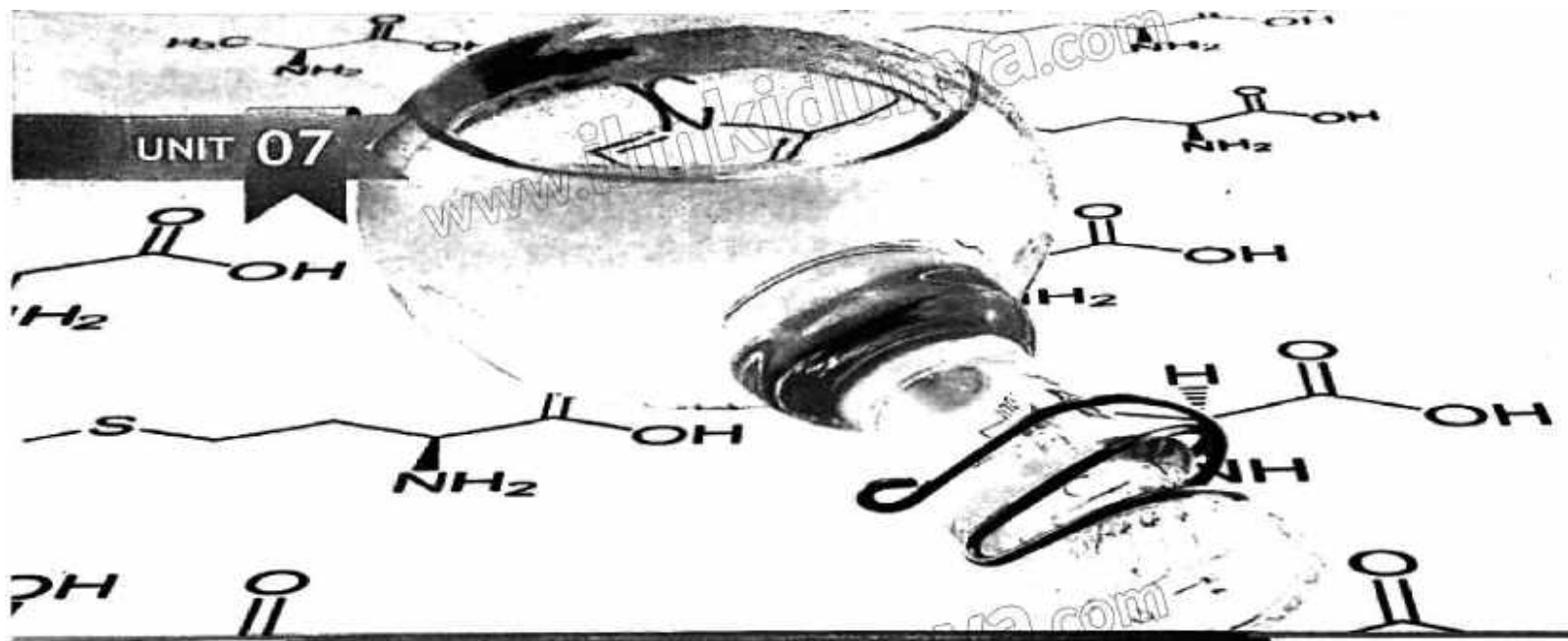




UNIT 07

ORGANIC CHEMISTRY

Student Learning Outcomes (SLOs)

- Explain stereoisomerism and its division into geometric (cis/trans) and optical isomerism.
- Describe geometrical (cis/trans) isomerism in alkenes and explain its origin in terms of restricted rotation due to the presence of pi (π) bond.
- Describe the shape of benzene and other aromatic molecules, including sp^2 hybridisation in terms of sigma (σ) bonds and delocalized pi (π) system.
- Explain what is meant by chiral center and that such a center gives rise to two optical isomers (enantiomers).
- Describe that enantiomers have identical physical and chemical properties for their ability to rotate the plane of polarized light and potential biological activity.
- Apply the terms optically active, racemic mixture and mesocompounds on the given structure.
- Describe the effect of two optical isomers of a single substance on a plane polarized light.
- Explain the significance of chirality in synthetic preparation of drug molecules, including the potential different biological activity of enantiomers, the need to separate racemic mixtures, and the use of chiral catalysts to produce a single pure optical isomer using thalidomide as an example.

