(–) that we knew before are called relative configuration. If one the mirror image isomers (enantiomers) is d(+), the other enantiomer is bound to be l(–). Both have the same value of $\alpha_d^{po}$, only sign is opposite of each other. Such a molecule can contain one or more asymmetric carbon atoms (or chiral centres) as we know about that later but the molecule as a whole can be either (+) or (–). There is another relative configuration often used in carbohydrate and other biomolecules called D and L (do not confuse with ‘d’ and ‘l’), which we shall discuss a little later.

**Absolute Configuration:** (R/S)

Without having any idea, how a particular chiral molecule will respond to PPL, we can assign its configuration at each chiral centre by R or S notation. (R=Rectus: means Right Handed and S= Sinister: mean Left Handed in Latin). If a molecule has more than one asymmetric centre, then each such centre has to be assigned R or S. This is done by applying CIP Rule.

**CIP Rule (Cahn-Ingold-Prelog):**

1. The four different groups bonded to the asymmetric carbon atoms are assigned with decreasing priority or ranking; 1 to 4. The atomic number of the directly bonded atom is considered for fixing priority. Greater the atomic number, greater the priority (ranking). For example: $-\text{Cl} > -\text{OH} > -\text{CH}_3 > -\text{H}$

Dr. S. S. Tripathy
Organic : Stereoisomerism

If the directly bonded atoms are same, the subsequent atoms are compared till the first point of difference is found. The atom or group bonded to atom having greater atomic number at that point makes the group’s priority greater, irrespective of whether this group is bonded to one such atom and the other group is bonded to more than one atoms of lower priorities. Between –CH₃ and –COOH, the higher priority group is –COOH as, there is O atom after C while in –CH₃, there is H atom.

\[ -\text{Cl}(1) > -\text{OH}(2) > -\text{COOH}(3) > -\text{CH}_3(4) \]

(Do not mistake this to be priority to have any link with the priority that you studied in IUPAC nomenclature. There, –COOH has higher priority over –OH, but here in CIP rule, –OH has higher priority over –COOH, as the first atom O in –OH has greater atomic number than first atom C in –COOH group.

\[ -\text{CH}_2\text{Br} > -\text{COOH} \]

One Br atom at the point of difference makes the –CH₂Br group senior to –COOH group although the in the latter, C is bonded to more than one O atoms. You should not look to 2 H atoms bonded to –CH₂Br, once you find one Br atom.

(More about fixing priority will be discussed later).

2. The molecule is viewed opposite to the least priority group i.e Group 4. In the Wedge formula shown before i.e (I) and (III) look befitting to view the molecule opposite of the least priority group ‘r’ in case of formula (I) and ‘q’ in case of formula (III). The viewer(you) is to remain in front of the molecule projecting the groups 1, 2 and 3 towards you while group 4 has to remain at the rear side(back) of the viewer.

3. R/S : While viewing the groups in the sequence 1 → 2 → 3, if the our eye rotates in clockwise direction, then the configuration is R- and if our eye rotates in anticlockwise direction, then it is S- configuration.

Viewing Wedge Formula (I):

Look to the Wedge formula of lactic acid below. I have kept the least priority group(4), H- in this case, deliberately on the back side, to apply CIP rule correctly and assign the configuration. In the first formula, our eye rotates anticlockwise while viewing the groups in the sequence 1 → 2 → 3, hence it is S-configuration.

By switching between any two groups (here i have switched between –COOH and –CH₃ groups, we see the rotation of eye becoming clockwise while viewing in the same sequence. Hence the second one is R-configuration. R and S- lactic acids are mirror image isomers(enantiomers), though we cannot visualise that in the two formula given below. For that we have to manipulate the two models in two hands to visualise, they are the non-superimposable mirror images. Had you switched between OH and COOH in stead of COOH and CH₃, we could have visualised the mirror images with a conventional vertical mirror plane placed in between the formulae.

Note that S-lactic acid is d(+), hence R-lactic acid is l(–). While writing the IUPAC name, we are required to give absolute configurations(R/S) at each chiral centre before giving the name. If there is only one chiral centre, then only R or S is written before the name. But if there are more than one chiral centres, we have to write (2S, 3R) or (2R, 3R) like this. For molecule having three chiral centres, similarly we have to assign the configuration at each carbon and write three times. Note that the terms of + or – is associated with the molecule once. The

Dr. S. S. Tripathy
whole molecule can be either d(+) or l(−), if present in pure form. Otherwise a d/l mixture (equal or unequal %).

Viewing Flying Wedge formula (III):

In this case too, we kept the least priority group (H) below the plane (shown by broken line) so as to apply CIP rule correctly. Thus first one produces anticlockwise rotation, hence S- while the second one produces clockwise rotation, and so it is R-. We have switched between COOH and OH groups in this example to convert S- to R-.

Golden Rule: For molecule in which viewing is made on the same side of the least priority group, i.e group 4 does not lie opposite side of the viewer rather is projected towards you, in that case, we can just change the convention. If eye rotates clockwise in the sequence 1 → 2 → 3, then it S-configuration and if rotates anticlockwise, it is R-configuration. This is opposite to the CIP rule and sometimes referred to as Golden Rule. By that, one need not have to manipulate the model to take group 4 to the rear side. In stead, view the molecule, as it is given to you.

Caution: It is always risky to use Wedge formula for assigning configuration. Only Wedge formula (I) can give correct predictions. However the other two including flying wedge formula often will make wrong predictions while handling in pen and paper. Yes, when you are given a model to manipulate in your hand, then the prediction will be correct. Therefore, it is higly essential to convert the Wedge formula to Fischer formula and then apply normal CIP rule or Golden rule to assign the configuration correctly.

CIP Rule applied to Fischer Formula (FF):

(a) If the least priority group (group 4) occupies any of the two vertical positions (UP or DOWN) that means it is lying below the plane of the paper, then normal CIP conventions are followed.

Clockwise : R and Anticlockwise : S

In this case, group 4 i.e H is occupying a vertical position (DOWN), hence we applied normal |CIP rule to get its S-configuration.
Organic: Stereoisomerism

(b) If the least priority group (group 4) occupies any horizontal position (Left or Right) that means the group is lying above the plane, then it is brought to the vertical position by making two switches (retention of configuration). This can be easily achieved by keeping one group fixed (in this case, either UP or DOWN group) and making a sequential shift of the three groups either clockwise or anticlockwise. This is equivalent to two switches. You may not adopt the sequential shift method, and make any two switches to bring group 4 to any vertical position (UP or DOWN). Then normal CIP conventions followed to assign the configuration.

**Golden Rule:** This can be directly applied when the least priority group occupies any horizontal position (lying above the plane) in the Fischer formula. There is no need to bring group 4 to vertical position by making two switches and then apply normal CIP rule. This is opposite to the normal CIP conventions.

Clockwise: S and Anticlockwise: R

In the above example, we can directly use the Golden rule to get its S-configuration (shown below) in stead of making two switches and then applying normal rule. The latter is time consuming.

**Conclusion:** So for any Fischer formula carrying the least priority group in any vertical position (UP or DOWN), normal CIP rule is applied and if that group occupies any horizontal position (Left or Right) then Golden rule is applied assign the configuration.

* When you convert a flying wedge formula to Fischer formula you can preplan to put the least priority group in any vertical position. Look to this case.

Here while converting the flying wedge formula to Fischer formula, after putting the group lying below the plane (CH₃–) in a vertical position (Down here), I started with H from the other vertical position (UP), keeping in mind that I shall use normal CIP rule. I could have kept H in any horizontal position without making any preplanning of the rule I shall be following. In that case I would us Golden rule to get the same configuration.

Dr. S. S. Tripathy
Organic : Stereoisomerism

PRIORITY OF GROUPS/Ligand Precendnce Rule (Contd.)

(i) More the length or degree of branching in an alkyl group, more is the priority

\[
\text{CH}_3 \quad < \quad \text{CH}_3\text{CH}_2 \quad < \quad \text{CH}_3\text{CH}_2\text{CH}_2 \quad < \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2 \quad < \quad \ldots.
\]

In \( \text{CH}_3 \), carbon is bonded to 3 H atoms while in \( \text{CH}_3\text{CH}_2 \), carbon is bonded to one C and two H. Hence Ethyl has greater precedence over methyl. Similarly as the length increases, the point of difference is C compared to H.

\[
\text{CH}_3\text{CH}_2\text{CH}_2 \quad < \quad \text{CH}_3\text{CH} \quad \text{CH}_3
\]

In n-propyl, C is bonded to two H and one C while in isopropyl, C is bonded to two C atoms and one H atom. Hence isopropyl is senior to n-propyl.

(ii) More the bond order in C–C bond, more is the priority.

\[
\text{CH}_3\text{CH}_2 \quad < \quad \text{CH}==\text{CH} \quad < \quad \text{CH}==\text{C}
\]

For assigning priority, a double bond is presumed to be a single bond with an extra C atom attached to each carbon. Similarly a triple bond is presumed to be a single bond with two extra C atoms bonded to each carbon. So in ethyl, C is bonded to one C and two H, while in vinyl(ethenyl), C is bonded to two C and one H. In ethynyl, C is bonded to three C atoms. Hence it is the seniormost.

\[
\text{CH}_3\text{CH} \quad < \quad \text{CH}==\text{CH} \quad \text{CH}_3
\]

In vinyl and isopropyl, the first carbon atom in each has identical bonding situations (two C and one H). However when you move to the 2nd C atom, we find the difference. In vinyl, the 2nd C is bonded to one C and two H atoms while in isopropyl, the 2nd C is bonded to three H atoms. Hence vinyl is senior.

Dr. S. S. Tripathy
Organic: Stereoisomerism

Both phenyl group and ethynyl group have identical surroundings for 1st and 2nd C atoms, the point of difference lies in the 3rd carbon atom. But between phenyl and vinyl, the point of difference lies in the 1st carbon atom.

(iii) While comparing the number of other atoms bonded to an atom, you must start from higher atomic number atom to lower atomic number atoms. See this example.

\[
\begin{align*}
\text{CH}_3\text{-CH-} & < \text{CH}_2\text{-CH-} < \text{HOCH}_2\text{-} \\
\text{CH}_3 &
\end{align*}
\]

Hydroxymethyl group is senior to vinyl, because, in the former C is bonded to O atom and two H atoms, while in vinyl, C is bonded to two C atom and one H atoms. The presence of one higher atomic number atom (O) makes the hydroxymethyl group senior to vinyl, despite the latter having two C atoms bonded to C and the former having two H atoms bonded to carbon.

(iv) 

\[
\begin{align*}
\text{O-} & > \text{O-CH}_3 > \text{O-CH}_2\text{CH}_3 > \text{C-CH}_3 > \text{C-H} \\
\text{C-} & > \text{OH}
\end{align*}
\]

(v) 

\[
\begin{align*}
\text{CH}_2\text{Br} & > \text{HOH} \\
(\text{presence of one Br atom makes bromomethyl group senior to} \text{–COOH})
\end{align*}
\]

(vi) 

\[-\text{CH}_2\text{O-H} > -\text{CH}_2\text{CH}_2\text{Br} \ (\text{Br atom in the second is farther away from the 1st C})
\]

(vii) 

\[-\text{D} > -\text{H}
\]

(viii) 

\[-\text{cis(Z)} > \text{trans(E)}
\]

The application of priority orders given in (vi), (vii) and (viii), we shall see later.

Some more examples with Fischer Formula:

- **R-2-chloro-2-methylbutanal**
  (Golden Rule)

- **R-2-ethylbut3-ene-1,2-diol**
  (normal rule)

- **S-4-bromo-3-phenyl-3-(propan-2-yl)but-1-ene**
  (golden rule)

Dr. S. S. Tripathy
Simple Conversion Rules for one Chiral Centre:

1. If the Fischer formula is rotated 180° about a vertical axis i.e making upside down, then the configuration is retained.

\[
\text{S-lactic acid} \quad \overset{180^\circ}{\longrightarrow} \quad \text{S-lactic acid}
\]

2. If the Fischer formula is rotated 90° about a vertical axis, i.e then the configuration is inverted.

\[
\text{S-lactic acid} \quad \overset{90^\circ}{\longrightarrow} \quad \text{R-lactic acid}
\]

SAQ: Convert the following Wedge formula to Fischer formula and assign configuration (R/S). Also give IUPAC name of the compound.

(a) CH₃CH₂CHO
(b) CH₂CH₂Br
(c) CH₂CH₂OH
(d) H₂C
(e) H₂N
(f) CH₂CH₂OH

SAQ: Draw the Fischer formula for the following.
(a) R-butan-2-ol
(b) S-2-bromobutane
(c) S-2-methylbutanal

SAQ: Draw all the isomeric alcohols (including stereo) from the formula C₄H₁₀O.
Answer: total 5
(a) CH₃CH₂CH₂CH₂OH (achiral)
(b) (CH₃)₂CHCH₂OH (achiral)
(c) (CH₃)₃COH (achiral)
(d) and (e) are two stereoisomers of butan-2-ol (chiral)
Organic: Stereoisomerism

Out of four structural isomers, butan-2-ol has a chiral centre and hence exist in two enantiomeric forms (R and S). So total of 5 isomers exist with the formula given.

