

TOPICITY AND PROSTEREOMERISM

Structure

6.1 Introduction	6.5 Pseudoasymmetry
Expected Learning Outcomes	6.6 Stereogenic and Prochiral Centres
6.2 Topicity of Ligands and Faces and their Nomenclature	6.7 Summary
6.3 Stereogenicity	6.8 Terminal Questions
6.4 Chirogenicity	6.9 Answers

6.1 INTRODUCTION

In unit 5, you have studied about the *configuration* of an organic compound, its representation and determination. You also know that many a times, we need to synthesise a particular stereoisomer – either an enantiomer or a diastereomer of a particular compound. The reasons to do so may be many such as biological activity of a particular stereoisomer or using such synthesis to obtain molecules for a variety of interests.

While planning such a synthesis, we have to explore the suitable starting materials and exploit their structural features. Here, we will provide you an insight to look at the structure of molecules in such a way so as to explore how to utilise the different groups present in it to give the desirable product.

Also, in this unit, you will be introduced to few new terms such as topicity, stereogenicity, chirogenicity, pseudoasymmetry etc. A clear understanding about them will facilitate you in understanding the concepts dealt in this unit.

Expected Learning Outcomes

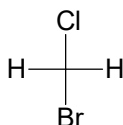
After studying this unit, you should be able to:

- ❖ explain topicity of ligands and faces;
- ❖ differentiate between enantiotopic and stereotopic ligands;

- ❖ describe the terms stereogenicity and chirogenity using suitable examples;
- ❖ discuss psuedoasymmetry and illustrate the presence of psuedoasymmetric centre; and
- ❖ identify stereogenic and prochiral centres present in a molecule.

6.2 TOPICITY OF LIGANDS AND FACES AND THEIR NOMENCLATURE

Let us first understand what is meant by a *ligand* here. *Ligands* are atoms or groups of atoms present in a molecule. Thus, in CH_2ClBr ,

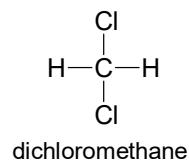
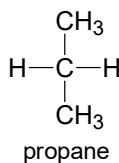


four *ligands* Cl, Br, H and H are attached to the carbon atom.

Ligands such as two H atoms in the compound shown above are apparently identical and are 'homomorphic'; (in Greek *homos* means *same* and *morphic* means *form*). Thus, such ligands when considered in isolation have same form and are indistinguishable. But, such ligands are distinguishable when present as a part of molecule. You will study about this aspect a little later in this section.

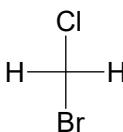
But, what if the homomorphic ligands are *not just the single same atoms* (as two H atoms above) and they are group of atoms such as methyl, secondary butyl groups etc; then, in that case, in addition to their identical nature, their *configuration* as *R* or *S* should also be *same*. Only then, these ligands would be homomorphic.

Further, homomorphic ligands, when present in a molecule, may occupy equivalent place or a different place. And, this *spatial relationship* of homomorphic ligands is referred to as the **topicity**. *Topas* means **place**. If the homomorphic ligands occupy the equivalent place, as shown below in case of propane and dichloromethane;



they are called *homotopic*. Thus, the two H atoms in the above two compounds are homotopic.

But what about the two H atoms in CH_2ClBr which we considered in the beginning?

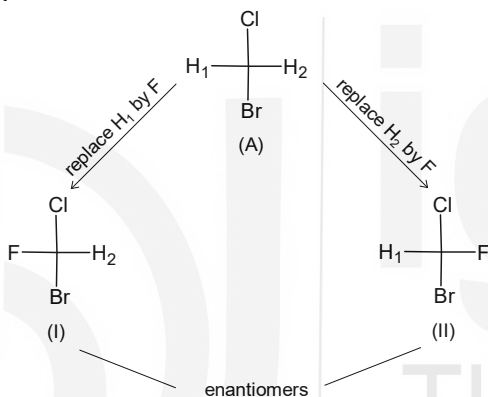


Two criteria are normally used to check whether the ligands are homotopic or not. When they are *not homotopic*, they are *heterotopic* and to be very precise *stereoheterotopic*. These criteria are:

- (i) Substitution-Addition Criterion
- (ii) Symmetry Criterion

We will discuss here the *substitution-addition* criterion which is familiar to you from your earlier studies. The *symmetry criterion* is based on the presence of symmetry elements in the molecule and point group of the molecule to which it belongs. It may also be referred to as and when possible and required in the present discussion.

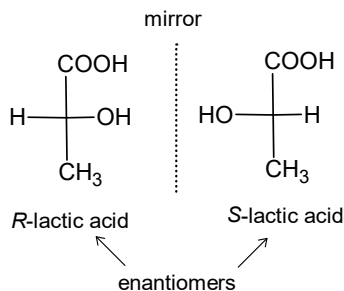
Let us apply the substitution-addition criterion to bromochloromethane which involves the replacement of one of the two H atoms, labeled as H₁ and H₂ (just for the sake of differentiation), by some other group one by one and see the resulting structures.



Now, as H₁ and H₂ are the same, i.e., just H, so the resulting structures (I) and (II) are **enantiomers**. Thus, the two H atoms in the original compound (A) were arranged *enantiotopically* and are called **enantiotopic**. So these two positions are different stereochemically and are **heterotopic**.

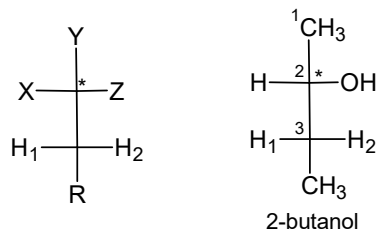
Please note that the terms *enantiotopic*, *heterotopic* or *homotopic* are relevant only when we are comparing the two atoms (or groups of atoms), otherwise it does not apply to any single atom or groups of atoms as there is nothing for the comparison.

