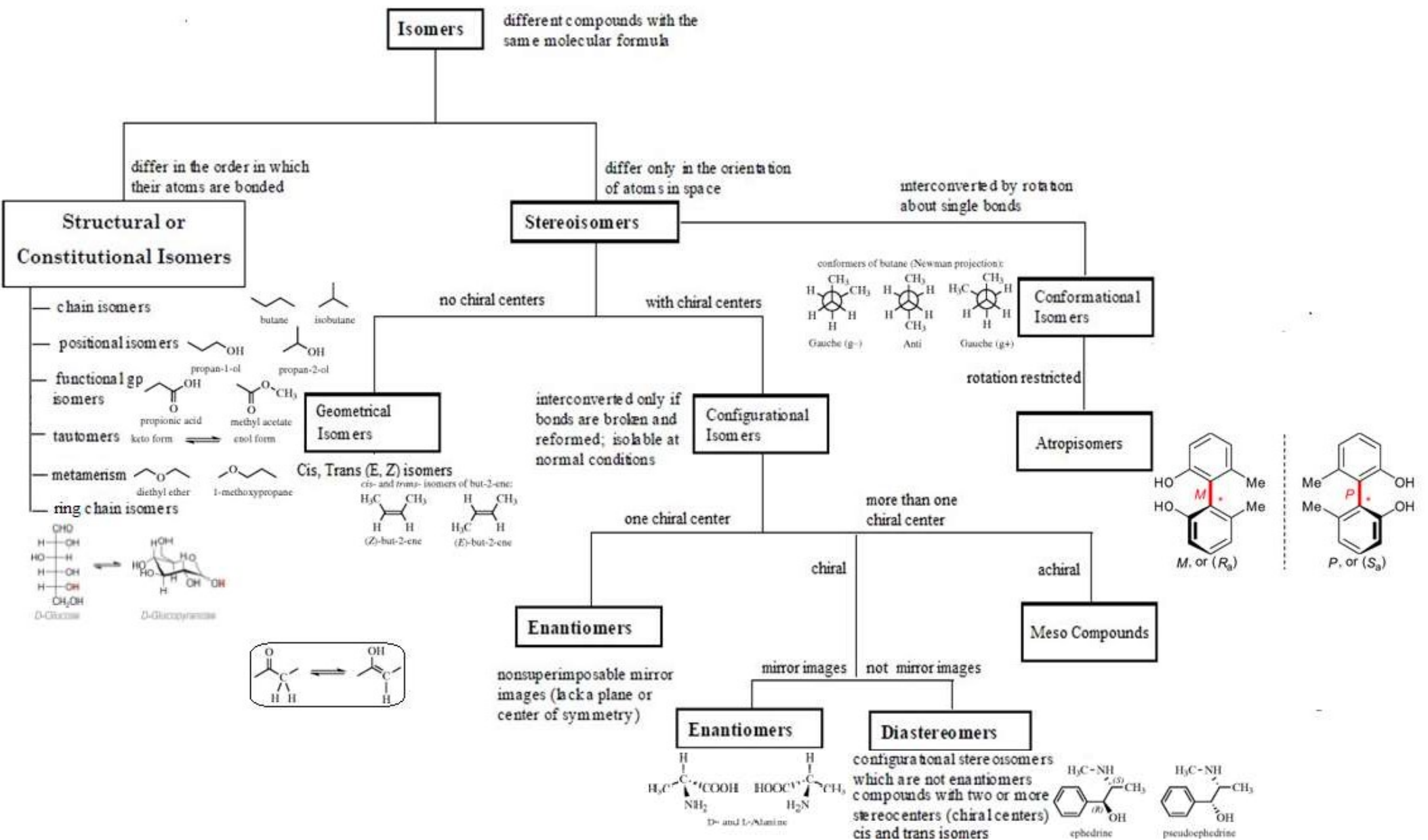


Classification of Isomers



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Course Instructor: Dr Bhar Saha

Dept. of Science & Mathematics

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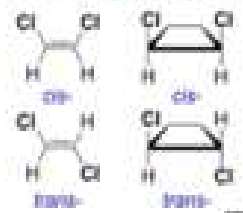
STEREISOMERISM

GEOMETRIC ISOMERISM

ABSOLUTE stereochemistry E/Z-ISOMER



RELATIVE stereochemistry cis/trans-ISOMER

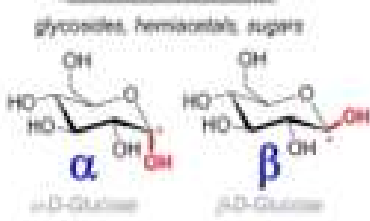


CONFIGURATIONAL ISOMERISM

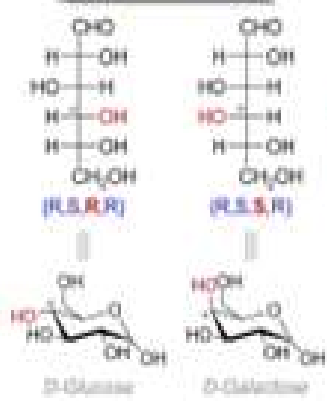
DIASTEREOMER



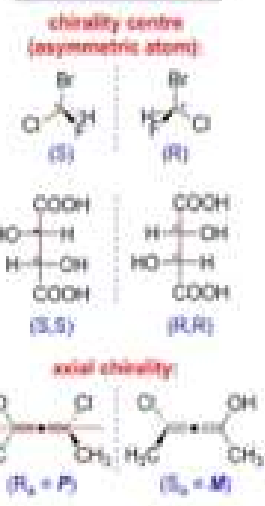
ANOMER



EPIMER



ENANTIOMER



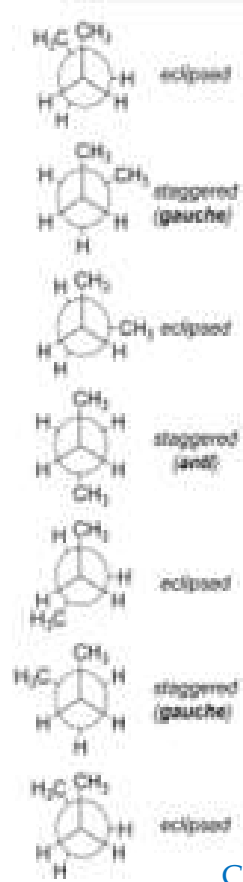
CONFORMATIONAL ISOMERISM

CONFORMER

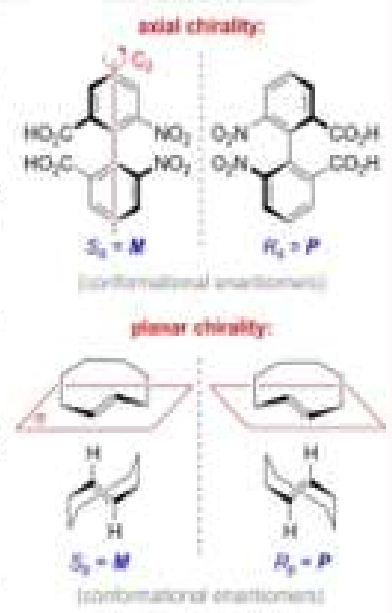
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ROTAMER



ATROPISOMER



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Isomers: are molecules that have the same molecular formula, but have different structures. i.e. They contain the same atoms bonded together in different ways.

