ISOMERS

These are different compounds that have the same molecular formula but the atoms are attached in different ways.

There are two classes of isomers

(1) Constitutional isomers or structural isomers: Constitutional isomers differ in their bonding sequence, and their atoms are connected differently and the number of constitutional isomers increases with the increase of carbon atoms in each compound.
Types of Structural isomers:
(i) Chain isomerism
(ii) Position isomerism
(iii) Functional isomerism
(iv) Metamerism
(v) Tautomerism

(2) Stereoisomers:

Stereoisomers are molecules that have the same molecular formula and differ only in how their atoms are arranged in three-dimensional space. They have the same connectivity but a different spatial orientation.

Stereoisomers do not differ from each other as a result of rotation around single (sigma) bonds. Stereoisomer can be further divided in to two categories (a) GEOMETRICAL ISOMERISM Geometric isomers are molecules that are locked into their spatial positions with respect to one another due to a double bond or a ring structure.

Geometrical Isomerism in Alkenes¬ The p-bond in an alkene does not permit rotation, thus all of the atoms attached directly to the alkene lie in a plane. Groups attached to the alkene could be positioned on the same side of the alkene or on opposite sides of the alkene. Such compounds are different in chemical and physical properties as well as in their geometry, and are called geometrical isomers. In other words Geometric isomers (also called cis/trans isomers) are a type of stereoisomer resulting from a double bond or a ring structure. The double bond or ring in the structure means that not all bonds are free to rotate; giving rise to geometric isomers whose shapes cannot interconvert.

Example:2-butene

In 2-butene the methyl groups can be located on the same side or on the opposite side of the double bond, giving rise to two geometrical isomers. The isomer with the methyl groups on the

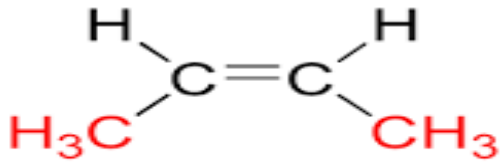
same side is called the cis isomer, while the isomer with the groups located on opposite sides is called the trans isomer. Trans isomers of compounds are usually more stable than cis isomers

Geometric Isomers of 2-Butene

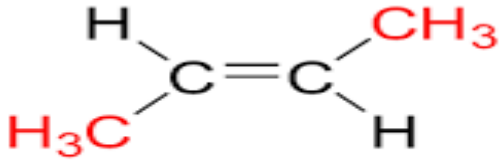
In each molecule, the double bond is between carbons 2 and 3.

A. In cis-2-butene, the methyl groups attached to carbons 2 and 3 are on the same side of the rigid double bond.

B. In trans-2-butene, the methyl groups are on opposite sides of the double bond.

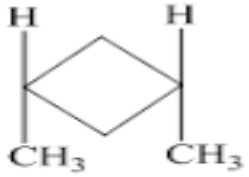


cis-2-butene

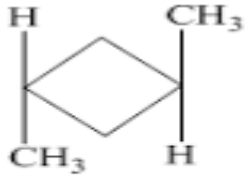


trans-2-butene

Geometrical Isomerism in Cyclic Systems¬ Substituents attached to a ring system will either be on the same side of the ring or on the opposite side of the ring. Thus, cyclic alkanes show cis and trans geometrical isomers Example: 1, 3-dimethylcyclobutane The cis and trans isomers of 1, 3-dimethylcyclobutane are shown below.