Also in compound (A) above, the two hydrogens compared for the enantiotopic relationship were present in the *same* molecule; so it is an example of **internal comparison**. We can further extend this logic and compare the groups present in different molecules, say the –OH group present in the enantiomers of lactic acid as shown below:

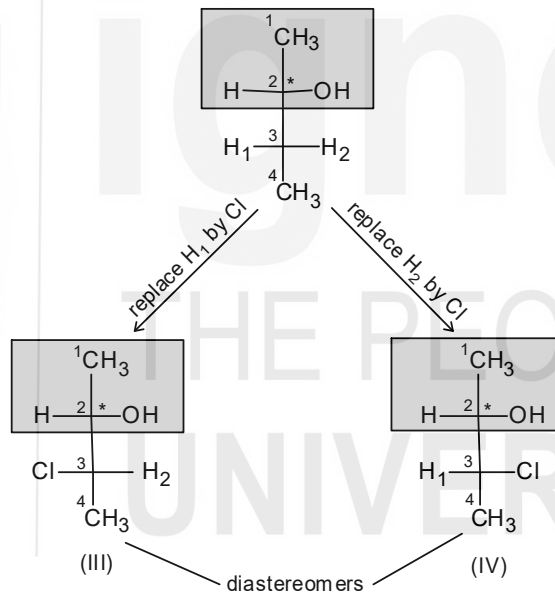


In case of comparison of –OH groups (or even –H atoms), the **external comparison** of the groups indicates that they are **enantiotopic**.

Let us understand another possibility when the two ligands are *diastereotopic*. You would definitely like to ask-When can this happen? Consider a molecule which already has a chiral centre (C*XYZ) and two atoms/groups of atoms occupying enantiotopic positions on the next carbon, as shown below:

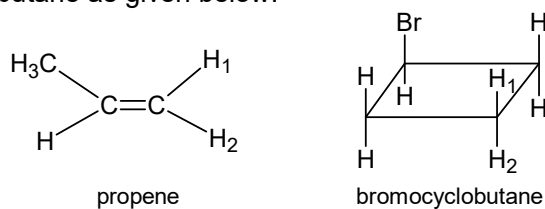


2-Butanol is an example of such a molecule in which C-2 is the chiral centre and two H atoms are present at C-3. Now, if we again use the substitution-addition criterion and replace H₁ and H₂, one by one - say by the Cl atom, we will get two compounds (III) and (IV).

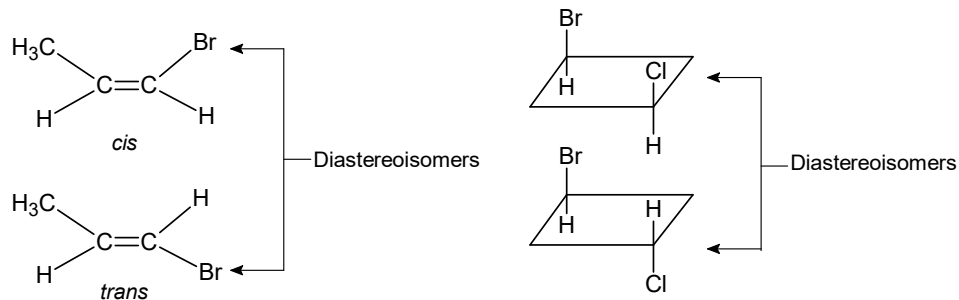


You can see that the upper portion in the box has remained as such in (III) and (IV) and so also the CH₃ group at the bottom. The only change by replacement of H by Cl has taken place is at C-3 and the two compounds – (III) and (IV), have opposite configuration at C-3. So, these are *diastereomers*. Therefore, the H₁ and H₂ at C-3 which have led to these diastereomers, are said to be *diastereotopic*.

Not only the presence of a chiral centre can make the two groups present at the carbon diastereotopic, but also in compounds like propene, CH₃–HC=CH₂ and bromocyclobutane as given below:

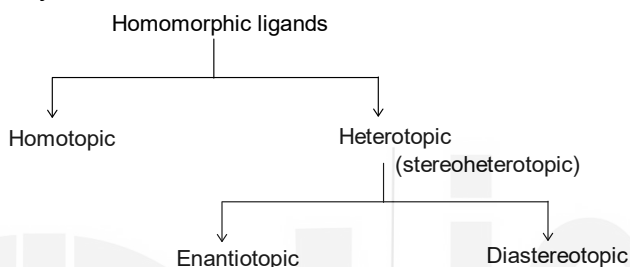


clearly indicate that H₁ and H₂ groups are sterically differently and when checked by substitution-addition criterion lead to diastereoisomers as shown below:

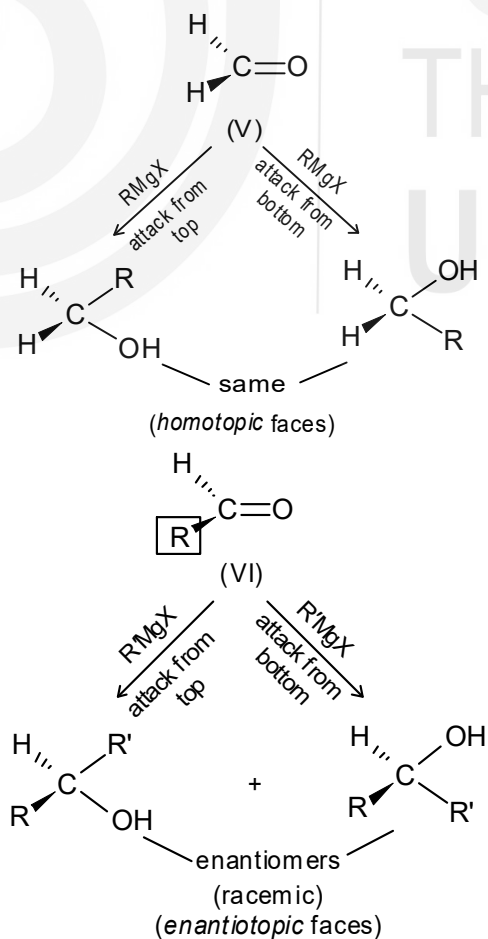


For clarity of visualisation, the two hydrogens at two carbons atoms are omitted in diastereoisomers in cyclic compounds.