Organic chemistry is the study of preparation, properties, identification, and modifications of organic compounds. All organic compounds have carbon as an essential element. They usually contain hydrogen element and may have other elements, like oxygen, nitrogen, halogens, and sulphur etc. There are millions of organic compounds with different uses in our lives. For example, carbohydrates, proteins, food, medicines, and cloths. Many industries produce organic compounds, like polymers, insecticides, cosmetics, and dyes.

Interesting Information

In the early nineteenth century, Jakob Berzelius classified chemical compounds into two groups based on their origin, organic compounds and inorganic compounds. Organic compounds come from plants and animals while inorganic compounds have mineral origin. A striking difference is in their way of burning. Organic compounds burn on heating (undergo combustion) while inorganic chemicals melt on heating.

Recall from grade 11, that organic compounds have a vast majority in nature. Nearly 19 millions organic compounds have been discovered so far. This enormous number of organic compounds is attributed to one of the factor which is isomerism. Organic compounds show isomerism because they exhibit different structures due to the directional character of covalent bond.

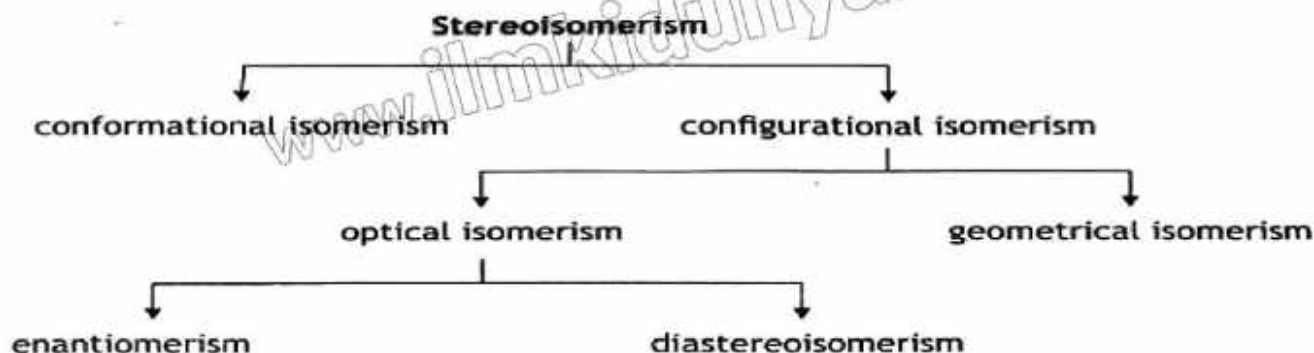
Organic compounds have a unique property of showing isomerism which is one of the factors held responsible for their vast majority in nature. The phenomenon which gives different structural formulae to organic compound with same molecular formulae is called isomerism. The compounds showing such phenomenon are called isomers.

Isomerism is broadly categorized into two classes: constitutional isomerism (structural isomerism) and stereoisomerism (configurational isomerism). The constitutional isomerism arises due to different connectivity of atoms in a molecule while stereoisomerism is due to different three- dimensional arrangement of atoms or groups of atoms in the space. We can interconvert constitutional isomers simply by rotation of one part of a molecule with reference to the other about single covalent bond, without breaking bonds, whereas stereoisomers can be interconverted by breaking and making bonds.

In the previous class, we have already studied both structural and stereoisomerism. However, in this chapter we will revisit stereoisomerism and study it in more detail.

7.1.1 Stereoisomerism

Most of the chemical reactions in our body involve molecules with specific stereochemistry. Metabolic reactions are catalyzed by enzymes which can interact with those stereoisomers that can fit in their active sites. The side effects of a medical drug is caused by the wrong stereoisomer whose structure does not fit into the active site of the enzyme. Stereoisomers are those molecules which have same chemical formulae, same structural formulae but different arrangement of atoms in space. The phenomenon of existence of such molecules is called stereoisomerism. This type of isomerism is further classified into two categories.



1. Geometric isomerism

Some organic compounds, like alkenes, have the same connectivity of atoms in their molecules, same structural formulae but different arrangement of atoms or groups of atoms around double bond. Such molecules are called geometric isomers, and this phenomenon is called geometric isomerism.