cis-1,3-dimethylcyclobutane

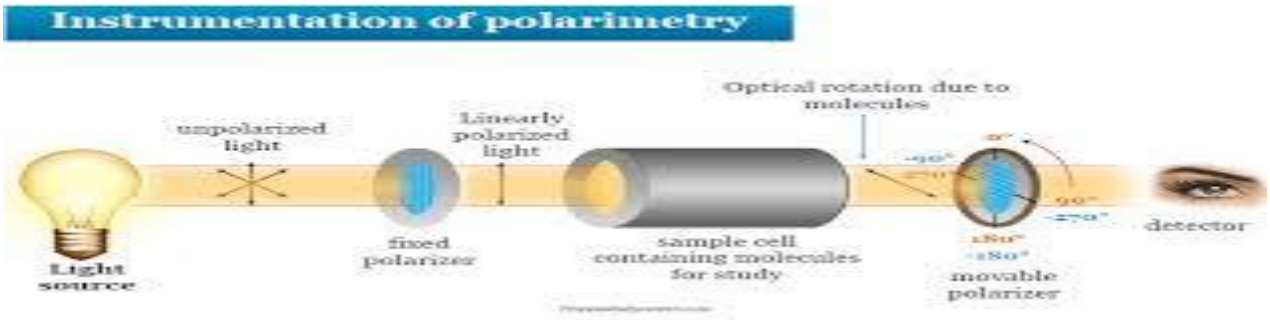


trans-1,3-dimethylcyclobutane

(b) OPTICAL ISOMERISM Optical isomers are two compounds which contain the same number and kinds of atoms, and bonds (i.e., the connectivity between atoms is the same), and different spatial arrangements of the atoms. It arises through the presence of a Chiral Centre. Optical isomers are Non Superimposable Mirror Images of each other; a set of optical isomers are called enantiomers. These shows optically active nature

Optical activity – The ability to rotate the plane of plane –polarized light and it can be detected by polarimeter.

Polarimeter – Device that measures the optical rotation of the chiral compound



A POLARIMETER is an instrument that allows plane-polarized light to travel through a sample tube containing an organic compound. After the light exits the sample tube, an analyzer slit is rotated to determine the direction of the plane of the polarized light exiting the sample tube. There are two possible results.

1. With achiral compounds, the light exits the sample tube unchanged, and the plane of the polarized light is in the same position it was before entering the sample tube. A compound that does not change the plane of polarized light is said to be optically inactive.
2. With chiral compounds, the plane of the polarized light is rotated through an angle α. The angle α, measured in degrees (°), is called the observed rotation. A compound that rotates the plane of polarized light is said to be optically active. The rotation of polarized light can be in the clockwise or counter clockwise direction.

1. If the rotation is clockwise (to the right from the noon position), the compound is called dextrorotatory. The rotation is labelled d or (+).
2. If the rotation is counterclockwise (to the left from noon), the compound is called levorotatory. The rotation is labeledl or (–).

Plane-Polarized Light

Ordinary light consists of electromagnetic waves that oscillate in all planes perpendicular to the direction in which the light travels. Passing light through a polarizer allows light in only one plane to come through. This is plane polarized light (or simply polarized light), and it has an electric vector that oscillates in a single plane.

Observed Rotation

a. The observed rotation depends on the number of chiral molecules that interact with polarized light. This in turn depends on the concentration of the sample and the length of the sample tube. To standardize optical rotation data, the quantity specific rotation (*α+) is defined using a specific sample tube length (usually 1 dm), concentration, temperature (25 °C), and wavelength (589 nm, the D line emitted by a sodium lamp).
b. Specific rotations are physical constants just like melting points or boiling points

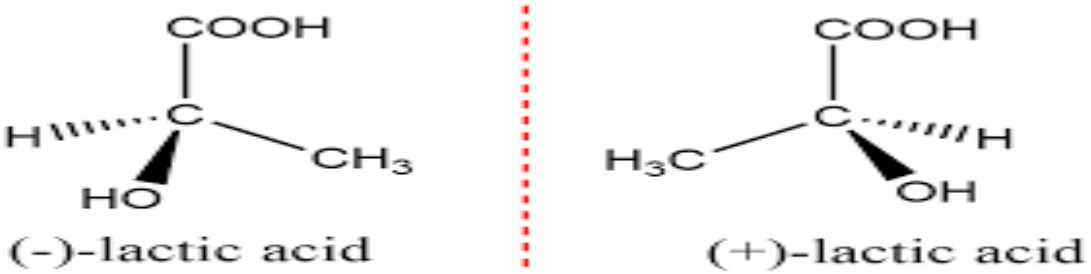
CONDITIONS FOR OPTICAL ACTIVITY

1. To exhibit optical activity molecule must possess asymmetric carbon: Asymmetric carbon compounds are optically active. But, presence of asymmetric is not only the requirement. (An asymmetric carbon atom (chiral carbon) is a carbon atom that is attached to four different types of atoms or groups of atoms.)
2. To exhibit optical activity molecule must not have the plane of symmetry

Plane of symmetry: A plane which bisects the molecules into two mirror images are called plane of symmetry. If the plane of symmetry is present then the molecule is optically inactive, if absent then optically active. Molecules that form non superimposable mirror images, and thus exist as enantiomers, are said to be chiral molecules. For a molecule to be chiral, it can not contain a plane of symmetry. A plane of symmetry is a plane that bisects an object (a molecule, in this case) in such a way that the two halves are identical mirror images. An example of a structure that has a plane of symmetry is a cylinder. Cutting a cylinder in half lengthwise generates two halves that are exact mirror images of each other. A molecule that possesses a plane of symmetry in any of its conformations is identical to its own mirror image. Such molecules are achiral, or nonchiral. Example: Butane is an achiral molecule, while 2-bromobutane is chiral.