Thus, we can say that



Similar to the topicity of ligands, *the two sides or faces* of the double bonds such as >C=C< or >C=O can also be same (or equivalent), enantiotopic or diastereotopic. These are illustrated below:



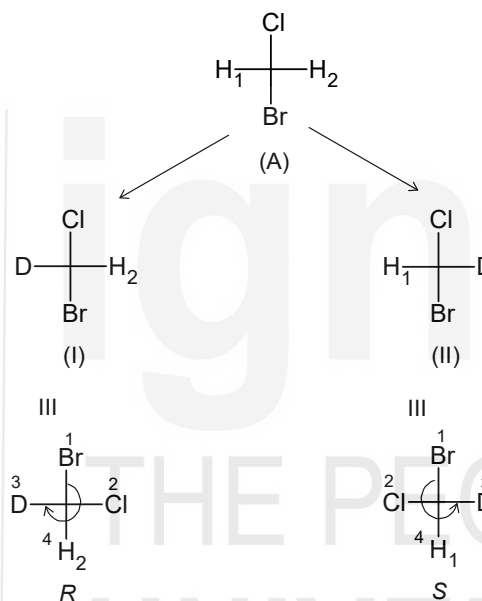
Having understood the topicity of ligands and faces, it will be appropriate here to understand their nomenclature.

A. Nomenclature of Stereoheterotopic Ligands

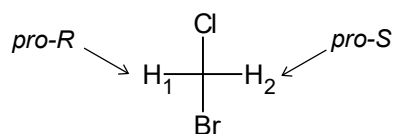
You already know that enantiomers can be designated by appropriate descriptions as *R* or *S* and the diastereomers with a rigid framework like a double bond (as on alkenes) can be designated as *E* or *Z*.

The, *R,S* descriptors are also used for stereocentres present in diastereomers.

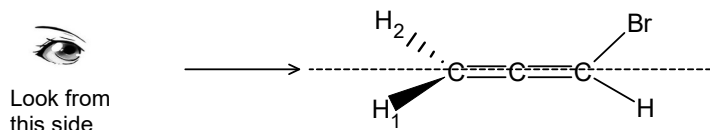
Let us take the example of compound A again and consider its conversion to the enantiomers (I) and (II) by replacing H_1 and H_2 , respectively by its higher isotope D as shown below. We will also assign them the configuration as *R* or *S* according to the Cahn-Ingold-Prelog rules.



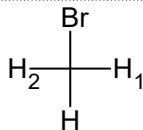
Here, the replacement of H_1 by D in compound A has led to *R* enantiomer; hence, H_1 is labeled as *pro-R* ligand. Similarly, replacement of H_2 in compound A is labeled as *pro-S*. This is shown below:



Similarly, a molecule having prochiral axis, has two stereoheterotopic hydrogen atoms labeled as H_1 and H_2 , as shown below;

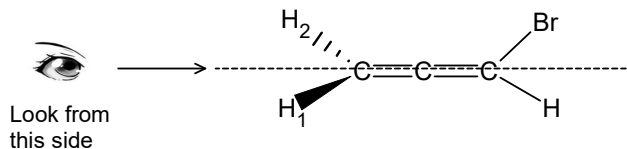


To know which H – i.e., H_1 or H_2 , is *pro-R* or *pro-S*, the molecule is looked along the axis from the side as shown above. Then, the molecule will appear as written below:

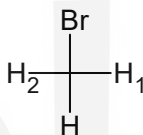


Again, if we replace H_1 and H_2 by say D, then H_1 will be *pro-R*. Repeating the same steps for H_2 will indicate that H_2 is *pro-S*.

Similarly, a molecule having prochiral axis, has two stereoheterotopic hydrogen atoms labeled as H_1 and H_2 , as shown below;



To know which H – i.e., H_1 or H_2 , is *pro-R* or *pro-S*, the molecule is looked along the axis from the side as shown above. Then, the molecule will appear as written below:



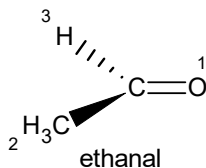
Again, if we replace H_1 and H_2 by say D, then H_1 will be *pro-R*. Repeating the same steps for H_2 will indicate that H_2 is *pro-S*.

B. Nomenclature of Stereoheterotopic Faces

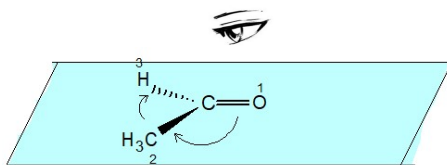
You have already studied about *homotopic*, *enantiotopic* and *diastereotopic* faces for the molecules labeled as (V), (VI) and (VIII), respectively. Let us study about their nomenclature for enantiotopic and diastereotopic faces.

(i) Nomenclature of Enantiotopic Faces

Let us take the example of ethanal which is a molecule of type (VI) structure wherein $\text{R} = \text{CH}_3$.

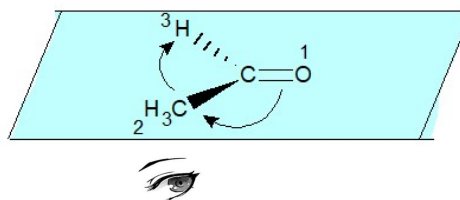


If we consider its top face and number the substituents attached to the carbonyl carbon as 1, 2 and 3 according to their decreasing order of priority as per the CIP rules, then you can see below that the path from 1 to 2 to 3 is



You have already studied about CIP rules in Unit 5.

clockwise; hence, this is called *Re* face. *Re* originates from the first two letters of the word *Rectus*. Alternatively, if we look this molecule from the opposite face, i.e., from below side as shown below,

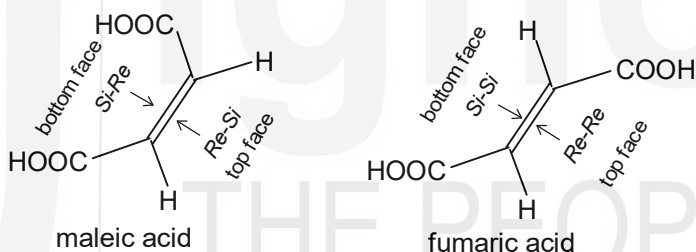


the path from 1 → 2 → 3 is *anticlockwise*. Thus, this face is called *Si* face from first two letters of the word *Sinister*.