Constitutional (structural) isomers: differ in the way their atoms are connected.

There are five types of structural isomerism:

- Chain isomerism

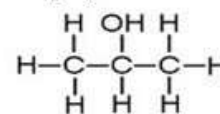
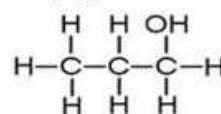


2-Methylpentane

3-Methylpentane

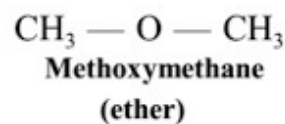
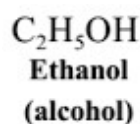
propane-1-ol

propane-2-ol

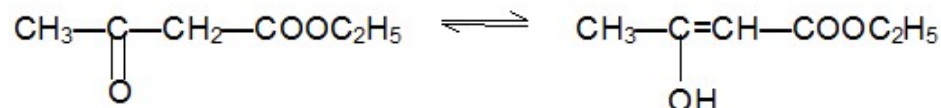


- Positional isomerism

- Functional isomerism



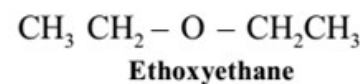
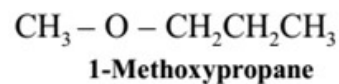
- Tautomerism (where there are two isomers are known as the keto and enol isomers)



keto form

enol form

- Metamerism



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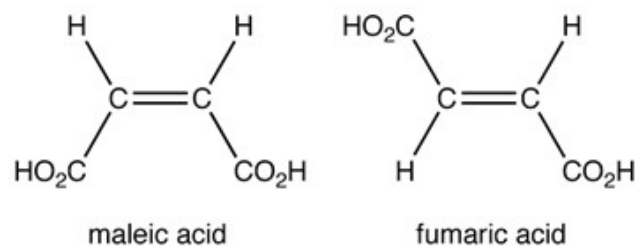
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Stereoisomers: differ in the way their atoms are arranged in space. They differ in presence or absence of chiral center, or difference in conformation (structures that can be interconverted simply by rotation about single bonds or rings)

Chiral molecules have no plane of symmetry. A tetrahedral carbon atom carrying four different groups: OH, CN, RCH_2 , and H is known as a stereogenic or chiral center. Only some chiral compounds have no stereogenic center.

Geometrical isomers (cis-trans): do not have any stereogenic centers (chiral /asymmetric atom). They can have very different physical properties, such as different melting points, but they tend to have the same chemical properties.



Chirality in terms of planes, centres, and axes of symmetry

Any molecule which has a plane of symmetry or a centre of symmetry is achiral.

Any molecule which has an axis of symmetry is chiral, provided it does not also have a plane or a centre of symmetry. An axis of symmetry is the only symmetry element compatible with chirality.

Configurational isomers: result from the breaking of bonds to form different molecules. Configurational isomers may have one or more chiral center. They may be optically active/inactive. In case of optically active isomers, they have the same chemical properties, except that one structure rotates the plane of polarized light to the right (+) [dextrorotatory] and the other rotates it to the left (-) [laevorotatory].

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Configurational isomers having one chiral center:

Enantiomers: are structures that are not identical, but are mirror images of each other, so not superimposable. Enantiomers can be described as (+) or (–), or D (dextrorotatory) or L (laevorotatory) depending on their rotation of plane polarized light. D and L enantiomers are non-superimposable images of each other. Structures that are not superimposable on their mirror image, and can therefore exist as two enantiomers, are simply chiral.

A racemic mixture is a mixture of two enantiomers in equal proportions. If all the starting materials and reagents in a reaction are achiral (lack an asymmetric center) and the products are chiral, they will be formed as a racemic mixture of two enantiomers.

Any compound which does not have a plane of symmetry is chiral. Any sample of a chiral compound that contains molecules all of the same enantiomer is enantiomerically pure. All isomers of alanine are chiral (no plane of symmetry) but chemically synthesized alanine is racemic (a 50:50 mixture of enantiomers) whereas naturally isolated alanine is enantiomerically pure (L-isomer).

A pair of enantiomers are mirror-image forms of the same compound and have opposite absolute stereochemistry, differing only in direction of rotation of plane polarized light. To convert one enantiomer to another (>1 chiral center), both/ all of the stereogenic centers are inverted.

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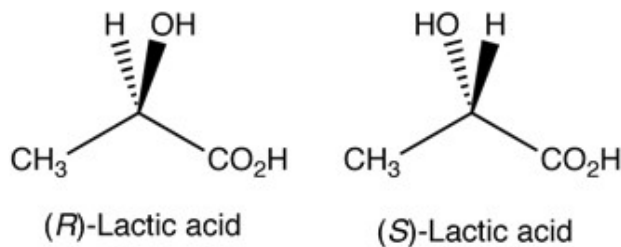
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Configuration of a chiral center can be labelled as R or S [Cahn-Ingold-Prelog rules]:

1. Each substituent at the asymmetric center is assigned a priority number in descending order of their atomic numbers.
2. Lowest priority substituent should be farthest from viewer (dotted line: perspective formula).
3. Moving from 1-2-3-4, clockwise is designated R, anticlockwise is designated S. However, for the configuration of a Fischer projection formula, only if the lowest priority substituent is on a vertical bond, will a clockwise arrow from the highest priority to the next highest priority substituent denote R-configuration & counterclockwise denote S. On the other hand, if the lowest priority substituent is on a horizontal bond, counterclockwise specifies R and clockwise specifies S configuration.

Enantiomers have same chemical & physical properties other than the direction of rotation of plane-polarized light, known as optical activity.