**Answer to Previous SAQs:**

**Answer to previous SAQs:**

(a)  
(b)  
(c)  

Always put the least priority group in any vertical position and then arrange the other three according to the requirement (R or S).

**Absolute vs. Relative Configurations:**
There is no fixed relationship between the two configurations. For example, R-lactic acid is l(−) i.e. it is laevorotatory with $\alpha_D^{20} = -3.33^\circ$, hence S-lactic acid is d(+) i.e. dextrorotatory with $\alpha_D^{20} = +3.33^\circ$. But R-methyl lactate (an ester of lactic acid) is d(+) and hence S-methyl lactate is l(−). So there is no obvious relationship between the two. A fixed compound has fixed relative configuration w.r.t a particular absolute configuration, which is available in the literature. But different compounds having same absolute configurations (say either both R or both S) may have same or may have different relative configurations (d/l).

**SAQ:** Draw Fischer formula of the simplest (smallest MM), (a) R-alkane   (b) S-alkene  (c) R-alkyne  (d) R-alcohol  (d) S-aldehyde

**Solution:** Put a cross mark to indicate the chiral centre. Then start putting groups from -H, then –CH₃, –CH₂-CH₃ etc. in increasing priority. If it contains a functional group, then one position is to be reserved for that.

(a)  
(b)  
(c)  

(We could put i-Pr in stead of n-Pr, (for alkene, the vinyl and alkyne, ethynyl group is a must) so there is another possibility)

(d)  
(e)  

Dr. S. S. Tripathy
Molecules containing Two Chiral Centres:

Case-I: Structurally symmetrical molecule: (Tartaric acid type)
In this case there are three pairs of identical groups. In tartaric acid, the they are OH pair, COOH pair and H pair. Each chiral centre is bonded to same four groups and hence the both are structurally identical.

Meso Form:

Here we have taken the eclipsed conformation of the molecule where 3 pairs of groups are eclipsed. We shall talk about conformational isomerism later. This form has a plane of symmetry(PS) and hence it is achiral and optically inactive. This is called MESO form. If we assign the configuration in the Fischer formula, we find that it is (R, S) from top to bottom. If the upper half of the molecule rotates the PPL to the right, the lower half will rotate to the left to the same extent and the molecule is as a whole optically inactive due to internal compensation.

Assignment of configuration:

We have to assign the configuration at each chiral centre by assigning the relative priorities. Here, the big group containing the other chiral centre kept inside a rectangular box is itself is one group whose priority is the 3rd. This is because the chiral C inside is bonded to one O and one C while the -COOH carbon is bonded to 3 O atoms as per our previous analysis. Normal CIP rule is followed here as the least priority group (H) is present in a vertical position in each case(below the plane of the paper). Had the least priority group occupied any horizontal position(lying above the plane), we would apply Golden rule to assign configuration.

Later we shall find that the meso-tartaric acid shown, has the stable anti conformation where the 3 pairs of identical groups lie opposite to each other. We have shown the eclipsed form which does not exist as it is energetically unstable. We already know from our knowledge about symmetry operations, that the anti form has an inversion centre(i), which makes it achiral. Later, we shall find that this has also has another stable form(though less stable than anti) called gauche form which is chiral, but it remains in as enantiomeric pair(d/l) which makes the mixture inactive. We shall discuss about this in details later in the heading “conformational enantiomorphism”. Note that meso- form has the configuration (R,S), irrespective of whether the conformation...
Organic : Stereoisomerism

is eclipsed, anti, gauche. By changing conformation effected by rotating C–C bond, the configuration does not change. The beginner to note that always configuration at the chiral centres are assgined best from the eclipsed formation as FF itself for 2 chiral centre systems is drawn from the eclipsed conformation.

We can play with a model and convert meso-tartaric acid to its mirror image form by making one switch at each chiral centre. (R,S) from top to bottom will be changed to (S,R) from top to bottom. But these two forms are one and the same i.e superimposable. So in such symmetrical molecule (R,S) = (S,R). We cannot write here (2R, 3S), because while naming from other side it will be (2S, 3R). Remember that if a form is meso then it has one unique form, as its mirror image form is the same as the original form. So the locants of chiral carbon atoms are dropped.

You can just try with two such moleculear models and see that they are indeed superimposable.

Active Forms:

By making one switch at any one chiral centre the meso form is converted to an active form. Such a form has no plane of symmetry, inversion centre or any improper axis of rotation. It has a C_2-axis and hence it is chiral molecule and so it has non-superimposable mirror image form. If you have already studied on symmetry and point groups given before, you must have understood this. If one form will be (R,R), the other form will be (S,S). One form is converted to the other by making one switch at each chiral centre.

(R,R) form was found to be (+) with $\alpha = +12^\circ$ and hence (S,S) form is (–) with $\alpha = -12^\circ$. Here we find that absolute configuration-wise we had to assign for each chiral centre. But relative configuration wise either d(+) or l(–). (R,R) and (S,S) forms are non-superimposable mirror image forms. They are enantiomers or optical antipodes. Both the active tartaric acids have same mp=172°C (N.B: Absolute configuration was determined by special X-rays technique while relative configuration is determined in a polarimeter).

Racemic Mixture(d/l) mixture:

A 50% mixture of d and l tartaric acid each will be called a Rac. mixture, which is optically inactive due to external compensation.

Conclusion: Symmetrical molecules like tartaric acid having two chiral centres can have three forms

(a) R,S = S,R (meso)  
(b) RR (active)  
(c) SS (active)

Dr. S. S. Tripathy
**Diastereoisomers/Diasteromers:**
Meso(RS=SR) and one of the active forms(RR/SS) of tartaric acids are not mirror images of each other. Such stereoisomers which are not mirror images of each other are called diastereoisomers. Note that we shall see this again in geometrical isomerism, in which we shall study that geometrical isomers also belong to diastereoisomers.

(R,R) and (R,S) tartaric acids are one pair of diastereosimers. Similarly (S,S) and (R,S) tartaric acids are antohter pair of diastereoisomers.

In enantiomers, each chiral centre has opposite configurations of each other, while in diastereoisomers at least one of the chiral centres have the same configuration.

Diastereoisomers have all physical properties different. They have different melting points (For example meso-tartaric acid has mp = 140°C, while the active one has mp = 172°C), different boiling points, solubility, refractive index etc. Hence it is extremely easy to separate the diastereoisomers. Since enantiomers have all physical properties same except rotation to PPL, it is extremely difficult to separate the enantiomers.

**Case-II: Structurally Unsymmetrical Molecule:**
When at least one pair of groups at the two chiral centres are different, then there cannot be any meso form(no σ, i or Sn), so it has two pairs of enantiomers namely (a) (R,R) and (S,S) (b) (R,S) and (S,R)

In this case, (R,S) and (S,R) are non-superimposable mirror images. Hence a total of four optical isomers.

When only one pair of groups (here Me and Et) are different and the two pairs are same, then we can use the term Erythro and Threo(burrowed from Carbohydrates Erythrose and Threose).

**Erythro d/l pair:** When the non-identical pair remains eclipsed or lie on the same side(in the above FF, they both lie below the plane: vertical lines), the the two identical pairs also remain eclipsed or remain on the same side(in this case OH groups lie on the same side, so also the H atoms), it is called Erthro d/l.

In the above FF, Golden Rule has been applied to assign the configurations at C₂ and C₃ as H atoms occupy horizontal positions(lie above the plane). (2S, 3R) and (2R, 3S) are found here for erythro pair. Unlike in symmetrical compound like tartaric acid in which (S, R) is same as (R,S), here the two are non-superimposable mirror images, in which one is d(+) and the other is l(−). They are enantiomers. But which is which, i cannot say now as i do not have the data with me. Literature has to be surveyed to know this. You already know that there is no obvious relationship between the absolute and relative configurations.

By making one switch at any chiral centre, Erythro is converted to Threo(just like meso tartaric acid converted to active form).

**Threo d/l pair:** When the non-identical pair(here Me and Et) remain on the same side(eclipsed), the other two identical pairs remain opposite to each other, then that is called Threo. In this case, OH groups lie on the opposite sides,

Dr. S. S. Tripathy
Organic : Stereoisomerism

so also H atoms. (2R,3R) and (2S, 3S) are the configurations of the two threo forms in this case. They are also enantiomers. If one of them is (+), the other is (–).

One of threo and the other from erythro constitute a diastereoisomeric pairs.

Diastereoisomeric pairs: (2R,3S) and (2S,3S) (ii) (2R,3S) and (2R,3R) (iii) (2S,3R) and (2S, 3S).

Thus there can be four pairs of diastereomers possible.

Conclusion:
(i) There will be four optically active stereoisomers in this case. (R,R) and (S,S); (R,S) and (S,R) i.e two pairs of enantiomers.
(ii) If only one pair is non-identical, then the term Erythro and Threo can be used to specify a particular pair.

SAQ: Assign the configuration (R/S) at each chiral centre. Indicate whereever required whether it is meso, active, erytro or threo.

(a) Br CH₃
    H CH₃
    Br CH₃

(b) CH₃ OH
    H CH₃
    HO CH₃

(c) Me Et
    H Me
    H Me

(d) Me OH
    Cl Me
    Et Et

Answers:

(a) (No PS in this case, so active)

(b) Meso(R,S)

Intelligently you can guess from the given question that it is a Meso form as CH₃ groups, H atoms and OH groups lie away from each other. No pair lie on the same side, like the previous case. Otherwise, you can either make two switches(sequential shifts among three groups) or make a 120° rotation about the C–C bond(conformation, you perhaps cannot capture now), you can get the 2nd form which is a homomer of the 1st one(identical). There you can clearly see a plane of symmetry. If it is meso, the configuration has to be R,S = S,R.

Dr. S. S. Tripathy
Organic : Stereoisomerism

We have to change it to the other homomer by a sequential shift (or rotation by 120°) to see whether belong to erythro or threo category? It is threo. While assigning configuration for C₃, note that the bulky group bearing Br- is no.1. Golden rule has been applied.

In this case, threo/erythro terms cannot be used. Only by assigning configuration, we can distinguish the isomers.

**SAQ:** Draw the F.F for the following: (a) meso-butane-2,3-diol (b) active(R,R)-2,3-dibromobutane (c) Threo(any one) 3-bromobutan-2-ol. Assign the configuration at each chiral centre for the one you give.

**Answer:**

(c) is Threo, since Br and OH lying on the same sides, the two identical pairs lie on opposite sides. If you cannot make out from 1st FF, you can make sequential switches at each chiral centre to get its homomer, in which everything looks crystal clear. The configuration i gave here is (2R,3R). Threo has another form (2S,3S) which is the enantiomer of the form drawn.

**IMPORTANT:** Except for a symmetrical compound having meso configuration(R,S), in all others, you have to assign the configuration at chiral centres w.r.t its locant in the IUPAC name. So first give its IUPAC name, and then assign configuration at the chiral centre with respect to the name, eg. (2R, 3S) or (2S, 3S) etc.

**Case-III: Unsymmetrical Structure having 3 Chiral Centres:**

In this case there are four pairs of enantiomers i.e a total of 8 optical isomers. Look to the following example.

This molecule has three chiral centres shown by star marks. The compound is structurally unsymmetrical, so
Organic: Stereoisomerism

we cannot think to have a meso form for this molecule. The four pairs of enantiomers are as follows.
(a) (2R, 3R, 4R) and (2S, 3S, 4S)  
(b) (2S, 3R, 4R) and (2R, 3S, 4S)  
(c) (2R, 3S, 4R) and (2S, 3R, 4S)  
(d) (2S, 3S, 4R) and (2R, 3R, 4S)

No other combination is possible for this. In each pair of enantiomers, each of the chiral centres are inverted (opposite configuration). But any one from each pair with any other from another pair are related as diastereoisomers in which there will at least one chiral centre having identical configuration.

\[
\begin{align*}
\text{(2R,3R,4R)} & \quad \text{(2S,3R,4R)} & \quad \text{(2R,3S,4R)} & \quad \text{(2S,3S,4R)} \\
\text{(-) ribose} & \quad \text{(-) arabinose} & \quad \text{ (+) xylose} & \quad \text{ (+) lyxose}
\end{align*}
\]

Four diastereomers are shown. The enantiomer of each has not been shown. So in total 8 optical isomers are there for such compound. These belong to a class of compounds called carbohydrates and this comes under aldopentose. The detailed discussion on carbohydrates will be done later. But one thing you can mark that the sign of optical rotation has nothing to do with absolute configuration. (2R, 3R, 4R) ribose is (-), hence its enantiomer (2S, 3S, 4S) ribose is (+), which is not shown.