SAQ 1

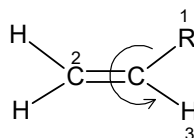
Draw the *Re* and *Si* faces for acetophenone molecule.

When *Re-Si* nomenclature is used for alkenes, the descriptors are assigned to both the carbon atoms of the alkenes. This is shown below for maleic acid and fumaric acid.



For maleic acid, the two faces are homotopic while for fumaric acid, the two faces are enantiotopic. The priority order is $\text{COOH} > \text{C} > \text{H}$.

However, in case of monosubstituted alkenes, the two faces are enantiotopic and only one symbol needs to be specified for each face. This is shown below:



Top face is *Si* face as the path from 1 → 2 → 3 is anticlockwise. What about the other face? It is *Re* face when viewed from the bottom.

(ii) Nomenclature of Distereotopic Faces

The nomenclature of distereotopic faces can be done similarly.

6.3 STEREOGENICITY

After studying the topicity of ligands and faces of molecules and their nomenclature, let us have a deeper insight into different terms being used in the context of stereochemistry of molecules.

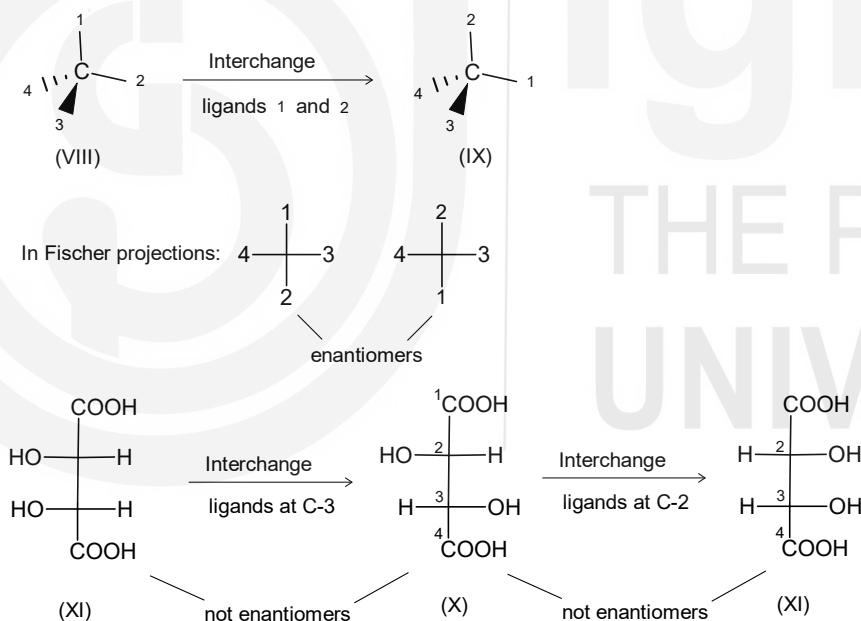
In Block 1, Units 1 and 2 of this course, you have studied about chiral centres, axial and planar chirality etc. But, have you got a clear idea about the chirality of molecule if it possesses one or more chiral centres.

In the due course of time, chemists also preferred the use of terms *asymmetric centre* for the chiral carbon as molecule does not have any symmetry elements when four different groups or ligands are attached to a carbon atom.

Another term *stereogenic centre* was used by Milton and Seigel in 1984 who said that *elements of chirality are more properly related to stereogenicity rather than molecular chirality*. Let us understand this now in a more detail.

A *stereogenic centre* is such a structural unit present in a molecule which can *generate stereoisomers*. And, the phenomenon associated with it is called *stereogenicity*.

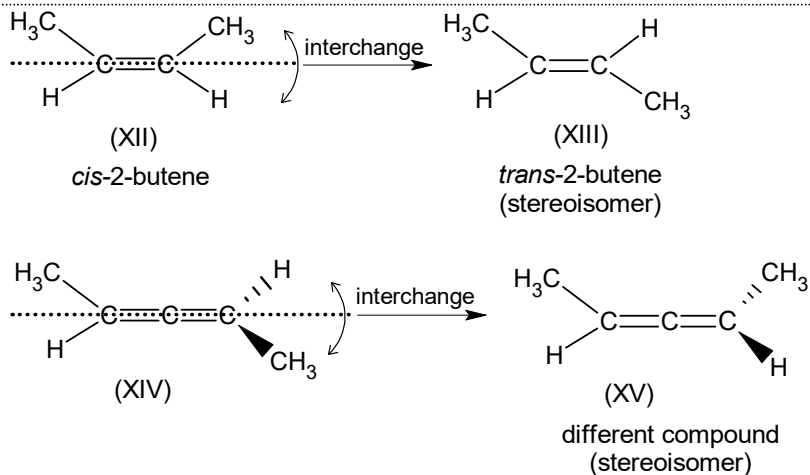
Now you may be curious to know what is a stereocentre. A **stereocentre is an atom or a group of atoms if the interchange of two ligands attached to it results in a new stereoisomer**. As the stereoisomerism is generated by such a centre, it is called *stereogenic centre*. You can see yourself in the figure given below that interchange of ligands attached to the central carbon atom leads to a different stereoisomer.



Interchange of two ligands in (VIII) gives its enantiomer (IX). But what about interchange of ligands in (X)? You can see that if we change the ligands at C-2 or C-3 in compound (X), we get the some new stereoisomer (XI), i.e., *meso* tartaric acid in this case. (XI) is not enantiomer of (X). Here, both C-2 and C-3 of (X) are stereogenic centres and also the central C atom in compound (VIII). So presence of a *chiral centre does not always ensure chirality*.

Also, *some molecules without chiral centres may be chiral*; you have already studied about *axial* and *planar chirality* in earlier units. Thus, interchange of ligands both in alkenes and allenes lead to different stereoisomers as shown below:

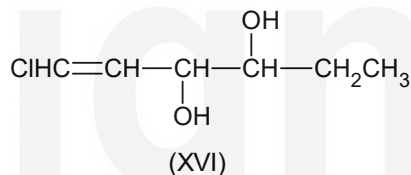
Remember that *chirality* is related to *handedness*. The word *chiral* came from Greek word *cheir* meaning *hand*. So our hands are mirror images of each other but they are not superimposable on each other.