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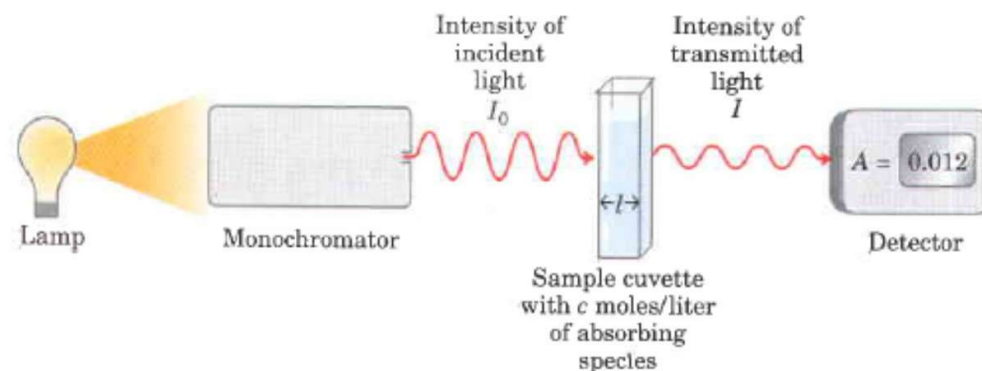
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Plane polarized light is a beam of light in which all of the light waves are aligned parallel to their direction of vibration. It is produced by shining light through a polarizing filter.

Polarimetry can deduce whether a sample is racemic or comprises of more of one enantiomer than the other. A polarimeter has a monochromatic (single wavelength) light source with a filter, a sample holder and a detector.



α is the observed angle through which the light is rotated. By dividing this value by the path length (in dm) and the concentration c (in g cm^{-3}) we get $[\alpha]$, characteristic of the compound, known as the compound's specific rotation.

$$[\alpha] = \frac{\alpha}{cl}$$

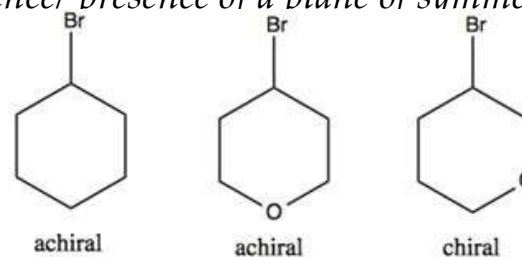
$[\alpha]_D^{20} = \alpha/cl$ where D refers to the wavelength of 589 nm, the 'D line' of a sodium lamp) or $[\alpha]_D^{20}$, the 20 indicating 20°C

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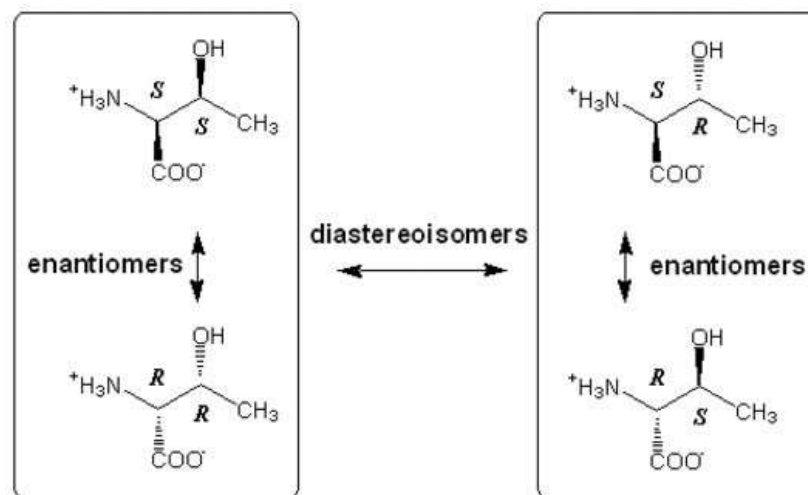
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Diastereoisomers: are stereoisomers that are not mirror images of each other (not enantiomers). These stereoisomers may be chemically and physically different from each other. Diastereoisomers are different compounds, having different relative stereochemistry. Diastereoisomers may be chiral or achiral (have no plane of symmetry) depending on the absence/ presence of a plane of symmetry. Diastereoisomers may have more than one stereogenic center.



To convert one diastereoisomer to another, any one of the two stereogenic centers is inverted. To convert one enantiomer to another (>1 chiral center), both/ all of the stereogenic centers are inverted.



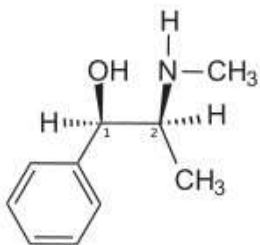
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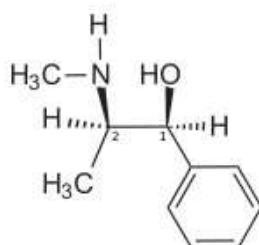
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The natural compound ephedrine and its diastereoisomer pseudoephedrine are both naturally occurring drugs. Ephedrine and pseudoephedrine are stereoisomers (non-mirror images) belonging to the amphetamine class of stimulants, emulating the action of hormone adrenaline in the human body. The two diastereoisomers are each a pair of enantiomers.

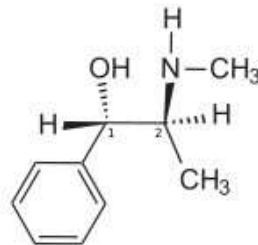
(1R,2S)-(-)-Ephedrine
(-)-erythro-Ephedrine



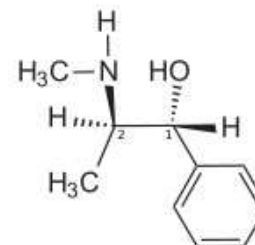
(1S,2R)-(+)-Ephedrine
(+)-erythro-Ephedrine



(1S,2S)-(+)-Pseudoephedrine
(+)-threo-Ephedrine



(1R,2R)-(-)-Pseudoephedrine
(-)-threo-Ephedrine



	(1R,2S)-(-)- ephedrine	(1S,2R)-(+)- ephedrine	(1S,2S)- -(+)-pseudoephedrine	(1R,2R)- -(-)-pseudoephedrine
mp	40–40.5 °C	40–40.5 °C	117–118 °C	117–118 °C
$[\alpha]_D^{20}$	-6.3	+6.3	+52	-52

Both ephedrine and pseudoephedrine are produced in enantiomerically pure form by plants, as single enantiomers of single diastereoisomers.