In alkenes, each carbon atom of double bond shows sp^2 hybridization. The double bond consists of one sigma (σ) bond and one pi (π) bond. The sigma (σ) bond is formed by head-on overlap between one of the three sp^2 hybrid orbitals on each carbon atom of double bond whereas pi (π) bond is formed by parallel overlap between unhybridized " p_z " orbitals on each carbon atom of double bond.

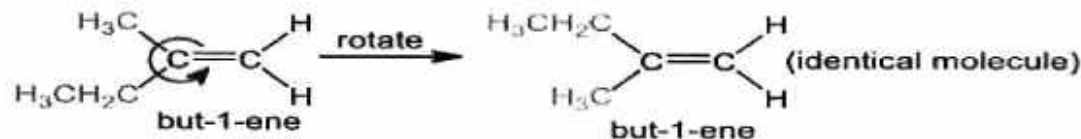
Since pi (π) bond between carbon atoms in alkenes restricts rotation about double bond at room temperature and does not allow free rotation of substituents around. To rotate the carbon atoms in a double bond of alkenes relative to each other, the pi (π) bond must be broken. Breaking pi (π) bond in ethene requires approximately 264 kJ/mol energy. This restricted rotation of carbon atoms of double bond is responsible for geometric isomerism in alkenes.

Alkanes, on the other hand, cannot show this type of isomerism because a single bond can easily be rotated at room temperature. For example, rotating carbon-carbon single bond in ethane requires almost 12 kJ/mol energy.

In the light of this discussion, we can say that one major difference between alkanes and alkenes is the degree of freedom of rotation about carbon-carbon single and double bonds.



Remember that alkenes molecules with same atoms or groups of atoms on same carbon atom of double bond cannot show geometric isomerism. This is because we get identical molecules even after breaking pi (π) bond and rotating the molecule across carbon-carbon double bond as shown.



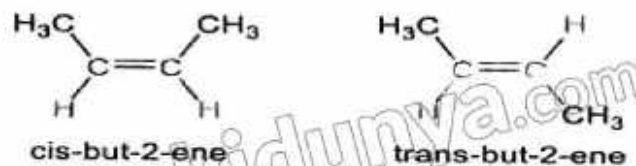
On the other hand, alkenes molecules with different substituents bonded to each carbon atom of double bond exist as two different molecules. For example, the physical properties of but-2-ene, depends on orientation of substituents around carbon-carbon double bond which means that different arrangement of substituents around double bond gives birth to different molecules as shown.



Remember that molecule (a) cannot be converted to molecule (b) simply by twisting one carbon of double bond with respect to the other due to restriction of pi (π) bond. To differentiate between such molecules based on different orientation of atoms or groups of atoms around double bond, IUPAC nomenclature recommends two types of designations for geometric isomers.

1. The cis-trans isomerism

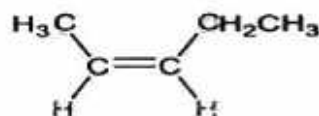
The cis-trans isomerism is originally used for naming disubstituted alkenes. We have some molecules that have the same substituents on the same side of double bond. Such type of molecules is called cis-isomers (Cis is a Latin word meaning "same side"). Conversely, the molecules having same atoms or groups of atoms on the opposite side of carbon-carbon double bond are called trans-isomers. In this system, the arrangement of carbon atoms of the parent chain decides whether the isomer is cis or trans. The but-2-ene molecule can show cis-trans isomerism as shown.



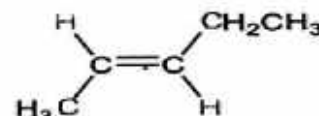
In cis-but-2-ene, the two methyl groups (carbon 1 and carbon 4 of the main chain) lie on the same side of carbon-carbon double bond whereas, in trans-but-2-ene, the two methyl groups stand on the opposite side of double bond.

The pent-2-ene molecule becomes relatively more difficult to designate it cis and trans-isomers in the sense that it has three different substituents, ethyl, methyl and hydrogen. Chemists decide cis and trans-isomerism in such molecules based on carbon atoms (carbon 1 and 4 in pent-2-ene) of alkyl groups bonded to the carbon atoms of double bond and treat all alkyl groups as same substituents. Similarly, cis-trans isomerism is studied based on orientation of hydrogen atoms bonded to carbon atoms of the double bond.

In pent-2-ene, the cis-isomer has alkyl groups and hydrogen atoms on same side of double bond whereas the trans-isomer carries alkyl groups and hydrogen atoms on opposite side of double bond.