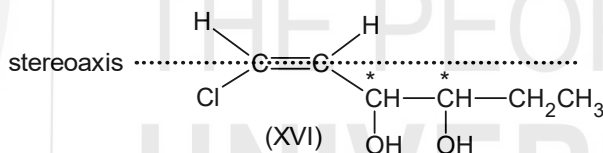
Hence, the *chirality axis in alkenes and allenes is a stereogenic axis*.

It would also be interesting to note that in some more complex molecules more than one stereocentres and/or stereoaxis may be present in a single molecule. For example, the following molecule (XVI),

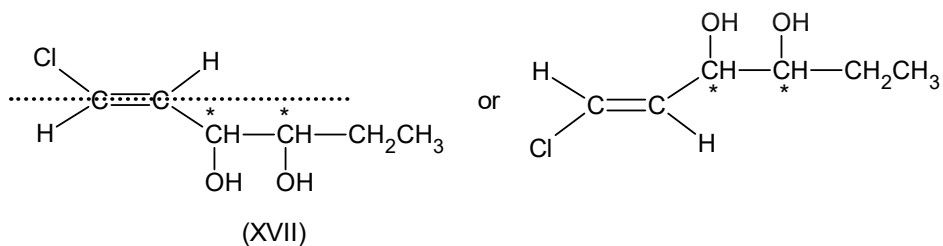
A chirotopic point in a molecule need not to be coincident with the material point i.e., an atom or a group. It can just be any point.



when looked as shown below clearly indicates the presence of two stereocentres marked by asterisks (*) and a stereoaxis.

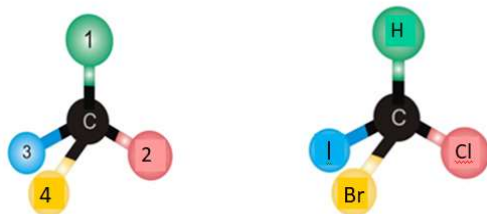


The interchange of two groups at any one of the carbon atoms forming the double bond would lead to *trans* arrangement as shown below:



6.4 CHIROPICITY

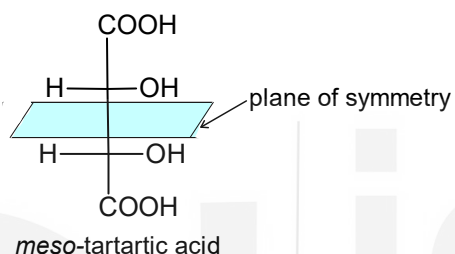
Chirotopicity is yet another term suggested by Milton and Siegel in 1984. Let us understand it now. Chirotopicity is the phenomenon related to presence of *chirotopic atom*. A *chirotopic atom is an atom which resides in a chiral environment*. This concepts involves the local or site symmetry within a molecule. Thus, *within a chiral molecule, all points are chiral*. For example, in a molecule (XVIII) as shown below, all five atoms, i.e., C, H, Cl, Br and I



(XVIII)

are present in the *chiral environment* and are *chirotopic*. Also, as discussed above carbon atom is *stereogenic also*.

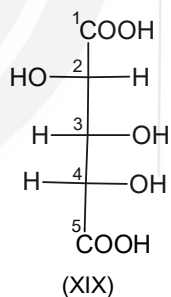
However, achiral molecules may also have many chirotopic atoms (or points). This is illustrated in case of *meso*-tartaric acid



Locate the centre of symmetry in *meso*-tartaric acid.

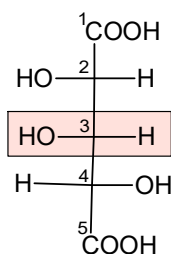
All points in *meso*-tartaric acid except those lying in the plane of symmetry, are chirotopic in this molecule. This argument is also valid for the centre of symmetry when present in a molecule. The centre of symmetry is also *achirotopic* in a molecule.

Let us study one more example and analyse chirotopic and stereogenic centre in compound (XIX).

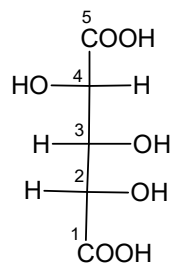


(XIX)

As this molecule is chiral, all the points in it should be chirotopic. Let us explore the stereogenicity at C-3. If we interchange the two groups i.e., -H and -OH, in the molecule, we get the following structure:



Let us check whether the structure so obtained is different, i.e., a stereoisomer of the compound or not. Let us rotate this by 180° as shown below:



Note the numbering of carbon atoms shown after rotation. What have we got? This is the *same structure* as of the starting compound.

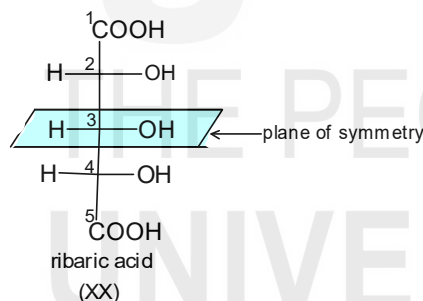
So, we have *not* got a stereoisomer after interchanging the groups (ligands) at C-3; hence, C-3 is *not stereogenic but it is chirotopic*.

So, this was an example in which one atom was *non-stereogenic but chirotopic*. But can there be molecules in which there is reverse situation. In other words, *are there molecules which have stereogenic centres and are achirotopic?*

Let us find an answer to this in the next section on pseudoasymmetry.

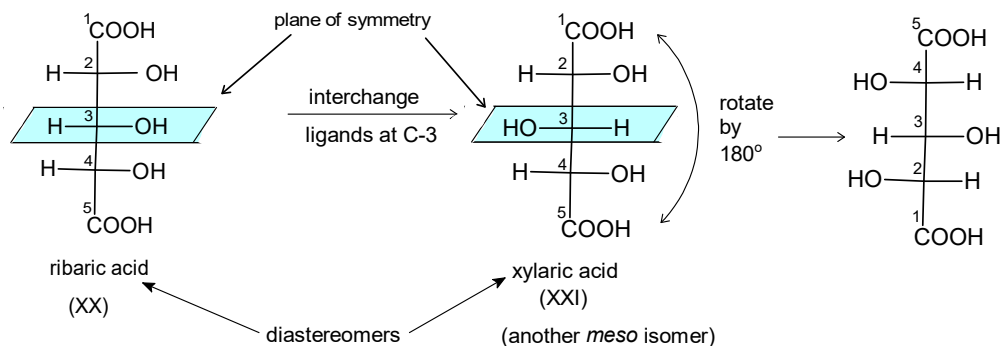
6.5 PSEUDOASYMMETRY

Let us consider *meso*-isomer of 2, 3, 4-trihydroxydicarboxylic acid (XX) which is a stereoisomer of compound XIX).