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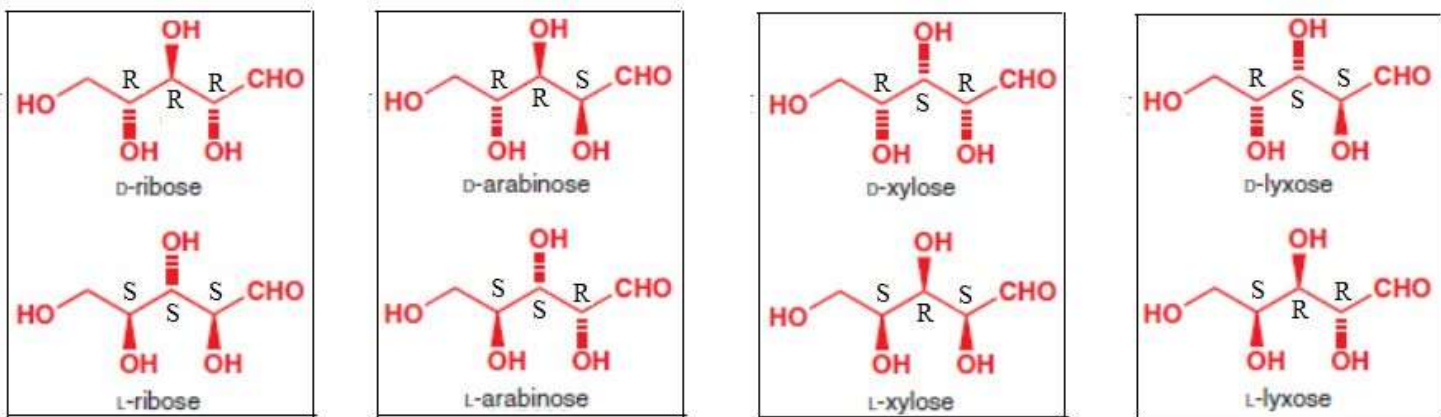
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D-Ribose is a pentose sugar that contains three stereogenic centers, each having the R configuration. These stereoisomers are

<i>RRR</i>	<i>RRS</i>	<i>RSR</i>	<i>RSS</i>
<i>SSS</i>	<i>SSR</i>	<i>SRS</i>	<i>SRR</i>

The top row and the bottom row it are enantiomers (all three centres are inverted); the four columns are diastereoisomers. Three stereogenic centers therefore give four diastereoisomers.



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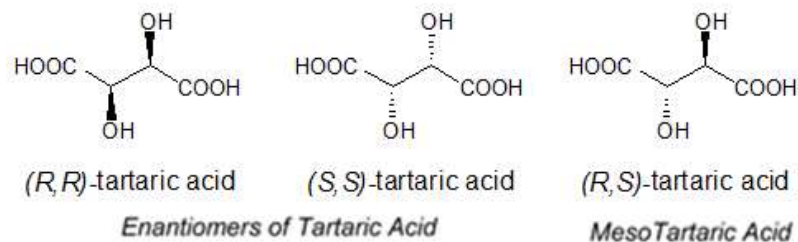
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(1R,2S)-Tartaric acid and (1S,2R)-tartaric acid are not enantiomers, but they are identical because, even though they contain stereogenic centres, they are achiral. By drawing (1R,2S)- tartaric acid after a 180° rotation about the central bond, you can easily see that it has a mirror plane, and so must be achiral. Since the molecule has a plane of symmetry, and R is the mirror image of S, the R,S diastereoisomer cannot be chiral.

Meso compounds: Stereoisomers that contain stereogenic centers but are themselves achiral are called meso compounds. This means that there is a plane of symmetry with R stereochemistry on one side and S stereochemistry on the other.

A compound with n stereogenic centres has 2^{n-1} diastereoisomers, each having a pair of enantiomers. First work out how many diastereoisomers there are, and then to decide whether or not each one is chiral, and therefore whether or not it has a pair of enantiomers.



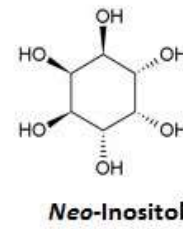
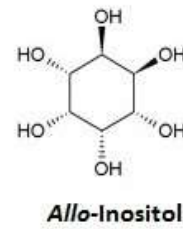
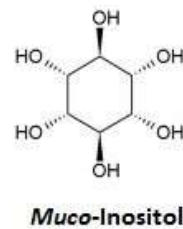
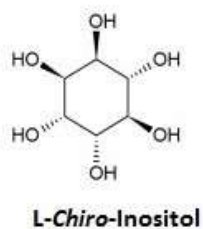
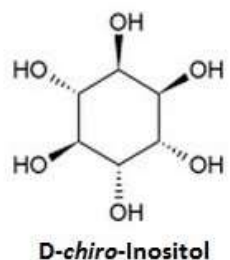
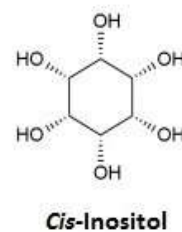
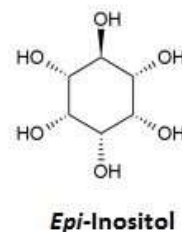
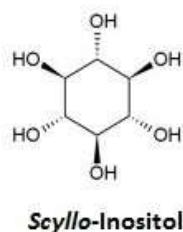
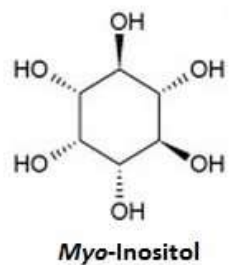
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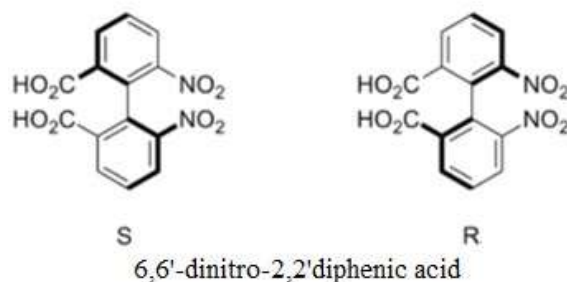
Isomers of Inositol:

Inositol is a mixture of hexahydroxycyclohexane stereoisomers. Of these, seven are achiral meso compounds and two are enantiomers. The chief natural isomer is cis-1,2,3,5-trans-4,6-cyclohexanehexol, known as myo-inositol.

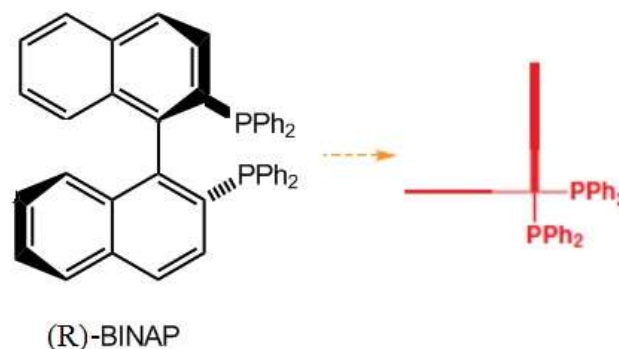
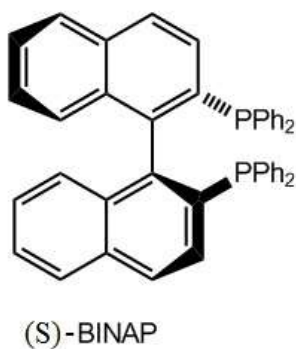
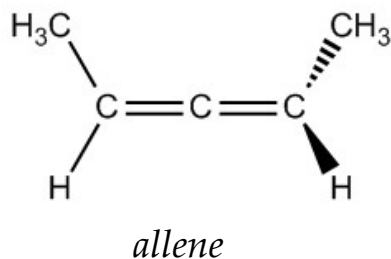


Atropisomers:

Compounds that are chiral because of restricted rotation about a single bond are called atropisomers. Atropisomerism was first detected in 6,6'-dinitro-2,2'-diphenic acid.