**Case-IV: Symmetrical Structure having 3 Chiral Centres:** *(Pseudosymmetry)*

Look to the following compound.

\[
\begin{align*}
\text{HOOC—CH(OH)}*\text{—CH(OH)—CH(OH)—COOH} & \\
2,3,4-trihydroxy pentanedioic acid
\end{align*}
\]

From a layman’s point of view, the middle carbon (C₃) does not look like a chiral centre as the two bulky groups on either side (each carrying a chiral centre) are structurally identical. But we are forgetting that they might also be different if their configurations are different, i.e. one is R and the other is S(R > S). In that situation, the middle carbon does act as a chiral centre. Yes, when the terminal chiral centres have same configurations i.e. either both R or both S, then middle carbon (C₃) becomes achiral. That is why such a carbon atom is often called a *pseudochiral centre*. It means, it can be chiral and also achiral depending on the surrounding.

Dr. S. S. Tripathy
Applying Golden rule, you can find the configuration of the C₃ (pseudochiral centre), taking R > S. Note that there are two meso forms in this molecule which are diastereomers. Also note that the mirror image of meso-I (S,s,R) is superimposable with the form shown (R,r,S). Similarly the mirror image of meso-II (S,r,R) is superimposable with the form shown (R,s,S).

Pseudochiral centres are customarily shown with small letter (r,s) to distinguish them from normal chiral centres. Note that while counting for number of chiral centres in a molecule, the pseudochiral centre is taken into consideration.

In the active form, the two terminal chiral centres become identical and C₃ becomes achiral.

There are two active forms of this compound i.e (R,R) and (S,S) which are enantiomers. C₃ now is not a chiral centre. So we do not talk about it for the active forms.

So such molecule has two meso forms and two active forms.

**Formula For Finding Number of Optical Isomers:**

(A) **Structurally unsymmetrical Molecule: (Cannot have a PS)**

(i) No of d/l (active forms) = \( \frac{2^n}{2} \) (where \( n \) = number of chiral centres)

Hence number of enantiomeric pairs = \( \frac{2^n}{2} \)

(ii) No. of meso forms = 0

Example:

(i) \( n = 2 \); No. of optically active forms = 4 i.e two pairs of enantiomers. (see the following example)

- (2S,3R)-pentane-1,2-diol  
  (Erythro d/l pair)

- (2R,3S)

- (2R,3R)

- (2S,3S)

  (Three d/l pair)
Organic: Stereoisomerism

(ii) OHC—CH(OH)—CH(OH)—CH(OH)—CH(OH)—CH₂OH;  \( n = 3 \), No of active forms = 8

2,3,4,5-tetrahydroxypentanal

We have already seen this compound has 4 pairs of enantiomers i.e a total of 8 optically active isomers. Such molecule cannot have a meso form.

(B) Structurally Symmetrical Molecule (Can have a PSE) P:

Case-I: \( n = \) even

(i) No. of d/l (active) forms = \( 2^{n-1} \)

No. of enantiomeric pairs = \( \frac{2^{n-1}}{2} \)

(ii) No. of meso forms = \( \frac{\left(\frac{n}{2}\right)+1}{2} \)

Examples: Tartaric acid  HOOC—CH(OH)—CH(OH)—COOH

\( n = 2; \) No of active forms = 2 i.e \((R,R)\) and \((S,S)\)

No. of meso form = 1 i.e \((R,S = S,R)\)

(you can refer the FFs of these already given before)

Case-II: \( n = \) odd

(i) No. of d/l(active) forms = \( 2^{n-1} - 2^{0.5n-0.5} \)

No. of enantiomeric pairs = \( \frac{2^{n-1} - 2^{0.5n-0.5}}{2} \)

(ii) No. of meso forms = \( 2^{0.5n-0.5} \)

Example:

pseudochiral centre

\[
\begin{align*}
&\text{HOOC—CH(OH)—CH(OH)—CH(OH)—COOH} \\
&\text{2,3,4-trihydroxy pentanedioic acid}
\end{align*}
\]

Here we have to count the pseudochiral centre to make \( n = 3 \), So apply formula to get

No. of active forms = 2 (one pair) i.e \((R,R)\) and \((S,S)\)

No. of meso forms = 2 \((R,r,S)\) and \((R,s,S)\)

(FF are already given before)

SAQ: Indicate the number of optically active forms and meso forms for the following compounds.

(a) CH₂—CH(OH)—CH(Cl)—CH(OH)—CH₂
(b) HO—CH₂—CH(CH₃)—CH(OH)—CH₃
(c) OHC—CH(OH)—CH(OH)—CH(OH)—CH(OH)—CH₂OH
(d) HOOC—CH(OH)—CH(Cl)—CH(Cl)—CH(OH)—COOH

Answer:
(a) symmetrical molecule with \( n = 3 \) (having one pseudochiral centre).

No. of active forms = 2, No. of meso forms = 2

(b) Unsymmetrical molecule with \( n = 2 \), So No. of active forms = \( 2^2 = 4 \), No. of meso form = 0

(c) Unsymmetrical molecule with \( n = 4 \), no. of active forms = \( 2^4 = 16 \) (8 pairs). No. of meso forms = 0

Note that one of the 8 pairs is Glucose, about which every one knows. We shall discuss more about it later.

(d) Symmetrical molecule with \( n = 4 \) (all pseudo type), No. of meso forms = 2, No of active forms = 8

Dr. S. S. Tripathy
Zig-Zag Notation (Line) Formula:
Many scientists prefer the zig-zag line formula to represent configuration instead of Fischer formula. Carbon atoms placed in one plane in a zigzag manner. Two groups bonded to each carbon are shown by wedges and broken lines. See the example of tartaric acid.

\[
\text{HOOC} \quad \text{COOH} \\
\text{HO} \quad \text{H} \\
\text{OH} \\
\text{S} \\
\text{R} \\
\text{S}_{\text{meso-tartaric acid}} \\
\text{HOOC} \quad \text{COOH} \\
\text{HO} \quad \text{H} \\
\text{HHO} \\
\text{HHO} \\
\text{RR}_{\text{active(R,R)-tartaric acid}} \\
\text{HOOC} \quad \text{S}_{\text{active(S,S)-tartaric acid}} \quad \text{COOH} \\
\text{HO} \\
\text{H} \\
\text{HHO} \\
\text{S} \\
\text{S} \\
\text{S}_{\text{active(S,S)-tartaric acid}}
\]

You can apply the CIP rule to view at each chiral centre in this zig-zag formula. Wherever the least priority group lies below the plane (broken line), apply normal CIP rule and wherever it is lying above the plane (wedge), apply Golden rule to assign configuration. In this formula, all the carbon atoms lie in one plane and are placed in a zig-zag conformation (all anti configuration which is the most stable).

**SAQ:** Draw the zig-zag line formula for (R,R) 2,3-dichlorobutane.
Solution:

\[
\text{CH}_3 \quad \text{H} \quad \text{Cl} \\
\text{CH}_3 \\
\text{R} \\
\text{R}_{\text{Golden rule can be applied in both the centres}} \\
\text{CH}_3 \quad \text{CH(OH)} \quad \text{CH(OH)} \quad \text{CH(OH)} \quad \text{CH}_3
\]

For Meso-I, (R,r,S) and its mirror image (S,s,R) are superimposable. For Meso-II (R,s,S) and its mirror image (S,r,R) are superimposable. So there are two meso compounds which have the pseudochiral centres at the middle. In the two active forms, the middle carbon is achiral. (R,R) and (S,S) are the two enantiomers.

Dr. S. S. Tripathy
**D/L Configuration:**
This configuration is often associated with carbohydrates and amino acids. The conventionally, in the FF, the more reduced group is written at the bottom and more oxidised group is written at the top. Take for example, arabinose (an aldopentose), about which we have already discussed.

![Diagram of D and L configurations]

CH$_2$OH group is more reduced group (carries more number of H atoms) and has been kept at the bottom.
CHO is more oxidised group (less number of H atoms) and is kept at the top. The three chiral centres have their absolute configurations shown.

If in the FF, the bottom-most carbon has the OH group lying to the right, it is called D-configuration and if the OH group lies to the left, it is called L-configuration. This D and L notations have come from the simplest carbohydrate D(+)glyceraldehyde and L(–)glyceraldehyde. Except glyceraldehyde, there is no fixed relationship between D/L with (+) and (–). Ribose has two enantiomers, the (R,R,R) is the D form in which the bottommost chiral carbon has the OH group to the right, and (S,S,S) is the L form in which this OH lies to the left. Note that in this case (D) is (–) while (L) is (+). Hence beginners are not to confuse D and L with d and l. While the former is based on the configuration at one chiral centre (bottommost), while the latter is the sign of optical rotation of the molecule as a whole.

**Zig-zag line formula of D-Ribose:**

![Zig-zag line formula of D-Ribose]

To write L:-Ribose

**SAQ:** Assign the configuration of the following molecule given in zig-zag line formula for a monosachharide (simple sugar), which is called D-glucose. D-glucose is d(+). Convert this to FF.

![Zig-zag line formula of D-glucose]

**Solution:** 2R, 3S, 4R, 5R

**Fischer Formula**

![Fischer Formula of D(-)glucose]
**SAQ:** Draw FF of D and L-alanine (2-aminopropanoic acid)

**Solution:**

Note that the 20 natural $\alpha$-amino acids obtained from proteins are all have L configuration in which $\text{-NH}_2$ lies to the left in FF. In FF, the oxidised group $\text{-COOH}$ is kept at the top and the reduced group $\text{-CH}_3$ to be kept at the bottom. In place of $\text{-OH}$ in carbohydrate, here $\text{-NH}_2$ group is considered for assigning D/L. Note that L-alanine has S-configuration and is dextrorotatory (+). Thus, there is no obvious relation between D/L with (+)/(–). Note that all L-amino acids are also having S-configuration as the priority order is $\text{-NH}_2$ (1) and $\text{-COOH}$ (2). But we cannot say, all of these are (+), it may be (+) in some cases and (–) in other cases.

**SAQ:** Cysteine is a natural $\alpha$-amino acid with group $\text{-CH}_2\text{SH}$ in place of $\text{-CH}_3$ in alanine. Draw the FF for this and also assign the configuration. Note that it is laevorotatory (–). Comment.

**Solution:**

This is only one $\alpha$-amino acid which has R-configurations. Note that it is L-$\text{(NH}_2$ lies to the left), but has R-configuration. Can you tell why? Because $\text{-CH}_2\text{SH}$ has greater priority than $\text{-COOH}$. One $\text{-S}$ atom linked to C- will make $\text{-CH}_2\text{SH}$ senior to one C bonded to 3 O atoms in $\text{-COOH}$. Note that this is laevorotatory unlike the case of L-alanine discussed before which is (+).
Chirality in the absence of Chiral Centre:
(Presence of a Chiral Axis)

There might not be any tetrahedral asymmetric centre or chiral centre, still the molecule can be disymmetric and has non-superimposable mirror image form. This is possible when there is a chiral axis. Just like we can have two types of screws (right handed and left handed) which are non-superimposable mirror images. We can also have two types of sloping staircase buildings which are non-superimposable mirror images.

(In the building written as Right hand, your left hand will remain inwards towards the axis (building) while you are ascending the slope upwards, while in Left hand building your right hand will remain inwards if you are ascending. It is told that kings were constructing left-handed sloping building, because when the enemy soldiers will climb up, their right hands will remain inwards and so they cannot use their swords or weapons effectively. But the soldiers of the king who will be descending from above will have their right hands lying outwards and so can freely operate onto the enemy soldiers.)

These are called helical configurations (noun- helix). If you hold the helix pointing away from you and it twists clockwise moving away, it is right-handed (P: plus), if anticlockwise it is left-handed (M: minus). These models are mirror images and cannot be converted one into the other by rotation. Note that a left handed helix appears the same whether you see it from one end or from the other end. Same is the case with a right hand helix. Unless you see the model yourself, you may feel as if the direction of twist becomes opposite when you view from the other end. In the diagram below, the helices are shown in a vertical manner, but you will have to view it keeping in front of you in a horizontal manner.

Such systems are said to have a chiral axis. It is an axis about which a set of substituents is held in a spatial arrangement that is not superposable on its mirror image. Such molecule is disymmetric w.r.t the molecular axis. There are two cases in this category i.e they have chiral axis. Although their structures (shapes) are not helical, but we can include under helical chirality.

I: Chirality due to Frozen Rotation
Case-II: Conformational Enantiotropism

I: Chirality due to Frozen Rotation:
In this case there is C=C or its a spiro compound in which the rotation is prohibited or frozen. We shall consider three different types under this category.

