Module-III

1. SUBSTITUTION REACTIONS

A reaction in which one group or atom is replaced by another is called a substitution reaction. The incoming group is bonded to the same carbon to which the leaving group was bonded. Substitution reaction has been classified according to the nature of the substituents involved. Thus-

A. Free radical substitution $A:B + \overset{\bullet}{Q} \rightarrow A:Q + \overset{\bullet}{B}$

B. Nucleophilic substitution $A:B + :\overset{\ominus}{Q} \rightarrow A:Q + :\overset{\ominus}{B}$

C. Electrophilic substitution $A:B + \overset{\oplus}{Q} \rightarrow A:Q + \overset{\oplus}{B}$

It will be seen that in all types of substitutions, the displaced species belong to the same class as the attacking species.

A. Free Radical Substitution

Radical substitution reactions are initiated by radicals in the gas phase or in non-polar solvents.

Thus, methane and chlorine react in the presence of sunlight or heat to give methyl chloride.

$$CH_4 + Cl_2 \xrightarrow[300°C]{h\nu \text{ or}} + CH_3Cl + HCl$$

Light energy or heat causes homolytic fission of chlorine producing chlorine radicals which attack methane to form methyl chloride.

$Cl:Cl \xrightarrow{h\nu \text{ or } 300°C} \overset{\bullet}{Cl} + \overset{\bullet}{Cl}$ .....(i)

$H_3C:H + \overset{\bullet}{Cl} \longrightarrow H_3C + HCl$ ..... (ii)

$H_3C + Cl:Cl \longrightarrow H_3C:Cl + \overset{\bullet}{Cl}$ .....(iii)

B. Nucleophilic Substitution (Common in aliphatic compounds):

- Nucleophilic substitution is one of the two main reactions of alkyl halides. A nucleophile replaces a leaving group on an sp^3 hybridized carbon.

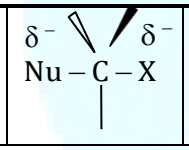
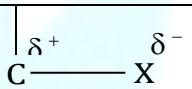
$$R - X + :Nu^- \longrightarrow R - Nu + X:^-$$

nucleophile — leaving group

The electron pair in the C – Nu bond comes from the nucleophile.

- One σ bond is broken and one σ bond is formed.
- There are two possible mechanisms: **S_N1 and S_N2**

S_N1 and S_N2 Mechanisms Compared

	S_N2 Mechanism	S_N1 Mechanism
[1] **Mechanism**	One step	Two steps
[2] **Alkyl halide**	Order of reactivity : $CH_3X > RCH_2X > R_2CHX > R_2CX$	Order of reactivity : $R_3CX > R_2CHX > RCH_2X > CH_3X$
[3] **Rate equation**	Rate = $k[RX][:Nu]$ Second – order kinetics	Rate = $k[RX]$ First – order kinetics
[4] **Stereochemistry**	Backside attack of the nucleophile Inversion of configuration at a stereogenic center	Trigonal planar carbocation intermediate Racemization at a single stereogenic center
[5] **Nucleophile**	Favored by stronger nucleophiles	Favored by weaker nucleophiles
[6] **Leaving group**	Better leaving group $\rightarrow$faster reaction	Better leaving group faster reaction
[7] **Solvent**	Favored by polar aprotic solvents	Favored by polar protic solvents
[8] **Reactivity structure of R-determining factor. Nature of X**	$3° > 2° > 1° > CH_3$ Stability of R^+ RI > RBr > RCl > RF	$CH_3 > 1° > 2° > 3°$ Steric hindrance in R group RI > RBr > RCl > RF
[9] **Effect of nucleophile**	Rate depends on nucleophilicity $I^- > Br^- > Cl^-$; RS > RO^-	No effect on rate
[10] **Catalysis**	Lewis acid, e.g. Ag^+, AlC_3, $ZnCl_2$	None of these
[11]**Competition reactions**	Elimination, rearrangement	Elimination
[12] **TS of slow step**		

- **Factors to decide whether S_N1 or S_N2 :**

Any factors that affects the energy of activation of a given type of reaction will affect the rate and / or mechanism. These factors are useful to decide whether S_N1 or S_N2 occurs :

1. Electronic effect
2. Steric effect
3. The nature of the leaving group.
4. The nature of the nucleophile.
5. Participation of neighbouring group.
6. Effect of solvent.

1. ELECTRONIC EFFECT :-

I-effect, R-effect, hyperconjugation etc. which can affect the stability of carbocation are collectively termed as electronic effect. Clearly if electronic effects stabilise the carbocation, S_N1 will more probable than S_N2 .

$C-X(1°)$ $\quad$ $C-X(2°)$ $\quad$ $C-X(3°)$

S_N2 $\quad$ S_N2 or S_N1 $\quad$ S_N1

2. **STERIC EFFECT :-**

More steric restriction opposes S_N2 mechanism. Simple alkyl halides show the following general order of reactivity in S_N2 reactions:

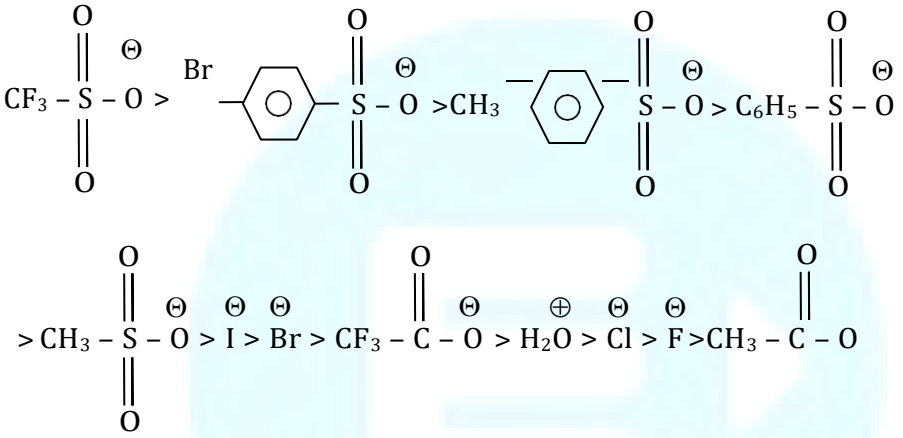
methyl > primary > secondary >>(tertiary)

Methyl halides react most react most rapidly and tertiary halides react so slowly as to be unreactive by the S_N2 mechanism.

3. **THE NATURE OF LEAVING GROUP :-**

The ease of formation of carbocation supports S_N1 and this formation depend upon nature of leaving group. The best leaving group is the weakest base. Leaving group ability increases left-to-right across a row and down a column of the periodic table. The ease of leaving is as follows :

The leaving power of some nucleophilic groups is given below in decreasing order :



4. **THE NATURE OF THE NUCLEOPHILE :-**

Stronger nucleophile supports S_N2 mechanism. Strength of nucleophile is as follows :

$$PhS^- > CN^- > I^- > Et-O^- > OH^- > Br^- > PhO^- > Cl^- > Me_3N$$:

5. **Participation of Neighbouring Groups :** Some neighbouring groups as : COO^- , $X, OH, -O-\overset{O}{\overset{\|}{C}}-Ph^-$ etc. can also participate and determine the nucleophilic substitution.

6. **Effect of solvent :** As the dielectric constant (i.e., polarity) of solvent increases, the rate of S_N1 reaction increases.

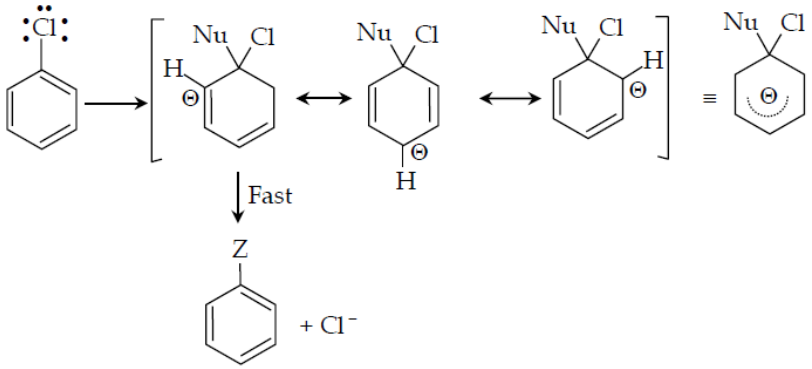
(C) Nucleophilic Substitution in Aromatic Compounds :

Aryl halides are less reactive towards SN reaction due to the donation of lone pair electrons to the benzene ring via resonance. Aryl halides undergo SN reaction when a strong electron-withdrawing group (or activating group) is present at the ortho and para positions. ArSN reactions are of two types viz.

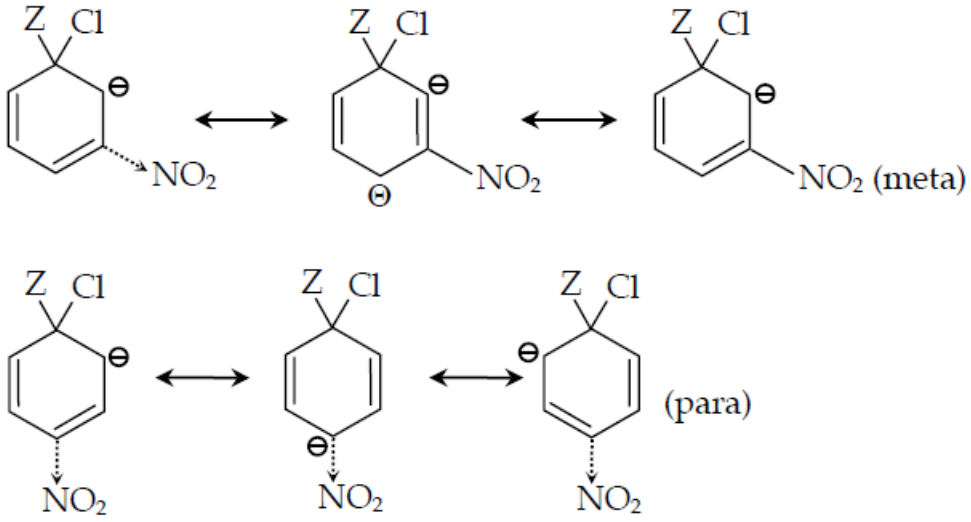
(i) **Addition-Elimination** reaction

(ii) **Elimination-Addition** reaction via ***benzyne*** mechanism

(i) **Addition-Elimination reaction (**also called *Bimolecular displacement* mechanism)



Any factor that stabilizes the carbanion will increase the rate of nucleophilic substitution reaction by dispersion the charge presence on resonating structures. An electron withdrawing group present at *meta* position does not activate the ring as much as it does from *ortho* and *para* position. This can be known by looking at following resonance structures.



(ii) Elimination-Addition Mechanism :
(Please refer to RARE MECHANISMS at the end of this chapter)

(D) Electrophilic Substitution (Common in Aromatic compounds) :

Electrophilic Substitution involves the attack by an electrophile. It is represented as S_E. If the order of the reaction is 1, it is abbreviated as S_E1 (unimolecular) and if the order is 2, it is S_E2 (bimolecular).

(a) S_E1 Mechanism :

Electrophilic substitution in aliphatic compounds (S_E1) are very rare. Some of the important examples are :

(i) Replacement of metal atom in an organo-metallic compound by hydrogen

$R\text{---}M + H^+ \rightarrow R\text{—}H + M^+$

(ii) Isotopic exchange of hydrogen for deuterium or tritium

$R\text{---}H + D^+ \rightarrow R\text{—}D + H^+$

$R\text{---}H + T^+ \rightarrow R\text{—}T + H^+$

(b) S_E2 Mechanism :

Electrophilic substitution (SE2) is every common in benzene nucleus (aromatic compounds) in which π electrons are highly delocalized and an electrophile can attack the region of high electron density. Aromatic electrophilic substitution reactions involve the following 3 steps mechanism :

Step-1 : The formation of an electrophile.

Step-2 : The electrophile attacks the aromatic ring to form carbocation (or arenium ion) which is stabilized by resonance.

Step-3 : Carbocation loses the proton to form the substitution product.

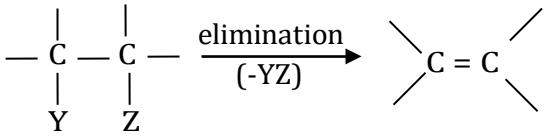
e.g. Bromination of Benzene, Nitration, Sulphonation & Friedel-Crafts reactions of benzene are classic examples of electrophilic substitution reactions.

NB: (i) The second step is found to be rate – determining step by isotopic studies.

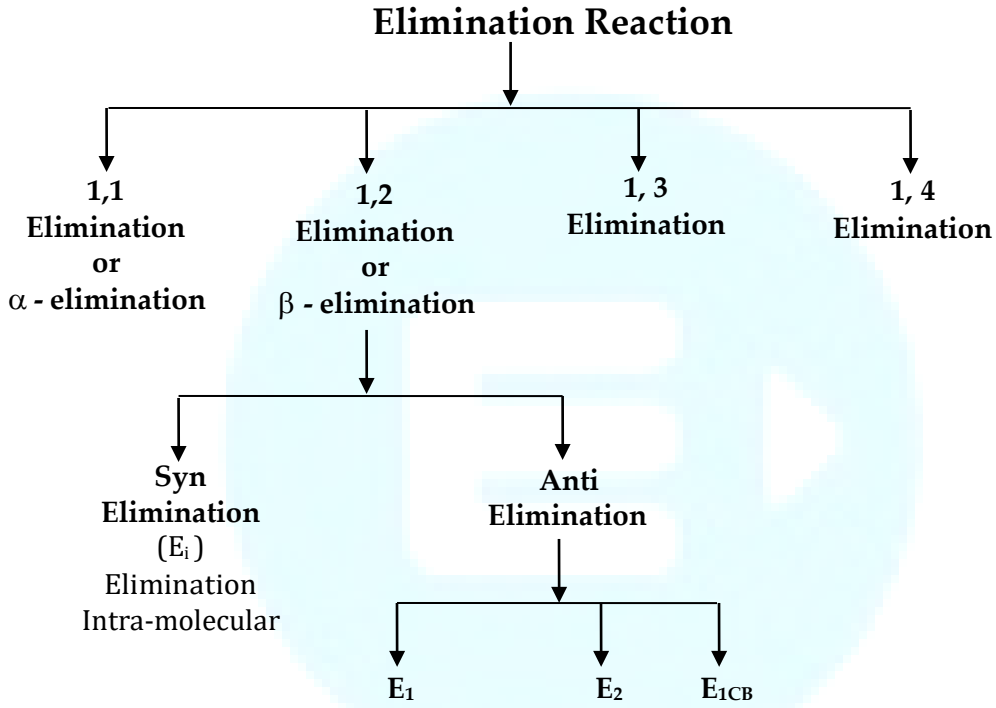
(ii) The intermediate carbocation is stabilized by resonance; a minimum of three resonance structures can be drawn. The positive charge is always located *ortho* or *para* to the new C – W bond. Refer to Chapter 5 or lecture notes for more clarity on the S_E2 mechanism.

2. ELIMINATION REACTIONS

Elimination reactions of alkyl halides are important reactions that compete with substitution reactions. In an **elimination reaction,** the fragments of some molecule (YZ) are removed (eliminated) from adjacent atoms of the reactant. This elimination leads to the introduction of a multiple bond:



The reaction in which two atoms or groups are removed from a compound is referred to as an elimination reaction. The elimination reaction can be classified as shown below:



E1 & E2 Mechanisms Compared

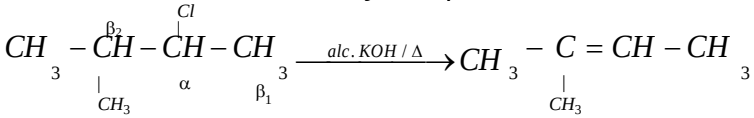
	***E*2 Mechanism**	***E*1 Mechanism**
Mechanism	One step	Two step
Alkyl halide	Rate : $R_3CX > R_2CHX > RCH_2X$	Rate : $R_3CX > R_2CHX > RCH_2X$
Rate equation	Rate = $k[RX][B:]$ Second – order kinetics	Rate = $k[RX]$ First – order kinetics
Stereochemistry	Anti periplanar arrangement of *H* and *X*	Trigonal planar carbocation intermediate
Base	Favored by strong bases	Favored by weak base
Leaving group	Better leaving group → faster reaction	Better leaving group → faster reaction
Solvent	Favored by polar aprotic solvents	Favored by polar protic solvents
Product	More substituted alkene favored	More substituted alkene favored (Zaitsev rule (Satyzeff's)

Regioselectivity : ORENTATION IN ELIMINATION REACTIONS :-

If substrate is unsymmetrical, then this will give more than one product. Major product of the reaction can be known by two empirical rules.

(1) *Saytzeff*'s Rule (also spelled as *Zaitsev's* Rule by some books) :-

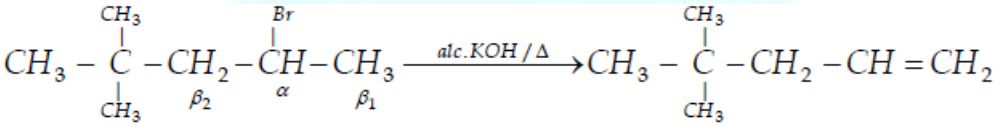
According to this rule, major product is the most substituted alkene, *i.e.,* major product is obtained by elimination of $\overset{\oplus}{H}$ from that β - carbon which has the least number of hydrogens. Product of the reaction in this case is known as *Saytzeff* product.



Saytzeff product

(2) Hofmann Rule :-

According to this rule, major product is always least substituted alkene, *i.e.,* major product is formed from β – carbon which has maximum number of hydrogens. Product of the reaction in this case is known as Hofmann product.



Hofmann Product

All nucleophiles are potential bases and all bases are potential nucleophiles. This is because the reactive part of both nucleophiles and bases is an unshared electron pair. It should not be surprising, then, that nucleophilic substitution reactions and elimination reactions often compete with each other.

Thus, elimination reactions are usually accompanied by substitution reactions. When the reagent is a good base, it accepts protons to yield elimination products (alkenes) and if it is a good nucleophile, then it attacks the carbon to give substitution products. The proportion of elimination and substitution depends upon the following:

(i) Structure of the Substrate
(ii) Nature of the Base
(iii) Nature of Solvent
(iv) Effect of Temperature

In general, the proportion of elimination increases on using a strong base of high concentration and a solvent of low polarity. On the other hand, the proportion of substitution increases by using a weak base of low concentration and a solvent of high polarity

3. ADDITION REACTIONS :

(1) Addition reactions are given by those compound which have at least one π – bond, *i.e.,*

$$(> C = C <, -C \equiv C -, -\overset{O}{\overset{\|}{C}} -, C \equiv N).$$

(2) In this reaction, there is loss of one *pi* bond and gain of two *sigma* bonds. Thus product of the reaction is generally more stable than reactant.

(3) The Addition reaction is a spontaneous reaction.

Types of Addition reactions : Addition reaction can be classified into three categories on the basis of the nature of initiating species :

(1) Electrophilic Addition (2) Nucleophilic Addition, and (3) Free radical Addition

- **Electrophilic Addition Reactions**

(1) This reaction is mainly given by alkenes and alkynes

(2) Electrophilic addition reactions of alkenes and alkynes are generally two – step reactions.

(3) Alkenes and alkynes give electrophilic addition with those reagents which, on dissociation, give electrophile as well as nucleophile.

(4) If the reagent is a weak acid then electrophilic adition is catalysed by strong acids (generally H_2SO_4)

(5) Unsymmetrical alkenes and alkynes give addition reaction with unsymmetrical regents according to Markovnikov's rule.

Regio-selective Study : (Markovnikov's & Anti-Markovnikov's Rules)

Addition Reaction of Alkenes : Markovnikov's Rule

According to Markovnikov's rule, the negative part of the reagent adds on that doubly bonded carbon if the alkene which has least number of hydrogen (s).

Conditions for the use of Markovnikov's Rule :

This rule can be used only in those alkenes which fulfill the following conditions:

(a) Alkenes should be unsymmetrical

(b) Substituent/substituents present on doubly bonded carbon /(s) should only be + I group.

(c) If phenyl group is present on doubly bonded carbon, then both doubly bonded carbons should be substituted by phenyl groups.