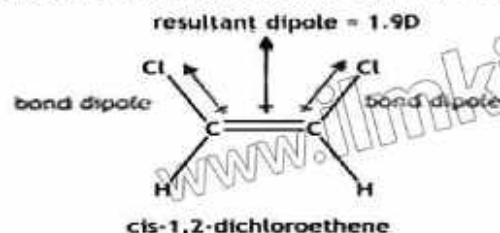


cis-pent-2-ene

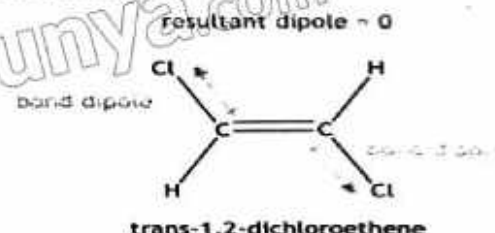


trans-pent-2-ene

The physical properties of cis-trans isomers, like melting points, boiling points, and solubility are different from one another. Cis-isomers are polar because they have dipole moment while trans-isomers are non-polar as they have zero dipole moment.



cis-1,2-dichloroethene



trans-1,2-dichloroethene

Their chemical properties are similar because they have the same functional groups, but not identical. They differ widely in biological systems due to their different shapes. Generally, cis-isomers are more reactive than trans-isomers. The closeness of bulky groups around carbon-carbon double bond causes steric hindrance, making the cis-isomer less stable compared to its trans-counterpart. Moreover, the electron cloud in cis-isomer is shifted to one side, making it more exposed to electrophilic attack compared to trans-isomer.

Interesting Information

Cis-platin has shape able to bond to the base guanine in DNA, causing DNA damage and kills cancer cells. This is why cis-platin is used in chemotherapy of different types of cancer. Trans-platin cannot play this role.

Key Information

We can also designate cis-trans isomers based on hydrogen atoms bonded to the carbon atoms of double bond.

How Isomerism Works in Our Eye?

In 1950s, an American chemist, George Wald discovered that the chemistry of vision involves cis-trans isomerization. The retina of eye contains rhodopsin which consists of protein and a cis-isomer called cis-retinal. When light enters our eye, the rhodopsin absorbs energy from photons of light high enough to break the π bond in the cis-isomer. Then rotation around sigma (σ) bond takes place followed by reformation of π bond and thus the trans-isomer, called trans-retinal, is formed. The energy released during reformation of π bond is responsible for the transmittance of nerve impulse to the brain. This absorption of light changes the shape of protein, creating flow of ions into retinal cells, initiating electric impulses which are carried by nerve cells to the brain where they are interpreted.

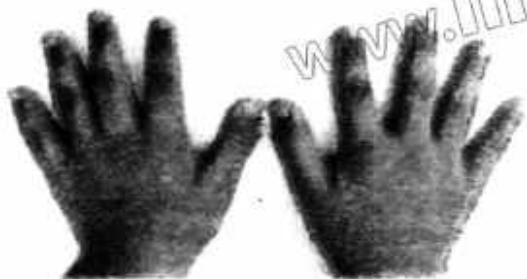
Concept Assessment Exercise 7.1

1. Which of the following compounds can and cannot show cis-trans isomerism and why?

- i. 1-chloroprop-1-ene ii. 3-chloroprop-1-ene iii. hex-2-ene

7.1.2 Optical Isomerism

The easiest way to understand the concept of optical isomerism is to look at our hands. Our right hand is the reflection of our left hand in a mirror which means that our left-hand reflection looks just like our right hand. In nutshell, our right and left hands are mirror images of one another. Your right and left hands are nonsuperimposable mirror images, meaning they cannot align perfectly one above the other, regardless of how you orient them as shown.



Interesting Information

If our hands were superimposable we would have either two rights hands or two left hands, instead of one right and one left.