The most common cause of chirality in an organic molecule is a carbon atom with four different atoms or groups bonded to it. This carbon atom is called a stereogenic, chiral, or asymmetric center

Enantiomers: Enantiomers are chiral molecules that are mirror images of one another. Furthermore, the molecules are non-superimposable on one another. This means that the molecules cannot be placed on top of one another and give the same molecule. Chiral molecules with one or more stereocenters can be enantiomers. It is sometimes difficult to determine whether or not two molecules are enantiomers. A stereocenter is an atom, typically carbon, that has four attachments that are different from each other.



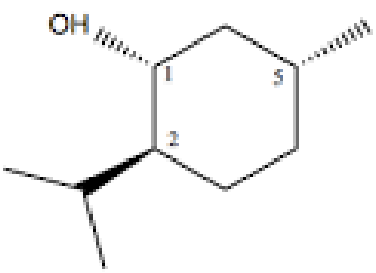
Enantiomers

Diastereomers

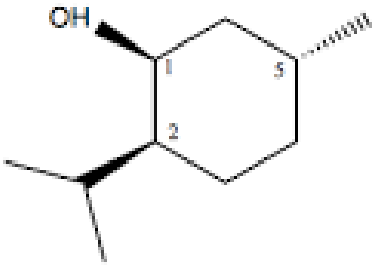
These are stereoisomers that are not mirror images of one another and are nonsuperimposable on one another. Stereoisomers with two or more stereocenters can be diastereomers

Example

these two are diastereomers



(1R,2S,5R)-(-)-menthol

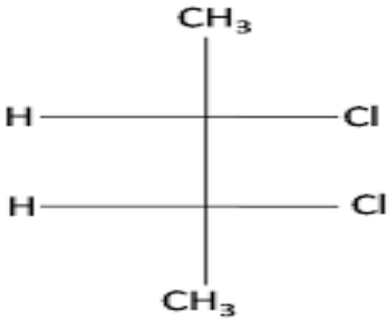


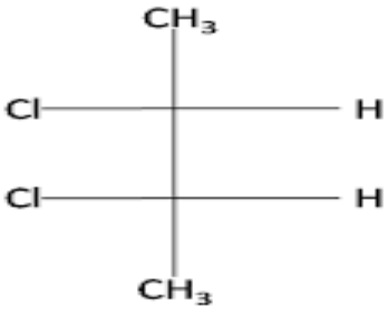
neomenthol

Meso compound: A meso compound is a stereoisomer and, thus, by default must have a stereocenter. Meso compounds require at least two stereocenters. A compound with only one stereocenter cannot be considered a meso compound as it would not be achiral and would not have another stereocenter to oppose its optical behaviour The meso compound must be symmetric about the internal mirror plane. Each opposing stereocenter must have differing absolute configurations and the attachments on each stereocenter must be the same. If the opposing stereocenters have the same absolute configurations or the attachments on either side are different, then one half will not be a mirror image of the other half.

Example :2,3-dichlorobutane

Meso compounds are symmetric compounds that have an internal mirror plane, so that the left and right side of the plane are mirror images of each other.