For example, the following alkenes **will give** addition according to Markovnikov's rule:

$$CH_3 - CH = CH_2, \quad \begin{matrix} H_3C \\ \diagdown \\ C = CH_2 \\ \diagup \\ H_3C \end{matrix}, \quad \begin{matrix} H_3C \\ \diagdown \\ C = CH - CH_3 \\ \diagup \\ H_3C \end{matrix}, \quad \begin{matrix} H_3C \\ \diagdown \\ C = CH - C_6H_5 \\ \diagup \\ H_3C \end{matrix}, \quad C_6H_5 - CH = CH_2$$

Following alkenes will **not give** addition reaction according to Markovnikov's rule.

$$CH_2 = CH_2, \quad R - CH = CH - R \quad \begin{matrix} R \\ \diagdown \\ C = C \\ \diagup \\ R \end{matrix}^{\diagup R}_{\diagdown R}, \quad \begin{matrix} C_6H_5 \\ \diagdown \\ \\ \diagup \\ C_6H_5 \end{matrix} \diagup \quad C = C$$

C_6 ^{5} C H

H ^{6} ^{5}

$CH_2 = CH - CF_3$; $CH_2 = CH - NO_2$

Substituted Alkenes which give Addition Reaction according to Anti – Markovnikov's Rule :

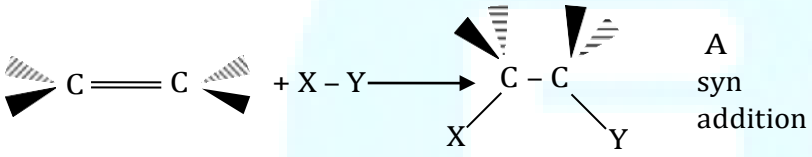
Unsymmetrical alkenes having the following general structure give addition reaction according to *anti* – Markovnikov's rule.

$H_2C = CH - G$ where, *G* is a strong – *I* group such as :

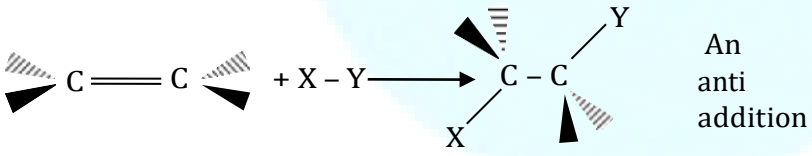
$-CX_3$,$-NO_2$,$-CN$,$-CHO$,$-C(=O)OR$,$-COOH$, $-C(=O)-Z(Z = Cl,OH,OR,NH_2)$

Stereo-selective Study (Syn & Anti Addition)

An addition that places the parts of the adding reagent on the same side (or face) of the reactant is called ***syn* addition**. We have just seen that the platinum-catalyzed addition of hydrogen (X = Y = H) is a syn addition



The opposite of a syn addition is an ***anti* addition**. An anti addition places the parts of the adding reagent on opposite faces of the reactant.



- **Nucleophilic Addition Reactions**

Addition of nucleophile in the first step and electrophile in the second step is called nucleophilic addition reaction. Thus this reaction is two – step reaction. In this reaction, addition of nucleophile is rate determining step. Nucleophilic addition reaction is given by :

(1) Alkenes (2) Alkynes (3) Carbonyl compounds and (4) Nitriles.

A reaction in which the substrate and the reagent add up to form a product is called addition reaction. The reaction occurs at the site of unsaturation in a molecule. Thus, compounds having multiple bonds such as :

$>C = C<$,$-C \equiv C-$ $>C = O$, $-C \equiv N$, etc.

undergo addition reactions.The reactivity of these compounds is due to the more exposed and easily

available π electrons tothe electron-seeking (electrophilic) reagent.

Free Radical Addition

Radicals, like cations are electron-deficient species. Thus radicals will attack the *pi*-system of a double bond of an alkene because *pi*-electrons of an alkene can provide the electron needed to complete the outer shell of a radical. The net result of this usually is the addition of some species across the double bond. These reactions involve radical intermediate. Free radical addition reactions occur either in the gas phase or in inert non-polar solvents in the presence of UV light or sunlight, heat or catalytic amount of radical initiators such as organic peroxides, labile azo compounds like azoisobutyronitrile (AIBN), etc. The mode of the addition reaction involves the' general steps for the radical reactions, *i.e.,* initiation, chain propagation and termination. The most important reaction of this category is hydrobromination.

Hydrobromination **:-** The radical addition of HBr to a carbon-carbon double bond occurs in the presence of UV light or a small amount of initiators such as dibenzoyl peroxide. HF, HCl and HI do not, give this addition.

When propene reacts with hydrogen bromide in the presence of dibenzoyl peroxide, the product is 1-bromopropane.

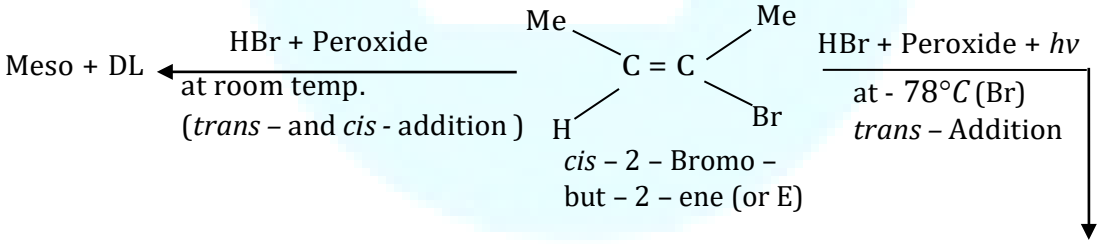
$$CH_3-CH=CH_2+HBr \xrightarrow{\text{dibenzoyl peroxide}} CH_3-CH_2-CH_2-Br$$

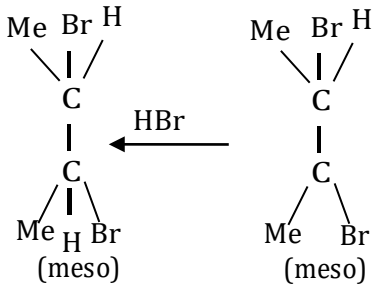
In this addition the hydrogen that is being added ends up on the carbon bearing the smaller number of hydrogens. Therefore, this is an *anti*-Markonikov addition. In general, unsymmetrical alkenes add, HBr, in the presence of a radical initiator, in an *anti*-Markonikov manner.

$$R-CH=CH_2+HBr \xrightarrow[\text{source}]{\text{radical}} R-CH_2-CH_2-Br$$

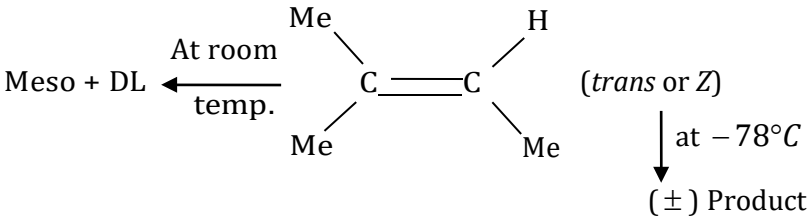
The addition of HBr to alkenes in the presence of light or peroxide is a free radical reaction and is trans-addition at low temperature but at room temperature two isomers give the same mixture of diastereomers, e.g.,

I.

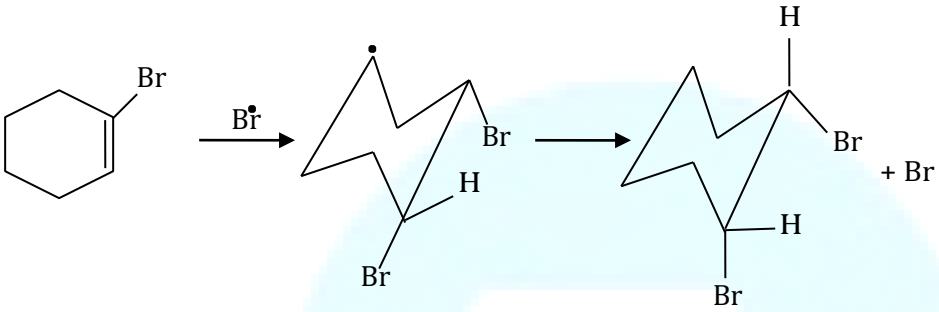




II.



At room temperature, the less stable radical (from *cis* butene) equilibrates with the more stable radical (from *trans* butene) by internal rotation which is now faster than the hydrogen abstraction. The result is that both butenes give the same mixture of diastereomers. In both cases, the addition of hydrogen is *trans* with respect to the bromine atom.
Free radical addition to alkenes is *trans;* no rotation is now possible, e.g.,



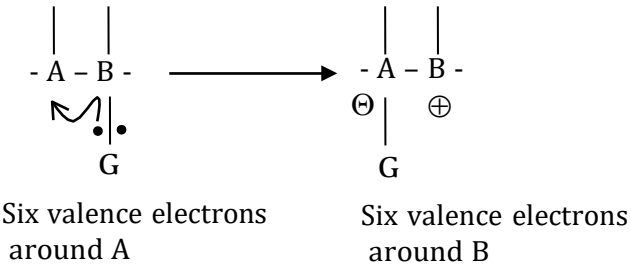
(4) REARRANGEMENT REACTIONS

Rearrangement refers to structural changes within a species. Rearrangements, in general are of two types:
(a) Shifting of a group from one atom to the other
(b) Rearrangement because of resonance

(A) SHIFTING OF A GROUP FROM ONE ATOM TO THE OTHER ATOM

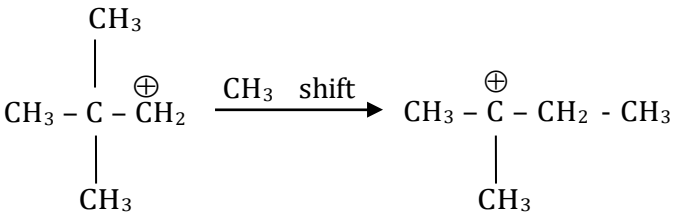
Although shifting of a group can occur from an atom to any other atom yet most of the shifts occur to adjacent atoms only. The main reason for this shifting is presence of six valence electrons and a vacant orbital on an atom. Such an atom has tendency to complete its octet for which the group from the adjacent atom migrates with the bonding electrons. There are two different conditions around an atom with six valence electrons.

(a) When atom with six valence electrons and a vacant orbital:

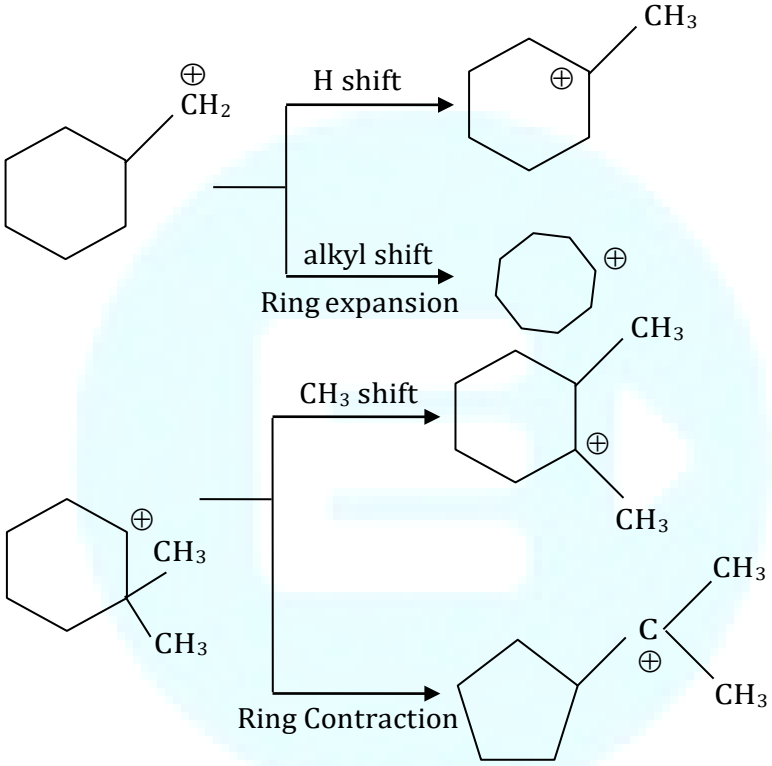


In this case when a group is shifted from atom S, the octet of S becomes incomplete which is not favourble condition. So we can say that this shift will occur only if it increases stability.

$$CH_3 - \underset{\oplus}{CH_2} - CH_2 \xrightarrow{H\ /\ Shift} CH_3 - CH - CH_3$$



Ring expansion and ring contraction can also result because of adjacent shift.

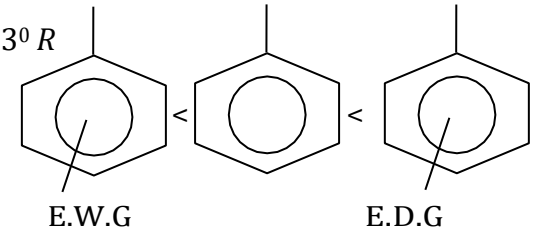


If migration of two (or more) different groups from adjacent atom can take place, major migration depends on the migrating tendency of the migrating groups (migration of group With higher migrating tendency is favoured) and the stability of resultant species (more stable resultant species is more favoured). Migrating tendency of a group is generally higher if it is more electron rich i.e. more electron donating. The general order of migrating tendency (or migratory aptitude) is as given below:

Hydride < *Alkyl* < *Aryl* < *Hydride*

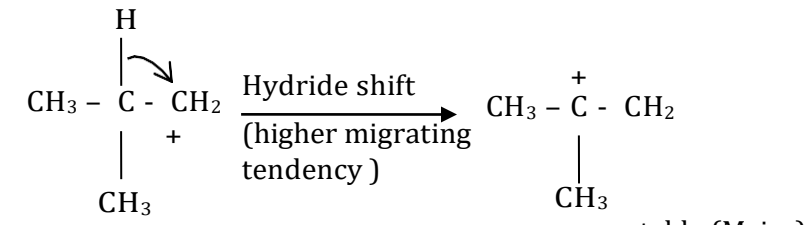
(If not involved in hyperconjugation with atom having 6 valence electrons)

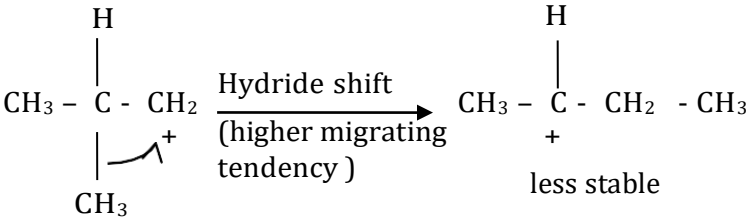
$1^0\ R < 2^0\ R < 3^0\ R$

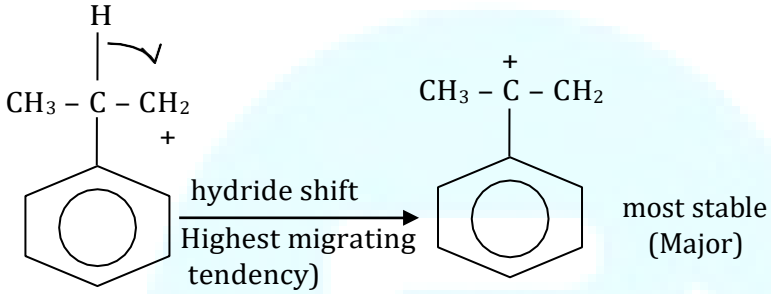


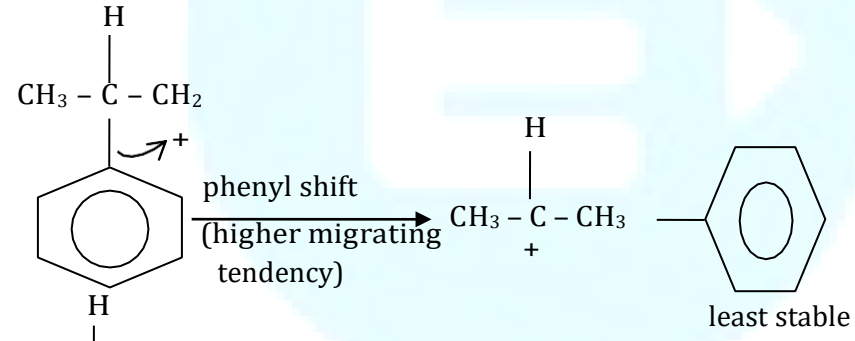
(If involved in hyperconjugation with atom having 6 valence electron)

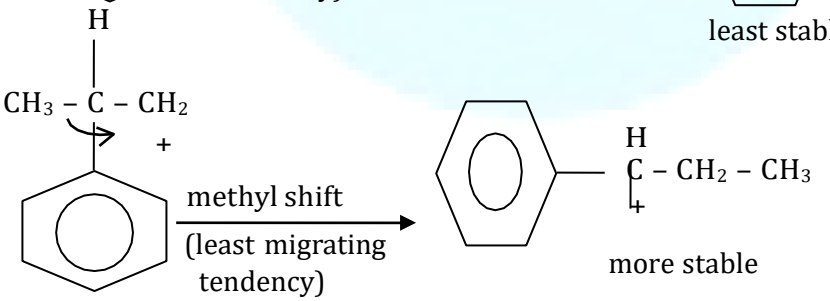
In several cases migrating tendency and the stability of resultant species favours the same migration. In such cases it will be easier to predict the major migration product.





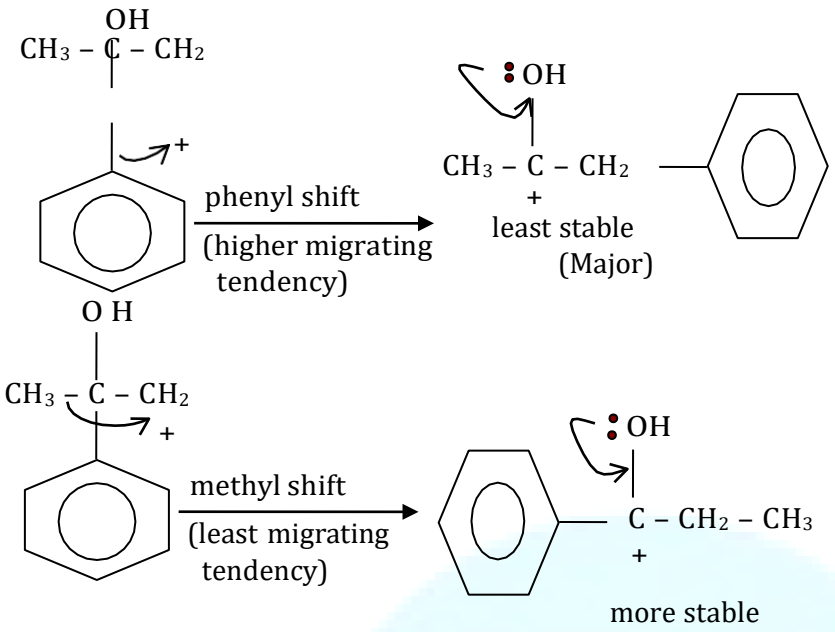




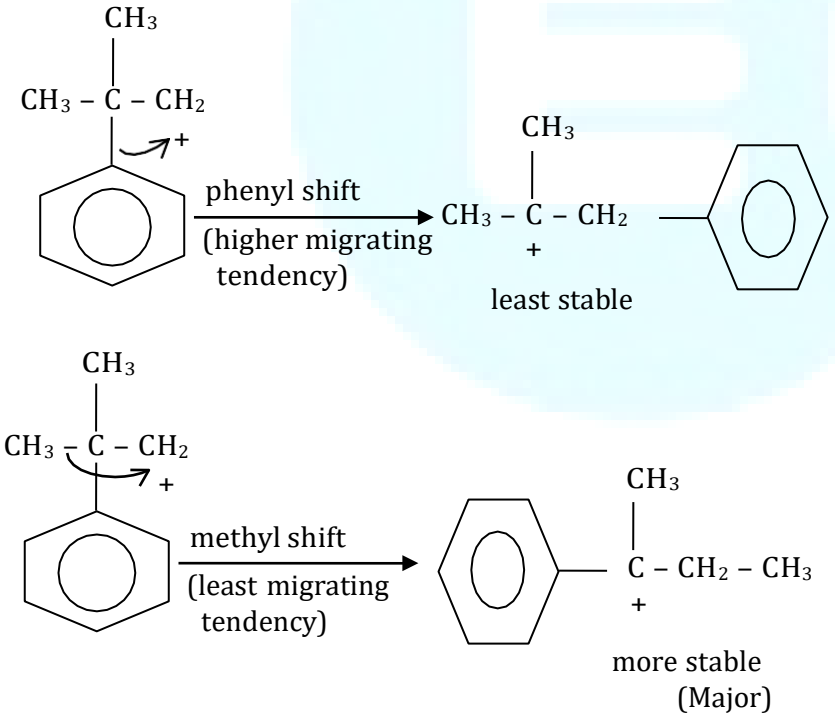


However, if migrating tendency and stability of resultant species oppose each other, following logics can be applied to predict the major product.

(i) If both resultant species are very highly stabilized (stabilized by resonance of/one pair or stabilized by formation of additional bond), small amount of stability does not matter a lot. Therefore, major migration occurs according to migrating aptitude.

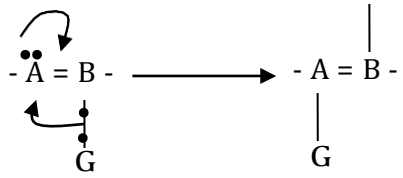


(ii) If both resultant species are not very highly stabilized (not stabilized by resonance of lone pair or not stabilized by formation of additional bond), small amount of stability also matters a lot. Therefore, major migration occurs according to stability of resultant species.