(a) Optical isomerism in substituted allenes (cumulated dienes)
Molecules containing even number of cumulated (consecutive) doubles bonds are non-planar (as the central C atom is sp hybridised having two π-bonds on either side perpendicular to each other) and if different groups are attached to the terminal carbon atoms, they will be chiral molecules. Therefore these are called axial allenes.
The groups lie in perpendicular planes and there is no plane of symmetry if the two groups are different (a,b or d,e). If the four groups are all different, then it appears to have a chiral centre while viewing along the direction of molecular axis. Hence the term ‘asymmetric’ is given to it. But truly there is no asymmetric centre. When only two different groups are there (a and b on each C), then it is disymmetric. By making one switch at any one stereogenic centre, we get its mirror image (enantiomeric) form. If one is (+), the other is (−), i.e., a d/l pair.

Assigning Configuration:
Subscript ‘a’ is given to R/S notations as this is due to a chiral axis i.e R_a and S_a configurations. The chiral axis is viewed end-on and the two "near" and two "far" substituents on the axial unit are ranked. The two near groups are given relative priority 1 and 2 and the two far groups given 3 and 4 according to CIP rule. The priorities are determined two times for the two pairs. The rear pair always gets 3,4 (for 1,2 respectively). Thus the 3D formula is converted to a Newman projection like formula (not FF) in which the near (front) groups are connected to the centre of the circle and the far groups are shown from outside of the circumference of circle. Note that the near groups may occupy vertical or horizontal positions depending on from which side you view. Then view the formula in the sequence 1 → 2 → 3 → 4, if eye rotates clockwise, then R_a configuration, if anticlockwise, then S_a. Here we do not have normal CIP rule and Golden rule while viewing as we did for molecules having chiral centres. In the FF, the projections of the four groups are made on the plane carrying the chiral centres. But here the projection is on the plane passing through the middle carbon which do not carry the stereogenic carbon atoms (terminal carbon atoms) bonded to the four groups. Hence the rule is different. While viewing from the top (near) groups (designated as 1,2) and then to rear groups (3,4), if the eye rotates clockwise, it is R_a, if anticlockwise, it is S_a. Note that the configuration will remain the same, whether you view from the side having horizontal groups or from the side having vertical groups. You already know that you have to view along the line of the chiral axis.
Organic : Stereoisomerism

N.B: Cumulated polyenes containing 3 or any odd number of C=C is planar and is achiral.

(b) Optical isomerism in alkylidene cycloalkanes: (Ring having exocyclic double bond)

When groups bonded to the two stereogenic centres are different then it will lack a plane of symmetry. Note that like axial allenes, the two pair of groups lie in perpendicular planes. Configuration is assigned in this case also in a similar manner as we did for axial allenes. One is converted to the other by making one switch at any one stereogenic centre.

(c) Optical isomerism in substituted spiro compounds:

Here also if the two groups are different in 2,6 positions of the spiro compound, then it will be disymmetric as the pair of groups lie in perpendicular planes. Only Sₐ - configuration is shown, you can draw its mirror image isomer and find for yourself that it is Rₐ. This can actually be done done in model, by making one switch at any one stereogenic centre bonded to substituents.

N.B: These cases cited are not regarded as geometrical isomers (which are diastereoisomers). These are enantiomers under optical isomerism.

II: Conformational Enantiotropism:

(please read this part after finishing conformational isomerism)

When the two conformers are also enantiomers, this is a case of conformational enantiotropism. In this case too, there is a chiral axis, but groups are arranged about a C–C, where rotation is possible. There might be enough hindrance to rotation which can make it equivalent to frozen rotation(atropisomerism in substituted biphenyls) in which the enantiomers can be separated(isolable) or hindrance to rotation is small enough for their separation and isolation not possible. The latter case, we shall discuss first.

Dr. S. S. Tripathy
(a) Chirality in n-butane:

It is hard to believe that the gauche form of butane is chiral as it is non-superimposable with its mirror image. The two gauche forms in n-butane are non-superimposable. The molecule has a chiral axis. But n-butane is achiral because 50% of each form exists always at equilibrium (racemic mixture). Due to very small hindrance to rotation, the two forms cannot be separated.

(b) Meso-tartaric acid type:

We know that meso compound is achiral, but which meso form is achiral? It is eclipsed conformation, which really does not exist (having a PS) and the anti (OH pair anti and COOH pair anti) conformation (having an Inversion Centre), which exists are achiral. But we never talked about the staggered form in which OH pair is gauche and COOH pair is also gauche w.r.t each other. There are two such conformations which are both chiral due to presence of chiral axis. Both are mirror images of each other and are non-superimposable. But again they form a racemate (50% each) and hence the net result is it is optically inactive. The hindrance to rotation about C–C is small enough for their isolation/separation. You can manipulate the models for staggered (I) and staggered (III) to ensure that they are non-superimposable and also are mirror images of each other. In the following diagram, the two do not appear to be mirror images. In reality they are.

(c) Atropisomerism:

When the rotation about C–C is highly hindered, which enable the enantiomers to be isolated, then it is called atropisomers (atropos: without turn: German). It is shown by tetrasubstituted biphenyls at the ortho positions. The two rings lie perpendicular to each other. The steric/dipolar repulsion coupled with stiffness of the bond (sp²-sp²) make the rotation highly hindered. One conformation is converted to other by 180° rotation of one ring w.r.t to the other about the chiral axis. The conformers are enantiomers, as it is already told; it is a case of conformational enantiotropism. The molecule does not have a PS. But if two groups are same, then there will be a PS and it will be achiral.

The absolute configuration here is assigned by converting to a Newmann projection type of formula as we did for allenes and then arranging each pair of groups with relative priorities. The designations given for

Dr. S. S. Tripathy
configurations here is $\textbf{M}$ (minus: left handed helix) and $\textbf{P}$ (plus: right handed helix) in stead of $\textit{R}_s$ and $\textit{S}_s$. $A/A'$ are higher priority groups while $B/B'$ are lower priority groups. While moving from top higher priority group ($A$ or $A'$) to rear higher priority group ($A'/A$), if eye rotates anticlockwise then it is $\textbf{M}$-configuration, if clockwise, then $\textbf{P}$ configuration.

(The reader is not to mistake the $(+)$ and $(-)$ signs given here with signs of optical rotation. The signs here mean right handed helix and left handed helix respectively which have no obvious relationship with signs of optical rotation.)

Helical chirality:
The molecules having chiral axes are customarily referred to exhibit helical chirality. The case of biphenyl, allenes etc. that we have discussed come under this category. Although for allenes, we often use $\textit{R}_a$ and $\textit{S}_a$ (like a tetrahedral chiral centre) for assigning absolute configurations, in biphenyls we use the Right($\textbf{P}$) and Left($\textbf{M}$) handed helix configurations. However the shapes of such molecules are not helical, though they come under helical chirality.

It is more appropriate to coin the term helical chirality, if the shape of the molecule becomes helical. One example of a chiral molecule having helical shape is $\textit{hexahelicene}$, which has six benzene rings twisted like left and right handed helices (enantiomers). Some natural species like snails also remain in helical pair.

Dr. S. S. Tripathy
Resolution of Racemic Mixture:
When a chiral molecule is synthesised, often the result is a 50% mixture of d/l mixture. This happens particularly when the new chiral molecule is obtained from a planar carbocation intermediate (we shall see this later). Only in stereospecific reactions or stereoselective reactions (we will discuss both later), racemic mixture is not obtained. In the former case only one configuration, and the latter case, an excess of one configuration is obtained. But most often we get a racemic mixture.

Since all physical properties of enantiomers are same (except optical rotation), it is difficult to separate them.

(A) Mechanical Separation: (Hand Picking from Crystals)
This was the earliest method initiated by Louis Pasteur in 1848. He crystallised sodium ammonium tartarate racemic mixture. He observed two types of crystals which were non-superimposable mirror images of each other. One is called left-handed and the other right-handed (like right hand and left hands are mirror images). Simultaneous inspection through a microscope and with the help of a pair of tweezers, the two types of crystals are separately hand picked. This technique has been obsolete now.

(B) Chemical Method (Diastereomeric method):
(R/S) mixture to be separated is allowed to chemically react with another pure R or pure S reactant to form two diastereoisomeric products (RR and SR/ RS and SS) having different physical properties, which are separated by fractional crystallisation or by chromatographic method. Then individual isomer is chemically hydrolysed and the original pure compound is separated from the other pure reactant.

Separation of C. acid Rac mix:
R-Acid + S-amine → (R,S)-salt
S-Acid + S-amine → (S,S)-salt
The chiral amine often used are 2-aminobutan-1-ol or 1-phenylethanamine etc.
Separation of Alcohols:
Alcohol mixture is converted to diastereomeric esters by reacting with chiral carboxylic acid.
Enantiomeric alcohols are converted to diastereomeric esters by reacting with chiral carboxylic acid such as (+) tartaric acid or (-) malic acid (HOOC-CH₂-CH(OH)-COOH) or (-) mandelic acid [Ph-CH(OH)COOH] and others.

Separation of Bases:
Same pure chiral carboxylic acids used for alcohols is used to get diastereomeric salts which then separated and later from them, the original enantiomers are separated.

Chromatographic method of separation diastereoisomers:
In any chromatographic method (HPLC or GC etc.), if the static phase should possess a pure chiral compound which will have different affinities for the enantiomers to be separated, they will be eluted at different times.

Dr. S. S. Tripathy
**SAQ:** Why do chiral molecules rotate PPL?

**Answer:**
Linear polarization of a light is equivalent to superposition of or vector sum of two opposite circularly polarized light (left handed and right handed helix). The two travel in same speed and hence in same phase but in opposite directions and the resultant lies in the direction of linearly polarized light (i.e no deviation). If the two circularly polarized light (CPL) pass through a disymmetric molecule, then they interact to different extents (as CPL helices are chiral and enantiomeric). The disymmetric molecule will have different refractive indices for the two CPLs and the speed of one will be less than the other. Thus the vectors will have different magnitudes and directions. The resultant vector either progressively shifts to right (+) or left (–). If for one enantiomer the net shift is to right (+), for the other enantiomer, the net shift is to the left (–).
Geometrical Isomerism (E-Z) Isomerism:

The stereoisomerism in compounds containing double bonds come under this category. This was formerly called cis-trans isomerism.

1. Each carbon atom of C=C should be bonded to two different groups. \( C(a)(b)=C(p)(q) \)

2. Cis-trans terms can be used only when the two groups bonded to \( sp^2 \) carbon atom of the double bond are same. \( C(a)(b)=C(a)(b) \), or each \( sp^2 \)-C bears one H atom. \( C(H)(a)=C(H)(b) \). In no other cases, these terms can be used. In fact, cis and trans are old notations which have been obsolete now even for the above mentioned compounds.

3. They are also diastereoisomers (stereoisomers which are not mirror images) having different properties, mostly in physical properties.

4. One isomer is converted to the other by making one switch on any of the two stereogenic centres (\( sp^2 \) C of C=C).

(In the last example, we cannot use the term Cis/Trans here as priorities of CH\(_3\) groups are different at the two centres. It is not correct to tell the first compound as Cis and second as Trans. Hence you have to give the modern notations E/Z for the purpose. So it is preferable to totally avoid using of Cis/Trans for Geometrical Isomers.)

Dr. S. S. Tripathy
Assignment of E/Z:

German words: E=Entegen: opposite Z=Zusammen: together

The two groups bonded to each stereogenic centre are assigned relative priorities separately. Suppose, (1,2) given for one centre, (1',2') for the other centre according to CIP rule already discussed in Optical isomerism.

Z-Configuration: If the higher priority groups (1, 1') remain on the same side (so also the lower priority groups remain on the same side), it is called Z-isomer.

E-Configuration: If the higher priority groups (1, 1') lie on the opposite sides (so also the lower priority groups lie on the opposite sides), it is called E-ismomers.

If there are more than one C=C which show E/Z isomerism, then you have to write the configurations with the proper locants of ‘ene’. See this example.

Note that the priority order has been given four times, two on each C=C. Do not mistake the notations 1,2, 1', 2' given in the above formula with the locants of the carbon chain. The carbon chain has not been numbered in the formula. You get the IUPAC name by yourself. We had to write the configurations at each C=C i.e (1E,4Z), before the name of the compound. If there are four stereogenic C=C, then we have to use the Z/E notations four times with respective locants of the C=C (the first carbon of each double bond). Follow the SAQ:

SAQ: Draw the formula of the following compound in proper stereochemical format.

(2E, 4E, 6Z, 8E)-3,7-dimethyl-9-(2,4,6-trimethylcyclohexyl)nona-2,4,6,8-tetraenoic acid.

Answer:
SAQ: Give the name with proper E/Z notation in the beginning.