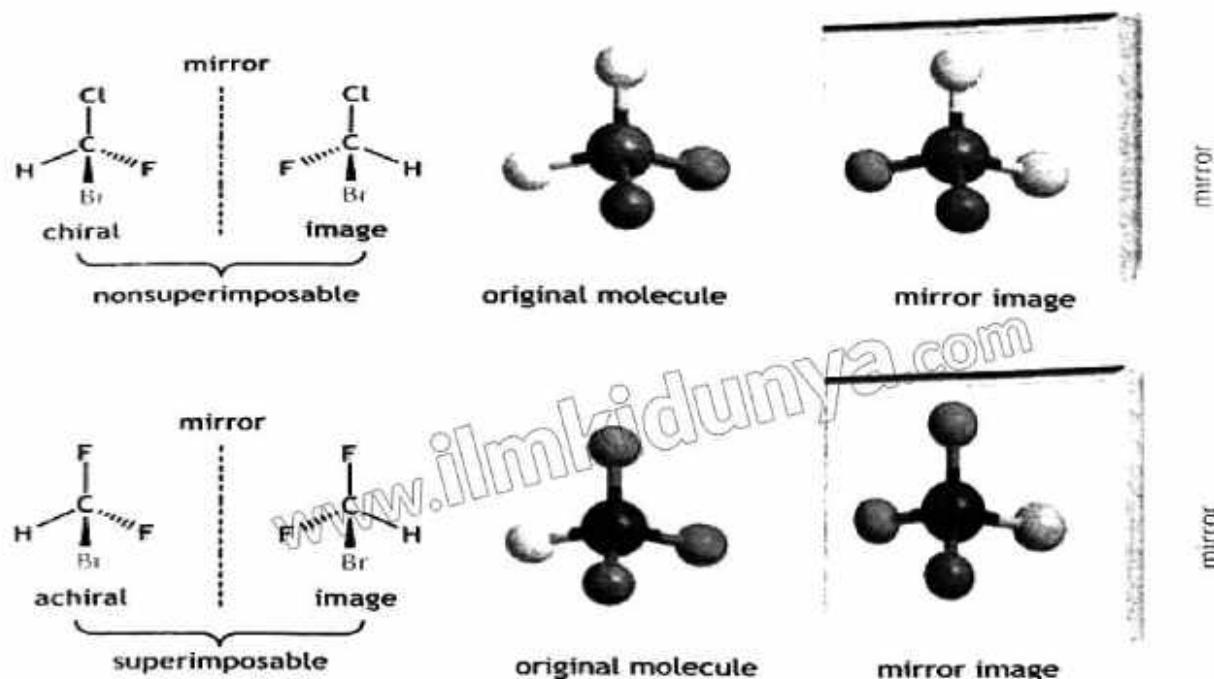
Similarly, try to put your right-handed glove on your left hand, it does not fit. All objects that are nonsuperimposable on their mirror images are called chiral (Greek word "cheir" meaning 'hand').

All chiral objects show handedness (chirality), with examples including scissors, keyboards, and cars. To understand chirality, hold your left hand outstretched (palm away) before a mirror and your right hand (palm toward you) next to it. The mirror image of your left hand will appear identical to your right hand, demonstrating chirality.

Many organic molecules exist in pairs which are non-superimposable mirror images of one another. Such molecules have carbon atom bonded to four different groups and are called

chiral molecules. The carbon which is bonded to four different atoms or groups of atoms are chiral or asymmetric carbon.

On the contrary, achiral molecules have a central carbon bonded to identical groups, making their mirror images superimposable and identical. For example, bromochlorofluoromethane has a non-superimposable mirror image.



The pair of stereoisomers that are nonsuperimposable mirror images of one another, just like our right hand is mirror are called enantiomers and this phenomenon is called enantiomerism. The word enantiomer comes from Greek word 'enantion' which means opposite. Consider 3-methylhexane shown.



We have studied in previous class that ordinary light has waves oscillating in all planes perpendicular to its direction of propagation. When ordinary light is passed through a polarizing

filter, such as calcite or Polaroid filter, only that part of light will be allowed to pass which can vibrate in parallel plane. The light vibrating in one plane is called plane polarized light.

The isomers that can rotate the plane of polarized light either in clockwise or anticlockwise direction are called optical isomers and this phenomenon is called optical isomerism. Optical isomers can exist in pairs called enantiomers or diastereomers. A solution of one enantiomer rotates the plane of polarized light in one direction whereas a solution of the other enantiomer rotates the plane of polarized light in the other direction.