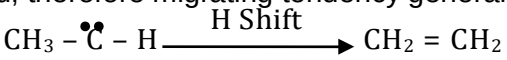


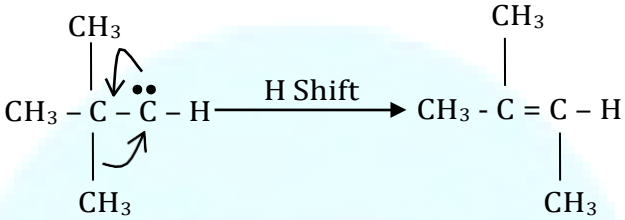
(iii) If the difference of stability is large, stability will dominate over the migrating tendency. Therefore, groups containing lone pairs migrate rarely.

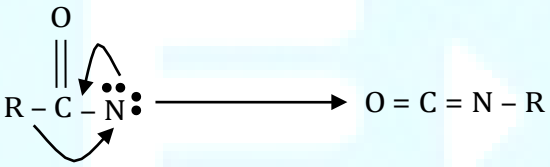
(b) When atom with six valence electrons and a vacant also has lone pair



In this case when a group from atom B is shifted, octet of B becomes incomplete which can be completed (stabilized) by lone pairs present on A atom. Hence under these conditions stability increases always and these rearrangements are, in general, bound to take place in the given species. Moreover, in such cases formation of additional bond or stabilization by resonance of lone pair will be generally observed, therefore migrating tendency generally dominates.



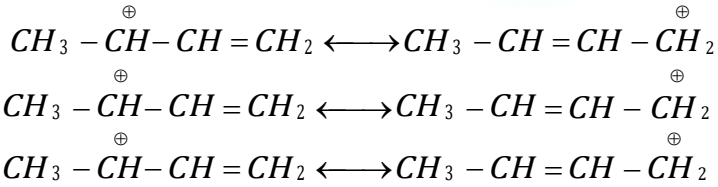




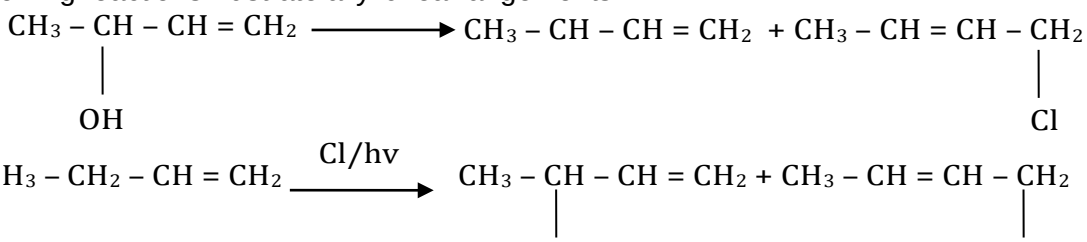
(B) <u>REARRANGEMENT BECAUSE OF RESONANCE (ALLYLIC REARRANGEMENT)</u>

In these cases, actually rearrangements do not occur but more-than one product is formed because of the resonance in the intermediate. These rearrangements are also called pseudo rearrangements. These rearrangements are possible when the intermediates like carbocation, carbanion or carbon free radical etc. are resonance stabilized and more than one different resonating structure are possible.

e.g.



Following reactions illustrate allylic rearrangements:



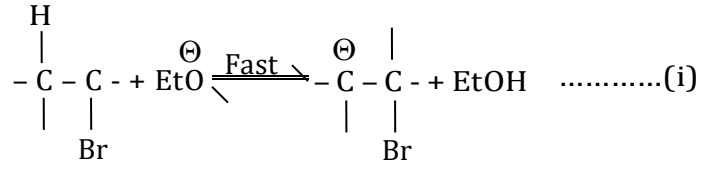
High temp

Cl Cl

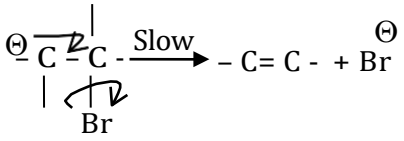
$$CH_3 - \underset{\displaystyle Cl}{\underset{|}{CH}} - CH = CH_2 \xrightarrow[\text{(ii) } H_2O]{\text{(i) Mg/dry ether}} CH_3 - CH_2 - CH = CH_2 + CH_3 - CH = CH - CH_3$$

$$CH_3 - \underset{\displaystyle OH}{\underset{|}{CH}} - CH = CH_2 \underset{}{\overset{H^{\oplus}}{\rightleftharpoons}} CH_3 - CH = CH - \underset{\displaystyle OH}{\underset{|}{CH_2}}$$

1. **E1 cb Mechanism** It may be argued that a second-order elimination reaction may as well proceed in two steps as in E1 reaction. The first step involves a fast and reversible removal of a proton from the β -carbon with the formation of a carbanion which then loses the leaving group in the second slow rate-determining step.



.....(i)

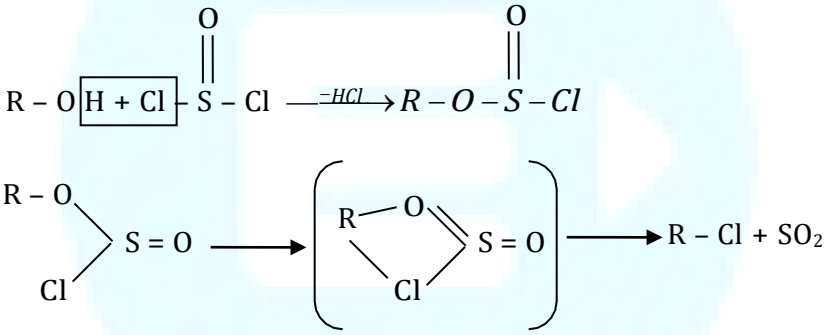


.....(ii)

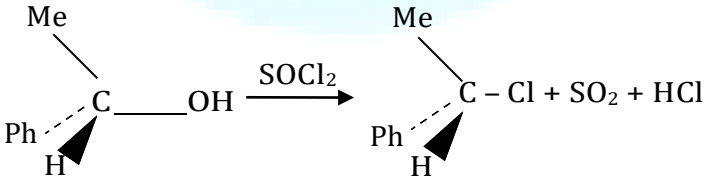
The overall rate of this reaction is thus dependent on the concentration of the conjugate base of the substrate (carbanion). Hence, this mechanism has been designated as E1cB (Elimination, Unimolecular from conjugate base).

2. **S_Ni Mechanism** :

Most common example of this type of mechanism is the mechanism of the reaction between alcohol and $SOCl_2$ It is actually substitution nucleophilic internal.



In this type of mechanism the configuration is retained. *i.e.*, R form of alcohol gives R type of halide and 5 form gives 5 type of alkyl halide. One reaction in which this has been shown to occur is in the replacement of OH by Cl through the use of thionyl chloride, $SOCl_2$:

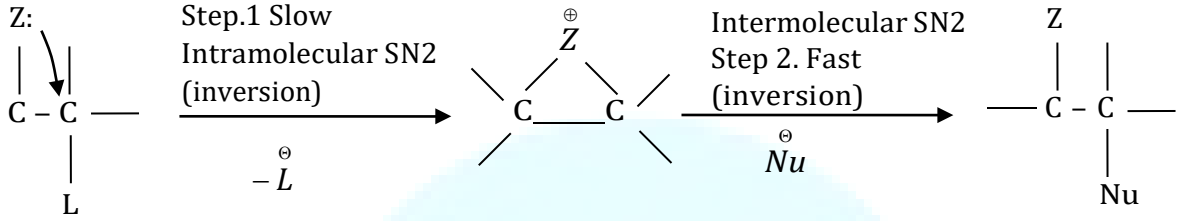


The reaction has been shown to follow a second order rate equation,

Rate = $k_2[ROH][SOCl_2]$, but clearly cannot proceed by the simple S_N2 mode for this would lead to inversion of configuration in the product, which is not observed.

3. Neighbouring Group Participation (N.G.P.)

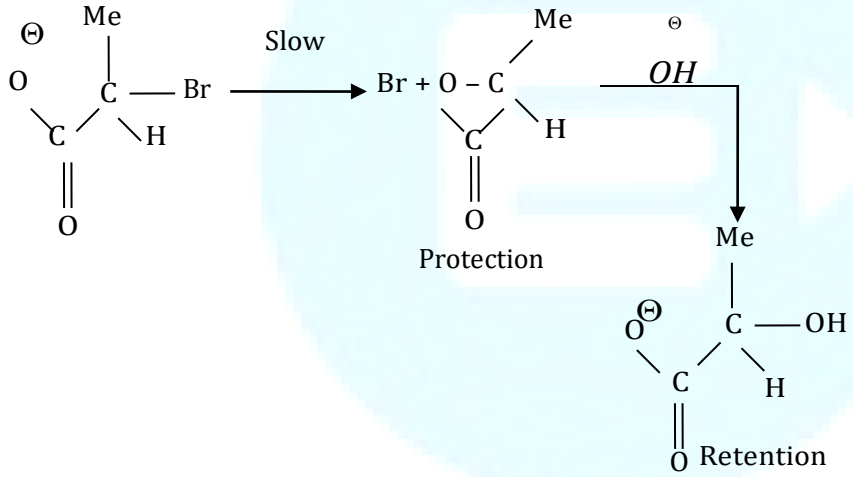
A number of nucleophilic substitution reactions are known which occur with complete retention (not inversion or racemisation) of configuration and with unexpectedly greater rate of reaction. In these cases usually there is atom or group with an unshared electron pair β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called *neighbouring group mechanism or neighbouring participation*. It consists of two consecutive SN2 substitutions with inversion of configuration, thus, the net result is retention of configuration. In the first step of this reaction the neighbouring group acts as a nucleophile pushing out the leaving group. In the second step the external nucleophile pushes out the neighbouring group. A *common feature of all neighbouring group mechanisms is the formation of a cyclic intermediate*.



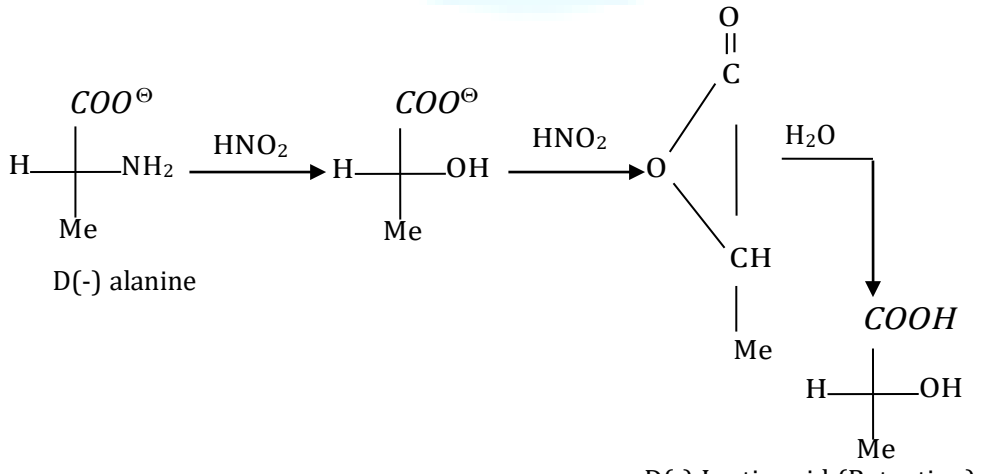
Net result is retention of configuration

(a). Neighbouring carboxylate anion

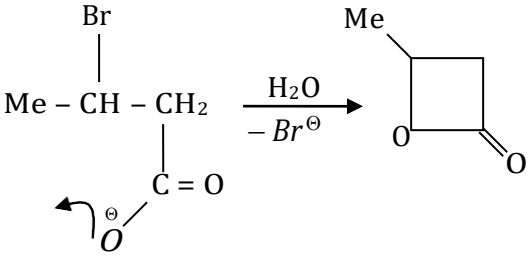
i.



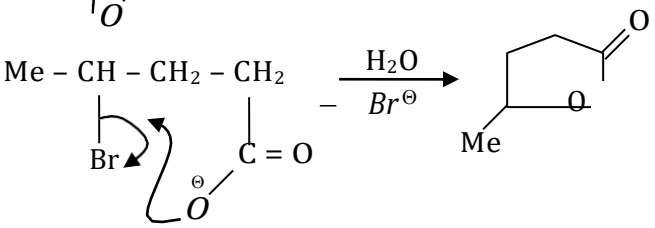
ii.



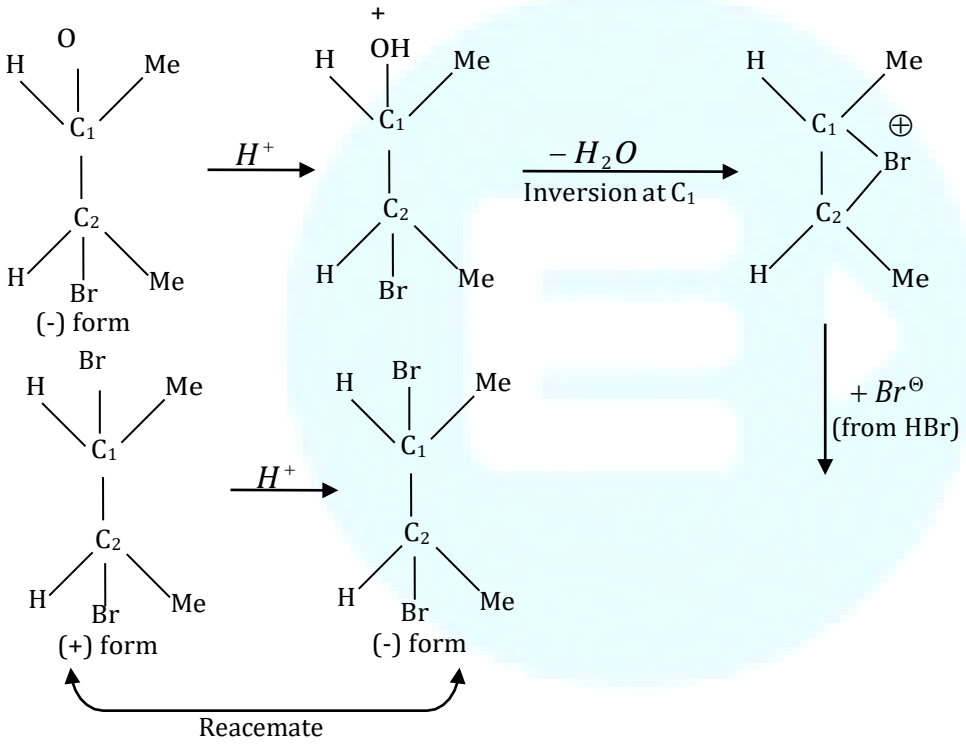
iii.



iv.



(b). <u>Neighbouring halogen atoms</u> : Reaction of HBr on (-) threo – 3 – bromo – butan – 2- ol

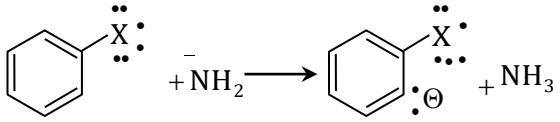


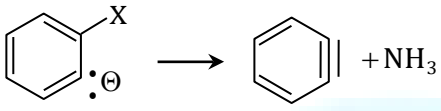
If no N.G.P. of Br occurred and the reaction was SN^2, complete inversion would have occurred only at C_1. If the reaction was SN^I, C_1 would have been a classical carbonium ion (flat), so inversion and retention (racemisation) would have occurred only at C_1. Since either retention or inversion occurs at both C_1 and C_2, the results are explained by the N.G.P. of bromine atom. Similarly, optically active erythro -3-bromobutane 2 - ol with fuming HBr gives meso-2-3-dibromo-butane.

(4) Elimination - Addition Mechanism (Benzyne Mechanism)

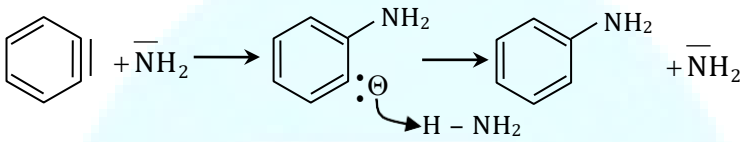
In the absence of an electron withdrawing group, nucleophilic substitution takes place in presence of very strong bases, but the mechanism is entirely different from that what we have seen in bimolecular nucleophilic substitution reactions. These reactions proceed by a mechanism called benzyne mechanism the positions.

.

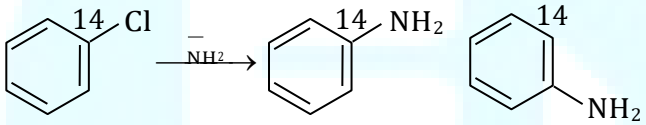




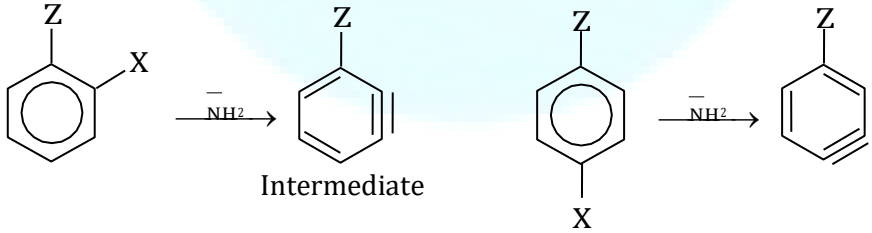
Benzyne



Benzyne is a symmetrical intermediate and can be attacked by nucleophile at both.

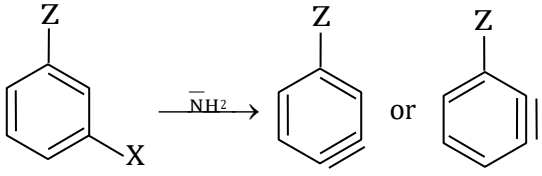


Isotopic labelling confirmed that there is an equal chance of abstraction from both carbons. An equal halide which does not contain alpha hydrogen with respect to halogen does not undergo this reaction. In the reactions involving/ benzyne intermediates, two factors affect the position of incoming group, the first one is direction of aryne formation. When there are groups *ortho* or *para* to the leaving group, then, the following intermediates should be formed.



Intermediate

When a meta group is present, aryne can form in two ways, in such cases.



More acidic hydrogen is removed, i.e. an electron attacking 'Z' favours removal of *para* hydrogen.

(5) SN' MECHANISM :

Allylic substrates undergo nucleophilic substitution reactions rapidly, and are usually accompanied by a rearrangement known as an *allylic rearrangement* or an allylic shift. When allylic substrates are treated with nuc1eophiles under SN1 conditions, two products are usually formed the normal product and a rearranged product:

$$R-CH=CH-CH_2X \xrightarrow{Y^{\ominus}} \underset{\text{Normal product}}{R-CH=CH-CH_2Y} + \underset{\text{Rearranged product}}{R-\underset{\displaystyle Y}{\underset{|}{CH}}-CH=CH_2}$$

The formation of two products can be easily explained because the allyl cation is resonance hybrid of two structures:

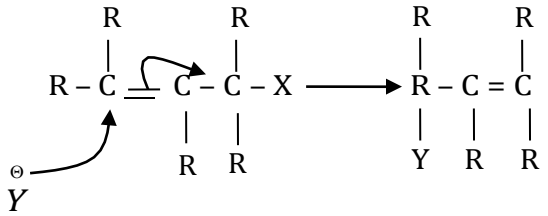
$$R-CH=CH-\overset{\oplus}{C}H_3 \longleftrightarrow R-\overset{\oplus}{C}H-CH=CH_2$$

Thus, C - 1 and C - 2 each carry a partial positive charge, and both are attacked by $Y^{\ominus}$ (nucleophile) resulting in the formation of two products. This mechanism is called SN1' *mechanism*. In SN1' reactions at equilibrium more stable product (thermodynamically controlled product) is formed in greater amount, whereas if equilibrium is not reached, less stable product (kinetically controlled) is formed in greater amount. If the double bond in one isomer is in conjugation with an aromatic ring, a triple bond, another double bond or a carbonyl group, then that isomer is more stable and predominates at equilibrium, e.g.,

$$Ph-CH=CH-CH_2-X \xrightarrow{{}^{\ominus}OH} \underset{\text{100\% at equilibrium}}{\underset{\text{I}}{Ph-CH=CH-CH_2-OH}} + \underset{\text{major product if equilibrium not reached}}{\underset{\text{II}}{Ph-\underset{\displaystyle OH}{\underset{|}{CH}}-CH=CH_2}}$$

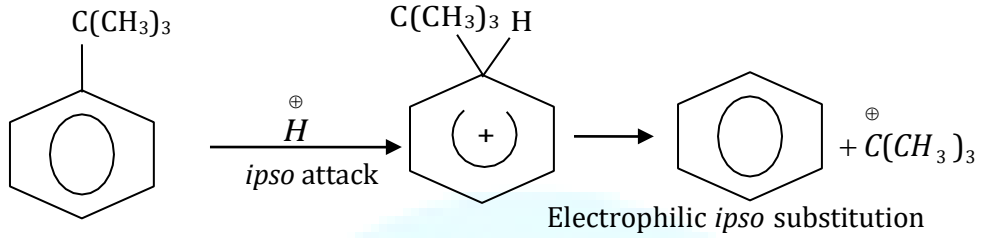
100% of the I is formed at equilibrium because it is more stable due to conjugation of its double bond with the phenyl ring. If equilibrium is not reached, then II is the major product. Nucleophilic substitution at an allylic carbon may also take place by SN2 mechanism without allylic rearrangement. However, allylic rearrangement can also take place under SN2 conditions through the following mechanism in which the nuc1eophile attacks at the γ -carbon instead of at the usual position. This mechanism is called SN2' *mechanism* and is an allylic rearrangement:

SN2' mechanism takes place under SN2 conditions where a substitution sterically retards the normal SN2 mechanism.