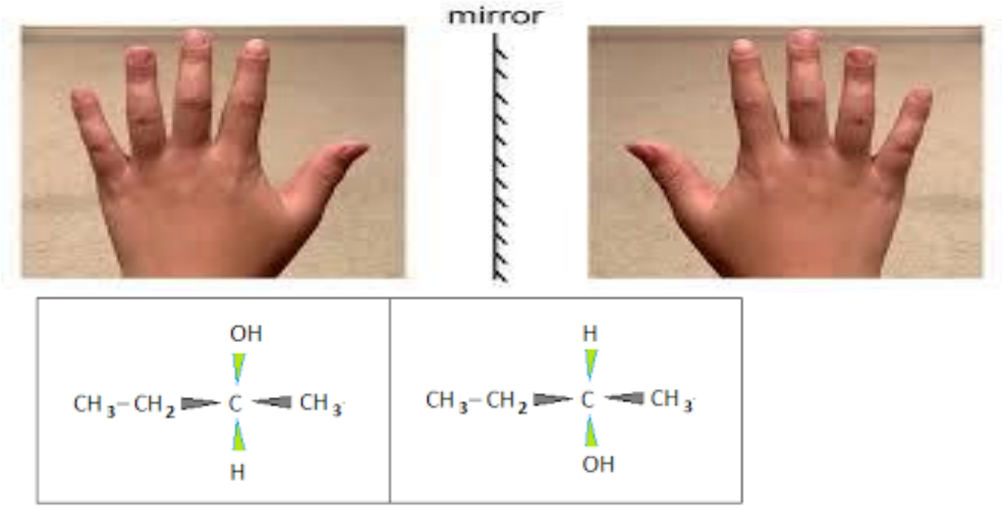




Chiral and Achiral Molecules

A carbon atom that contains four different groups will be chiral. We call that atom a chiral center, or chirality center. When two of the groups on a carbon atom are the same, that carbon is not a chiral centerTheexistance of these molecules are determined by concept known as chirality. The word "chiral" was derived from the Greek word for hand, because our hands display a good example of chirality.They are non-superimposable mirror images of each other. EXAMPLE - like our hands, are non-superimposable mirror images of each other

And other example is2-butanol

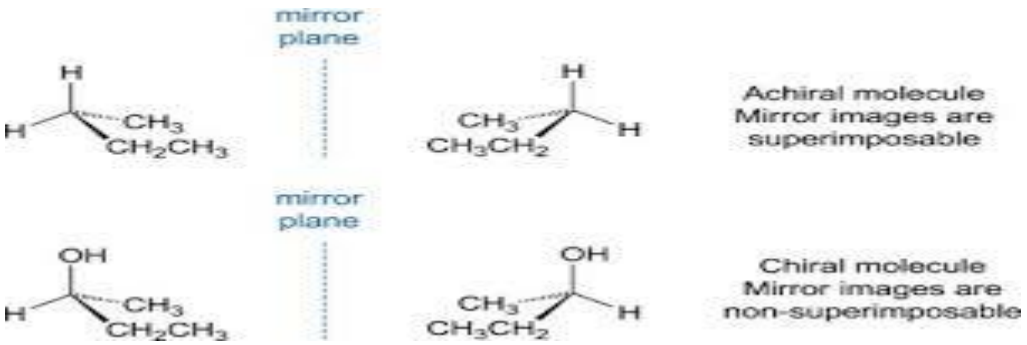


(L/R) 2-butanol

In This carbon two has four different groups: an ethyl group, a hydrogen atom, a hydroxyl group, and a methyl group. The opposite of chiral is achiral. Achiral objects are superimposable with their mirror images. Most achiral molecules have a plane of symmetry. Achiral molecules that contain a stereocenter are called meso.

Example -Two pieces of paper are achiral

Some other examples are:



RACEMIC MIXTURE A racemic mixture is a 1:1 mix of two enantiomers (Each of a pair of molecules that are mirror images of each other). No matter how many molecules are in a mixture, it is racemic if there are equal numbers of the two enantiomers. The racemic mixture produces a net optical rotation - of plane polarized light - of zero degrees. This is because the mixture contains equal amounts - equimolar mixture - of both enantiomers that have opposite rotations. A racemic mixture is a solution containing equal amounts of a pair of enantiomers

A solution containing equal amounts of (R)-2-butanol and (S)-2-butanol is a racemic mixture.

A solution containing an excess of either the (R)-enantiomer or the (S)-enantiomer would be ENANTIOENRICHED.

A solution containing only the (R)-enantiomer or the (S)-enantiomer will be ENANTIOMERICALLY PURE.

RESOLUTION OF RACEMIC MIXTURES

The separation of a racemic mixture into the individual enantiomerically pure enantiomers is called resolution. Since enantiomers have identical physical properties, such as solubility, boiling point and melting point, they cannot be resolved by common physical techniques such as direct crystallization, distillation or basic chromatography. The main difficulty in a process of resolution is that d or (+) and l or (–) forms have identical physical and chemical properties, so they cannot be separated by ordinary methods. However, the following methods can be used for this purpose.