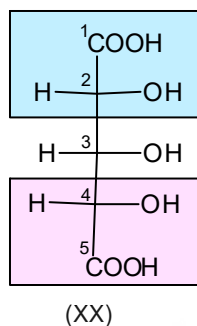
As it is a *meso*-isomer and has a plane of symmetry, all the points lying on this plane are achirotopic. So, C-3 will be *achirotopic*.

Let us check whether C-3 carbon is stereogenic or not? Again, we will interchange the ligands at C-3 and see if we get the stereoisomer or the same compound.

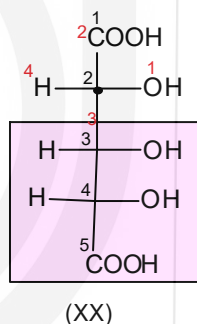


Here, the interchange of ligands at C-3 gives a stereoisomer which is another *meso* isomer. Even rotation of 180° of (XXI) does not give XX; so it is a *different stereoisomer*. As XX and XXI are not enantiomers; they are diastereomers. Thus, chirotopicity and stereogenicity are *two distinct aspects* and *are delinked from each other*.

Now such a centre which is achirotopic but stereogenic centre has four different ligands attached to it. You will say – how? Let us see below.

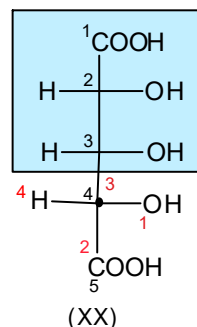


The C-3 carbon in XX has –H, –OH and two bulky groups shown in blue and pink coloured boxes. At the first sight, you can say that these two groups are same. They are same in the sense of their constitution, i.e., they have –H, –OH and –COOH attached to C. But do they have the same configuration? Let us check.



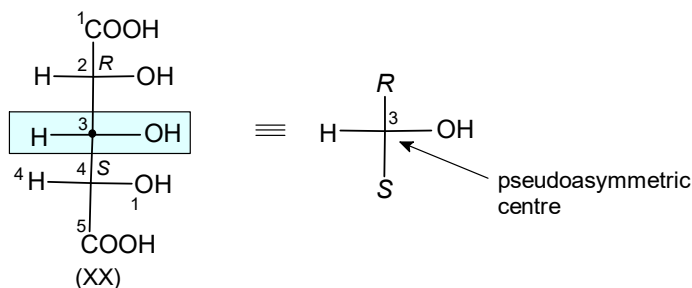
At C-2, the configuration is *R*. We have to prioritise the groups attached to C-2 as shown by numbers in red colour, this time to differentiate from the numbering of carbon atoms of the main chain done in black colour. Then, using the CIP rules, you can yourself verify the configuration at C-2 is *R*.

Similarly, we can check for the configuration of C-4 carbon atom. This time again, we can assign the priorities by using the CIP rules to four as groups as shown by numbers in red colour and then the path from 1 to 2 to 3 indicates



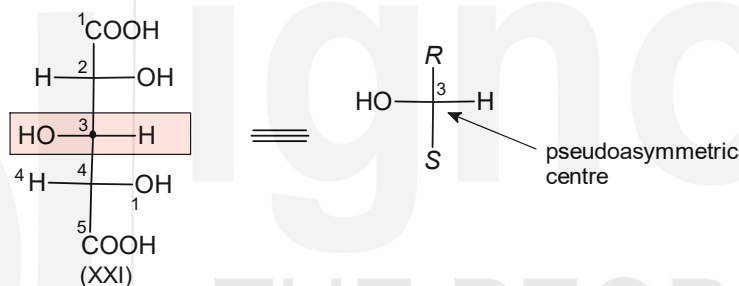
that the configuration of C-4 so obtained is *S*.

Now, we can write the structure of compound XX with configurations at C-2 and C-4 as shown below:



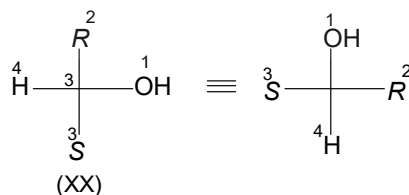
If we focus on C-3, we can represent the structure of XX attached to four different groups where *two* of them are *configurationally different* i.e., one is *R* and another is *S*. Such a centre is called *pseudoasymmetric centre* and this phenomenon is called *pseudoasymmetry*.

Now what about compound XXI, the diastereomer of XX? On the same lines as above, we can write it as shown below.



You can see that the pseudoasymmetric centres in XX and XXI have different arrangement of two groups –H and –OH. We can assign the stereodescriptors to such pseudoasymmetric centres also by using the CIP rules.

Thus, for compound XX, the priorities of different groups will be as shown below:



Here, *R* group is given priority over *S* as per CIP rules because *R* alphabet comes before *S*. As the path from 1 → 2 → 3 is clockwise, the stereodescriptor *r* designates this centre, i.e., C-3. Note that lower case letter *r* has been used here to differentiate from *R/S* descriptors for chiral centres.

Similarly, you can repeat the same steps for XXI and arrive at the configuration for pseudoasymmetric centre C-3 in it.

As you might have checked and expected the C-3 pseudocentre in XXI has *s* configuration.

You can now answer the following SAQs to check your understanding.

SAQ 2

What will happen if rbaric acid (XX) is reflected in a mirror? Will you get its enantiomer or the same compound?