Solution: (a) E-1-bromo-2-(methoxymethyl)pent-1-en-3-yne (∴CH₂–OCH₃ is senior to prop-1-ynyl)
(b) Z-1-chloro-2-ethylbuta-1,3-diene (here the other C=C does not show E/Z isomerism)

SAQ: Draw the stereochemical formula for (a) Z-2-phenylpent-2-ene (b) E-3-hydroxy-4-methylhexa-3,5-dien-2-one
(You draw of your own)

**General Formula for finding number of GIs:**

(A) Structurally symmetrical molecule having identical terminal groups:

Case-I: \( n = \text{even} \) (where \( n \) = number of stereogenic C=C)

\[
\text{No. of GIs} = 2^{n-1} + 2^{\left(\frac{n-1}{2}\right)}
\]

Case-II: \( n = \text{odd} \)

\[
\text{No. of GIs} = 2^{n-1} + 2^{\left(\frac{n-1}{2}\right)}
\]

(B) Structurally unsymmetrical molecule having different terminal groups:

\[
\text{No. of GIs} = 2^n.
\]

Examples:

A-I: \( \text{CH}_3–\text{CH}=\text{CH}–\text{CH}=\text{CH}–\text{CH}_3 \):

No. of GIs = 3 (EE, ZZ, ZE=EZ)

(2Z,4E)-hexa-2,4-diene (2E,4Z)-hexa-2,4-diene

Note that in a symmetrical molecule like this, (2Z,4E) is superimposable with (2E,4Z) and hence there are three GIs as calculated from the formula.

A-II: Similarly we can get the number of GIs for a molecule having three C=C (odd) which is symmetrical by using the other formula.

\[ \text{CH}_3–\text{CH}=\text{CH}–\text{CH}=\text{CH}–\text{CH}–\text{CH}_3 \]

No. of GIs = 6; (Find for yourself, which are the six by notation eg. (ZZZ), (EEE)......

Dr. S. S. Tripathy
Organic : Stereoisomerism

B: For unsummetrical molecule like \( \text{CH}_2=\text{CH}=\text{CH}=\text{CH} \text{--C}_2\text{H}_5 \), the number of GIs = 4
Here (EZ) and (ZE) are non-superimposable.
So the four GIs are : (ZZ), (EE), (EZ) and (ZE)

Properties of Geometrical Isomers:
We shall make case study of a few compounds to assess the difference in properties between a \( E \) and \( Z \) isomer of compounds. This can be regarded as a Rough Rule of Thumb, not a concrete one, as there are many exceptions to this.

Boiling and Melting Points:
We shall take the examples of \( Z \) & \( E \) but-2-ene and \( Z \) & \( E \) 1,2-dichloroethene for our analysis.
The boiling point of \( Z \) (cis) isomer is greater than \( E \) (trans) isomer as the V.W forces in the former is greater. However, the melting points of \( E \) (trans) isomer is greater than \( Z \) (cis isomer) due to greater symmetry in \( E \)-isomer which favours greater packing of molecules in the crystal.

\begin{align*}
\text{But-2-ene} & : \text{bp: } Z = 40^\circ \text{C} & E = 10^\circ \text{C} \\
& : \text{mp: } Z = -140^\circ \text{C} & E = -105^\circ \text{C} \\
\text{1,2-dichloroethene} & : \text{bp: } Z = 60^\circ \text{C} & E = 48^\circ \text{C} \\
& : \text{mp: } Z = -80^\circ \text{C} & E = -50^\circ \text{C}
\end{align*}

Dipole Moment:
\( Z \) (cis) > \( E \) (trans)
For structurally symmetrical molecule like 1,2-dichloroethene \( E \) isomer is non-polar \( (\mu = 0) \). The \( Z \) (cis) isomer has a net resultant dipole moment. Refer the chapter “Chemical Bond” for details on dipole moment.

Acid Strength:
Case of Fumaric and Maleic acid will be considered for studying relative acid strength.

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]
Z-but-2-enedioic acid
(Maleic acid)

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]
E-but-2-enedioic acid
(Fumaric acid)

Maleic acid is more acidic than fumaric acid. Because, the first formed carboxylate ion(conjugate base) from maleic acid is stabilised by intramolecular H-bonding. Hence the dissociation is favoured. Such factor is absent in fumaric acid.
Moreover maleic acid can undergo dehydration to give maleic anhydride because the two –COOH lie on the same side. Fumaric acid has no anhydride as the two –COOH lie on the opposite sides.

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]
maleate ion

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]
maleic anhydride

Density and Solubility:
\( E > Z \) (for solid state only)
As the packing density is more in \( E \)-isomer, its density is greater than \( Z \). For the same reason, the solubility in a solvent is lower for \( E \)-isomer than the \( Z \)-isomer. This is the case when the compound is a solid at room

Dr. S. S. Tripathy
Organic : Stereoisomerism

Maleic acid : density = 1.59 g/cc solubility in water = 78.8 g per 100 mL(25°C)
Fumaric acid: density = 1.64 g/cc solubility in water = 0.7 g per 100 mL(25°C)

Note that this is not the case with 1,2-dichloroethene, which is a liquid at room temperature. Density of Z-isomer(1.265 g/cc) is greater than the E isomer(1.259 g/cc). I do not have their solubility data for comparison.

Heat of Hydrogenation:

Trans(E)-alkenes are thermodynamically more stable than Cis(Z)-alkene due to greater steric crowding (hence greater steric strain) in the molecule. Therefore, trans-alkene give slightly lower numerical value of heat of hydrogenation than the isomeric cis-alkene.

Standard Heat of Hydrogenation(ΔH°): E-but-ene = –27.6 kcals/mole
Z-but-2-ene = –28.6 kcals/mole

Geometrical Isomerism in Cyclic compounds:

Cyclopropane, cyclobutane, cyclopentane, cyclohexane etc. show geometrical isomerism(Cis and Trans) as their cyclic structure prohibits bond rotation about C–C. A ring is to be treated like a C=C. If the substituents lie on the same side, then Z(Cis) and if lie on the opposite sides then E(Trans).

1,2-dichlorocyclopropane:

Geometrical Isomerism in compounds containing N=N and C=N:

(A) Compounds of the type R–N=N –R’ are called azo compounds. R/R’ = alkyl, aryl group or H. The lone pair plays a crucial role(sp^2 hybridised) in pushing R and R’ to remain either on the same side or opposite side.
Organic : Stereoisomerism

(B) Compounds of containing

$R \neq R'$ : alkyl, aryl or H (obtained from ketone/aldehyde by reacting with a N-nucleophile)

$X = –OH$ (oxime), $H/R-/Ph-$ (amines), $–NH_2$ (hydrazone), $-NH-Ph$ (phenylhydrazone etc.)

Then we have $Z$(syn) and $E$(anti) isomers. If the higher priority groups remain on the same side, then $Z$(syn) and if remain on opposite sides then $E$(anti). In this case, syn and anti terms are often used for cis and trans respectively.

Aldoximes:

Molecules having exhibiting both GI and OI:

Acyclic:

$C_3$ is chiral while $C_3-C_4$ is a double bond is stereogenic. The configuration at $C_3$ is R while at $C=C$, it is Z, hence the name $(3R, 4Z)$-hex-4-en-3-ol.

N.B: This compound has four stereoisomers including namely $(3R,4Z)$, $(3S,4Z)$, $(3S, 4E)$ and $(3R,4E)$.

The first two are enantiomers, so also the last two. But one from each enantiomeric pair are diastereoisomers.

Formula for finding maximum number of stereoisomers (GI and OI) = $2^{(n+m)}$

Where $n$ = number chiral centres; $m$ = number of steroactive $C=C$.

In the above example: $n=1$, and $m=1$. Hence, the total number of stereoisomers = 4(already give)

N.B: Note that if the molecule is structurally symmetrical, then the total number of isomers will be less than the number obtained by using the above formula. The example given before is a structurally unsymmetrical compound and hence the formula gives the actual number of stereoisomers obtained by using the given formula.

Dr. S. S. Tripathy
Organic : Stereoisomerism

Review of Isomerism (both structural and stereoisomerism):

\( \text{C}_4\text{H}_8 \):
Look to structural isomerism again. We knew that \( \text{C}_4\text{H}_8 \) exists as 3 acyclic isomers namely but-1-ene, but-2-ene, isobutene(2-methylprop-1-ene) and two are cyclic namely cyclobutane and methylcyclopropane. But from among them but-2-ene is a candidate for showing GIs(stereoisomers)
So total number of isomers including stereoisomers = 4 + 1 GI pair = 6

![Structural Isomers of C4H8](image1)

Alkenes (I) and (IV) do not show GI, as it does not satisfy the condition to have different groups at each stereocentre.

N.B: Now on, whenever, you see a structure, first ensure whether there is one or more chiral centre or not. If present, then you have to draw all the optical isomers(whether optically active or meso). You also have to ensure the presence of stereogenic C=C. If present, then you have to draw the GIs for it. If it is a cyclic compound it may exhibit both GI and OI. We shall consider such cases later.

(2) \( \text{C}_4\text{H}_{10}\text{O} \):
From this formula, there are four alcohols namely butan-1-ol, butan-2-ol, 2-methylpropan-1-ol and 2-methylpropan-2-ol and three ethers namely diethyl ether, methyl n-propyl ether, methyl isopropyl ether. But one of the alcohol i.e butan-2-ol is a candidate for showing OI, as it has a chiral centre.

![Alcohols and Ethers](image2)

Dr. S. S. Tripathy
Only butan-2-ol has a chiral centre and exists in two enantiomeric forms (R and S), others are achiral. Hence total of 5 alcohols are possible from the formula. None from three ethers has a chiral centre and hence all are achiral. So total number of isomers is \((5+3) = 8\), which includes stereoisomers.

N.B: You are advised to look to a question to ascertain, whether you are asked all possible isomers including stereo or only structural and accordingly you answer.

**Cyclic:**
In cyclic compounds too, if there is one or more chiral centre, then besides showing GI (explained before), it will also show OI.

**Cyclopropane:**

\[
\begin{array}{c}
\text{achiral} \\
\text{d/l pair (NO GI)} \\
\text{Cis(d/l) pair} \\
\text{Trans(d/l) pair}
\end{array}
\]

N.B: While assigning configuration in cyclic compound, if the least priority group (say H atom) is lying down, then normal CIP rule is applied, if it is lying UP, then Golden Rule is applied. In the Trans pair, one H is lying UP in each enantiomer. For the \(C_3\), we had to apply Golden Rule to assign the configuration.

This is similar to acyclic compound having two dissimilar chiral centres (unsymmetrical structure) having \(2^n\) optical isomers. Here one pair belongs to Z(cis) and the other pair belongs to E(trans). In acyclic compound there was no E and Z. They were merely (2R,3R) & (2S,3S) pair and (2R,3S) & (2S,3R) pairs. One from each pair makes a diastereoisomeric pair.

**Cyclobutane:**

\[
\begin{array}{c}
\text{Z-(1S,2R)} \\
\text{Z-(1R,2S)} \\
\text{E-(1S,2S)} \\
\text{E-(1R,2R)}
\end{array}
\]

Dr. S. S. Tripathy
Note that had the structure been symmetrical, e.g., both OH or both Br, then the first pair (1S,2R) and (1R,2S) would have been superimposable MESO form. We would have three isomers, the Cis form is MESO and the Trans form exists in d/l pair.

**4-bromocyclobutan-1-ol:**

In both Z and E, there is no chiral centre and moreover there is a PS passing through C₁ and C₄, hence are achiral. Only it exists as two GIs.

**SAQ:** Will the following molecule show GI and OI?

**Ans:** No GI and No OI

N.B: The extensive discussion on GI and OI for substituted cyclohexane will be made after we study conformation of cyclohexane. Just wait.
Conformational Isomerism

Rotation about single bonds in acyclic molecules is allowed as the barrier to rotation is less. If this barrier > 84 kJ/mole, then the rotation is prohibited. In alkenes and alkynes, the rotation about the multiple bond is prohibited at room temperature as the barrier is > 84 kJ/mole. But this barrier is much less than the above figure for C–C and hence it is allowed. Rotation about single bond results infinite number of conformations out of which a few are stable and the molecules spend most time in assuming those stable conformations. Those stable ones are called conformational isomers or conformers or rotamers.

Conformation of Ethane:

Newman Projection Formula:
The following diagram is a representation of the conformations of ethane in Newman Projection formula. In this, the front carbon (Numbered 1) lies at the centre of the circle shown and is bonded to three H atoms. The rear C atom is not visible as it is below the plane carrying the C₁. To give a 3D feel, the single bonds linked to the rear carbon are shown (projected) outside of the circumference of the circle. To study the conformations in an easy manner, we shall be making rotation of one –CH₃ group relative to the other. In other words, keeping one –CH₃ group (in the diagram the front –CH₃ group) fixed, the other –CH₃ (in this case, the rear one) is to be moved by rotating the C–C bond. As if, you are holding the front C(1) in your left hand in a model, and rotating the the rear –CH₃ group in a clockwise direction as shown.