(i) Mechanical separation: If the d or (+) and l or (–) forms of a substance exits in well-defined crystalline forms, the separation can be done by hand picking with the help of magnifying lens and a pair of tweezers. Example The d and l forms of sodium ammonium tartarate can be separated by this method. Louis Pasteur was the first to resolve a racemate - (±)-sodium ammonium tartrate. He was lucky in that this salt crystallized below 28°C as separate mirror-image crystals, one type containing only (+)-enantiomers and the other type containing only (-)-enantiomers. Thus, Pasteur was able to separate them using only magnification and tweezers. This kind of racemate is called a racemic mixture.

Many other kinds of racemates (e.g., racemic compounds, whose (+)- and (-)-enantiomers are in the same crystal type) cannot be separated (resolved) in this way, but there are

many alternative methods of resolution are available. The process by which an optically active substance is transformed into the corresponding racemic modification is known as racemization The method has very limited application and applies to only few crystalline constituents having different shape.

(ii) Biochemical separation: In this method, the resolution is done by the use of microorganisms. When certain bacteria or moulds are added to a solution of a racemic mixture, they decompose one of the optically active forms more rapidly than the other.

Example When thePenicilliumglaucum is allowed to grow in ammonia salt, it destroythe dextro chemical compound than the levo chemical compound.the mould completely decomposes the d form white l form is left practically unaffected. The main drawback of the method is that half of the material is destroyed during resolution. The process is very slow and only small amounts of the materials can be separated.

(iii) Chemical separation: This is probably the best method of resolution. The racemic mixture is made to combine with another optically active compound and the resulting solubility in various solvents. By fractional crystallization from a suitable solvent, they can be separated. For example, the racemic mixture of lactic acid is allowed to combine with the optically active base (-) strachnine or (+) brucine.

Advantages of racemic modification

The use of a single isomer must be seriously taken after long clinical assessments between racemate and single enantiomer actions because in some cases, racemates have more therapeutic advantages than single isomers.

Disadvantages of racemic modification

Side effects of "other" enantiomer could be dangerous. Larger or double doses of the drug will have to be taken if drug contains a mixture of enantiomers.

ADVANTAGES OF RESOLUTION OF RACEMIC MODIFICATION

Single enantiomers have less complex and more selective pharmacodynamics profile as compared to racemic mixture so have lesser adverse drug reactions, improved therapeutic profile, and less chances of drug interactions than racemic mixtures. Single enantiomers seem to be more advantageous over racemic mixtures as adverse drug reactions occurring due to one enantiomers are avoided, patients are exposed to less amount of drug, so the body is exposed to the lesser metabolic, renal, and hepatic load of drug, there is easier therapeutic drug monitoring of the active pure active enantiomers.

Reduction in the therapeutic dose. Reduction in the interpatient variability in metabolism and in response to treatment. Simplification ofthe relationship between the dose and the response to treatment. Reduction in the toxicity and side effects due to the greater specificity of action of the isomer with the relevant biological processes. Cuts cost. Reduces patients dosage by half as pure is more potent.

Example

1. Levorotary isomer of all β-blockers is more potent in blocking β-adrenoceptors than their dextrorotary-isomer, such as S (-)- propranolol is 100 times more active than its R(+)-antipode.
2. All ACE inhibitors such as captopril, benazepril, enalapril, and imidapril are chiral compounds under diastereoisomeric form, and most of them are marketed as single isomer. Valsartan, an angiotensin II receptor antagonist, is used as a single Senantiomer and the activity of the R-enantiomer is clearly lower than the Senantiomer.

Asymmetric synthesis or Stereoselective synthesis A chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts.Traditionally called Asymmetric synthesis.

Asymmetric synthesis relates to any synthetic process that introduces one or more new elements of chirality during a functional group transformation. In asymmetric synthesis, the reactions are either highly enantioselective or enantiospecifi. But, resolution is not very efficient as the maximum yield of the desired enantiomer is only 50%.

Asymmetric synthesis, also known as chiral or enantioselective synthesis, is a chemical reaction that produces unequal amounts of stereoisomers (enantiomers or diastereomers) from achiral or chiral starting materials. It's a crucial area in organic chemistry, particularly for synthesizing molecules with specific biological activities, as enantiomers can have drastically different effects.

Creating a Chiral Center:
The reaction introduces a new chiral center (or alters an existing one) in a molecule

Preferential Formation:
The reaction favors the formation of one stereoisomer over its counterpart(s), leading to an enantiomeric excess (ee) or diastereomeric excess

Chiral Influences:
This preference is achieved by using a chiral starting material, chiral reagent, chiral catalyst, or by employing chiral reaction conditions.