(6) *IPSO* reaction :

A position which is already occupied by a non-hydrogen substituent in an aromatic ring is called *ipso* position (Latin: *ipso,* on itself), the attack on this position is called *ipso* attack (or *ipso* addition), and the aromatic substitution in which a substituent already present is replaced is called *ipso* substitution. For example, protodealkylation of an alkylbenzene (reverse of Friedel-Crafts alkylation). In this reaction, tertiary alkyl groups are most easily removed, since they depart as stabler carbocations. Thus, *t*-butyl group is used to protect the most reactive position in a compound to effect reaction elsewhere. The mechanism is as follows :



Electrophilic *ipso* substitution

$$(CH_3)_3\overset{\oplus}{C} \longrightarrow (CH_3)_2C = CH_2 + H^{\oplus}$$

Aromaticity:

Benzene is a planar compound with a cyclic cloud of delocalized electrons both above and below the plane of the ring as shown above. Because its π-electrons are delocalized, all the C-C bonds in benzene have the equal length- partway between the length of a typical single and double bonds. We have noticed that the benzene is a particularly stable compound because it has extraordinarily large resonance energy (36 Kcal/mol). The compounds such as benzene with unusually large resonance energies are typically called aromatic compounds, and the cause which explains the extra stability of such cyclic molecules is termed as 'aromaticity'. In aromatic compounds, resonance phenomenon (for details, see resonance section) typically increases the stability of the molecule, and therefore, the energy is called resonance energy. The concept of aromaticity can be best explained based on the Hückel's rule as discussed below:

Hückel's rule: For a compound to be aromatic, the following conditions must be followed

(i) A compound must have an uninterrupted cyclic cloud of π-electrons. For the πcloud to be cyclic, a compound must be cyclic and planar or nearly planar.

(ii) The πcloud must contain an odd number of pairs of π-electron.

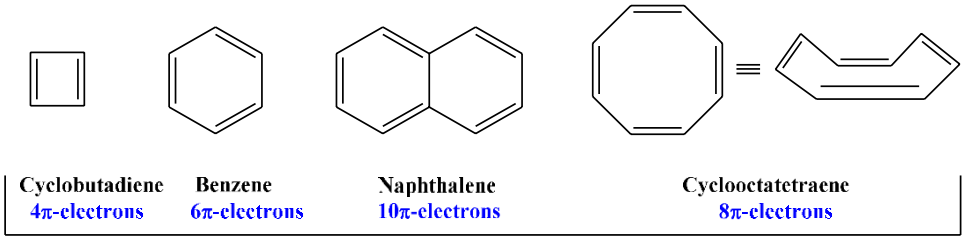
(iii) The German chemist Erich Hückel was the first to recognize that an aromatic compound must obeys [4n + 2] π-electron rule. The rule states that a cyclic and planar compound would be aromatic, if its uninterrupted πcloud contains [4n + 2] π-electrons, where n = 0,1,2,3… n is generally called Hückel's number or aromaticity index

<table>
<tr><th colspan="3">[4n + 2] π-electrons</th><th colspan="3">4n π-electrons</th></tr>
<tr><td>Resonance</td><td rowspan="4">Never Anti-Aromatic</td><td>Resonance</td><td>Resonance</td><td rowspan="4">Never Aromatic</td><td>Resonance</td></tr>
<tr><td>Planar</td><td>Non-Planar</td><td>Planar</td><td>Non-Planar</td></tr>
<tr><td>Aromatic</td><td>Non-</td><td>Anti-</td><td>Non-</td></tr>
<tr><td></td><td>Aromatic</td><td>Aromatic</td><td>Aromatic</td></tr>
</table>

Concept of aromaticity

For applying Hückel's rule in any system, one will need to count the number of π-electrons.The number of π-electrons can be calculated as follows:

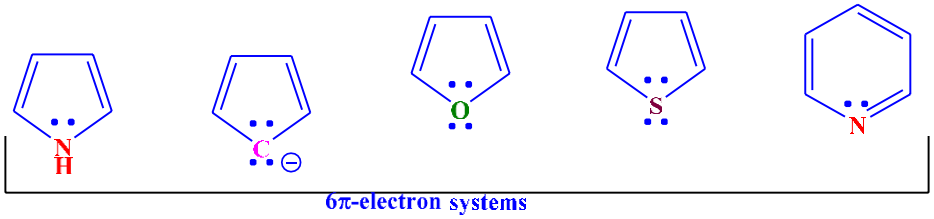
- Double bond or triple bond contributes 2 π-electrons to the system.



Cyclobutadiene, benzene, naphthalene and cyclooctatetraene has two, three, five and four pairs of π-electrons, respectively. Benzene and naphthalene fulfill the conditions for aromaticity but cyclobutadiene and cyclooctatetraene are not aromatic because they have an even number of pairs of π-electrons. There is an additional reason why cyclooctatetraene is not aromatic – it is not planar but, instead tub-shaped.

- Negative charge or lone pair of electron also contributes 2p electrons, if they are in conjugation with π-electrons. However, if they are not involved in resonance, then not counted.

Aromaticity in heterocyclic compounds: So far, we have only considered compounds having a carbon skeleton. However, many compounds found in nature are cyclic compounds with an element other than carbon in the ring. These are called Heterocyclic compounds. Further, some of them may be aromatic compounds and are termed as heteroaromatic compounds as given below.



ANTI-AROMATICITY

Cyclic conjugated flat or planar molecules having 4n π-electrons are termed as anti-aromatic compounds. Unlike highly stable aromatic compounds, which typically follow Hückel's

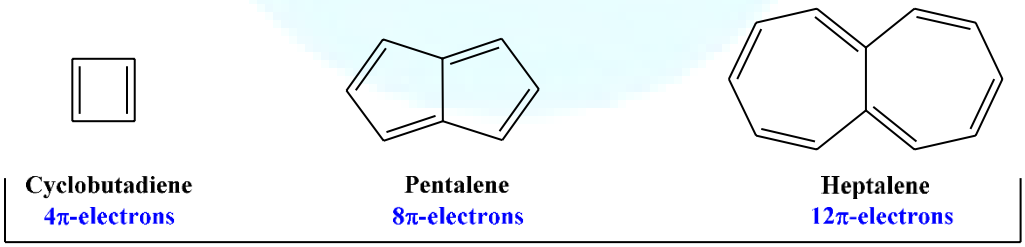
rule ([4*n* + 2] π electrons), anti-aromatic compounds are highly unstable as well as quite reactive.

The unexpected instability of 4n π-electron cyclic conjugated system has been termed as "anti-aromaticity". For instance, the cyclopentadienyl cation is extremely unstable and difficult to make. Similarly, the oxirene itself has never been observed despite having an exciting trace of its fleeting existence, and by the way, neither has the 1H-azirene and/or thiirene, the nitrogen analogues.

Cyclopentadienyl cation **Oxirene** **1H-Azirene** **Thiirene**

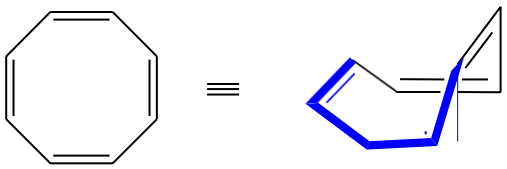
Structures of cyclopentadienyl cation and some elusive three-membered anti-aromatic ring compounds

The simple pentalene hydrocarbon is quite unstable above -100°C and does not exist while its hexaphenyl derivative is air sensitive. Similarly, though the 12π-electron-containing planar heptalene has been prepared yet is found to be extremely reactive (even more than that of cyclooctatetraene). Apart from that, all attempts to isolate 1,3-cyclobutadiene (4π-electron system) have always resulted a dimer.



Cyclobutadiene **Pentalene** **Heptalene**
4π-electrons **8π-electrons** **12π-electrons**

Planar and very unstable



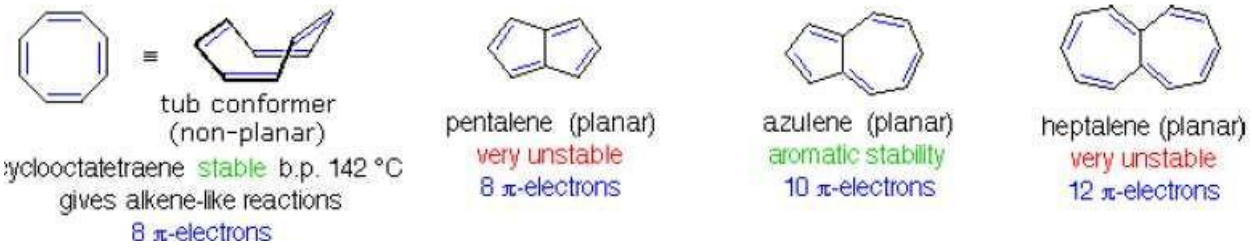
Cyclooctatetraene **Tub-conformer (non-planar)**
8π

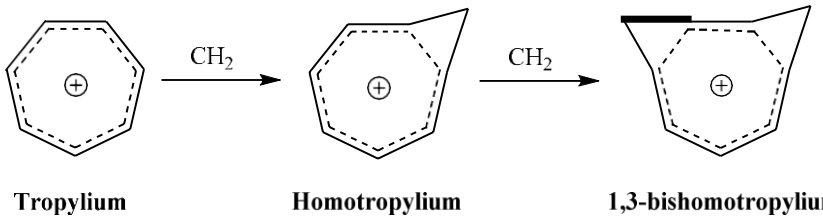
Upper column: Structures of some typical anti-aromatic compounds; Lower column: structure of cyclooctatetraene and its tub conformer

It would be worthwhile to mention here that some molecules may change shape and become non-planar in order to avoid the instability due to anti-aromaticity. As such, the molecules can break some of the typical π interactions. For instance, 1,3,5,7-cyclooctatetraene is a non-planar compound and adopts a tub-shaped conformation to avoid the destabilization that results from anti-aromaticity (Figure 11, lower column). If it were planar, it would have a single 8π-electron system around the ring, but it instead adopts a boat-like shape having four individual π bonds. The compound can be readily prepared and undergoes addition reactions, typical of alkenes. The catalytic hydrogenation of this cyclooctatetraene produces cyclooctane.

HOMOAROMATICITY

In the previous section, we discussed about aromaticity. In 1959, Saul Winstein introduced a new class of aromatic compounds based on the structural properties of "tris- homocyclopropenyl" cation. In this cation, aromaticity was found to be discontinued due to the presence of single sp^3-hybridized atom. These types of molecules were termed as homoaromatic molecules. Thus, we can say that **homoaromaticity** refers to a special case of aromaticity in which conjugation is interrupted by a single sp^3-hybridized carbon atom. Due to the poor overlapping of p-orbitals, these compounds are definitely less stable than the aromatic compounds (having complete delocalization of electron). To date, homoaromatic compounds are known to exist as both cationic and anionic species while some studies also support the existence of neutral homoaromatic molecules, though these are less common. Among these, the cationic homoaromatic compounds are the most studied species for homoaromaticity. For example, the homotropylium cation. Similar to those of cationic counterparts, the anionic homoaromatics have also been accepted to exhibit the "true" homoaromaticity. The anionic homoaromatics are generally prepared from their neutral parent compounds through reduction with lithium metal. Notably, in bis, tris, (etc.) homoaromatic species, two, three, (etc.) single sp^3-hybridized centres separately interrupt the pi-electron system.

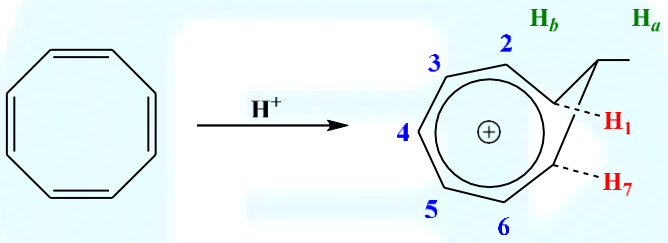




Structures of different tropylium cations

Synthesis of homotropylium cation:

When cyclooctatetraene is dissolved in concentrated sulfuric acid, a proton adds to one of the double bonds to form the homotropylium ion. In this species, an aromatic sextet extends over seven carbon atoms similar to that of tropylium ion. As the eighth carbon atom is sp^3-hybridized, it cannot take part in the aromaticity.



Synthesis of homotropylium cation from cyclooctatetraene

BENZENOID AND NON-BENZONOID AROMATIC COMPOUNDS

Benzene is simplest aromatic compound. There are three alternative π-bonds in the cyclic ring of benzene. However, it is not essential that all aromatic compounds contain a benzene ring. On these ground, aromatic compounds can be classified as benzenoid and non-benzenoid compounds.

Benzenoid compounds: Those compounds which are derived from benzene are known asbenzenoid compounds. These compounds show a complete delocalization in the ring. benzenoid compounds can be further divided into isolated and fused benzenoid compounds.

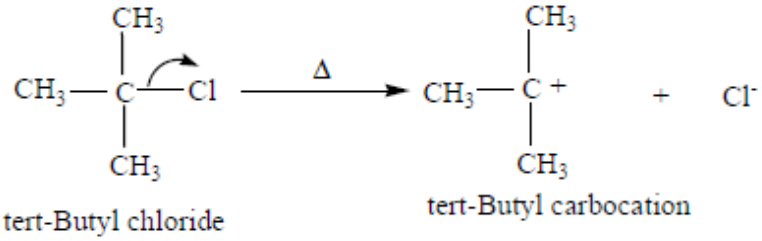
Isolated benzenoid compounds: These types of compounds usually contain a benzene ring or benzene ring is connected by only one bond. Some selected examples of isolated benzenoid compounds including benzene are given below.

REACTION INTERMEDIATES

Carbocations:

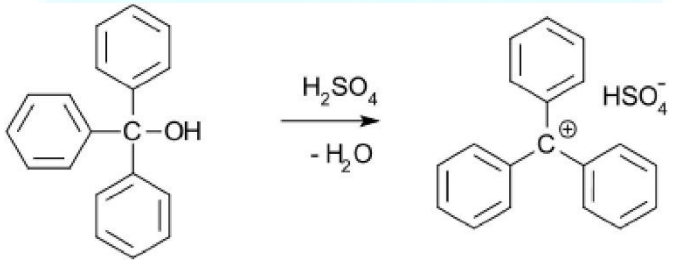
An Organic species which has a carbon atom containing only six electrons in its outermost shell and has appositive charge is called a carbocation reaction intermediate. The carbon atom of the carbocation is Sp^2 hybridized, it use the three hybrid orbitals for single bonding to three substituents and remaining p- orbital is empty. The carbocations thus has a planner structure having all the three covalent bonds are in plane with the bond angle of 120^0 between them.

Formation of carbocations: These are formed by the heterolytic cleavage of the covalent bonds



tert-Butyl chloride tert-Butyl carbocation

in which the leaving in which the leaving group takes away with it the shared pair of electrons.



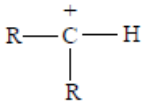
For example,

Classification of carbonium ion: Carbocations are classified as primary (1^0), secondary (2^0) andtertiary (3^0) according to the positive charge is present on a primary, secondary and tertiary carbon atom respectively.

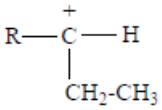
For examples:

1. **Alkyl Carbonium ion:**

   Like free radical carbinium ion also classified in to three classes-



a. Primary carbonium ion: In this type of carbonium ion one carbon atom is attached with



the positive carbon atom.

Where R is the alkyl group

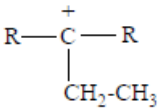
Where R is the alkyl group

b. Secondary carbonium ion-

In this type of carbonium ion two H atoms are replaced by two alkyl groups from the + charge bearing carbon.

Where R is the alkyl group

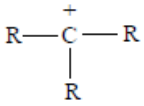
Isopropyl carbonium ion



Where R is the alkyl group

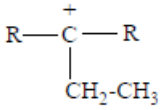
c. Tertary carbonium ion:

In this type of carbonium ion 3 hydrogen atoms are replaced by 3 alkyl groups from the positive charge bearing carbon.



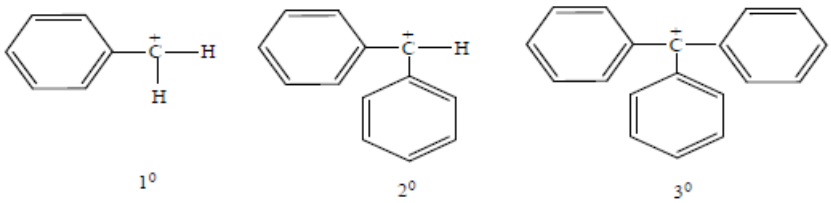
Where R is the alkyl group

tert. Butyl carbonium ion

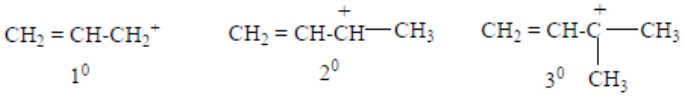


Where R is the alkyl group

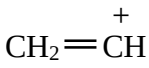
2. **Benzylic carbocations:**



3. **Allylic carbocations:**



4. **Vinylic carbocation:**

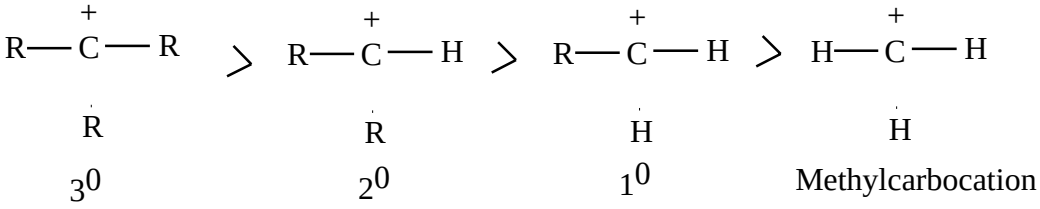


5. **clopropylmethyl carbocation**

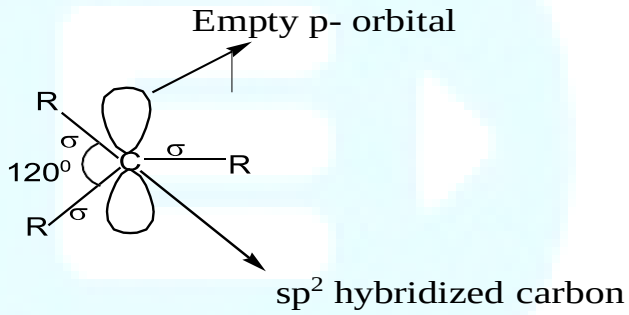
Stability of carbonium ion:

The relative stability of carbonium ion is explained with the help of Inductive effect. In the case of 1^0 carbonium ion the CH_3 group contains +I affect, so it release the electron towards the

carbon that bearing positive charge. So some charge neutralize and also somewhat positive charge created on the methyl group carbon, so the + charge become dispersed and gives the stability. Hence 3^0 carbocation is most stable in compare to 2^0, 1^0 and methyl cabocation.

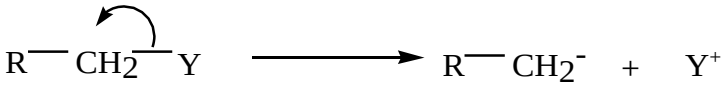


Orbital structure: The carbocations are planner species. The carbon atom carrying the positive charge is sp^2 hybrized. The three sp^2 hybrised orbitals of this carbon form three σ bonds with monovalent atoms or groups which lie in a plane and are inclined to each other at an angle of 120^0. The unhybridized 2p orbital which is perpendicular to the plane of the three σ- bonds is, however, empty which are given as follow:



Carbanaions:

These are chemical species which possess a negatively charged on carbon and possessing eight electrons in its valence shell are called carbanions. Like the Carbocations the Carbanions are also formed by *hetertolytic fission* of covalent C-Y molecules

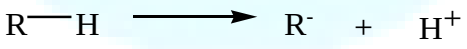


Here Y is an atom which is more electropositive than Carbon. This is why during the heterolytic fission the shared pair of electrons is drawn towards the Carbon atom to develop a negative charge over it.

Generation of carbanions: Carbanions are generated as intermediate in various organic reactions. Some of the methods for the generation of carbanion are given as:

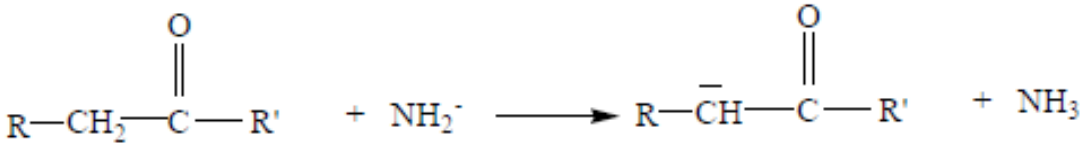
a) Proton abstraction
b) Decarboxylation
c) Addition of nucleophile to alkene
d) Formation of organometallic compounds

(a) Proton abstraction: When proton is abstracted from a carbon centre then the resulting anion is called a carbanion.