SAQ 3

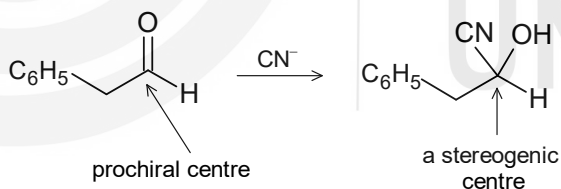
Has any change taken place in the descriptor of C-3 of ribaric acid when it is reflected in the mirror? Arrive at the answer by performing the necessary steps using CIP rules.

6.6 STEREOGENIC AND PROCHIRAL CENTRES

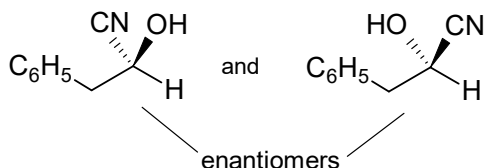
So far you have studied about the *stereogenic centre* on which exchange of two ligands yields stereoisomers – whether enantiomers or diastereomers. One way of how these stereogenic centres are created is from *an archiral centre*. Such an archiral centre is a planar trigonal carbon atom of the carbonyl group. For example, in the formation of a cyanohydrin a new stereocentre can be created, as shown below.



For the cyanohydrin formed to be *enantiomeric*, the two groups R and R' have to be *different*. Only then a new stereogenic centre would be formed in the cyanohydrins. In such a situation, the carbonyl carbon in the starting carbonyl compound is called a *prochiral centre*.

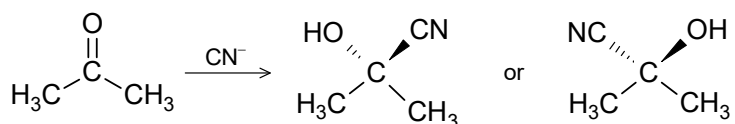


As the two enantiomers so formed would be as shown below:



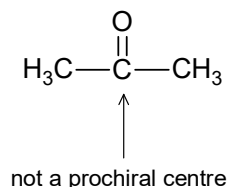
But, what would happen if the two groups, R and R' are the same?

Let us see.



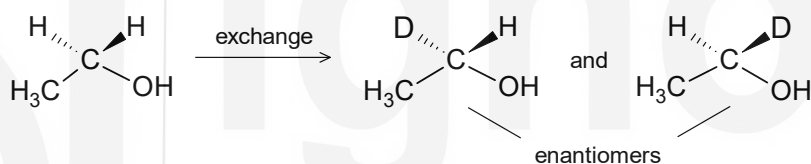
In whatever way the cyanohydrins so formed is presented – it is the same compound, the *two stereoisomers are not formed in this case*.

Hence, the no new stereogenic centre is created this time. Therefore, the carbonyl carbon is not prochiral in the starting carbonyl compound which is propanone here.

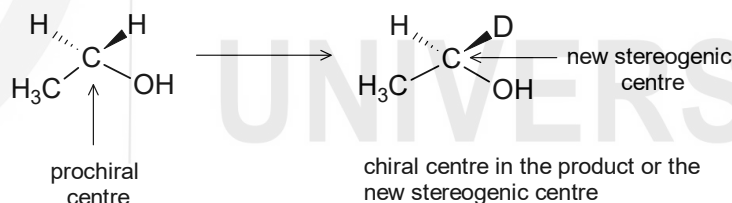


Thus, it is important to note here that the *prochiral centres are those centres which can be converted to chiral centres by one single transformation*. If two such chemical transformations are required then, such a centre is called a *proprochiral centre*.

Let us see another example of a prochiral centre. This time, we explore for a tetrahedral carbon atom. The two hydrogen atoms of the ethyl group, as in ethanol, on exchange with another group, say D lead to two compounds which



are enantiomers, i.e., there is generation of a chiral centre in the product. Hence, the carbon bearing these two hydrogens in ethanol is a prochiral centre. This is illustrated below.



SAQ 4

Differentiate between a prochiral and a proprochiral centre.

6.7 SUMMARY

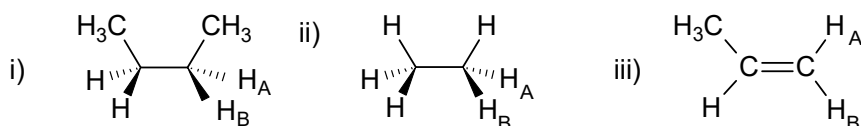
In this unit you have learnt that

- ligands are atoms or groups of atoms present in a molecule
- homomorphic ligands are ligands having the same atoms or groups of atoms with same configuration.
- the spatial relationship of homomorphic ligands is referred to as the topicity.

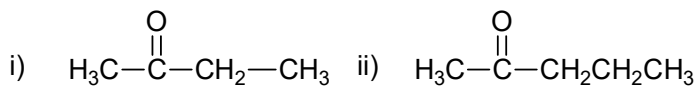
- whether the ligands are homotopic or not can be checked by the following criteria
 - ❖ substitution-Addition Criterion
 - ❖ symmetry Criterion
- stereoheterotopic Ligands can be classified as *pro-R* or *pro-S* ligands.
- stereoheterotopic Faces can be classified as *Re* or *Si* faces.
- a stereocentre is an atom or a group atoms if the interchange of two ligands attached to it results in a new stereoisomer.
- the presence of a chiral centre does not always ensure chirality and some molecules without chiral centres are also chiral;
- chirotopicity is the phenomenon related to presence of chirotopic atom. A chirotopic atom is an atom which resides in a chiral environment.
- within a chiral molecule, all points are chiral.
- *chirotopicity and stereogenicity are two distinct aspects and are delinked from each other.*
- the configuration of pseudoasymmetric centre is denoted by *r* or *s*.
- prochiral centres are those centres which can be converted to chiral centres by one single transformation. If two such are chemical transformations are required then, such a centre is called a proprochiral centre and
- stereogenic centre is one on which exchange of two ligands yields stereoisomers – whether enantiomers or diastereomers

6.8 TERMINAL QUESTIONS

1. Identify the hydrogen atoms present in ethanol as *pro-R* and *pro-S*.
2. In the following compounds, identify the hydrogens indicated by H_A and H_B as homotopic, enantiotopic or diastereotopic.