Dihedral Angle (φ):
It is angle between two planes: one containing C₁, C₂ and Hₐ and the other containing C₁, C₂ and Hₐ. Two H atoms are subscripted ‘a’ and ‘b’ only to monitor their positions during the course of rotation. So φ is a solid angle. You can get a clear idea about φ, if you look to the 2nd conformation. We start our analysis from φ=0, when all the three pairs of H atoms are eclipsed. This is called Eclipsed conformation. We shall be rotating the rear –CH₃ group in a clockwise direction thereby increasing the φ value progressively to 60° → 120° → 180° → 240° → 300° → 360° to see the changes in the conformations. Note that even during change of φ by 60°, we come across with infinite number conformations, but the study of conformation with an increment of 60° gives us significant information. Here we have kept Hₐ bonded to front carbon atom fixed while Hₐ bonded to rear carbon atom is moving. Hence the increment of φ between Hₐ and Hₐ from 0 to 360° is discussed in the energy profile diagram.

Eclipsed Conformation (SYN conformation):
This is the most unstable conformation possessing the highest energy. This is due to maximum torsional strain (also called eclipsing strain/Bond opposition strain) arising due to repulsion between bond pairs which are at their closest proximity.

Staggered Conformation:
This is the most stable conformation possessing the minimum energy. Although φ between Hₐ and Hₐ is 60°, there are three pairs of H atoms lying anti (opposite) to each other and therefore torsional strain is minimum. For every increment of φ by 60°, the conformation alternates between between eclipsed and staggered form.

Energy Profile:
The Gibbs free energy (G) versus dihedral angle (φ) is shown in the following diagram. What is written as PE (potential energy) is actually Free energy (G).

Energy Difference:
The eclipsed and staggered form differs by nearly 3 Kcals/mole or 12.5 kJ/mole, which is too small to prevent rapid interconversion between the different staggered forms via the unstable eclipsed form. It is estimated that the molecule changes conformations 5 million times per sec. But at any instant, the percentage of staggered form is 99.9% at 25°C, the remaining are the combined conformations within a span of φ=60°.

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Saw Horse Projection Formula:

The terms “Saw Horse” has come from the wooden device having four legs on which a wooden beam is mounted. This is used by carpenters for sawing and other wood processing work. The legs look like an inverted Y. See the following figures. Like Newman formula, here also we have kept the front CH₃ bearing H₃ fixed and rotated the rear CH₃ about the C–C. The projection of this formula on a vertical plane at the mid position gives the Newman projection formula. You are advised to familiarise with this formula too alongwith the Newman formula for writing the stereo structure of a compound with proper conformation.

Dr. S. S. Tripathy
Organic : Stereoisomerism

Dr. S. S. Tripathy

Butane:

**Newman Projection Formula:**
We shall considered the two middle carbon atoms (C₂ and C₃) to depict the Newman formula. One of them to be kept on the front and the other at the rear (back). Each of these carbon is bonded to one –CH₃ group and two H atoms. We start with Eclipsed conformation in which the two –CH₃ groups are eclipsed, so also the two pairs of H atoms. Then increase the dihedral angle while keeping one CH₃ group fixed (designated as ‘b’) and moving the other CH₃ (designated as ‘a’) by rotating C₂–C₃ bond in clockwise direction from \( \phi = 0 \) to \( \phi = 360^\circ \) (back to pavillion) like we did for ethane.

**Eclipsed(I):** (\( \phi = 0^\circ \))
This is the most unstable conformation of butane because both Torsional Strain and Steric Strain are maximum. Steric strain arises due the repulsion between electron clouds of substituents (eg. –Me, –Et etc) bonded to adjacent carbon atoms in space coming close to each other (syn). Note that torsional strain arises due to repulsion between bond pairs on adjacent carbon atoms, while steric strain is due to Van der Waals repulsion between adacent groups in space.

**GAUCHE:** (\( \phi = 60^\circ \)) (to be pronounced as *gauss*, not gachi or gache, or gasssi)
This belongs to Staggered conformation where 3 pairs of bonds are opposite to each other and the torsional strain is at the minium (like staggered ethane.) But there is some amount of steric strain as the two –CH₃ groups are nearer (at a dihedral angle of 60°). This is a stable conformation and hence is called a conformer/rotamer. This is more stable than the Eclipsed-I by 4.1 kcals/mole.

**Eclipsed-II:** (\( \phi = 120^\circ \))
This is an unstable conformation of butane but relatively less unstable than Eclipsed (I). Here –CH₃ groups are adjacent to H atoms. Hence the steric strain is less than (I). This form is more stable than Eclipsed (I) by 1.5 kcals/mole.

Dr. S. S. Tripathy
Organic: Stereoisomerism

**ANTI**: $(\phi=180^\circ)$
This is another staggered conformation where the torsional strain is minimum. However, the steric strain is also minimum as the two $-\text{CH}_3$ groups are opposite (anti) to each other. This is the most stable conformer, more stable than Gache by 0.9 kcal/mol. This is small barrier for which there is a rapid conversion between Anti and Gache conformers via the unstable TS i.e Eclipsed-II and Eclipsed-I, mostly the former. But at a given instant the % of Anti form is more than the Gauche.

**Gauche-II**: The other Gauche at $\phi=300^\circ$, is the non-superimposable mirror image of the 1st Gauche($\phi=60^\circ$). They always remain as racemate (already discussed in conformational enantiotropism).
Similarly there are two Eclipsed-II at $\phi=120^\circ$ and $240^\circ$ which are also mirror images. Since they are the TSs, not the rotamers, it is meaningless to say that they constitute also a racemate (theoretically they do).

**Energy Profile Diagram:**
Standard Free Energy($G$) vs. dihedral angle for full rotation is given below. The energy differences between different forms are listed below. (Please read $G$ for $\Delta G$ in the diagram. It is burrowed from Wikipedia)

- $\Delta G$ (Gauche and Anti) = $-0.9$ kcal/mol
- $\Delta G$ (Eclipsed-I one and Gauche) = $-4.1$ kcal/mol
- $\Delta G$ (E-I and Anti) = $-5.0$ kcal/mol
- $\Delta G$ (Eclipsed-II and Anti) = $-3.5$ kcal/mol
- $\Delta G$ (E-I and E-II) = $-1.5$ kcal/mol

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Equilibrium between Anti and Gauche:

Applying principle of thermodynamics to correlate between equilibrium constant ($K$) with free energy change ($\Delta G^0$), we have

\[
\Delta G^0 = -2.303RT \log K
\]

\[
\Rightarrow -0.9 = -2.303 \times 0.002 \times 298 \times \log K
\]

\[
\Rightarrow K = 4.5
\]

So at 25°C, it corresponds to 82% Anti and 18% Gauche forms coexisting in equilibrium.

**Effect of Temperature on Equilibrium:**

As temperature is increased, more and more molecules pass on to Gauche form by absorbing 0.9 kcals/mole and hence % of Gauche form increases at the expense of Anti.

400K:

\[
-0.9 = -2.303 \times 0.002 \times 400 \times \log K
\]

\[
\Rightarrow \log K = 0.489
\]

\[
\Rightarrow K = 3.16
\]

700K:

\[
-0.9 = -2.303 \times 0.002 \times 700 \times \log K
\]

\[
\Rightarrow \log K = 0.28
\]

\[
\Rightarrow K = 2.82
\]

So at 400K, the % of Anti form is as high as 76% and Gauche 24%. Though % of Anti has decreased by increasing temperature frm 298 to 400K, but still the Anti dominates over Gauche. At 700K too still the Anti form predominates although its % has further decreased to about 74%. See while temperature is increased from 400 to 700K, the % of Anti form decreases by 2%. In fact, if you are bit conversant in thermodynamics, you will realise that as long as $\Delta G^0$ is negative, $K$ value will always be greater than 1 and hence Anti has a greater abundance than Gauche at all temperatures. Although $\Delta G^0$ values also change with temperature, although for a narrow range of temperature, it remains nearly constant, in this case the Anti will always more stable than Gauche at all temperatures, though the numeral values might change, $\Delta G^0$ will be always –ve. So
Organic : Stereoisomerism

remember that % of Gauche form superceding Anti will not be possible whatever may be the temperature rise.

Saw Horse Projection Formula for butane:

N.B: Note that both Anti and Gauche are Staggered conformation. While drawing the conformers henceforth for analysis, do not draw eclipsed conformations, which do not exist.

Propane:
This is treated similar to ethane. The conformation alternates between staggered and eclipsed in every 60° rotation.

Here the eclipsed form is more unstable than that in ethane.

n-pentane and n-hexane:
Similar to ethane, butane, higher alkanes like n-pentane has many conformations, however the most stable among them is the one having the dihedral angle at each C–C is 180°. This is called Zig-Zag conformation or allled ALL ANTI(All Trans) conformation. Other conformation do exist which are less stable. In n-pentane, there will be anti-anti (most stable), anti-gauche, gauche-gauche(I) and gauche-gauche(syn). In the last

Dr. S. S. Tripathy
conformation the two terminal CH₃ groups remain gauche w.r.t each other and hence it is the least stable.

The above Anti-Anti form of n-pentane is a repetition of the zig-zag conformation already given in the previous diagram along with n-hexane. In this, w.r.t C₂–C₃, the CH₃(1) and rest group(C₂H₅) are anti, also w.r.t C₃–C₄ bond C₂H₅ and CH₃ are anti. This is ALL ANTI conformation which is most stable.

Next to it, is Anti-Gauche form. Between C₃–C₄, C₂H₅ and CH₃ are gauche(dihedral angle of 60°) with respect to each other.

Still less stable is Gauche-Gauche(I), in which you shall find both about C₂–C₃ and C₄–C₅, the groups are lying gauche w.r.t each other.

The most unstable among them is Gauche-Gauche(syn), in which there is two CH₃ group at C₂ and C₄ lying eclipsed although farther away from each other. This will give additional instability due to both torsional and steric interactions.

N.B: From this insight, you can treat any longer chain or substituted alkane.

Conformation of molecule of X–CH₂–CH₂–Y type:
The conformation of the above type of molecule is similar to conformation in butane. In place the two terminal Me- groups we have here X and Y groups.

1. 1,2-dichloroethane (Anti and Gauche)
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Anti is more stable than gauche form, as in the latter, there is greater dipolar strain along with steric strain. Dipolar strain arises due to repulsion between poles of identical sign. In gauche, the two Cl(–δ) poles are close to each other. Note that anti conformer has zero dipole moment while gauche form has finite dipole moment.

Since there is certain percentage of gauche form in equilibrium with anti form, the compound show a net dipole moment. This can be verified by studying the net dipole moment of equilibrium mixture at different temperatures. As the percentage of gauche form increases with increase in temperature, the net dipole moment of the compound also will increase.

Exception:
In ethane-1,2-diol(ethylene glycol), the gauche form is more stable than the anti form due to latter’s stabilisation by intramolecular H-bonding. This has to be verified only in a non-polar solvent where there will be almost no intermolecular H-bonding. If taken in a polar solvent or the neat liquid, then obviously the anti form will be more stable and more abundant, as the strength of intermolecular H-bonding and its network structure will stabilise the anti form more than gauche.

Configuration vs. Conformation:
So far we have not discussed the conformation of acyclic compounds bearing chiral centres. The cases studied before are all achiral molecules. Let us now see the marriage between configuration with conformation.

1,2-dichloro-1,2-diphenylethane (stilbene dichloride)

IMPORTANT: The reader to note that for such compounds, you will have to draw three rotamers(all staggered) by making rotation of 120° two times from the starting rotamer. You have to keep one carbon atom fixed(say front carbon atom) and rotate the rear carbon atom two times with 120° each time. If you find two of them are identical, then you remove one of them. If two of them are enantiomeric, then mention that without removing any of them.

Meso Compound:
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Out of the three staggered conformation, the first one is most stable as the steric strain between the bulky Ph-groups is minimum (anti to each other) and also the dipolar strain between Cl groups is minimum (anti to each other). The other two conformers are enantiomers and are less stable, as both steric strain due to Ph-groups and dipolar strain due to Cl groups are maximum (gauch w.r.t each other). Since the first conformer as zero dipole moment and it contributes more to the equilibrium, the net dipole moment of the meso compound is less ($\mu = 1.27$ D). See what happens in the active (d or l) compound.