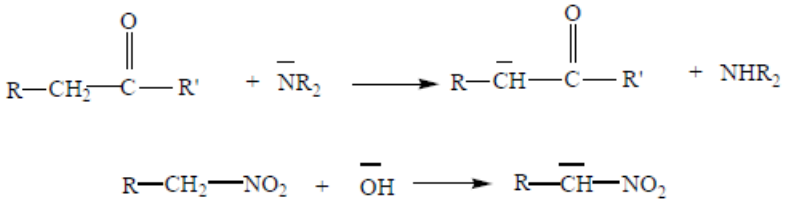


The acidic hydrogen of an organic substrate can be abstracted by an appropriate base. For example carbanion generated from carbonyl compounds.

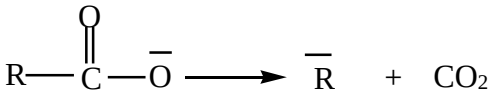
Here, are some examples showing generation of carbanion by abstraction of the acidic proton



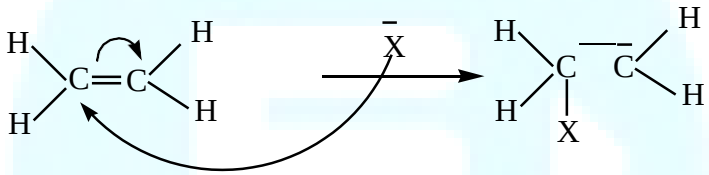
using a base (OH^-, NH_2^- and RO^-).



(a) Decarboxylation: Decarboxylation of carboxylates ion to form carbanion intermediate.

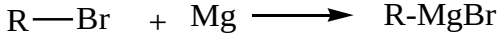


(b) Addition of nucleophile to alkene: Carbanions are generated by the attack of nucleophiles on one of the carbon of an alkene. It results into the development of negative charge on the other carbon atom.



(c) Formation of organometallic compounds: Metals which are less electronegative than carbon (such as magnesium, lithium, potassium, sodium, zinc, mercury, lead, thallium) react with alkyl halides under appropriate conditions to form a carbon-metal bond where the carbon carries negative charge and metal positive charge.

For example, alkyl bromides react with magnesium in the presence of dry diethyl ether to form alkyl magnesium halides also known as Grignard reagent.

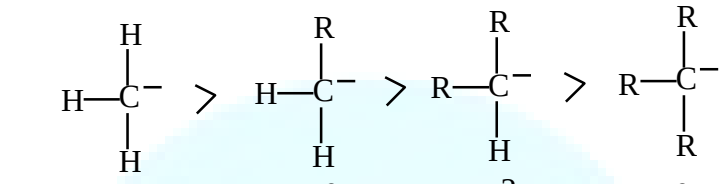


Stability of Carbanion: Factors which can stabilize the negative charge on carbon will stabilize a carbanion. The stability of carbanion depends on the following factors:

a) Inductive effect
b) Extent of conjugation of the anion
c) Hybridization of the charge-bearing atom
d) Aromaticity

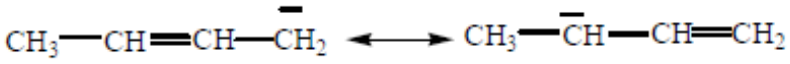
(a) Inductive effect: If the electron donating groups are attached to carbanion they will increase the negative charge on carbon and thus destabilize it. However, electron withdrawing groups adjacent to the negatively charged carbon will stabilize the carbanion.

All alkyl groups are electron donating in nature due to inductive effect (+I effect). More the number of alkyl groups attached lesser will be the stability. Therefore the order of stability order of alkyl carbanion is methyl > 1^o > 2^o > 3^o carbanion.

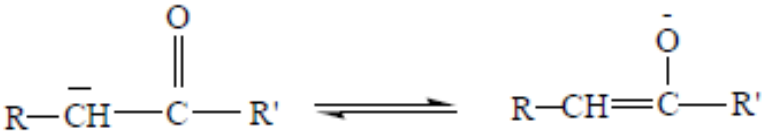


methyal carbanion 1^0 2^2 3^0

(b) Extent of conjugation of the anion: If negatively charged carbon is in conjugation with a double bond the resonance effects will stabilize the anion by spreading out the charge by

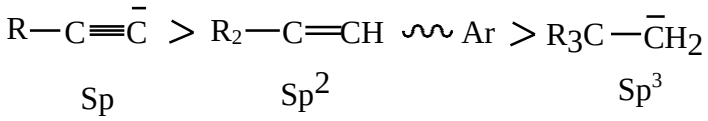


rearranging the electron pairs.



Enolate of ester:

(c) Hybridization of the charge bearing atom: Stability of anion will depend upon the s character of carbanion i.e. more the s character, higher will be the stability of anion. The percentage s character in the hybrid orbitals is as follows: sp (50%) > sp^2 (33.33%) > sp^3 (25%).



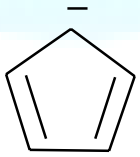
Explanation of the order of stability:

Propargyl anion > propenyl anion > propyl anion

The order of stability can be understood as follows. In propargyl anion, the triply bonded carbon is sp hybridized, in propenyl anion the doubly bonded carbon is sp^2 hybridized while in propyl anion the carbon is sp^3 hybridized. Orbital with greater s character is more close to the nucleus and having more nuclear charge. The sp hybridized atoms are more electronegative than sp^2 and sp^3. The distance of lone pair and nucleus is less if the lone pair is sp hybridized than in a sp^2 hybrid orbital. Since, it is more favorable for the negative charge of an anion to be in an orbital close to the positively charged nucleus. Therefore sp hybrid anion is more stable than sp^2.

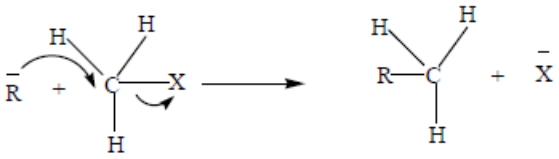
(d) Aromaticity: In some carbanions, the lone pair of electrons of the negative charge is involved in delocalization to add on to the aromatic character of the molecule which gives them extra stability**.**

For example, in cyclopentadienyl anion there are 6π electron and thus it obeys Huckel aromaticity rule, (4n+2)π electron. This anion is stabilized by aromatization.

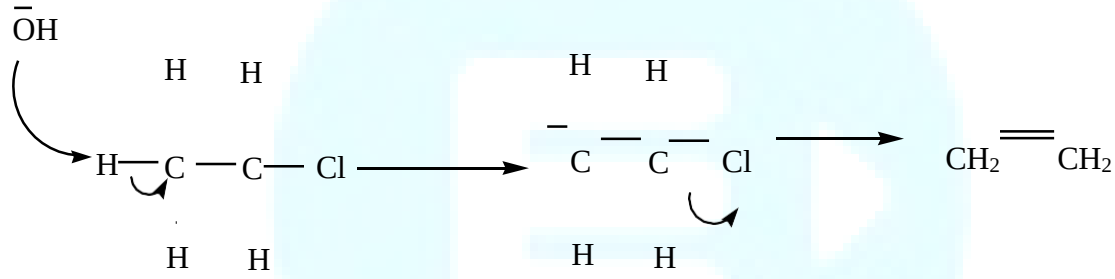


Reactivity of Carbanion: Carbocations are strong Lewis acids while carbanions are strong bases (Lewis and Bronsted bases). Carbanions are part of most of the common reaction types such as displacement, elimination, condensation, addition, rearrangement, polymerisation etc.

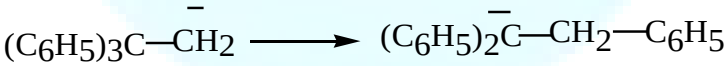
1. Displacement Reaction: Such reactions are nucleophilic substitu (SN^2) reactions observed in alkyl halide.



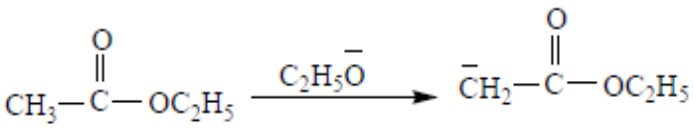
2. Elimination reaction: In a Conjugate Base Elimination reaction (E_1cb) the C-H bond breaks with formation of carbanion as intermediate. The developed negative charge on carbon assist in the loss of leaving group, leading to the formation of alkene.



3. Rearrangement reactions: In some cases, carbanions may rearrange to form more stable species. Consider the rearrangement in triphennylmethyl carbanion.



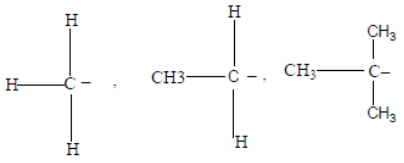
4. Condensation reactions:



Claisen condensation: Formation of β-keto esters from carboxylic esters is known as Clasien ester condensation.

It is generated by heterolytic fission and bearing - ve Charge and the number of valence electrons are 8 in it called carbanion reaction intermediate.

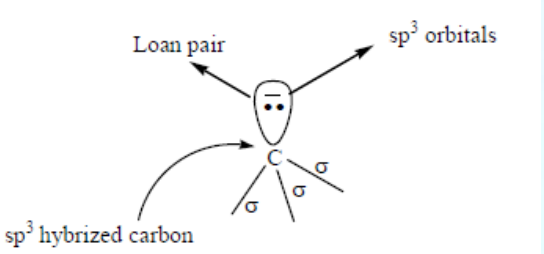
Example:



Hybridization in carbanion ion:

The carbanion ion shows SP^3 hybridization with one loan pair of electron. Hence its geometry will be tetrahedral.

Structure of Carbanion: The structure of simple carbanion is usually pyramidal just like those of ammonia and amines. The carbon atom carrying the negative charge is sp^3 hybridized. Three of the four sp^3 hybridized orbitals from three σ- bonds with monovalent atoms while the four sp^3

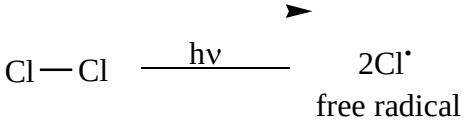


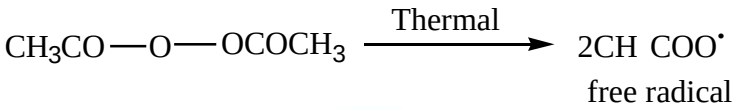
orbital contains the loan pair of electrons.

Carbon Free Radicals:

A free radical (often simply called a radical) may be defined as a species that containsone or more unpaired electrons. Note that this definition includes certain stable inorganic molecules (e.g., NO and NO2), as well as many individual atoms (e.g., Na and Cl). As with carbocations and carbanions, simple alkyl radicals are very reactive. Their lifetimes are extremely short in solution, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules. Since the lifetime of a radical depends not only on its inherent stability, but also on the conditions under which it is generated, the terms persistent and stableare usually used for the different senses. A stable radical is inherently stable; a persistent radical has a relatively long lifetime under the conditions at which it is generated, although it may not bevery stable.

Generation of Free Radicals: Formation of free radicals is favoured by the presence of UV light, heat and organic peroxide. An important characteristic of free radical reactions is that, once initiated, they proceed very fast. The free radicals can be detected by magnetic susceptibility measurement.





Example: CH_3^o, $CH_3CH_2^o$, H^o etc.

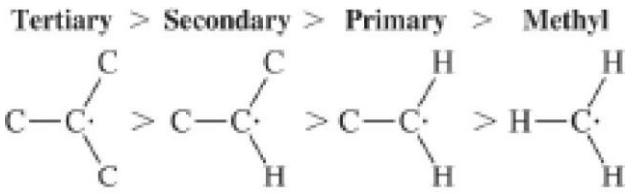
The free radicals are strongly reactive because they have stronger tendency to become paired and their nature is paramagnetic.

Stability of free radicals: The bond dissociation energies give us an idea of the ease with which radicals can form; they can also give us an idea of the stability of those radicals once they have formed. The lower the bond dissociation energy, the higher will be the stability. Alkyl radicals are stabilized by adjacent lone-pair-bearing heteroatom and by the π bonds. The various factors responsible for the stability of free radicals are:

1. Inductive effect
2. Hyperconjugative effect
3. Resonance effect

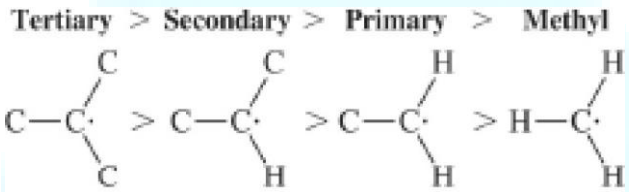
Inductive effect: Greater the number of alkyl groups attached to the free radical carbon centre more will be the stability of the radical. This is due to the electron donating inductive effect **(+ I effect)** of the alkyl groups which decrease the electron deficiency of the radical.

The bond dissociation energies, of the C-H bonds for the formation of a free radical of methane, ethane, and other alkanes, clearly shows that radical centres are stabilized by the replacement of one, two, or three of the hydrogens of the methyl radical by alkyl groups.
Thus, the order of stability is $3^o > 2^o > 1^o$.



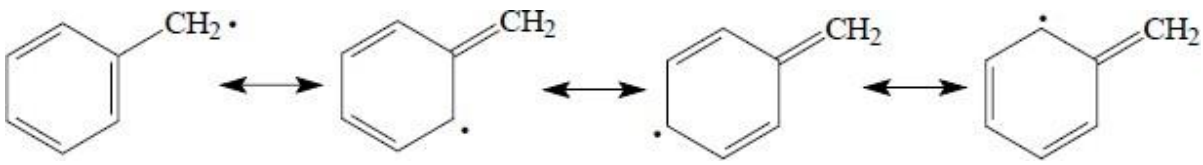
Hyperconjugative effect: Hyperconjugative effect also gives stability to free radicals as in the case of carbocations. Thus, Greater the number of hyperconjugative structures more will be the Stability of the radical. The

Stability order of alkyl free radicals is tertiary > secondary > primary > CH_3.



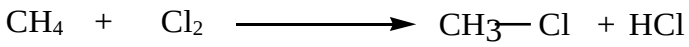
Resonance Effect: In the free radicals where the carbon centre is in conjugation to a double bond, the resonance effect leads to stabilisation of these molecules. The stabilising effects of vinyl groups (in allyl radicals) and phenyl groups (in benzyl radicals) are very significant and can be satisfactorily explained by resonance. Allyl and benzyl free radicals are more stable than alkyl free radicals but still have only a transient existence under ordinary conditions.

Resonance in benzyl free radical:



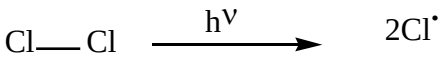
Reactivity of free radical: Some important reactions of free radicals are described below:

Halogenation of aliphatic hydrocarbons: In the presence of sunlight, halogenation of saturated hydrocarbons like alkane gives haloalkane.

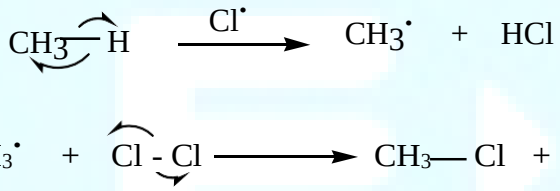

CH4 + Cl2 CH3—Cl + HCl

Mechanism of Halogenation: It involves three main steps (i) Initiation (ii) Propagation and (ii) Termination.

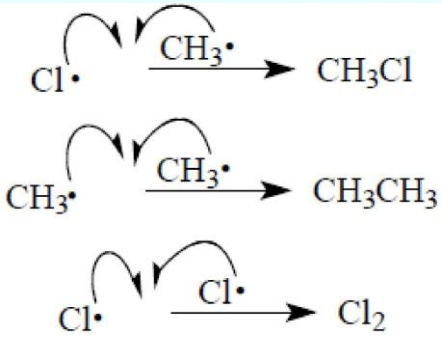
(i) Initiation: In this step, free radicals required for the reaction are generated in situ by irradiation or heating of the reagent or by carrying out the reaction in the presence of an initiator like peroxides. The process is always endothermic.



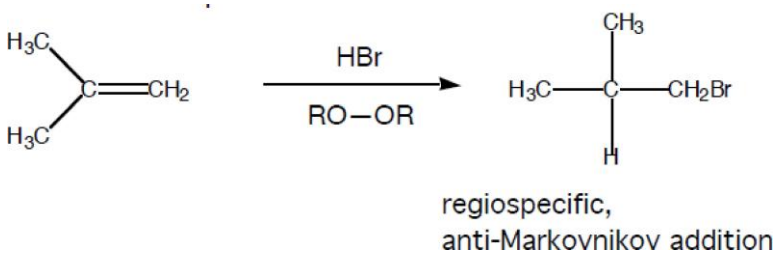
(ii) Chain propagation: Second step is chain propagation. In this step the highly reactive chlorine radicals with unpaired electron reacts further. They are electrophilic, thus each seeks an electron to complete its unfilled shell of electrons. In a reaction with methane, a chlorine atom readily removes hydrogen from the methane. Free radical chain reactions work best when all propagation steps are exothermic.



(iii) Chain termination: The final step is chain termination in which two reactive radicals combine together.

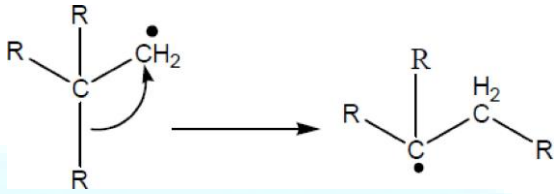


Addition reaction: The anti-Markovnikov addition of HBr to alkenes was probably the firstfree radical addition reaction to be discovered.



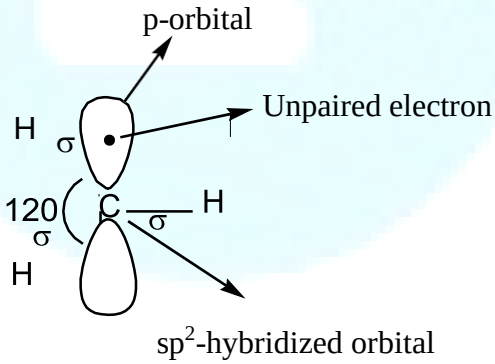
regiospecific,
anti-Markovnikov addition

Rearrangement reaction: Free radicals may also undergo rearrangement to form a morestable radical and then the final product.



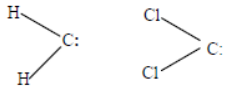
Structure:

Alkyl free radicals like carbocationa are planner species. The only difference being that in carbocations, the unhybridized p- orbital is empty while in free radicals, it contains the odd electron.



Carbene Reaction intermediate:

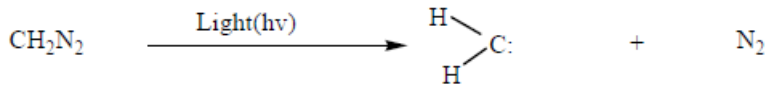
Carbenes are netural, divalent, highly reactive intermediate carbon species. It is defined as a netural reactive divalent species which consist six electrons in its outermost shell is known as Carbene.


H
C:
H
Cl
C:
Cl

Carbenes are highly reactive because they have stronger tendency to complete their octate.

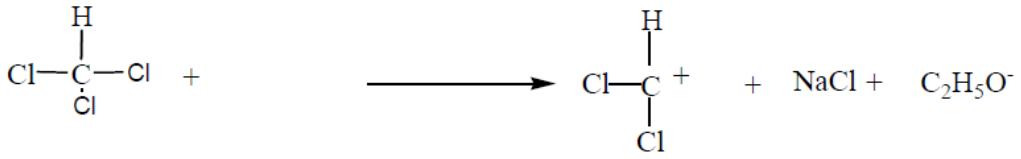
Methods of preparation

1. **From diazomethane:** Diazomethane on decomposition under the action of light gives carbene.

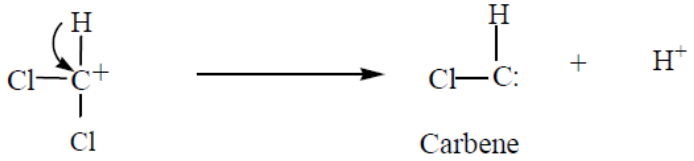


2. **From chlororm:** hloroform on react with sodium ethoxide gives dichloro carbine by releasing C_2H_5OH.

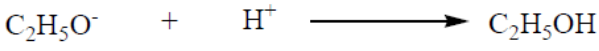
Step 1



Step 2



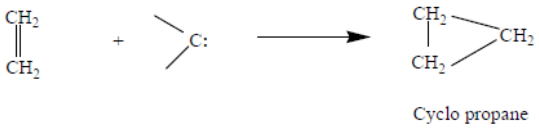
Step 3



Properties of carbine:

Carbene is a highly reactive reaction intermediate and it gives easily reaction.

1. **Reaction with Alkene:** carbine on react alkene gives cycloalkanes.