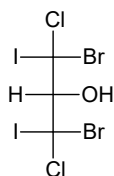


3. Mark the prochiral centre(s) in the following compounds.



4. Give an example of a compound which does not have a prochiral centre.

5. Assign the configuration to C-3 carbon atom of the following compound:

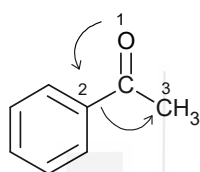


6. What descriptors are used to assign configuration to a pseudoasymmetric centre?
7. Draw the wedge and dash structures of (i) (*S*)-alanine and (ii) (*R*)-lactic acid.

6.9 ANSWERS

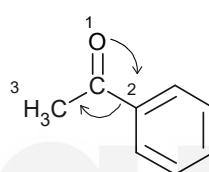
Self-Assessment Questions

1.



Top face: *Si* face

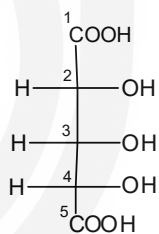
Anticlockwise path
from 1 → 2 → 3



Bottom face: *Re* face

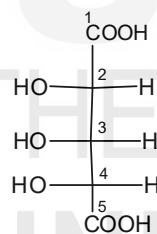
Clockwise path
from 1 → 2 → 3

2.



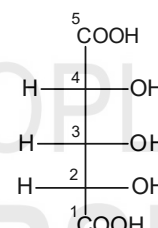
ribaric acid
(XX)

mirror



mirror image of
(XX)

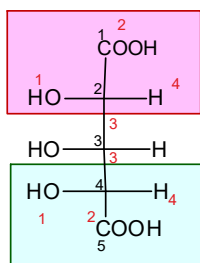
rotate by
180°



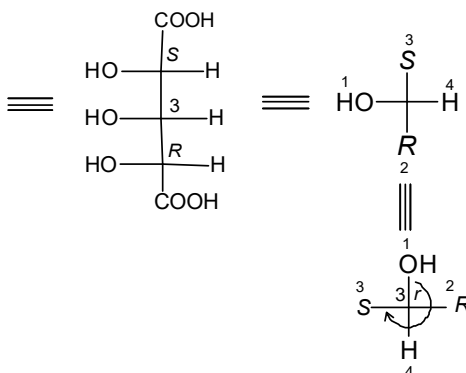
(XX)

Rotation of mirror image by 180° in the plane of paper gives (XX) again, the same compound.

3. The mirror image of ribaric acid (XX) shown below gives C-2 and C-4 with stereodescriptors as *R* and *S*, respectively. In its equivalent form when the path is traced from 1 → 2 → 3, it is clockwise.



mirror image of
ribaric acid
(XX)



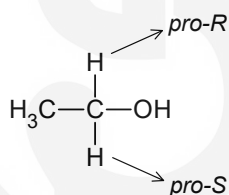
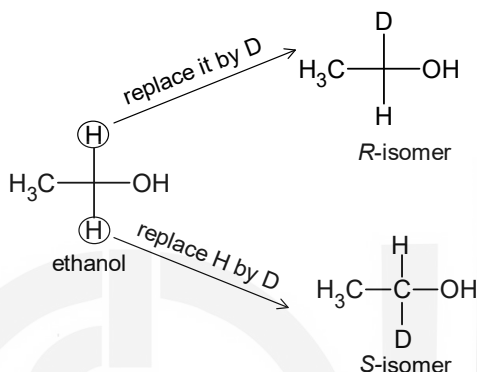
Therefore, stereodescriptor at C-3 would be *r*. The stereodescriptor for C-3 of ribaric acid is also small *r* which you had studied above in Sec. 6.5.

Thus, stereodescriptor for a pseudoasymmetric centre has not changed when it is reflected through a mirror; hence, we can say that the stereodescriptors (*r* or *s*) are invariant on reflection through mirror.

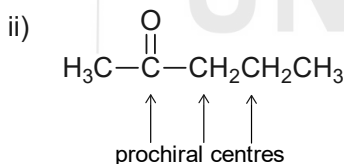
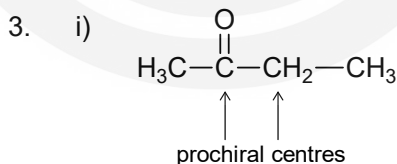
4. The *prochiral centres* are those centres which can be converted to chiral centres by one single transformation. If two such are chemical transformations are required then, such a centre is called a *proprochiral* centre.

Terminal Questions

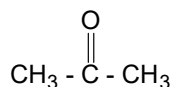
1.



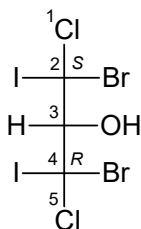
2. i) Enantiotopic; ii) Homotopic; iii) Diastereotopic



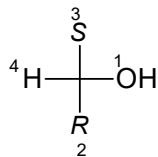
4.



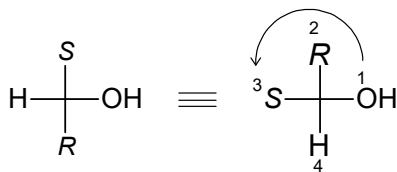
5. We have to first determine the configurations of C-2 and C-4 by using CIP rules. These were as found to be *S* and *R*, respectively as shown below:



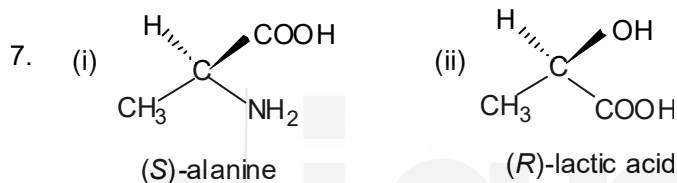
The above compound can then be written as follows:



Now, again using the CIP rules, as the path from 1 → 2 → 3 is *anticlockwise*: hence, the configuration of C-3 will be *s* as shown below.



6. *r* and *s*.



(i) As the groups attached to the chiral centre in alanine are COOH, NH₂, CH₃ and H; their priority order is NH₂ > COOH > CH₃ > H

For *S* configuration, these groups are to be arranged and placed in anticlockwise path from 1 → 2 → 3. The H can be placed at the backside being the last in the priority order.



Hence, the above structure.

(ii) argument as in (i) above give the structure of *R*-Lactic acid as shown above.