Concept Assessment 7.2

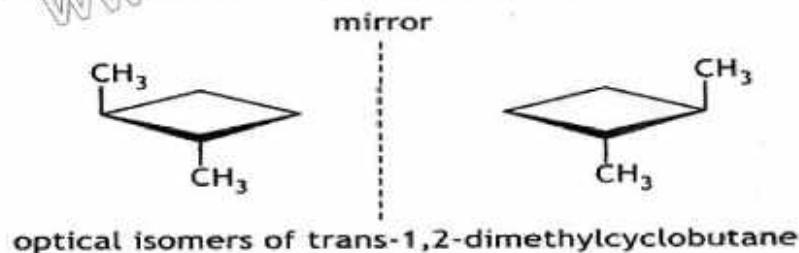
Separate chiral and achiral molecules in the following.

- | | | |
|---|---|--|
| a. $\text{CF}_3\text{CH}_2\text{CCl}_3$ | b. $\text{CF}_2\text{HCHFCCl}_3$ | c. $\text{CHCl}_2(\text{CH}_2)_3\text{CH}(\text{OH})\text{CH}_3$ |
| d. $\text{CH}(\text{OH})\text{ClCH}_2\text{CH}_3$ | e. $\text{CH}_2\text{ClCH}(\text{OH})\text{CH}_3$ | f. $\text{CF}_3\text{CH}_2\text{CCl}_3$ |

If the mixture contains 50-50 mixture of the two types of isomers, it is called racemic mixture. It has 50% dextrorotatory (Latin 'dexter' meaning 'right') isomer which rotates the plane of polarized light in clockwise direction while the other has 50% levorotatory (a Latin word 'laevus' meaning 'left') isomer which rotates the plane of polarized light in anticlockwise direction. The symbols "l" for levo and "d" for dextro are now obsolete and IUPAC recommends symbols "+" for dextro and "-" for levo isomers. The trans-isomer of 1,2-dimethylcyclobutane shows optical isomerism as follows.

Interesting Information

Optical isomers are molecules which can have non-superimposable images while enantiomers are the pairs of molecules that are non-superimposable images of one another.



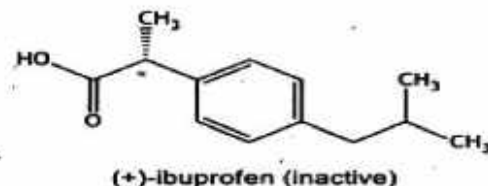
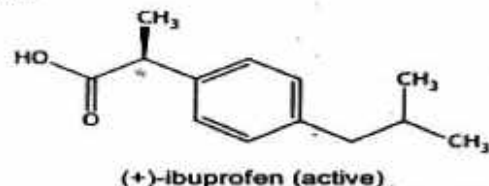
Similarly, nicotine molecules naturally synthesized by tobacco plant are chiral showing optical isomerism. Note the red star shows chiral carbon in nicotine molecule.



It is evident that a racemic mixture lacks the ability to rotate the plane of polarized light in either direction, making it optically inactive. The two isomers within such a mixture rotate polarized light equally, but in opposite directions. They cancel out their collective impact on the rotation of plane of polarized light in either direction.

Interesting Information

While administering racemic mixture of drugs, one enantiomer puts intended therapeutic effect while the other have damaging effect on the body. For example, a common painkiller, ibuprofen is chiral molecule, whose one enantiomer is active while the other is inactive as shown.

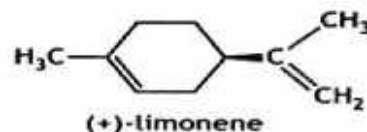


7.1.3 Properties of Optical Isomers

The physical and chemical properties of optical isomers are similar. For example, the optical isomers of the same compound possess the same density and melting points. Optical isomers of a compound can be differentiated based on their ability to rotate the plane of plane-polarized light in opposite directions.

However, they show different physiological effects in human body highlighting the fact that biological sensors and biochemical reactions are dependent on the shapes of molecules. For instance, one enantiomer of amino acid (asparagine) has a bitter taste whereas the other counterpart gives sweet taste.

Similarly, limonene molecule has chirality, and the body can distinguish between the taste and odour of its two enantiomers. Lemons and oranges contain the same isomer, (+)-limonene. In contrast, (-)-limonene is found in pine needles, peppermint, and spearmint and is different in smell or taste to the (+)-isomer. The (+)- and (-)-enantiomers of limonene (+)-limonene (-)-limonene.