Some biaryl compounds, like bisphosphines, known as BINAP, exist as two separate enantiomers because rotation about a single bond is restricted. The two flat rings are at right angles to each other and so the molecule has a twist in it as in the allene.



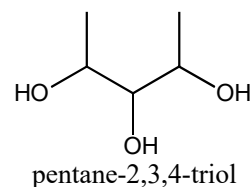
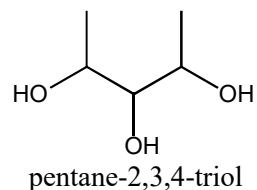
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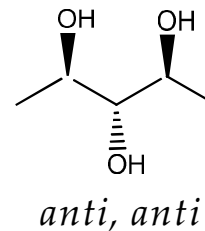
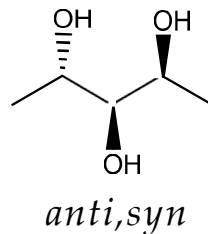
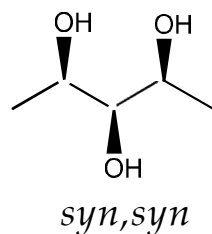
Finding the stereochemistry of a compound

1. Draw the compound in planar manner with zig-zag bonds with the carbon skeleton and substituents.

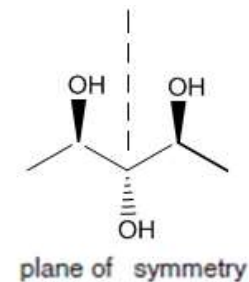
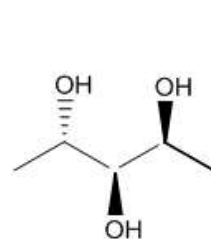
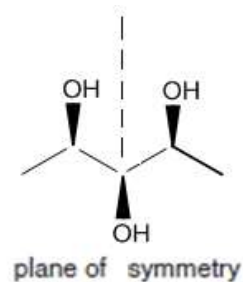


2. Identify the stereogenic centers.

3. Decide how many diastereoisomers there are by assigning the substituents up or down position.



4. By checking on possible planes of symmetry, see which diastereoisomers are chiral.

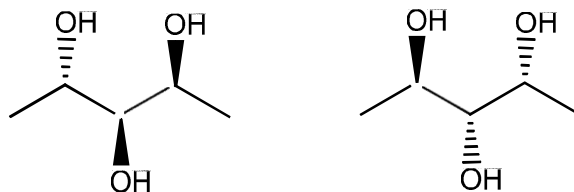


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5. Inverting all the stereogenic centers, draw the enantiomers of any chiral diastereoisomer obtained previously.

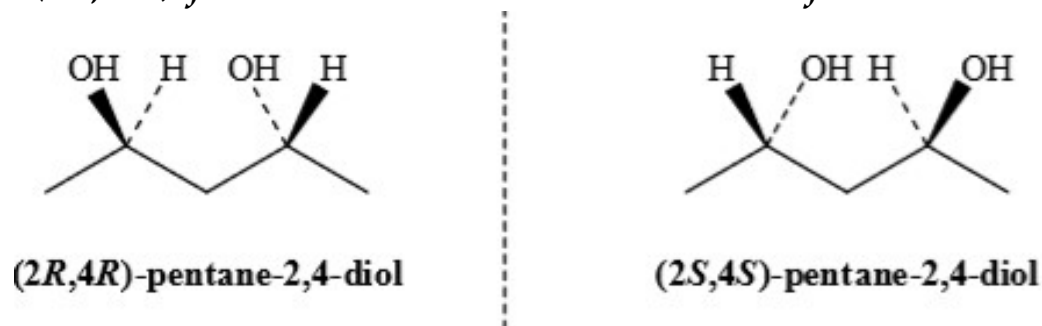


6. There are three diastereoisomers, the syn,syn, the syn,anti, and the anti,anti. The syn,syn and the anti,anti are achiral (meso) compounds but the syn,anti is chiral and has two enantiomers.

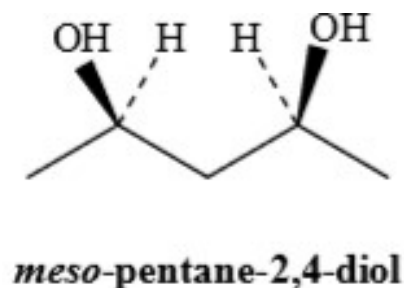
In case of 2,4-pentanediol

Two chiral centres would seem to give 2×2 combinations. However, only three isomers are possible.

The (2R, 4R) and (2S, 4S) forms below are enantiomers of each other.



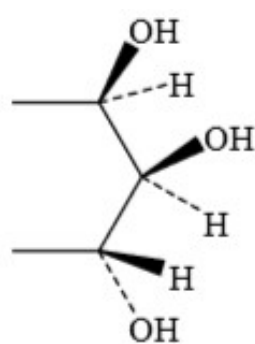
The third combination of chiral centres gives a form which is superimposable on the fourth combination, its mirror image. This is called the meso isomer which possesses a plane of symmetry through the centre of the molecule.



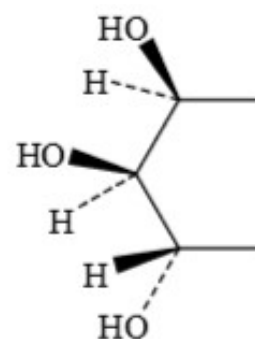
In case of 2,3,4-pentanetriol

Two chiral centres would seem to give 2×2 combinations. Thus, only 4 isomers are possible.