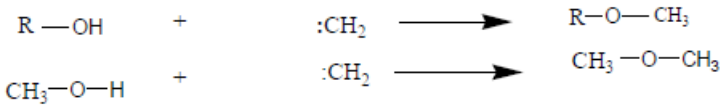


Cyclo propane

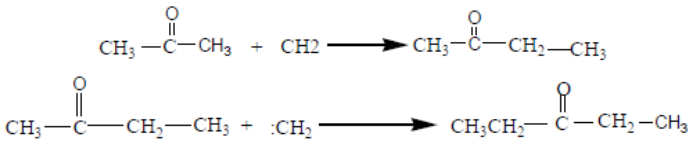
e.g.

Methyl cyclo propane

2. **Reaction with alcohol:** Carbene on react with alcohol gives addition compound ether.



3. **Insertation Reaction:** In this reaction carbine react with those functional groups which are bi-valent and from both sides they are link with another groups undergoes insertation reaction reaction with carbine.

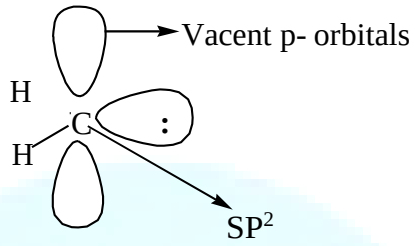


4. **Reaction with alcohol: Alkanes on react with carbene gives higher number of alkane series.**

Classification of carbene: Carbenes are classified in to two classes by name these are-

1. Singlate carbene
2. Triplet carbene

1. **Singlet carbene:** In this type of carbene SP^2 hybridization is observed and the unshared pair of electron is present in one p- orbital.



Multiplicity = S = 1/2n

(Where n is the number of unpaired electron)

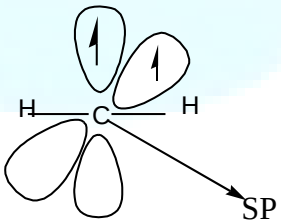
In this case n = 0

Since multiplicity = 2s + 1

= 2 x 0 + 1

= 1 (singlet)

2. Triplet carbene: In this type of carbene the unshared pair of electron is exist in to two unhybridised p- orbital. So they show Sp- hybridization with linear geometry.



S = ½ n

S = ½ x 2

S = 1

Since multiplicity = 2s + 1

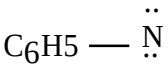
= 2 x1 + 1

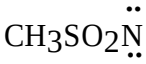
= 3 (Triplet)

Stability of singlet and triplet carbene: Out of singlet and triplet carbene is more stable because in singlet carbene there is the repulsion between unshared electrons.

3.3.3. Nitrenes:

Nitrenes are defined as "A neutral reactive monovalent species which consist six electron in its outermost shell is known as nitrene". The nomenclature follows that of carbene. Substituted nitrenes are simply named as substituted derivative of carbene. For example:


Phenylnitrene

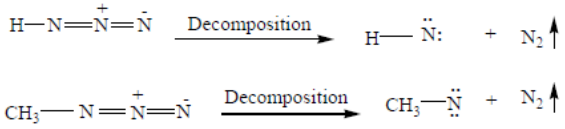

Methanesulphonyl nitrene


Alkylnitrene

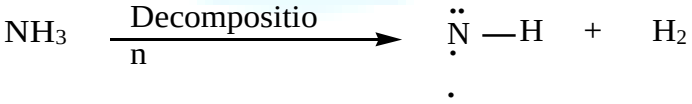
In nitrenes the nitrogen atom N has 1 l.p. of electron and 1 unshared pair of electron.

Method of preparation:

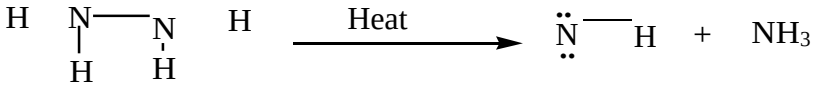
1. **From hydrozoic acid-** Hydrozoic acid **(**HN_3) on decomposition gives nitrene.



2. **From Ammonia:** Ammonia (NH_3) on decomposition gives nitrene by removing H_2 gas.

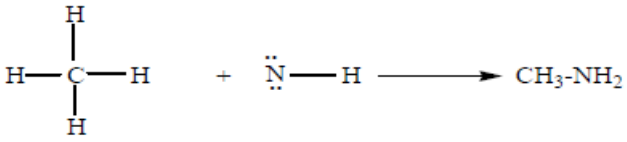


3. **From hydrazen:** Hydrazene on decomposition gives nitrene.



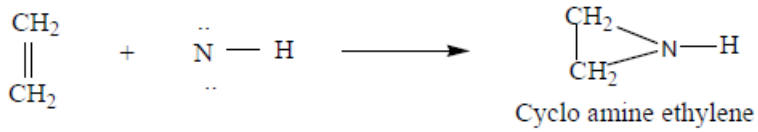
Properties: Nitrenes are highly reactive because they have stronger tendency to complete their octate.

1. **Insertion reaction:** In this type of reaction nitrene react with alkane to give amino derivative compound.



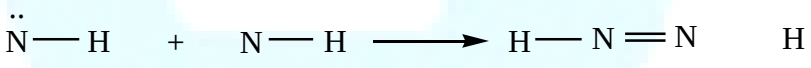
Aminomethane

2. **Reaction with alkene:** Nitrene on react with alkenes gives cyclic amino compounds.



Cyclo amine ethylene

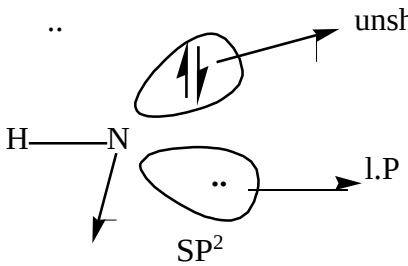
3. **Di- marization reaction:** In this type of reaction two nitrenes are combined together to form the product.



azo hydrogen

Classification of nitrenes: Nitrenes are classified into two classes one is singlet and other is triplet nitene.

1. **Singlet nitrene:** In this type of nitrene the unshared pair of electron is present in one p-orbital and it consist Sp2 hybridization, its geometry is as follow.



For multiplicity:

Unshaired pair of e^- n = 0

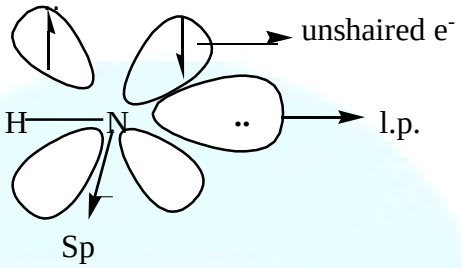
$$S = \frac{1}{2} n = \frac{1}{2} \times 0 = 0$$

Since multiplicity = 2s + 1

$$= 2 \times 0 + 1$$

$$= 1 \text{ (singlet)}$$

2. **Triplet nitrene:** In this type of nitrene N atom shows Sp hybridization and the unshared electron are present in to two different p- orbitals.



For multiplicity: No. of unpaired e^- (n= 2)

$s = \frac{1}{2} n = \frac{1}{2} \times 2 = 1$

So multiplicity = 2s + 1

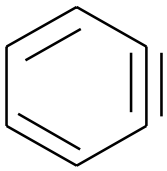
$= 2 \times 1 + 1$

= 3 (Triplet)

3.3.4. Benzyne:

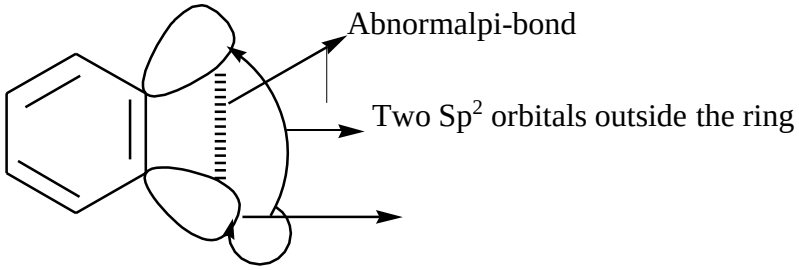
Benzynes or arynes are highly reactive species derived from an aromatic ring by removal of two ortho substituents. Arynes are usually best described as having a strained triple bond; however, they possess some biradical character as well.

The aryne nomenclature derives from the fact that the C6H4 can be represented as an alkyne, although systematically the species should be named as didehydro aromatic compounds, i.e. 1,2-didehydrobenzene.



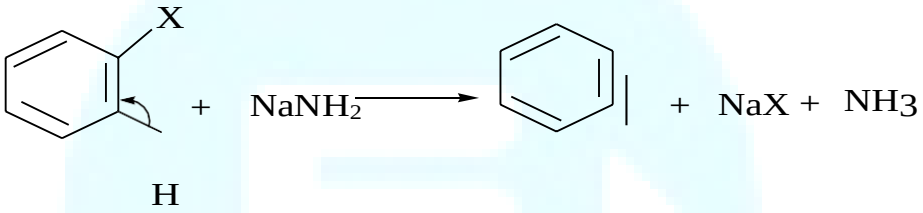
Benzyne can be represented as a singlet molecule with a carbob-carbon triple bond. Although it

has triple bond but it is not normal alkyne bond. In benzyne out of two π-bond of triple bond, one π-bondis normal and the other π-bond is abnormal and is formed by overlap of two Sp^2 orbitals outside the ring. This is called external π-bond.

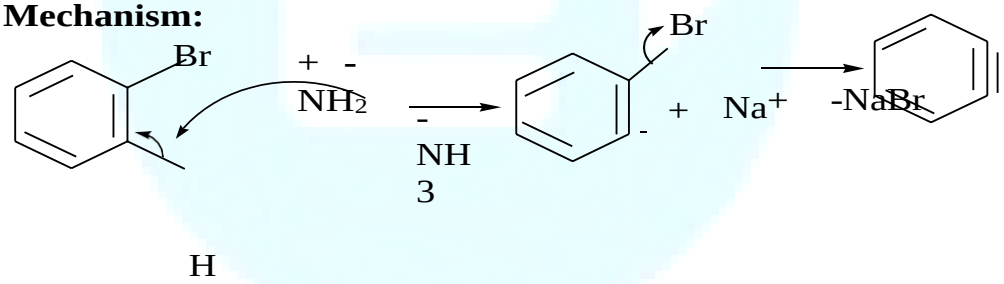


Preparation of benzyne:

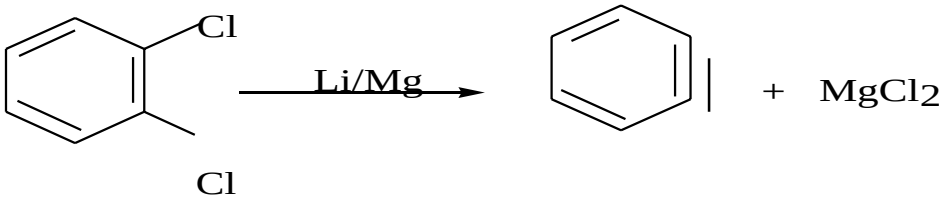
1. **From halobenzene:** When halogbenzene are react with sodamide in liquid ammonia then it gives benzyne.



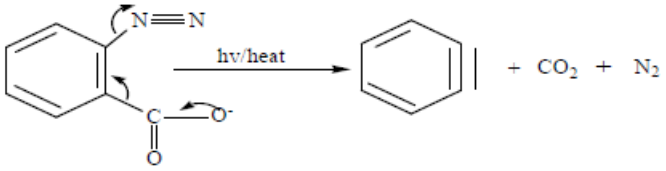
Mechanism:



2. **From 0- dihalobenzene:** When o-dihalobenzene is treated with lithium amalgam or Mg, then it gives benzyne.



3. **From benzenediazonium-2- carboxylic acid:** benzenediazonium-2- carboxylic acid when heated in the presence of heat and sun light then it gives benzynes.



STEREO (or CONFIGURATIONAL) ISOMERISM

Stereoisomerism is arises due to the difference in arrangement (configuration) of atoms or groups in space. When two or more than two isomers have the same structural formulae but having difference in the arrangement (configuration) of atoms in space are called stereo isomer and the phenomenon is called stereo isomerism.

Stereo isomerism can be further classified as

i. Geometrical or *cis-trans* isomerism
ii. Optical isomerism

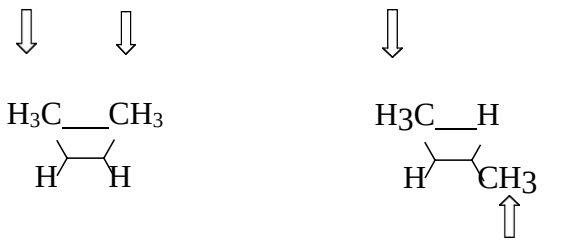
GEOMETRICAL ISOMERISM:

Geometrical isomerism is generally observed in alkenes and cyclic compounds due to their restricted rotation around carbon- carbon bond. The rotation about a double bond in alkene or about a single bond in a cyclic/ring like compound is restricted. Double bonded system consists of a σ (sigma) and a π (pi) bond perpendicular to each other. It is not possible to rotate the molecule about carbon-carbon bond. The rotation will break the π bond as a result the molecule will lose its identity. In some cased the rotation about single bond is also restricted due to steric hindrance. Geometrical isomerism is shown by various groups of compounds the major class of compounds that exhibit geometrical isomerism are classified as:

i. Compounds having double bond;

C=C, C=N, N=N

Example : *cis*- and *trans*- isomerism in 2-butene

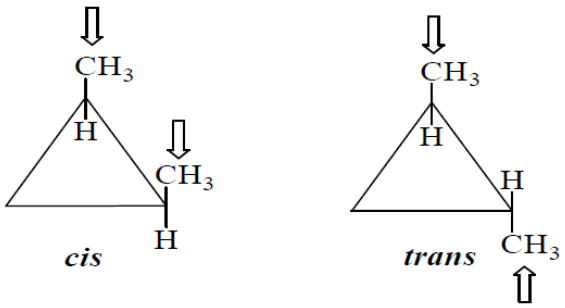


***cis*-2-butene** ***trans*-2-butene**

ii. Cyclic compounds like homocyclic, heterocyclic and fused-ring systems

You can easily observe that rotation around C-C bond is also not possible in cyclic compounds as the rotation would break the bonds and break the ring. Thus Geometrical isomerism is also possible in cyclic compounds.

Example: *cis*- and *trans*- isomers of 1,2-dimethylcyclopropane



Conditions for geometrical isomerism:

Following two conditions are necessary for any compounds to show geometrical isomerism

a) There should be restricted (not allowed) rotation about a bond in a molecule.
b) Both substituent/atoms on each carbon about which rotation is not allowed should (restricted) be different.

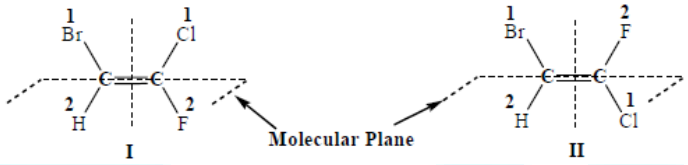
E & Z system of nomenclature for geometrical isomers:

The *cis*- and *trans*- nomenclature is the oldest and most fundamental nomenclature system for geometrical isomerism. The *cis*- and *trans*- nomenclature system is applicable only for those geometrical isomers in which at least one identical atoms/groups is bonded with each double bonded carbon. If both the identical groups/atoms are on same side of double bond the isomer is called as *cis*- isomer; whereas, if both identical groups/atoms are on opposite side of the double bond the isomer is called as *trans*- isomer.

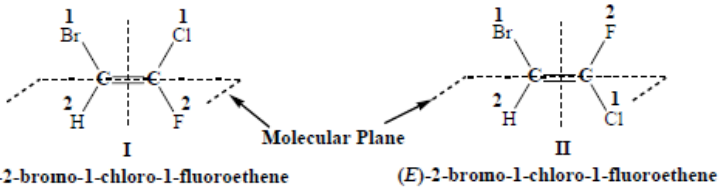
The *cis*- and *trans*- nomenclature method is limited to the molecule in which identical groups/atoms are attached to double bonded carbon. If all the atoms/groups on double bonded carbon are different then the configuration of such molecule could not be assigned as *cis*- and *trans*- nomenclature. A more general nomenclature (*i.e.* E/Z nomenclature) was introduced which was based on *Cahn*-

Ingold-Prelog system. In E/Z system the configuration is specified by the relative positions of two highest priority groups/atoms on the two carbons of the doublebond.

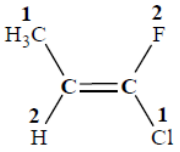
Because all four atoms attached to the carbon-carbon double bond are different, therefore it is not so simple that you can predict them as *cis*- and *trans*- to each other. The E/Z system of nomenclature provides the most appropriate solution to above problem. This system is based on the priority of the attached atoms/groups on each double bonded carbon. The priority of the atoms/groups can be assigned as per the 'Sequence Rule' or 'CIP Rule' given by Cahn-Ingold- Prelog. We have discussed the detail about 'Sequence Rule' in later part of this Unit. Now assign priority to atoms/groups attached to each double bonded carbon in above example.



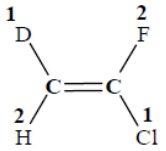
We can easily observe that the both higher priority atoms/groups on each double bonded carbon of isomer **I** are on same side; whereas, the higher priority atoms/groups on each double bonde carbon of isomer **II** are on opposite side. If the two groups with the higher priorities are on the same side of the double bond, such isomer is designated as the (*Z*)- isomer. So you would write it as (*Z*)-name of compound. The symbol *Z* comes from a German word *ZUSAMMEN*, which means together. If the two groups with the higher priorities are on opposite sides of the double bond, then such isomer is designated as (*E*)- isomer. *E* comes from the German *ENTGEGEN*, which means opposite. Thus in given example the isomer **I** is having both higher priority groups/atoms are on same side of double bond, hence it is *Z*- isomer; whereas, the isomer **II** is having both higher priority groups/atoms are on opposite side of the double bond, hence it is *E*- isomer.



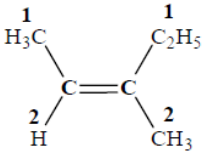
Some other examples of geometrical isomers with *E* and *Z* configuration



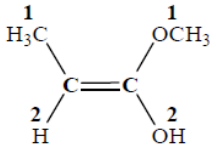
(*E*)-1-chloro-1-fluoroprop-1-ene



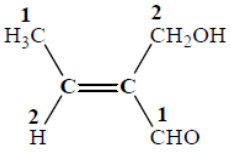
(*E*)-Deuterated1-chloro-1-fluoroprop-1-ene



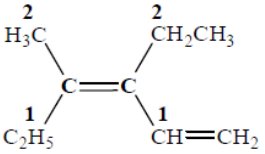
(*Z*)-3-methylpent-2-ene



(*Z*)-1-methoxyprop-1-en-1-ol



(*E*)-2-(hydroxymethyl)but-2-enal



(*Z*)-3-ethyl-4-methylhexa-1,3-diene

Geometrical isomerism in oximes and cyclic compounds:

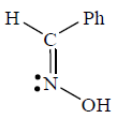
Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are:

(a) Oximes

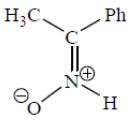
(b) Nitrones

(c) Semicarbazones

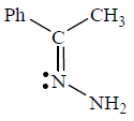
(d) Hydrazones



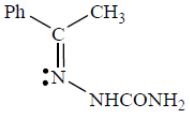
(*Z*)-benzaldehyde oxime



(*E*)-nitrone



(*E*)-1-(1-phenylethylidene) hydrazine

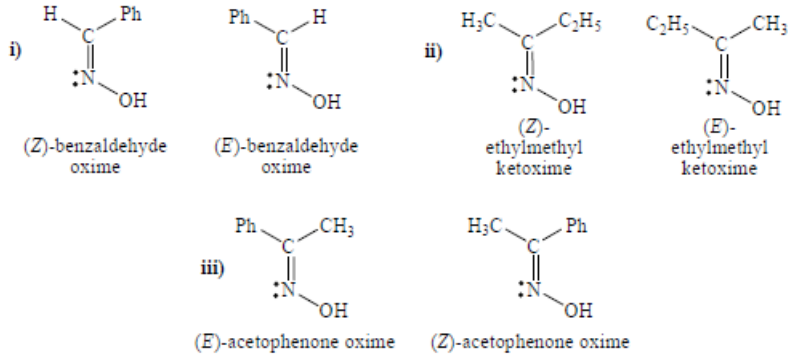


(*E*)-1-(1-phenylethylidene) semicarbazide

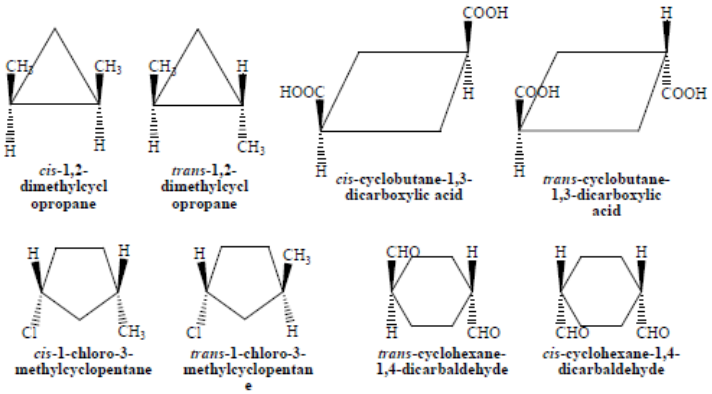
Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp^2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism. The configuration of such compounds is also based on priority of the groups/atoms attached to the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is

assigned as per the sequence rule which we have already discussed in Unit 4. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*- isomer.