Therapeutic drugs may also show optical isomerism as they are chiral molecules. One of the two enantiomers have desired pharmacokinetic and pharmacodynamic properties. Pharmacokinetics studies absorption, distribution, metabolism and excretion while pharmacodynamics is the study of actions administered drug on the system of the body and the way drug binds to the target site.

7.2.1 Separation of Drugs

It is of high industrial concern to design, develop and supply pharmaceutical drugs globally. One cannot neglect the importance of the therapeutic effects and the heavy financial issues of the development and marketing of new drugs.

The shape of biological systems and the biological-targeted chiral molecules are deeply linked in preparation of drugs. There is a potential difference between the biological activity of a particular drug. One enantiomer of a chiral molecule has differing effects on the human body compared to the other enantiomer of the same chiral molecule. For instance, one enantiomer of propoxyphene is an analgesic (pain relieving) whereas the other has anti-coughing properties, although the commercial names are mirror images of one another.

Another example of a chiral molecule which is used is called thalidomide. It was prescribed by medical practitioners as a sedative and treating morning sickness (nausea linked with pregnancy). Later, it was found that this drug caused birth defects in babies whose mothers took it during pregnancy. Further research proved that the (+)-enantiomer of thalidomide is active and used as sedative with no side effects whereas the (-)-enantiomer is a teratogenic, causing birth defects in babies whose mothers took the drug.



Unfortunately, the two enantiomers of thalidomide soon interconvert, making the administration of a single intended enantiomer ineffective to prevent the harmful effects.

7.2.1 Separation of Racemic Mixture of Thalidomide

Most chiral molecules in drugs exist in the form of racemic mixture, having 50 % (+) and 50 % (-) isomers. However, such drugs are not advised by healthcare professionals in racemic mixture form because the two isomers can have different effects on human body. One enantiomer may be therapeutically active and have desired effects while the other may be inactive, less effective or even harmful. This is evident from the case of thalidomide.

To address this issue in thalidomide drug, there are two methods. One method is optical resolution which involves the separation of the racemic mixture into two enantiomers of thalidomide, removing the (-)-thalidomide enantiomer. This can be done by high-performance liquid chromatography (HPLC), crystallization or use of some enzymes. The other method is called chiral synthesis or asymmetric synthesis which ensures the formation of single desired enantiomer, like (+)-thalidomide, suppressing the formation of the other enantiomer.

Asymmetric synthesis utilizes chiral catalysts to create an environment in the chemical reaction that favours the production of desired enantiomer, suppressing the other enantiomer. A BINOL (1,1-bi-2-naphthol) catalyst has palladium or rhodium used for asymmetric synthesis of (+)-thalidomide enantiomer, making thalidomide drug safer and reliable thereby minimizing the risks of harmful effects of (–)-thalidomide enantiomer.

In asymmetric synthesis reaction thalidomide, the double bond in thalidomide, is selectively hydrogenated in the presence of a chiral catalyst. The chiral catalyst supports the addition of hydrogen to the double bond in thalidomide molecule favoring the formation of one enantiomer over the other. In this way, a single pure isomer of thalidomide is produced which can be used for intended therapeutic effects on our body.

Interesting Information

Now-a-days, different drug authorities across the globe, like US Food and Drug Authority (FDA), recommends the assessment of enantiomer activity for racemic drugs in the body to ensure the development of a single desired enantiomer.

KEY POINTS

- Organic chemistry is the study of hydrocarbons or their derivatives.
- Almost 20 million of organic compounds are known.
- Isomerism is the phenomenon stems from same molecular formulae but different structural formulae of organic molecules.
- Stereoisomers have same molecular formulae and structural formulae but different arrangement of atoms or groups of atoms in the space.
- Geometric isomerism is shown by alkenes having different atoms or groups of atoms bonded to double bonded carbon atoms.
- Geometric isomerism is also called cis-trans isomerism.
- The double bond presents restricted rotation to the two doubly bonded carbon atoms giving different configuration to the molecule.
- The E/Z designation is used specifically for those molecules having different atoms or groups bonded to double bonded carbon atoms.
- A priority rule is established by IUPAC body to decide the right configuration.
- The IUPAC nomenclature recommends E/Z system for all alkenes molecules exclusively.
- However, chemists still continue to use cis-trans designations for simple molecules.
- According to IUPAC recommendation for organic chemistry 2013, both E/Z and cis-trans systems are used for alkenes, however, the E/Z nomenclature is preferred over cis-trans nomenclature.
- Optical isomerism is shown by molecules having no symmetry. Optical isomers rotate the plane of polarized light either clockwise or anticlock-wise.
- The clock-wise rotating isomers are designated d or + sign while the ones that rotate the plane of polarized light anticlock-wise are designated l or - sign.
- The plane polarized light is the one which travels or vibrates in one plane.
- Chiral molecules are those having carbon atoms bonded to four different atoms or groups of atoms.