The (2R, 4R) and (2S, 4S) forms pictured below are enantiomers of each other:

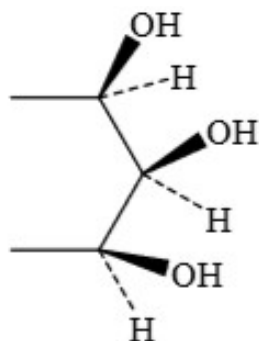


(2R,4R)-pentane-2,3,4-triol

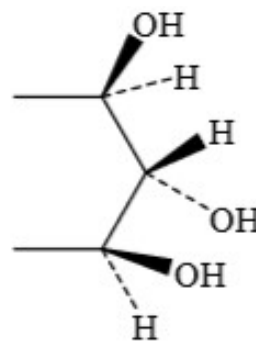


(2S,4S)-pentane-2,3,4-triol

There are also two meso forms (diastereoisomers):



(2R,3s,4S)-pentane-2,3,4-triol



(2R,3r,4S)-pentane-2,3,4-triol

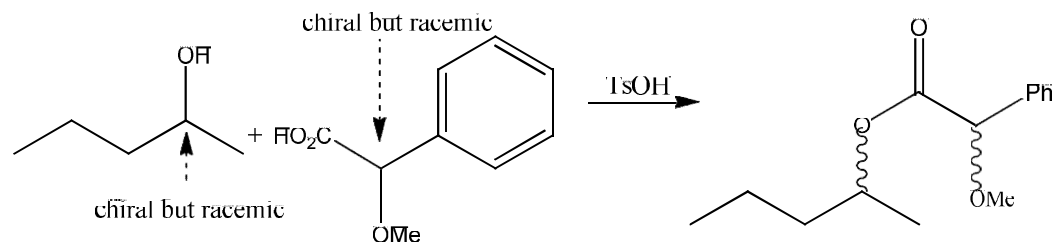
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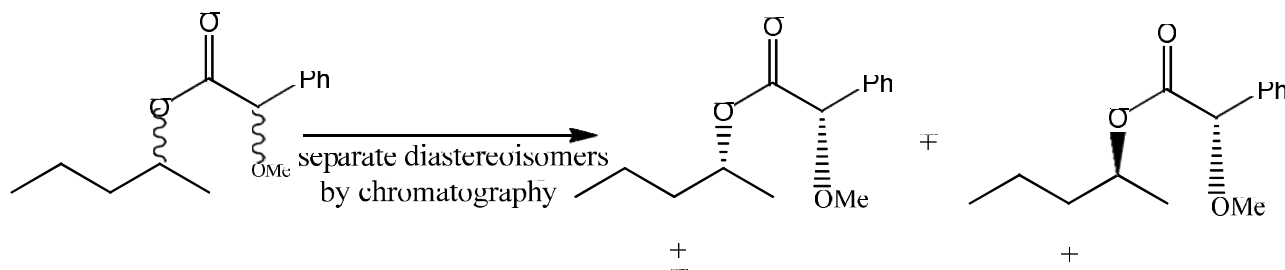
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Resolution of isomers:

The process of separation of enantiomers is called resolution. Using natural enantiomerically pure compounds to help us separate the components of a racemic mixture into its two enantiomers is called resolution. Consider an acid-catalyzed esterification reaction between chiral, racemic alcohol and a chiral, racemic carboxylic acid to give an ester.



We will get two diastereoisomers, each a racemic mixture of two enantiomers. Diastereoisomers have different physical properties, so they are easy to separate, by chromatography.

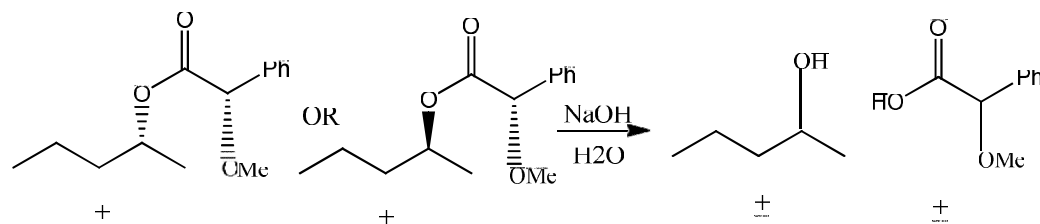


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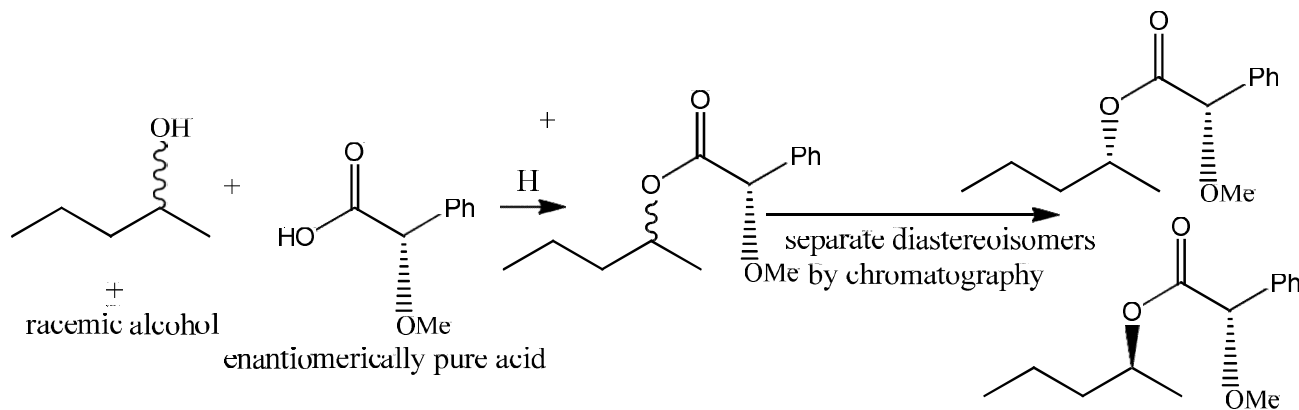
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Reverse the esterification step and hydrolyze either of these diastereoisomers, to regenerate racemic alcohol and racemic acid.



We repeat this reaction, this time using an enantiomerically pure sample of the acid, to get two diastereoisomeric products, but this time each one will be enantiomerically pure.

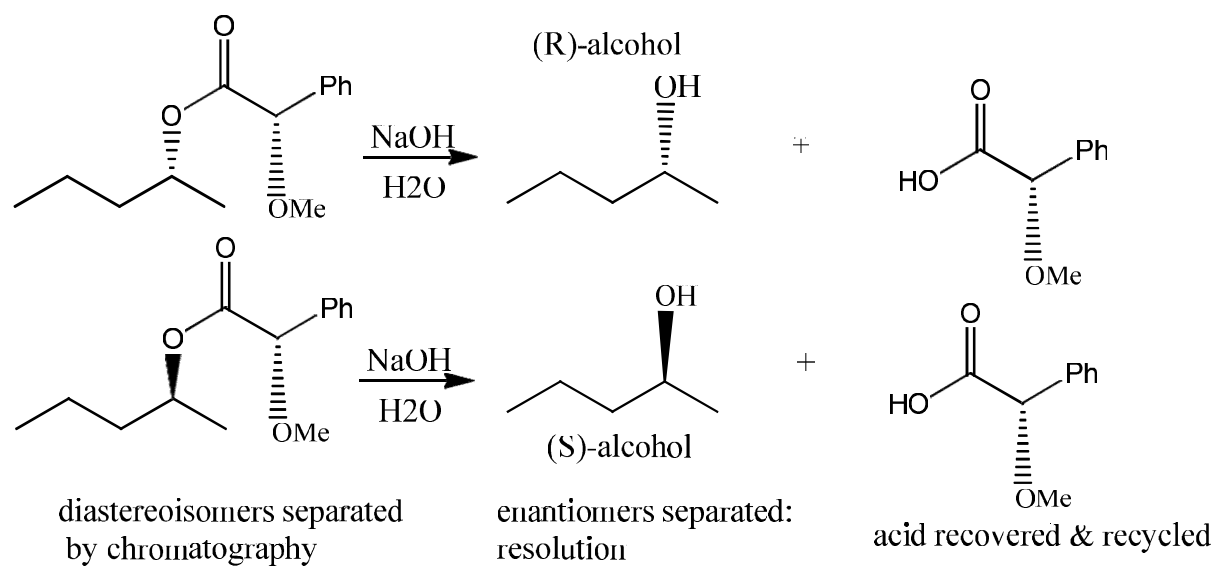


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If we now hydrolyze each diastereoisomer separately, we have separately two enantiomers of the starting alcohol.