**Active compound:**

Just by one switch (between H and Cl) in the front carbon atom, the meso has been converted to active. I have not redrawn the other two rotamers in the Marvin Sketch I am using for this. In all the three rotamers for meso, I have exchanged between H and Cl on the front carbon atom, then copy - pasted to get for the active form. The first conformer is most stable as the bulky phenyl groups are anti w.r.t each other, although the Cl atoms are gauche. Note that steric strain is more pronounced than the dipolar strain, particularly when the groups are as bulky as Ph-. In the other two, the Ph-groups are gauche to each other, although in the third one, Cl-atoms are anti. So the order of stability will be 1st > 3rd > 2nd. Since in the most stable conformer, there is a finite dipole moment, the net dipole moment is much higher for the active compound ($\mu = 2.75$ D) than for meso. Note that in this case, all the three rotamers are different and there is no repetition, nor enantiomeric pair.

(Did you appreciate, how the marriage between configuration and conformation added value to our discussion? We first fixed the configuration i.e whether meso or active. Then we found all the three rotamers in each case remaining in equilibrium. Also note that, the barrier to rotation in all these cases is small enough to prevent rapid rotation between the rotamers and hence separation between rotamers is not possible.

**Chiral vicinal diols [RCH(OH)CH(OHR)]**:

**Meso compound:**

In meso form, the equally stable enantiomeric gauche rotamers are more stable than anti conformer (first one) due the intramolecular H-bonding stabilisation which outweighs the effect of destabilisation by steric strain due to gauche R-groups, provided the groups are small like Me-, Et- etc. But if the R-groups is bulky like i-Pr or t-Bu, then the steric strain will outweigh the effect of intramolecular H-bonding stabilisation. Hence in such cases the anti form is more stable than the gauche forms.

Note that all the study on intramolecular H bonding is to be made by using non-polar solvent like hexane, benzene etc.
Organic : Stereoisomerism

**ACTIVE COMPOUND:**

Just by exchanging between H and OH on the front carbon atom in all the previous rotamers, the rotamers for the active compound have been drawn. It's easy. In this case the first rotamer is most stable as there is intramolecular H-bonding stabilisation as well as the steric strain is minimum (R groups are anti). So form 1 will be stable irrespective of the bulk of the R group, as they remain anti w.r.t each other.

**Assigning Configuration from the Saw-Horse and Newman Projection formula:**

I shall tell you the tricks to convert any of these formula to FF first and then assign R/S to each chiral centre.

**Saw-Horse Formula:**

Bring the formula to eclipsed conformation with each chiral carbon with $Y$ mode (not inverse Y) by making required rotation of C–C. Then put all the groups in FF and assign R/S. See this example.

![Saw-Horse Formula Example]

We have kept the front chiral carbon as such, as it is already in the Y- mode. Only the rear carbon is rotated 180°, to bring it from inverse Y mode to Y mode. After bringing the saw-horse formula to eclipsed conformation in which both chiral centres are in Y mode, then we took the projections for FF. Note that in this mode, the groups which are DOWN in the saw-horse formula will come UP and DOWN (i.e. vertical bonds actually lying below the plane) and the LHS and RHS groups will remain on the respective sides in the FF. If you take the inverse Y mode at each in the another eclipsed conformation, then, the LHS and RHS groups are lying below the plane and groups which are UP are above the the plane. That will not give the correct projections according FF rules. So remember this very carefully. If you use invese Y mode eclipsed, you get wrong configurations.

**Newman Formula:**

Convert it to eclipsed all Y mode in saw-horse formula by required rotation and then to FF.

![Newman Formula Example]

Dr. S. S. Tripathy
**Conformation in conjugated dienes:**
Buta1,3-diene can exist in two conformational isomers. With respect to C–C, the two C=C can remain cis or trans, giving two distinct stereoisomers called s-cis and s-trans. s- stands for single bond. s-trans is more stable and constitutes 98% of buta-1,3-diene at room temperature. Due to steric repulsion between the two closely located H-atoms in s-cis, it becomes less stable. When required for any reaction, s-trans converts to s-cis. It happens in a cycloaddition reaction of butadiene in Diels Alder reaction (to be discussed later).

In cyclic dienes like cyclohexa-1,3-diene, s-cis is the only conformation in which the ring structure is possible while in 3-methylidene cyclohexene, s-trans is the only stable conformation. The other conformation in each case is an impossibility.

Similarly when we take penta-1,3-diene, we shall find that in Z-pentadiene the s-cis conformation is 0% while in E-pentadiene the s-cis is has its presence felt (3%). In both the cases, the s-trans is the predominant conformation. This due to greater steric repulsion between CH₃⁻ and H- groups in Z- isomer.
Types of Strain in a Molecule:
Let us list the types of strain an organic molecule can have

(1) Angle Strain:
According to Baeyer Strain Theory, tetrahedral angle (190.28°) is regarded to have no angle strain. Any deviation from this produces strain (higher energy and hence instability) in the molecule.

\[
\text{Angle strain} = \frac{|Angle - 109.5|}{2}
\]

So the strain on either side of angle i.e the angle by which the each bond is compressed or expanded from the normal tetrahedral angle is regarded as the angle strain.

Presuming cyclopropane (BA=60°), cyclobutane(90°), cyclopentane(108°) to be planar, the angle strain is 24.75°, 9.75° and 0.75° respectively for the three rings. When it was known that six and higher membered rings remain in 3D puckered structure in which bond angles are nearly tetrahedral, then Baeyer strain theory became invalid for six and higher membered rings, which were believed to have no angle strain. Cyclopentane ring also have negligible angle strain, although it is not strictly planar. However, the strain theory is most applicable to cyclopropane and cyclobutane rings, the former having the maximum angle strain followed by the latter. Cyclobutane and cyclopentane rings are not truly planar, they are puckered which relieves the eclipsing strain.

Still the angle strain is in the order: cyclopropane > cyclobutane > cyclopentane. Cyclohexane has no angle strain. From cycloheptane onwards, there is very small angle strain like cyclopentane and in cyclotetradecane, again the angle strain is zero. Actually the relative angle strain in cyclic rings are measured in terms of the difference between actual heat of combustion of cyclic compound and their acyclic counterparts.

2. Torsional Strain/Eclipsing Strain/Bond Opposition Strain:
The repulsion between adjacent bond pairs gives rise to this strain, already discussed.

3. Steric strain:
Any substituent particularly alkyl, aryl etc. in adjacent or nearby positions produce Van der Waals repulsion between their electron clouds in space. This is called steric strain, which is directly proportional to the size (bulk) of the group. Tert-butyl group has a greater steric strain than isopropyl and so on.

\[
3^\circ \text{alkyl} > 2^\circ \text{alkyl} > 1^\circ \text{alkyl} > \text{CH}_3(1^\circ)
\]

In eclipsed(I) form of butane, there is highest steric strain due two -CH_3 groups coming nearest (eclipsed) to each other. This strain is lowered in gauche form as the -CH_3 group remain at a dihedral angle of 60° between each other. We have discussed this before.

4. Dipolar Strain:
When identical poles come closer there is electrostatic force of repulsion between the poles which give instability to the molecule. Gauche 1,2-dichloroethane is has greater dipolar strain than anti form, white the anti conformer has least least dipolar strain.

Dr. S. S. Tripathy
Coformation in Cyclohexane:
Cyclohexane has a 3D puckered structure having no angle strain. All the carbon atoms are sp³ hybridised and bond angles are all nearing 109.5°. It has the following conformations.
(a) Chair form
(b) Twist Boat (Skew Boat) form
(c) Boat Form
(d) Half boat form.

Stability order: Chair form > Twist Boat form > (Boat Form) > (Half Boat Form).
The forms given inside parenthesis are transition states (TS) and merely conformations but the first two are conformers (stable).

These conformations are interconvertible by the rotation of several single bonds simultaneously.

The two stable forms are Chair and Twist boat with an energy difference of 5.5 kcals/mole. These are the conformers of cyclohexane. The high energy transition state attained while converting from a chair form to skew boat form is the half chair form, which is nearly 10.85 kcals/mole higher energy than the chair form. The energy difference of 5.5 kcals/mole between the two conformer suggests a 99.99% chair form and the rest twisted boat form can be increased, but cannot supercede chair form at any temperature. At 1073K, the percentage of Twist boat form has been found to be 30%.

Twist boat forms can be interconvertible via another TS called the boat form. The energy gap between Twist boat and boat form is small (1.6 kcals/mole).

(Please forget the energy data given in the diagram below. I take the above mentioned data for record. The figures have been borrowed for net images on Google search. Hats up to Google.

There are two chair forms of equal energy. One chair form is converted to the other via two high energy half chair forms (TS). The energy profile below represent that.

At room temperature, this barrier of 10.85 kcals/mole is small enough to allow rapid interconversion between the two chair forms. Let us now see the different forms of cyclohexane.

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Dr. S. S. Tripathy
Organic: Stereoisomerism

**Chair Forms:**

Like a chair, it has a head resting region projected upwards and leg resting region projected downwards. In the first chair form the carbons 1, 2 and 6 form the head resting region while carbons 3, 4 and 5 form the leg resting region.

I suggest you to hold a cyclohexane model and manipulate onto it to get a full understanding on its conformation. There are two parallel planes on which the carbon atoms lie. One plane carrying C-1, C-3 and C-5 which in the first chair form makes the upper plane while the other plane carries C-2, C-4 and C-6 which in the first chair form makes the lower plane. These planes are interchanged while we convert one chair form to the other chair by pushing the head resting portion down to make it the leg resting region and the leg resting region is lifted up to make it the head resting region. If you number the carbon atoms from 1 - 6, you will find the parallel planes get interchanged. Plane carrying 1,3 and 5 converts from upper plane to lower plane while plane carrying 2,4 and 6 converts from lower plane to upper plane.

There are two types of bonds in cyclohexane.

(a) **axial bonds:** which lie alternately vertically UP and vertically DOWN.

(b) **Equatorial Bonds:** Which lie nearly horizontal: alternately Slanting Down and Slanting Up.

If a carbon atom carries an axial bond which is vertically UP, it has to carry the equatorial bond which is slanting down and vice versa.

When one chair form is converted to the other chair via two unstable half chair forms (transition states: to be shown later) and via skew boat form (another less stable conformer), the axial and equatorial bonds are interchanged. The bond which is axial at C-1 in one chair form, will be equatorial in the second chair form. Similarly the bond which is equatorial at C-1 in the first chair form will be axial in the the second chair form. Likewise in all the carbon atoms, you will find the axial and equatorial bonds are interchanged.

This change of conformation from one chair form to the other is called **FLIPPING** of the ring. At room temperature, this flipping is very rapid and axial – equatorial H atoms get exchanged rapidly. Each H atom spends 50% time as axial and 50% time as equatorial. But at low temperature of −78°C, the flipping can be totally stopped, and one can get two types of H atoms in cyclohexane i.e axial H and equatorial H static at their respective positions, which can be distinguished in Nuclear Magnetic Resonance Spectroscopy (not to be discussed here).

Chair conformation is the staggered form at any two C–C. You hold any two carbon atoms in your hand and take a frontal view of the model, you will find similar to staggered form of ethane. In this form you will find one pair of H atoms are anti and in each of the the other two pairs, one H is anti to the adjaent C–C bond on either side. So there is least torsional(bond opposition) strain. Hence it is the most stable form.

**Diaxial Interactions:** Note that if H atoms at C-1, 3 and 5 lie vertically UP then H atoms at C-2,4 and 6 will lie vertically DOWN. The interaction between any two adjacent axial pairs(either both UP or both DOWN) is called 1,3-diaxial interaction. This interaction becomes significant when there is a group like R- in place of H. The torsional strain is negligible at such distance, however the 1,3-diaxial steric strain due to alkyl or other substitutents is pronounced. We shall see this in analysis of substituted cyclohexane.
Symmetry Property: If you have by any chance studied Symmetry and Point Groups in this chapter, then you can understand the chair form of cyclohexane belongs to $D_{3d}$ point group. It has a $C_3$ axis perpendicular to parallel planes and passing through the centre, $3\cdot C_2$ perpendicular to $C_3$, $3\cdot \sigma_d$.

**Boat Form:**
Let us first study about boat form, although it is a TS conformation, not a conformer. Boat form is represented by an energy maximum point which is only about 1.6 Kcals/mole above the Twisted boat form. In boat form there are four pairs of H atoms which are eclipsed. If we consider C-1 an C-4 are upward projection parts of the boat form, then C-2, 3,5 and 6 lie in one plane while C-1 and C-4 lie in another parallel plane above the first plane. If you rotate the model from a boat like appearance by $90^\circ$, about a vertical axis and view in front of $C_2$–$C_3$ and $C_5$–$C_6$ bonds you will find two eclipsed form of ethane where you can see two pairs of eclipsed H atoms on each side. Please do not view in front of $C_1$–$C_2$ or $C_3$–$C_4$ or $C_6$–$C_1$ because this view will give you staggered form of ethane.