Types of Asymmetric Synthesis:

Partial Asymmetric Synthesis:

Achieved by using a chiral substrate, auxiliary, reagent, or catalyst to influence the stereochemical outcome of a reaction.

Examples:

1. Chiral Pool Synthesis:

Utilizing naturally occurring chiral molecules (like L-tyrosine) as starting materials to introduce chirality into a new molecule.

Example: Converting L-tyrosine into L-DOPA, where the existing chiral center in L-tyrosine is maintained during the synthesis.

2. Chiral Auxiliary Approach:

Employing a chiral molecule (chiral auxiliary) that temporarily binds to the substrate, influencing the stereochemical outcome of a reaction, and is later removed.

Example: Using a chiral auxiliary like proline in an aldol reaction to achieve enantioselective carbon-carbon bond formation.

3. Enzyme-Catalyzed Reactions:

Utilizing enzymes, which are chiral catalysts, to direct the stereochemical outcome of a reaction.

Example: The reduction of pyruvic acid to lactic acid using yeast, where the enzyme specifically catalyzes the formation of one enantiomer.

4. Sharpless Epoxidation:

A reaction where chiral titanium complexes are used to catalyze the epoxidation of allylic alcohols with high enantioselectivity.

Example: Epoxidation of allylic alcohol using a chiral titanium catalyst and diethyl tartrate as a chiral ligand

Absolute Asymmetric Synthesis:

Achieved using a physical phenomenon that breaks symmetry, like circularly polarized light, to induce chirality in the product.

Examples

Circulatory Polarized light: Irradiating achiral molecules with cirularly polarized light can lead to the formation of chiral products, as the light itself possesses chirality.

Crystallization: Some molecules, when crystallized, can adopt chiral crystal structures, even if the individual molecules are achiral. This can lead to absolute asymmetric synthesis if reactions occur within these chiral crystal lattices.

Helical Molecules: Reactions involving the formation of helical molecules, like some helicenes, can be induced to be chiral by using cirucularly polarized light.

STEREOSPECIFIC REACTIONS:

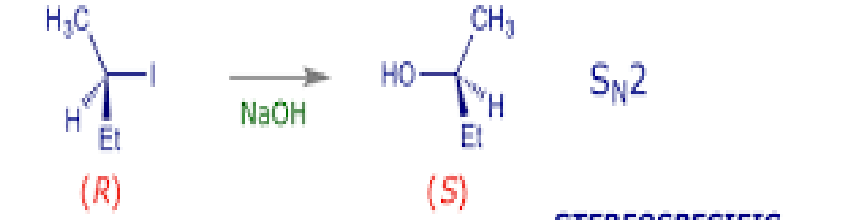
A stereospecific reaction is one which, when carried out with stereoisomeric starting materials, gives a product from one reactant t other. 'Stereospecific' relates to the mechanism of a reaction, the best SN2 reaction, which always proceeds with inversion of stereochemistry at the reacting centre. Stereo specificity in substitution reactions.

STEREOSELECTIVE REACTIONS:

A stereoselective process is one in which one stereoisomer predominates over another when two or more may be formed. If more than one reaction could occur between a set of reactants under the same conditions giving products that are stereoisomers and if one product forms in greater amounts than the others, the overall reaction is said to be stereo selective.

All stereospecific reactions are also stereoselective, but not all stereoselective reactions are stereospecific. Stereospecific reactions are more restrictive, as they require a specific mechanism for each stereoisomeric starting material, while stereoselective

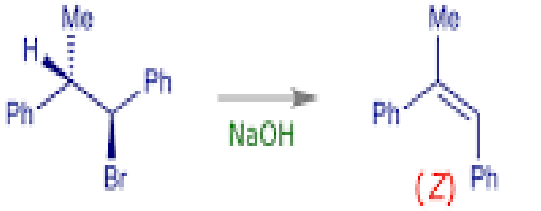
reactions simply favor one stereoisomer over others



(R) (S)

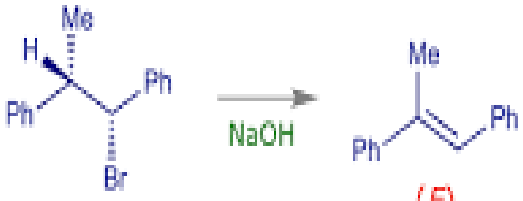
STEREOSPECIFIC
always inversion

(S) (R)



(Z)

STEREOSPECIFIC
always antiperiplanar TS



(E)