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Resolutions can be carried out by chromatography on chiral stationary phase

Interactions even weaker than ionic bonds (hydrogen bonds or van der Waals) can be used to separate enantiomers. Chromatographic separation relies on a difference in affinity between a stationary phase (silica/alumina) and a mobile phase (the solvent travelling through the stationary phase, eluent) effected by, hydrogen bonds or van der Waals interactions. If the stationary phase is made chiral by bonding it with an enantiomerically pure compound (generally a derivative of an amino acid), chromatography can be used to separate enantiomers.

This is done by passing a solution of the racemic mixture through a column of silica bonded to an amino-acid-derived chiral stationary phase. The enantiomer which shows a lower affinity for the stationary phase is eluted first from the column, followed by the other enantiomer.

Chromatography on a chiral stationary phase is especially important when the compounds being resolved have no functional groups suitable for making the derivatives (generally esters or salts).

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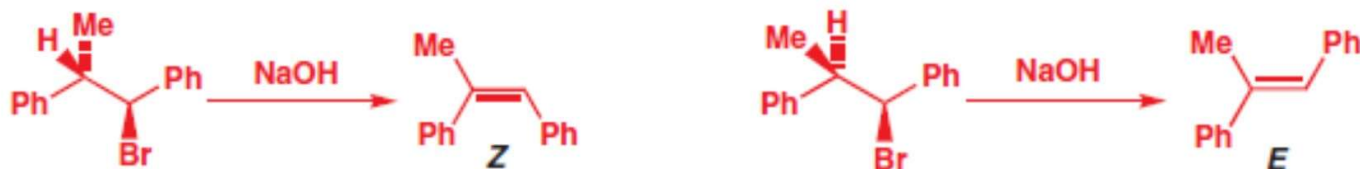
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Stereospecific reactions: lead to the production of a single isomer as a direct result of the mechanism of the reaction and the stereochemistry of the starting material. There is no choice. The reaction gives a different diastereoisomer of the product from each stereoisomer of the starting material.

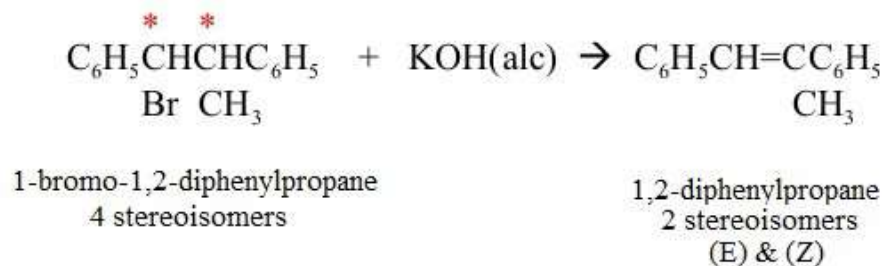
e.g. S_N2 reactions are stereospecific. They proceed with inversion of configuration so absolute stereochemistry of the starting material determines the absolute stereochemistry of the product.



E2 reactions are stereospecific: They proceed through an anti-periplanar transition state, with the relative stereochemistry of the starting material determining the geometry of the product.



Dehydrohalogenation of an alkyl halide via E2 mechanism:



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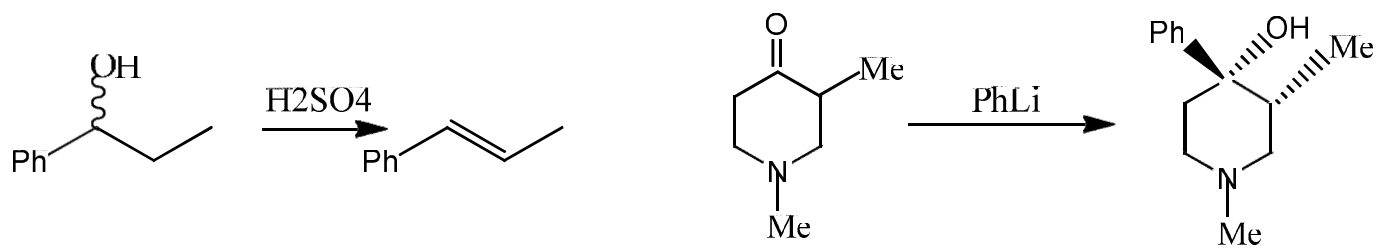
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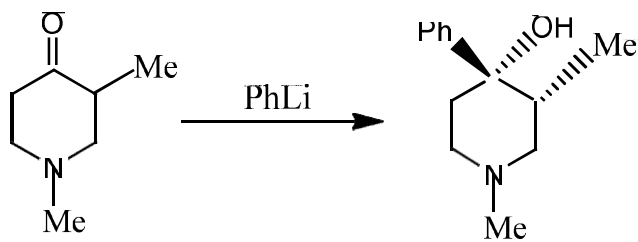
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Stereoselective reactions: are reactions that give one predominant product because the reaction pathway has a choice. Either the pathway of lower activation energy is preferred (kinetic control) or the more stable product is preferred (thermodynamic control).