Example:E/Z isomerism is shown by i) benzaldoxime, ii) ethylmethylketoxime and iii) methylphenylketoxime



The geometrical isomerism is usually arises due to restricted rotation about a bond. Since, there is no rotation possible about the carbon-carbon bond in a cyclic compound or cycloalkanes like cyclopropane, cyclobutane, cyclopantane, cyclohexane, etc. Hence, such molecule also exhibits geometrical isomerism, and can be designated as *cis*- and *trans*- isomer. In a disubstituted cycloalkanes, where the two atoms/groups are bonded ondifferent carbons, can be represented in to two geometrical isomers. The isomer in which the twoatoms/groups are located on the same side of the ring is called *cis*-isomer; whereas, the isomer in which the two atoms/groups are located on the opposite side of the ring is called *trans*-isomer.



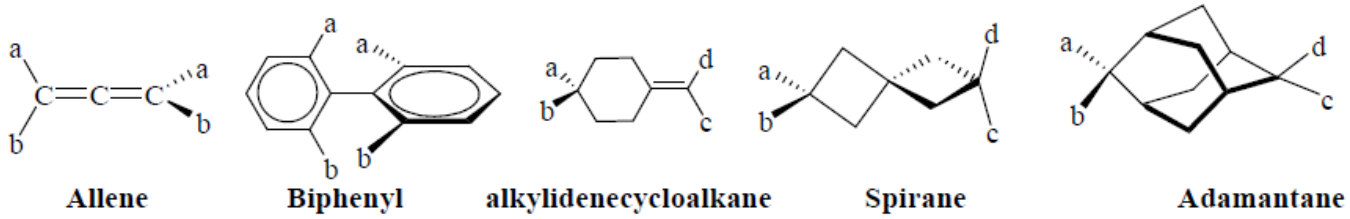
Example: Geometrical isomers of disubstituted cyclopropane, cyclobutane, cyclopantane and cyclohexane.

STEREOCHEMISTRY OF ALLENES and BIPHENYLS

There are a class of compounds with nonsuperimposable mirror images it is not possible to identify a stereocentre, then to predict the stereochemistry of such compounds it becomes necessary to focus our attention on other aspects of the molecule. Thus, the presence of stereocentre is not a necessary and sufficient condition for molecular dissymmetry. The overall chirality of a molecule can be categorised in to three elements; i) stereocentres; ii) stereoaxes; and iii) stereoplanes, one other element of chirality is still there and called helicity.

Chirality due to axes (Axial chirality): Such type of chirality is produced in a molecule when there is no chiral centre present in the molecule. As discussed, in order to produce chirality it is not necessary for all of the substituents to be different. However, it is sufficient to have each substituent different from its nearest neighbour.

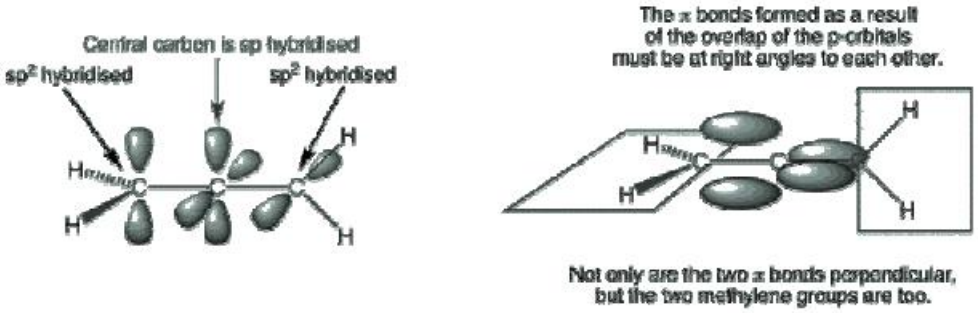
When four atoms/groups attached to a central atom are located on the corners of tetrahedron the central atom is termed as chiral centre. If the chiral centre is replaced by a linear grouping like C-C or C=C=C, the tetrahedron geometry get extended along the axis of the grouping and thus generates a chiral axis. Depending on the nature of groups attached with the carbon atoms, some examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes, spiranes, adamentanes etc.



Examples of molecules with chiral axis are allenes, biphenyls, alkylidenecycloalkanes,spiranes and adamentane

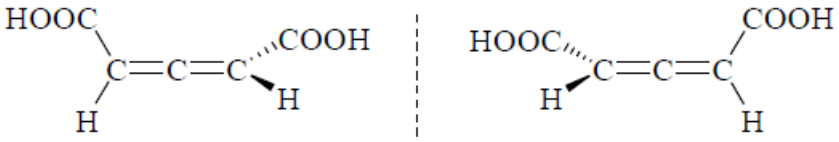
Allenes: Allenes are compounds with two or more double bonds side-by-side. Such bonds are called *cumulated double bonds.* The central carbon of allene forms two sigma bonds and two pi bonds. The central carbon is *sp*-hybridized and the two terminal carbons are sp^2-hybridized. The two π-bonds attached to the central carbon are perpendicular to each other. The geometry of the π-bonds causes the groups attached to the end carbon atoms to lie in perpendicular planes (Figure 4). The bond angle formed by the three carbons is 180°, indicating linear geometry for the

carbons of allene.



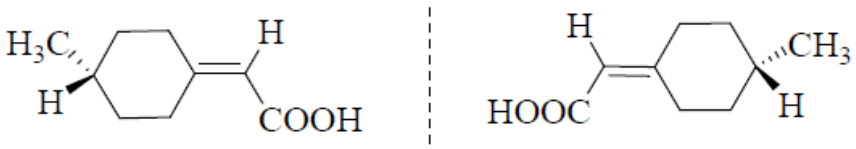
Planar depiction of allene molecule

Stereochemistry of Allenes: When three or more adjacent carbon atoms in a molecule are bonded by double bonds, the compounds is called cumulene or said to have cumulative double bonds. Allene is the simplest example of this class. Allenes are chiral and they have nonsuperimposable mirror images and exist as enantiomers although they have no chiral centre



Nonsuperimposable Mirror images (Enantiomeric Pair)

Stereochemistry of Alkylidenecycloalkanes: The replacement of double bonds in allene by a cycloalkane ring gives the alkylidenecycloalkane; such replacement does not change the basic geometry of the molecule. The suitably substituted alkylidenecycloalkanes also exhibit enantiomerism. The enantiomerism in such compounds is also due to the presence of chiral axis. For example, 4-methylcyclohexyldene acetic acid has been resolved into two enantiomers.



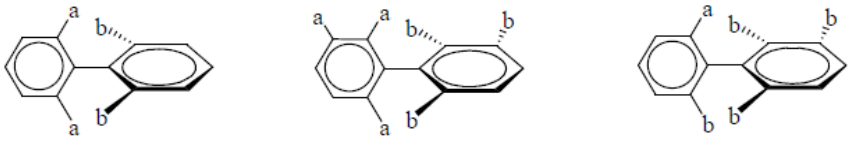
4-methylcyclohexyldene acetic acid

Stereochemistry of Biphenyls: Stereoisomers obtained due to the restricted rotation about

carbon-carbon single bond are called atropisomers and the phenomenon is called atropisomerism. Such compounds also have the chirality due to the axis. Suitably substituted biphenyls exhibit enantiomerism due to the presence of chiral axis. This enantiomerism arises due to atropisomerism *i.e.* restricted rotation around C-C bond between two phenyl rings. This steric hindrance of substituents at *ortho*- position of the each ring is responsible for such restricted rotation. To maintain the maximum stability, molecule orients itself in such a manner so that both the *ortho*- substituted phenyl rings lie in different plane.

Biphenyl shows the enantiomerism when the molecule has the following properties.

a) Each ring must be unsymmetrically substituted. Each of the rings should not contain any kind of symmetry element.



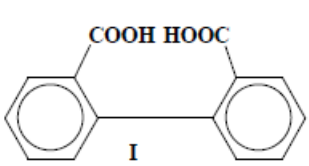
nonresolvable Biphenyl (optically inactive due to plane of symmetry)

resolvable Biphenyls (optically active due to absence of symmetry elements)

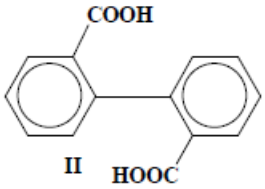
b) Suitable substitution (at least one substitution) at *ortho*- position must be there at each rings.

c) *othro*- substituents must be larger in size (-Cl, -Br, -I, -COOH, -NO_2, -$NHCOCH_3$, -SO_3H, -R groups etc.).

The smaller groups at *othro*- position make the compounds planar in nature and thus do notexhibit atropisomerism.



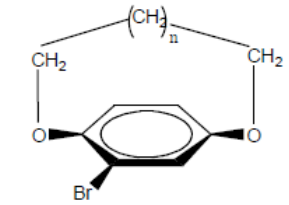
nonresolvable Biphenyl (optically inactive due to plane of symmetry)



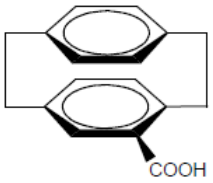
nonresolvable Biphenyl (optically inactive due to centre of symmetry)

Chirality due to Plane (Planar Chirality): Chirality shown by a molecule due to the asymmetry in molecular plane is called chirality due to plane. The chirality is particularly due to the out of the plane

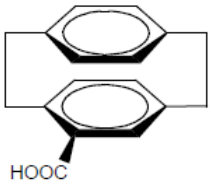
arrangement of atoms or groups in the molecule with respect to reference plane, hence called chiral plane. The most important example of the molecule with chiral plane iscyclophanes. Other examples are trans-cyclooctene, bridged annulenes and metallocenes etc.



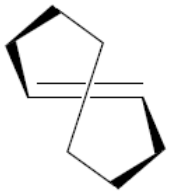
Polymethylene ether of hydroquinone



paracyclophane
(*S*)-



paracyclophane
(*R*)-

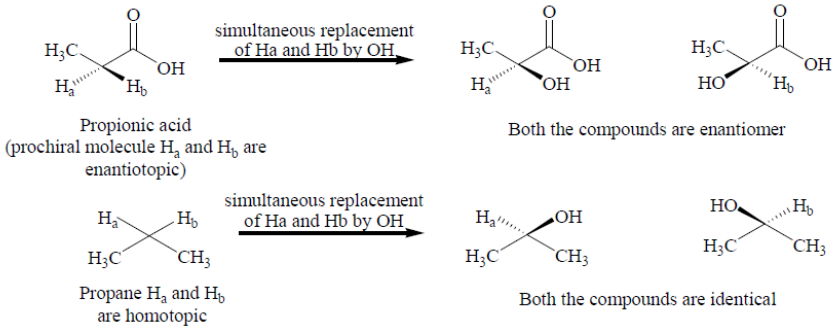

trans-cyclooctene

The polymethylene bridge is perpendicular to the plane of the benzene ring; the substituent Br restricts the rotation of the benzene nucleus inside the methyl bridge, that makes the molecule chiral. Similarly the simple paracyclophane can be resolved because the benzene ring cannot rotate in such a way that the carboxylic passes through the acyclic ring. The plane of both the aromatic rings is approximately parallel to each other. Similarly the *trans*-cyclooctene also exhibits the chirality due to the presence of chiral plane.

TOPOCITY

Stereo-chemical relationships between individual atoms or groups within a single molecule can be defined in terms of topicity. Thus, two atoms equated by a mirror reflection of the molecule are enantiotopic and two atoms in equivalent environments (i.e., the methylene protons in n-propane) are homotopic. Two protons placed in diastereomeric positions by a mirror reflection are in diastereotopic environments.

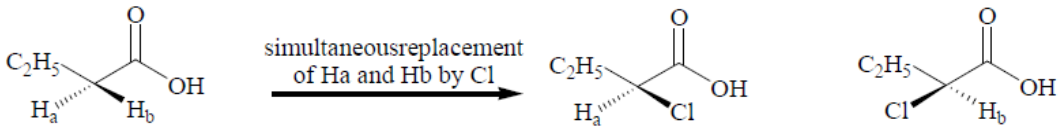
Propane has homotopic ligands; however, propionic acid has enantiotopic ligands



PROCHIRAL CENTER AND PROCHIRAL MOLECULE:

A tetrahedrally bonded atom with four different atoms or groups (**Cabcd**) is called a chiral molecule. However, a tetrahedrally bonded atom with two identical atoms or groups (**Cabbc**) is called an achiral molecule.

If replacement of one of the identical groups in an achiral molecule of type **Cabbc** with a different group when gives an asymmetric molecule then the achiral center is called prochiral center and the molecule is called prochiral molecule. This property is called prochirality.



Butanoic acid
(prochiral molecule H_a and H_b
are enantiotopic)

Both the compounds are enantiomer

Example: Propionic acid is a prochiral molecule with centre carbon atom as prochiral centre. Replacement of one of the hydrogen atom by a different group gives the optically active compound.

HOMOMORPHIC LIGANDS:

Two apparently identical atoms/groups of a prochiral centre are called homomorphic atoms/groups. These are also known as homomorphic ligands. Homomorphic is a Greek name where *homos* meaning similar and *morphe* meaning form. Thus two homomorphic ligands are indistinguishable during their isolation. Two hydrogen atoms of Propionic acid are apparently identical groups *i.e.* H atoms of methylene group are called homomorphic atoms or ligands.

STEREOHETEROTOPIC LIGANDS:

Consider two molecules, Butanoic acid in which two identical hydrogen atoms attached with methylene carbon, and 2-butanol in which two identical hydrogen atoms of methylene carbon. Replacement of any one of the homomorphic ligands in butanoic acid will give a pair of enantiomer; however, replacement of any one of the homomorphic ligands in 2-butanol will give the formation of two diastereomers. Since enantiomers and diastereomers are stereoisomers therefore the homomorphic groups or ligands are also called stereoheterotopic groups or ligands.

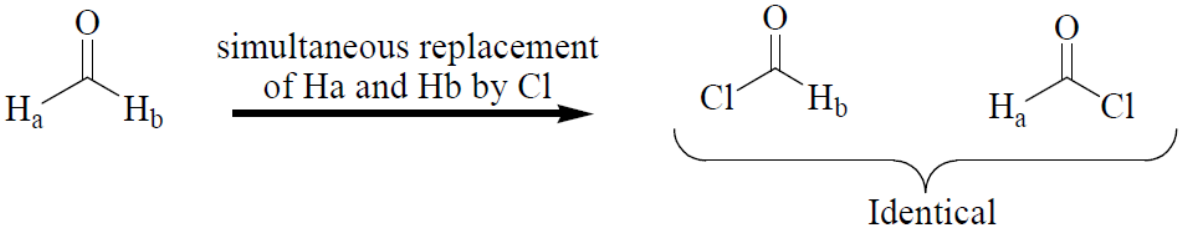
PROCHIRALITY:

It is the property of some molecules due to which these molecules can be converted in to stereoisomers (enantiomers or diastereomers) by replacing one of the identical atoms or groups by a different atom or group. It is also known as '*prostereoisomerism'* more specifically. If the replacement of such atoms or groups leads the formation of enantiomer the atoms or groups are called enantiotopic; whereas, if such replacement lead the formation of diastereomers the atoms or groups are termed as diastereotopic.

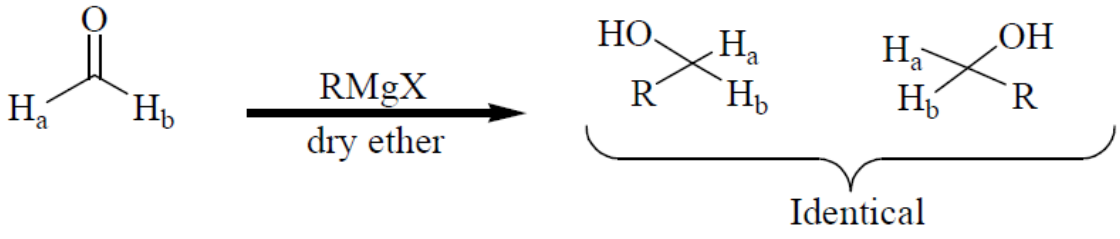
HOMOTOPIC LIGANDS AND FACES:

When replacement of two H atom in a methylene carbon of a molecule generates two identical compounds instead of stereoisomers, these two hydrogen atoms are called homotopic ligands.

Example: Let us consider the case of formaldehyde, the two hydrogen atoms of formaldehyde when replaced with a different atom or group generates two identical compounds hence both the hydrogen atom of formaldehyde molecules are homotopic atoms or homotopic groups.

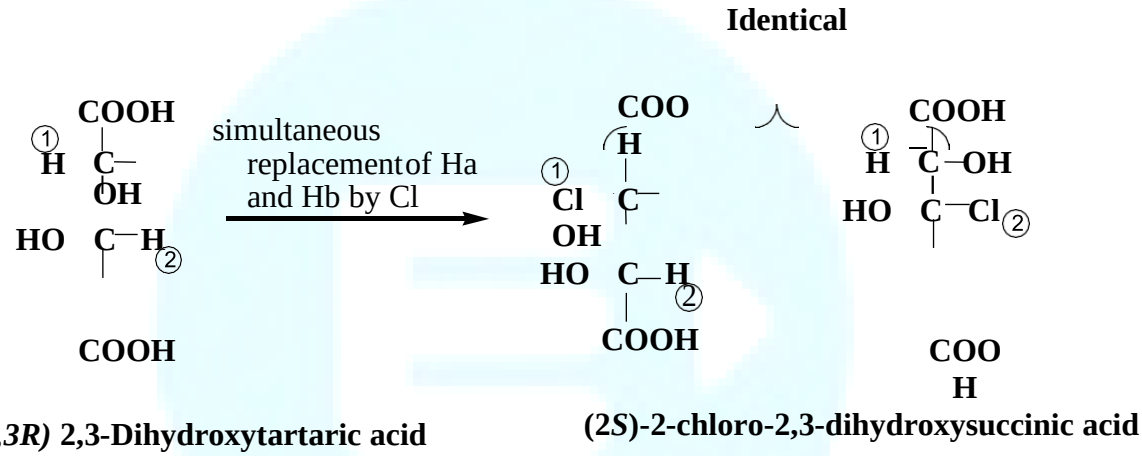


Example: Similarly there is no way to differentiate between the two faces of formaldehyde molecule. The addition of Grignard reagent RMgX to either faces gives the identical compound ethanol. Hence, two faces of formaldehyde are also homotopic faces.

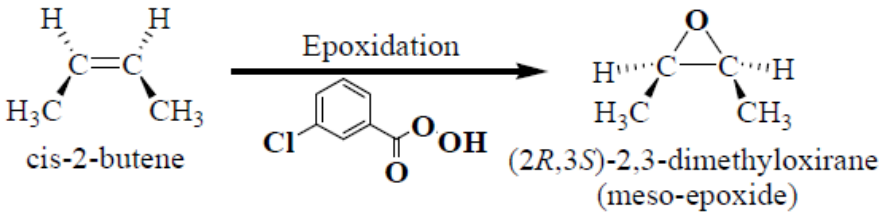


Substitution/addition and symmetry are the two key criteria to determine the topicity of homomorphic ligands and faces. Two homomorphic ligands are called homotopic if replacement of each one of them by another atom or group leads to the identical structure. Thus we can consider three hydrogen atom of acetic acid as homotopic hydrogen, similarly three hydrogen of toluene are also called homotopic hydrogen, because replacement of each one of them will lead the same structure.

Example: In (2*R*,3*R*)-2,3-dihydroxytartaric acid two homotopic hydrogen atoms are present; replacement of each one of them by a different atom gives identical compounds.

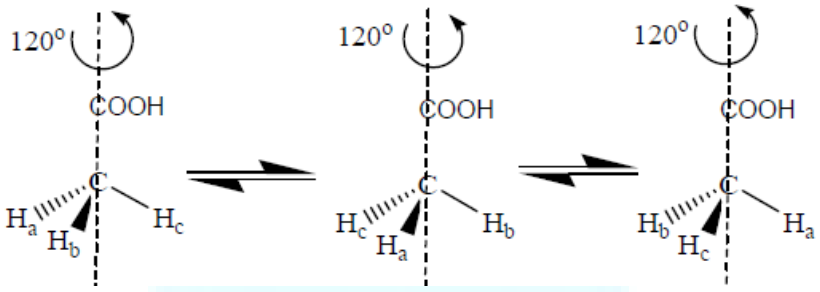


Example: In a double bonded compound like cis-2-butene, two faces of double bond are homotopic since addition on either faces gives the same product. The epoxidation of double bond on either face gives meso product [(*2R*,*3S*)-2,3-dimethyloxirane].