- Chirality means handedness. A chiral molecule has a mirror image related to it like left hand to right hand.
- A molecule may have more than one chiral carbon atoms.
- All optical isomers have chiral carbon atoms and are asymmetric.
- All optical isomers have chiral centers but all chiral molecules are not optically active.
- A meso isomer is the one which is optically inactive, although it has chiral carbon atoms. The reason is that it is internally compensated.
- A racemic mixture is the one having 50% dextro and 50% levo rotatory isomerism making it overall optically inactive.
- Polarimeter is the instrument that determines the optical activity of organic molecules.
- Optical isomers have different properties from one another.
- Optical isomers are used as drugs. One optical isomer has the desired effect on a patient while the other counterpart has harmful effects.
- It is recommended to separate the racemic mixture of optical isomers before using them as drugs.

References for Further Information

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- Chemistry by George Facer
- Chemistry-The molecular nature of matter and change by Silberberg.
- Chemistry by Peter Cann and Peter Hughes.
- Chemistry by Blackman, Bottle, Schmid, Mocerino and Wille.
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- Chemistry by Christopher Talbot, Richard Harwood and Christopher Coates.

EXERCISE

1. Multiple Choice Questions (MCQs)

- i. Which one of the following molecules will have the ability to rotate the plane of polarized light?



- a) I and II only
b) I and III only
c) I, II and IV only
d) II and IV only

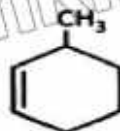
- ii. Which one of the following molecules shows optical isomerism/

- a) $\text{CH}_2=\text{CHCH}_2\text{CH}_3$
b) $(\text{CH}_3)_2\text{CHCl}$
c) $\text{CH}_2=\text{CHCH}(\text{Cl})\text{CH}_3$
d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$

How many chiral centers are present in this molecule?



CC1=CCCCC1



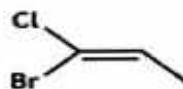
- cause different rotation of plane polarized light
have no functional groups
es cannot show optical isomerism
ouble bond carbon in alkenes acts chiral center

2. Short Answer Questions

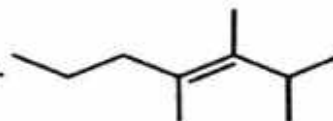
i.



b.



c.



- ii. Draw the cis-trans isomers of hex-3-ene.
- iii. Highlight the importance of chirality in drugs. Why do we need to separate optical isomers in the preparation of drugs?
- iv. What is meant by levo-rotatory and dextro-rotatory isomers? Give one example.
- v. Why can't geometric isomerism occur in alkenes where identical atoms or groups are attached to the same carbon atom of the double bond?
- vi. How does the presence of a π (pi) bond in alkenes restrict rotation, and what energy implication does this have for isomerism?
- vii. Why are cis-isomers generally more reactive but less stable than their trans-isomer counterparts?
- viii. How can a molecule be chiral yet remain optically inactive? Give the term used for such a molecule.
- ix. Why is it not effective to administer only the (+)-thalidomide enantiomer to patients?
- x. Why is the use of chiral catalysts preferred in the pharmaceutical industry for synthesizing optical isomers of drugs?

3. Long Answer Questions

- i. Define geometric isomerism. Draw cis-trans isomers of any alkene.
- ii. Why propene cannot show cis-trans isomerism?
- iii. Explain the way of separating a racemic mixture of thalidomide.
- iv. How a catalyst can play its role in this separation.
- v. Explain why the trans-isomer of but-2-ene is more stable than the cis-isomer. What role do steric interactions play?
Given the compound 1,2-dichloroethene, identify and draw all possible geometrical isomers.
- vi. Indicate which isomer would likely have a higher boiling point and why.
- vii. What structural features must a molecule have to exhibit optical isomerism? Give an example and explain why it is optically active.