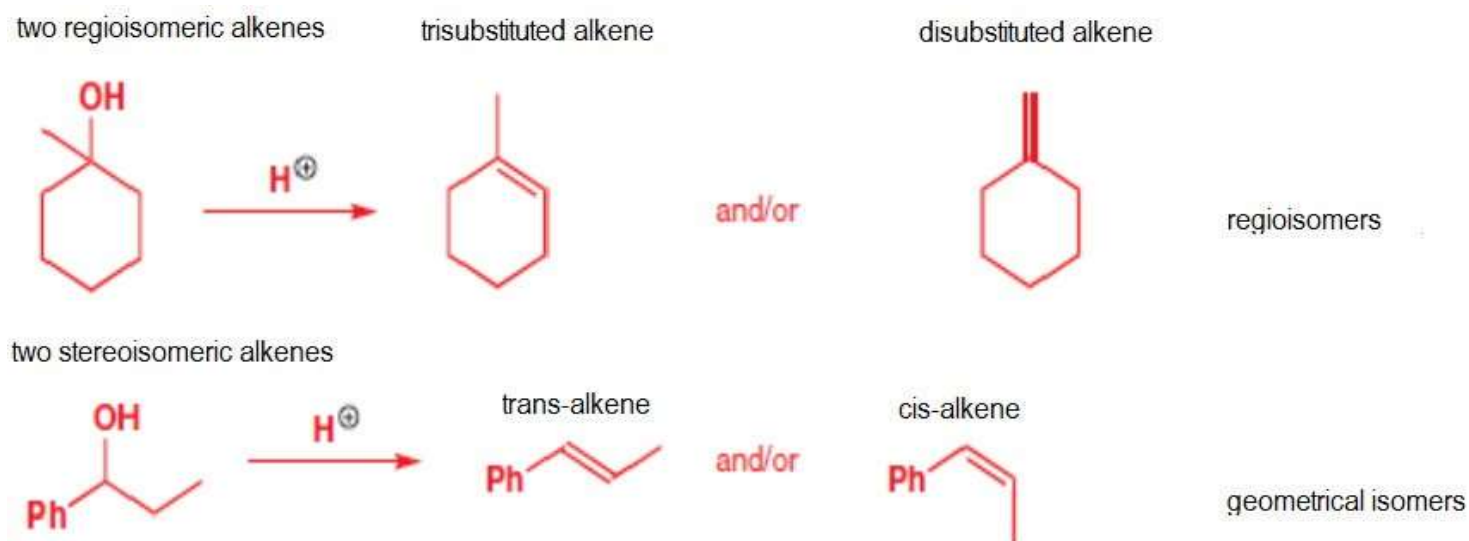
e.g. E1 reactions are stereoselective. They form predominantly the more stable alkene.



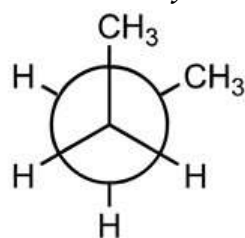
Nucleophilic attack on six-membered ring ketones is also a stereoselective reaction. Small nucleophiles attack axially and large ones equatorially.



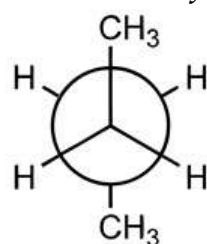
By analogy with stereospecific, a regiospecific reaction is defined as one in which the regiochemistry (that is, the location of the functional groups) of the product is determined by the regiochemistry (that is, where the double bond is) of the starting material.



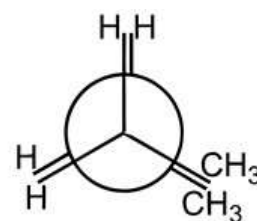
Conformers: If we managed to slow down the rapid interconversions in butane (by cooling to very low temperature, for example), we would be able to isolate the three stable conformations—the anti-periplanar and the two synclinal conformations. These different stable conformations of butane are some sort of isomers. They are called conformational isomers or conformers for short.



synclinal or gauche



anti-periplanar



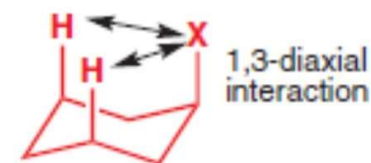
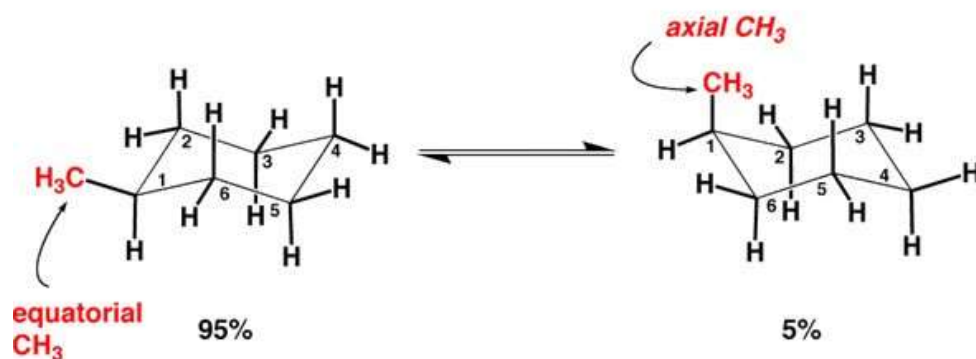
eclipsed

In a monosubstituted cyclohexane, there can exist two different chair conformers: one with the substituent axial, the other with it equatorial. The two chair conformers will be in rapid equilibrium (by the process we have just described) but they will not have the same energy. In almost all cases, the conformer with the substituent axial is higher in energy, which means there will be less of this form present at equilibrium.

There are two reasons for this:

1. The axial conformer is destabilized by the repulsion between axial group X and the two axial hydrogen atoms on the same side of the ring. This interaction is known as the 1,3-diaxial interaction. As the group X gets larger, this interaction becomes more severe and there is less of the conformer with the group axial.
2. The equatorial conformer has the C–X bond anti-periplanar to two C–C bonds, while, for the axial conformer, the C–X bond is synclinal (gauche) to two C–C bonds.

At equilibrium, methylcyclohexane exists as a 95:5 ratio of conformers, favoring the equatorial chair form.



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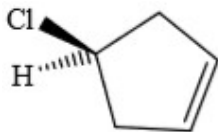
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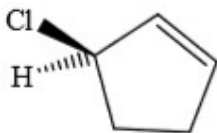
Problems for Practice:

Mark each stereogenic centre in the following compounds with an asterisk ():*

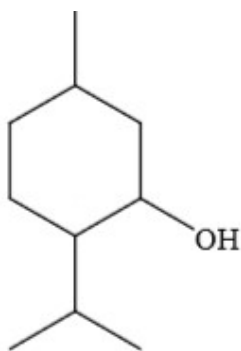
1.



2.



3.



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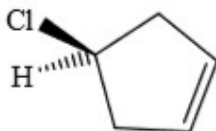
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Solutions:

1. There is no stereogenic centre: as the ring is symmetrical about the substituted carbon



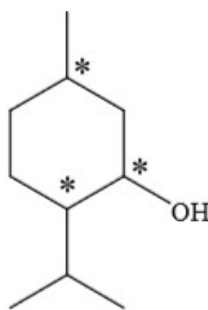
4-chlorocyclopent-1-ene

2. There is one stereogenic centre: ring is unsymmetrical about substituted carbon



3-chlorocyclopent-1-ene

3. There are three stereogenic centres: each has a hydrogen and three different groups around it.



2-isopropyl-5-methylcyclohexanol

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