In addition to eclipsing strain(torsional strain), there is severe 1,4-diaxial Van der Waals strain called 1,4-*flagpole interaction*. The distance between the axial H atoms at the 1,4 positions is 1.8 Åwhich is less than the sum of the Van der Waals radii of the two H atoms(2.4 Å). This is a kind of steric strain between H atoms which generally does not come into force in other forms(even in the eclipsed conformation) as the atoms remain at distance greater than 2.4 Å.

These two strains make the boat form less stable than the chair form by 7.1 kcals/mole. In fact, boat form is a TS between two Twisted boat forms and does not have any real existence.

Dr. S. S. Tripathy
**Symmetry:** Boat form belongs to $C_{2v}$ point group like $\text{H}_2\text{O}$, having a $C_2$ axis and two vertical mirror planes carrying the $C_2$ axis.

**Twist Boat (Skew Boat) Form:**
If you manipulate the boat model of cyclohexane by holding $C_1$-$C_2$ bond on your left hand and $C_4$-$C_5$ bond on your right hand, such that your left hand thumb is holding $C$-2 and right hand thumb holding $C$-4. If you give a clockwise motion to both of your hands (particularly the two thumbs), you will find the 1,4 diaxial H atoms will be go a bit farther away (relieving the flagpole interaction) and the 4 pairs of eclipsing H atoms will deviate bit away from the eclipsed conformation thereby relieving some torsional strain. You get a form, where C-2 will lie above C-6 and C-3 will go below C-5, while earlier in boat form C 2, 3, 5 and 6 were lying in one plane. Due to relief of both the types of strain, it is more stable than boat form by 1.6 kcals/mole.

Note that when you go in the reverse direction ie from twist boat form to boat form by giving anticlockwise twist to your hands, you will get back boat form and if you give a bit more anticlockwise twist you will get another twist boat form which is the mirror image of the previous twist boat form. In this, C-2 will lie below C-6 and C-3 lie above C-5.

**Symmetry:** Twist boat form belongs to $D_2$ point group having a $C_2$ axis and two more $C_2$ axes perpendicular to the first $C_2$. Hence this form is chiral and exist as inseparable $d$/l pair.

**Half Chair form:**
While lifting the leg portion up or head portion down in respect of any chair form, we get a form where four atoms lie in one plane and out of the remaining two, one lies above the plane and the other below the plane. Suppose in the above figure, C -2, 3, 4, 5 lie in one plane, C-1 lies above the plane while C-6 like below the plane. This has angle strain ($BA = 120^\circ$) in the planar portion (though $109.5^\circ$ in the puckered portion) along with eclipsing strain at two C–C. Hence it is most unstable form and is merely a TS between two chair forms. We come across with two such forms while changing the conformation from one chair to the other. **Symmetry:** From an academic point of view, we find that half chair form belongs to $C_2$ point group, it has only one $C_2$ axis. Hence the form is chiral form enantiomeric pair.

(N.B: If you want to see the animation showing the conversion of one chair to other chair via half chair, twist boat, boat, half chair forms, then visit this website: http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch03/ch3-cyclohexane.html)

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**Monosubstituted Cyclohexane:**

Let us take methyl cyclohexane as a representative example for any monosubstituted cyclohexane. It will have two conformations.

(a) **Axial Isomer:** where $R-$ occupy axial position in one chair form

(b) **Equatorial Isomer:** where $R-$ occupy equatorial position in the other chair form

The two forms have difference in energy and hence there will always be a preponderance of the more stable isomer. The axial isomer will have two Gauche-Butane type of interaction having energy of about $2 \times 0.9 = 1.8$ Kcals/mole, by which it is less stable than the equatorial isomer which has no such interaction. We have neglected the 1,3 diaxial interaction between $CH_3-$ group and the two axial H atoms lying on the same side. This energy difference makes the percentage of axial isomer of about 5% as against 95% of the more stable equatorial isomer. Note that the carbon bonded to the substituent is not a chiral centre, and so we cannot bring in optical isomerism in this case.

In the Axial isomer, you can see the two Gauche-Butane Interactions, one about C1-C2 in which $CH_3$ group and the C2–C3 bond is gauche the other about C1-C6 bond in which the $CH_3$ and C5–C6 bond are gauche. You hold a model in your hand and play with it to get a feel.

(If you do not have a good quality model box with you, you can ask your teacher who will surely lend you the model kit to get an on-hand experience of all these)

**Disubstituted Cyclohexane:**

Earlier we had seen the marriage between configuration(meso/active) with conformation(different staggered forms). Here we shall see the marriage between both the forms of configurational isomerism namely optical and geometrical with conformational isomerism. It will be really interesting.

1,2-disubstituted cyclohexane:

Let us take 1,2-dimethyl cyclohexane as representative of this type. This has two chiral centre of the type of tartaric acid and will definitely show optical isomerism, if it will be chiral. Again the geometrical relationship between the two Me- groups can have two GIs, i.e Cis and Trans. We have to look to optical isomerism in each of the GIs. 1,2-disubstituted cyclohexane two GIs.

(i) Trans:  
(ii) Cis

Note that these are diastereoisomers and cannot interconvert by flipping process. Bond breaking and making at the stereogenic centre will be required to convert one GI to the other.
Organic : Stereoisomerism

**Trans(1,2):**

This can have two possible conformations namely
* diequatorial (ee) : i.e both occupy equatorial positions
* diaxial (aa) : i.e both occupy diaxial positions

(ee) form is more stable than the (aa) form by \((4 \times 0.9 – 0.9) = 2.7\) kcals/mole. Diaxial has four Gauche Butane Interactions (GBI, lets abbreviate for this) while diequatorial has one GBI (between the two \(\text{CH}_3\) groups). This makes the abundance of (ee) form by 99% against 1% of (aa) form.

![Diagram of diequatorial (ee) and diaxial (aa) conformations](image)

**Optical activity:**

Both the conformations are chiral and exist in enantiomeric (d/l) pair. If one is (RR), the other one will be (S,S).

**Cis(1,2):**

This exist two equally stable conformations with 50% each
* axial-equatorial (ae) isomer
* equatorial - axial(ae) isomer

Let me tell you from the beginning that unlike tartaric acid, which has a meso form (achiral), in this case both the conformations are chiral (disymmetric) and interestingly the two are mirror images of each other. Since these are conformations which are in rapid interconversion, we cannot separate one from the other. This comes under conformational enantiotropism, which we had discussed before. In substituted biphenyls, the isomers are separable because the barrier to rotation is very high, which is not the case here. Here the barrier is about 12 Kcals/mole and so the rapid interconversion between chair forms cannot prevented.

If one of them will be (R,S), the other will be (S,R). Ironically, here, unlike the case of tartaric acid, are not superimposable and are enantiomers. The 3D puckered structure has made it disymmetric which was not the case with acyclic compound of similar type.

![Diagram of axial-equatorial (ae) and equatorial-axial (ae) isomers](image)

(To verify whether ‘ae’ isomer is mirror image of ‘ea’ isomer, you take the two chair models of the molecule and see for yourself. You have to make a rotation of one form about a vertical axis to realise the mirror image relationship.)

Dr. S. S. Tripathy
Each form has 3 GBIs, one between the two CH₃ groups and the axial CH₃ has two more GBIs. So the interaction energy is 2.7 kJ/mol relative to cyclohexane. Since both of them are of same energy, they have equal abundance and the mixture is a racemic mixture.

(Note that if we consider the planar model of cyclohexane, then cis isomer will appear to have a PS and we jump onto the conclusion that it is achiral and is inactive due to internal compensation. However, truly the cis isomer is chiral, but still the compound is inactive due to external compensation.)

Relative Stability between cis and trans 1,2-dimethyl cyclohexane:
- Interaction energy of cis = 2.7 kJ/mol
- Interaction energy of stable conformation (ee) of trans = 0.9

So trans isomer is more stable than cis by 1.8 kJ/mol. Do not forget that cis and trans are GIs (diastereoisomers) which have independent existence.

(Note that all the energy values given in cyclohexane topic are enthalpy changes (ΔH). For finding equilibrium constants for different equilibria, the entropy factor is to be included to find the ΔG, whose values are not given here.)

1,3-dissubstituted cyclohexane:

Trans(1,3):

It has two equally stable conformations like cis(1,2).
- * Axial-Equatorial (ae) form:
- * Equatorial-Axial (ea) form:

Interestingly the two forms are superimposable i.e., they are one and the same. But more interestingly its a chiral molecule. Hence remain either as (+) or (−). That means, if you are dealing with a racemic mixture, then the enantiomers are permanently resolvable as there is no question of conformational enantiotropism in this case. Each has an interaction energy of 2 GBIs (1.8 kJ/mol) for the axial CH₃ group.

Cis(1,3):

It has two interconvertible conformations like trans(1,2)
- * diequatorial (ee) form
- * diaxial (aa) form

‘ee’ has zero interaction energy while ‘aa’ has 4 GBIs (3.6 kJ/mol). In addition to GBIs there is severe 1,3-diaxial repulsion (steric strain) which itself amounts to an interaction energy of 5.5 kJ/mol, so total of 9.5 kJ/mol. Hence the ‘ee’ form exists almost exclusively (nearly 100%).

Optical Activity: Each of ‘ee’ and ‘aa’ (hypothetically) has a PS passing through the C2–C5 (w.r.t C1 and C3 carrying the CH₃ groups). Hence cis form is achiral i.e, in true sense it is meso.

Relative Stability between cis and trans 1,3-dimethyl cyclohexane:
- Interaction energy of (ee) form of Cis = Nil
- Interaction energy of trans = 1.8 kJ/mol

So Cis isomer is more stable than Trans by 1.8 kJ/mol.

Dr. S. S. Tripathy
Organic : Stereoisomerism

**1,4-disubstituted cyclohexane:**
We shall take 1,4-dimethyl cyclohexane for our analysis. The cis and trans forms are similar to (1,2) disubstituted compound.

**Trans(1,4):**
It has two interconvertible conformations like trans(1,2)
* (ee) form * (aa) form

(ee) form has zero interaction energy while (aa) form 4 GBIs (3.6 kcales/mole). Hence ‘ee’ form remains in exclusive abundance (>99%). Both are achiral as a PS pass through C1–C4 carrying the CH₃-groups. In fact none of the two carbons (C1 and C4) are chiral. Hence Trans form is optically inactive.

**Cis(1,4):**
It has two conformations like cis(1,2)
* ea form * ae form.
Each has an interaction energy of 2 GBIs (1.8 kcales/mole). Both have also a PS passing through C1–C4 and hence cis form too is optically inactive. Since there is no chiral centre, why shall we talk about optical activity? Trans-ee(1,4) is more stable than Cis(1,4) by 1.8 kcales/mole.
(Note that interaction energy based on GBIs given in all the substituted cyclohexane are calculated values. The experimental values do closely match with them, though are different).

**Exceptional cases in which Boat form is more stable:**

In the first compound, if it assumes boat form then the bulky tert-butyl groups will have huge 1,3-diaxial interaction with axial H atoms. Hence boat form is more stable.
In the second compound, the intramolecular H-bonding stabilises the boat form. Third bicyclic ring cannot be possible if the cyclohexane ring assumes chair form.

SAQ: Assign R/S to each chiral centre for the following and establish a relationship between them. The question ans answer are given together. This is the height !!!!!!!

I and II are enantiomers. I and III are diastereoisomers. II and III and also are diastereoisomers.
Dr. S. S. Tripathy
SAQ: Identify configurations at each chiral centre and establish relationship between them.

Solution:
I: (1S,2R) II: (1R,2R) III: (1R,2S) IV: (1R,2R) V: (1R,2S)
I and III: enantiomers; I and V: enantiomers; III and V: Homomers
I and II: diastereoisomers; II and II: diastereoisomers; IV and V: diastereoisomers
II and IV: Homomers I and IV: diastereoisomers

Note that before you assign configuration, you must name the compound, particularly when it is not symmetrical. For example, in (III) and (V) the rear carbon(1) bears the –Cl group while in (IV), the front carbon(1) bears Cl.

SAQ: Draw all the isomers (including stereoisomers) from the formula C_7H_{16}.

(Total 11 = structural isomers = 9 + Additional optical isomer = 2)

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Two of the structural isomers, namely 3-methylhexane and 2,3-dimethylpentane are chiral (having one chiral centres). Hence each of them remains in R/S or d/l pair. So altogether 11 isomers (inclusive of stereoisomers)

SAQ: Draw the structures of all isomers (including stereo) from the formula C₆H₁₂.

Solution:

Hex-1-ene, hex-2-ene and hex-3-ene are positional isomers.

Out of 10 structural isomers, four of them show E-Z isomerism (geometrical isomerism).

Structural isomers = 10 + additional 4 geometrical isomers = 14
So a total of 14 acyclic isomers (including stereoisomers) are possible from the above formula.

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