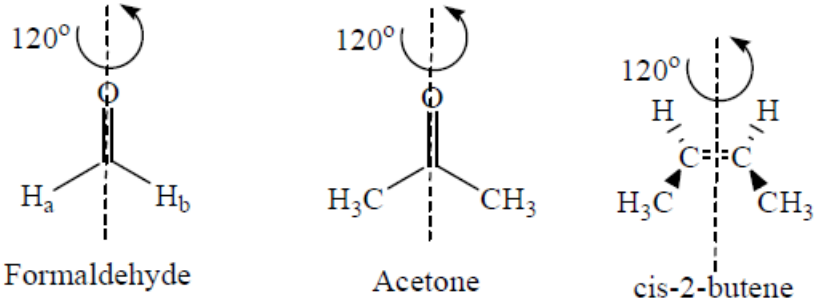
Homotopic ligands and faces can also be determined by employing symmetry operations on the molecule. Let us consider an example of acetic acid, in which all three hydrogen atom of methyl group are homotopic. Two successive rotation of methyl group around its C_3 axis (with the rotation

angle of 120°) allow each hydrogen atom to occupy the position of either of the othertwo hydrogen atoms without effecting any structural changes. As we know that hydrogen atom of methyl group interchanges their position rapidly in 3 dimensional planes, due to this rapid interchange of hydrogen atoms of methyl group leads the formation of indistinguishable structure, that's why these hydrogen atoms are called homotopic hydrogen (homotopic ligands).



All the hydrogen atoms of methyl group are homotopic (homotopic ligands)

Similarly, both the faces of cis-2-butene, formaldehyde and symmetrical ketones are homotopic,hence called homotopic faces.

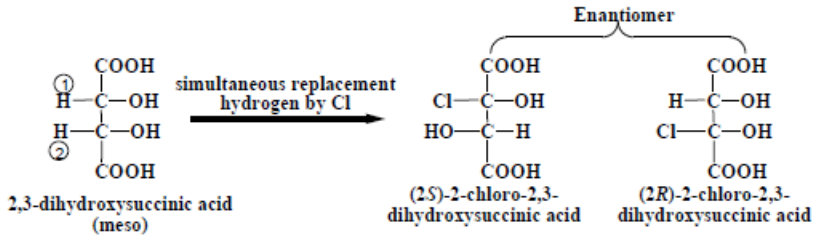


Homotopic Faces

ENANTIOTOPIC LIGANDS AND FACES:

When the replacement of each equivalent atom or groups by a different atom given enantiomeric products, such equivalent atoms or groups are called enantiotopic atoms or enantiotopic ligands.

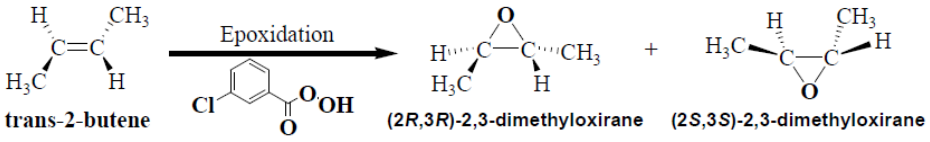
Example: For example, two hydrogen atoms of meso-tartaric acid are enantiotopic since the replacement of each one of them by a different atom or group gives the enantiomeric pair of



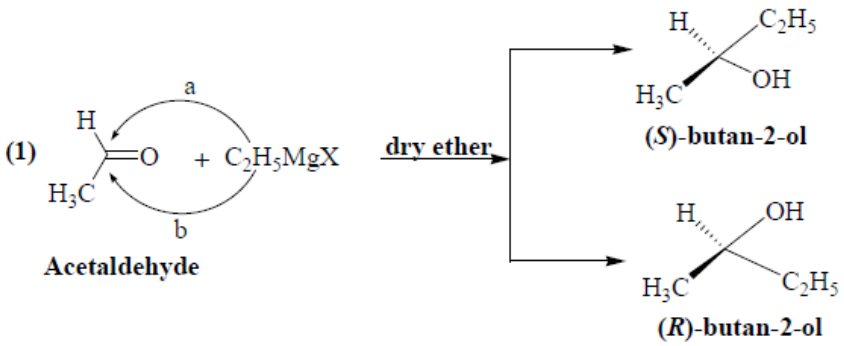
(*2S*)-2-chloro-2,3-dihydroxysuccinic acid and (*2R*)-2-chloro-2,3-dihydroxysuccinic acid.

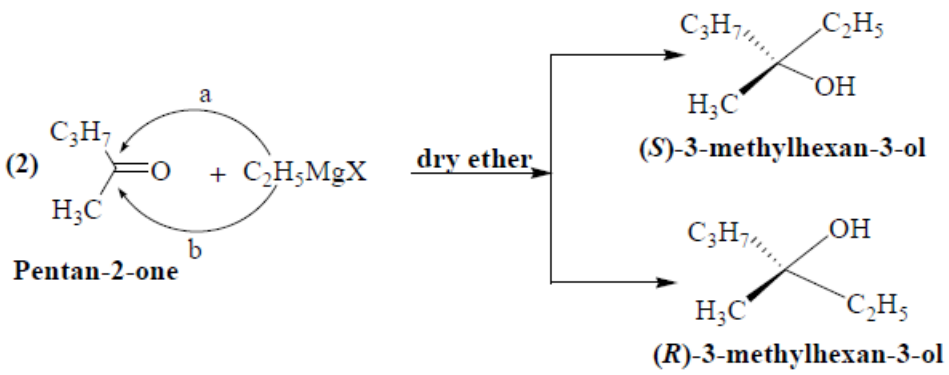
Similarly, when two faces of a double bond gives enantiomers on addition of suitable reagents, such faces are called enantiotopic faces. For example, trans-2-butene and unsymmetrical ketones have enantiotopic faces since they also give enantiomers on addition of suitable reagents.

Example: Epoxidation of trans-2-butene on either face of double bonds gives the enantiomeric pair of (*2R,3R*)-2,3-dimethyloxirane and (*2S,3S*)-2,3-dimethyloxirane.



Example: Similarly, addition of the Grignard reagent (RMgX; R=C_2H_5) or other organometallic reagents on either faces of unsymmetrical carbonyl compounds gives enantiomers. Hence, faces 'a' and 'b' of acetaldehyde **(1)** and Pentan-2-one **(2)** are called enantiotopic faces.



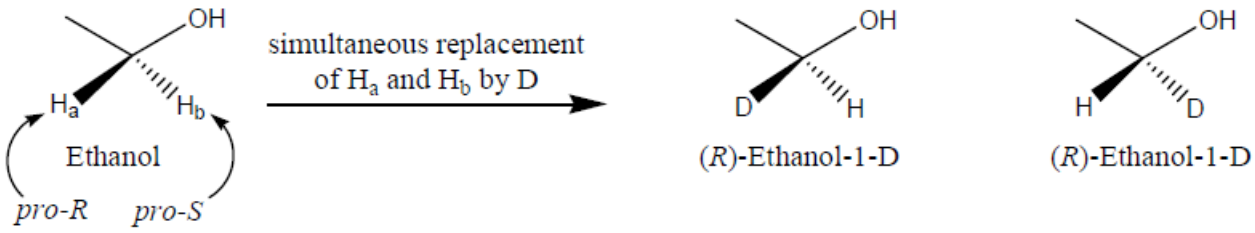


Unlike homotopic ligands and faces, enantiotopic ligands and faces cannot be interchanged by a simple axis of symmetry (C_n). However, they can be interchanged by plane of symmetry, center of symmetry (i) and alternative axis of symmetry (S_n).

NOMENCLATURE OF ENANTIOTOPIC LIGANDS AND FACES:

Naming of enantiotopic ligands and faces is based on the CIP sequence rule by arbitrarily assigning priority to the homomorphic groups/ligands/faces.

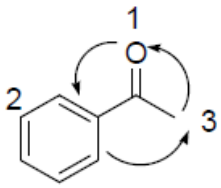
Example: Let us consider ethanol with two homomorphic ligands (H_a and H_b). If H_a is arbitrarily preferred over H_b in the sequence rule, the priority order of the attached groups at central carbon will be OH>CH_3> H_a> H_b and the hypothetical configuration of the stereocenter will be R, thus H_a is designated as *pro-R* and H_b is designated as *pro-S.* Similarly, if H_b was arbitrarily given higher priority over H_a in that case according to sequence rule priority order would have been OH>CH_3> H_b> H_a and the hypothetical configuration of ethanol would be S, thus H_b is designated as *pro-S* and H_a is designated as *pro-R.* Replacement of H_a by deuterium 'D' gives (*R*)-ethanol-1-*D*, hence, H_a is *pro-R;* similarly, replacement of H_b by D gives (*S*)- ethanol-1-*D*,



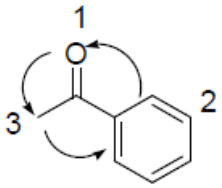
hence, H_b is *pro-S*.

Similalry, two faces of carbonyl carbon are termed as enantiotopic faces. These faces can be designated as *Re-Si* nomenclature. The groups around the carbonyl group are given priorities as per CIP

sequence rule for R and S nomenclature. While going from the highest priority group to the lowest priority group around the faces of carbonyl group, if the path followed is clockwisethe faces is *Re* and if it is anticlockwise, the face is *Si*.



Si-face

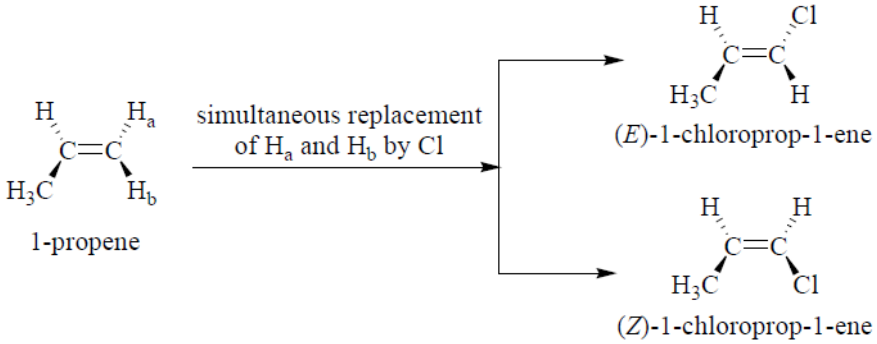


Re-face

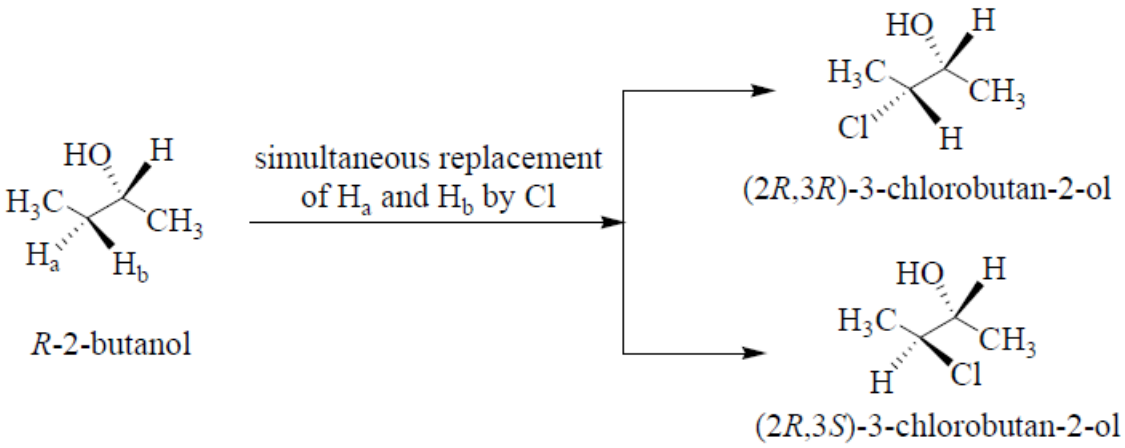
DIASTEREOTOPIC LIGANDS AND FACES:

When the replacement of either of two homomorphic ligands or atoms of a molecule by a different atom generates diastereomers, such homomorphic ligands or atoms are called diastereotopic ligands or atoms.

Example: Let us consider an example of propene in which two homomorphic hydrogen are present. Replacement of one of the homomorphic hydrogen with a hetero atom Cl gives *Z*-alkene ((*Z*)-1-chloroprop-1-ene) while replacement of other homomorphic hydrogen atom by Cl generates *E*-alkene ((*E*)-1-chloroprop-1-ene). Both, (*Z*)-1-chloroprop-1-ene and (*E*)-1- chloroprop-1-ene are stereoisomer but non mirror image of each other, hence are called diastereomer. Thus, two hydrogen atoms (*i.e.* H_a and H_b) of 1-propene are diastereotopic.

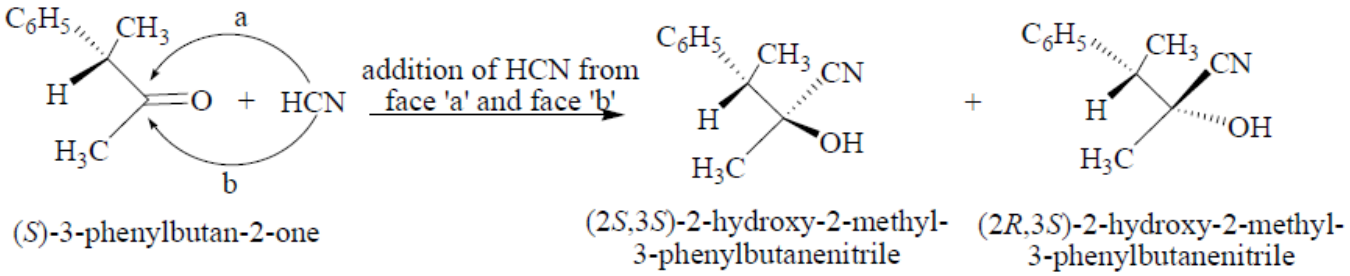


Example: Consider another interesting example of *R*-2-butanol with a stereocenter at C1 andtwo homomorphic hydrogen atoms (H_a and H_b) at C2. Replacement of H_a leads to the formation of (*2R,3R*)-3-chlorobutan-2-ol, and replacement of H_b leads the formation of (*2R,3S*)-3- chlorobutan-2-ol. Therefore, these two products are diastereomers, and the two protons (H_a and H_b) of *R*-2-butanol are diastereotopic.

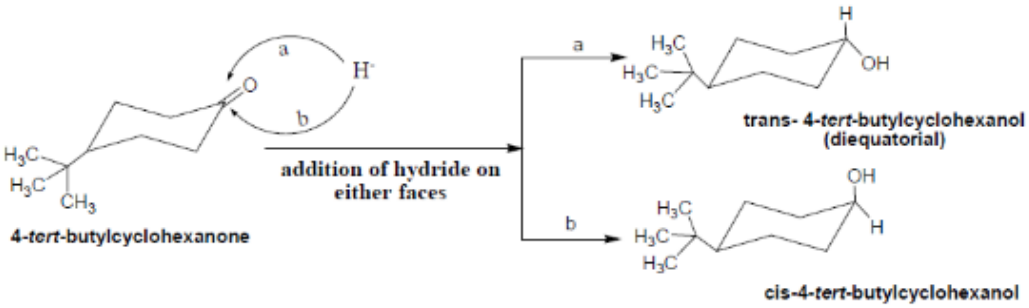


The two faces of carbonyl group next to a stereocenter are diastereotopic. Since, addition of reagents (like HCN, RMgX, HCl etc.) from either faces gives diastereomers. Thus, two faces of such carbonyl group are termed as diastereotopic faces.

Example: For example, let us consider addition of HCN to the either faces of carbonyl group of (*S*)-3-phenylbutan-2-one leads to the formation of, (*2S,3S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile and (*2R,3S*)-2-hydroxy-2-methyl-3-phenylbutanenitrile, a pair of diastereomers.



Example: Similarly, consider another example of 4-*t*-butylcyclohexanone in which addition of hydride on either faces of carbonyl group leads the formation of *trans*- and *cis*- 4-*t*- butylcyclohexanol (diastereomers). Thus two faces of 4-*t*-butylcyclohexanone are diastereotopic faces.



The addition of hydride on either faces of 4-*t*-butylcyclohexanone gives two diastereomers (achiral) products. Hence, the carbonyl carbon is considered as prostereo center rather than prochiral center.

ASYMMETRIC INDUCTION

Before 1940, the optically active compounds could be obtained in stereoisomerically pure form only by isolation of racemic mixture of optically active compounds from natural products and their subsequent enzymatic resolution. Since, equimolar amount of enantiomers (racemic mixture) is obtained when a prochiral molecule undergoes reaction in the absence of chiral environment. As we know the physical and chemical properties of enantiomers are always same in the absence of a chiral environment. However, enantiomers have entirely different reactivities in biological system.

Asymmetric induction is a stereo chemical transformation (reaction) that results the preferential formation of one enantiomer or diastereomer over other in the presence of a chiral substrate, reagent, catalyst or environment. This is also known as asymmetric synthesis. The chiral agent must play an active part in the asymmetric induction. Such chiral agent has an important role in the formation of transition state.

The direct synthesis of an optically active substance from optically inactive compound with or without the use of any optically active compound is called asymmetric synthesis. In general asymmetric synthesis can also be defined as the synthesis which converts a prochiral unit in to a chiral unit and formation of unequal amount of stereoisomers.

PRINCIPLE OF ASYMMETRIC SYNTHESIS:

There are three principle of asymmetric synthesis

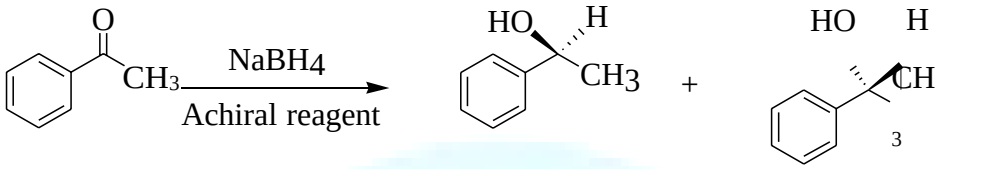
a) The substrate molecule must be prochiral i.e. the substrate must have either enantiotopic or diastereotopic ligands or faces.

b) There must be presence of chirality in the reaction/asymmetric transformation for the preferential formation of one stereoisomer over the other. Either the substrate, or the reagent, or the solvent, or the catalyst must be enantiomerically pure.

c) The chiral agent must play an important role in the reaction and must involve in the

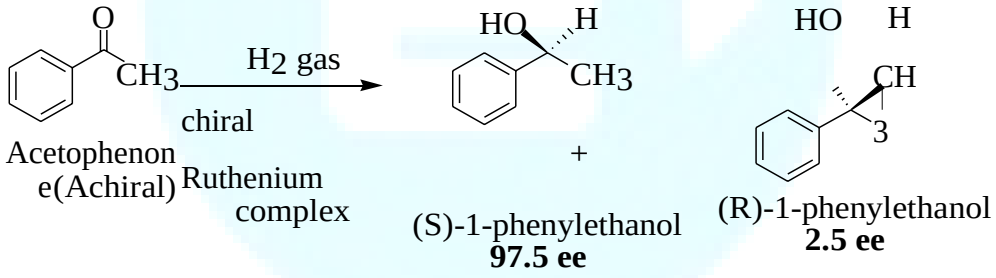
formation of two diastereomeric transition states.

Example: Let us consider hydrogenation of Acetphenone by sodiumborohydride ($NaBH_4$). Since, both the reagent and substrate are achiral (optically inactive) and also the reaction takes place in the medium of methanol (achiral), hence, equal amount of (R)-1-phenylethanol and (S)-1-phenylethanol (racemic mixture) is formed.

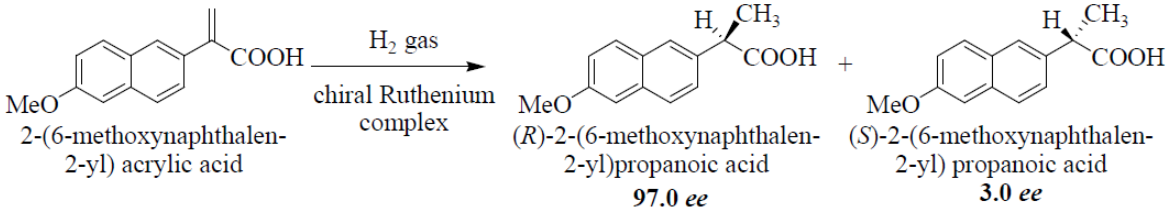


Acetophenone(Achiral) → (S)-1-phenylethanol50% + (R)-1-phenylethanol 50%

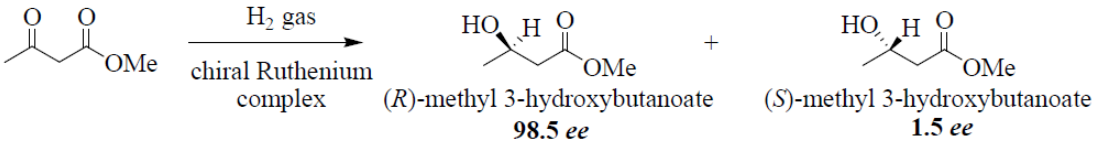
Example: However, when the above reaction is allowed to proceed in the presence of a chiralreagent the (S)-1-phenylethanol is formed preferentially over (R)-1-phenylethanol.



Acetophenone(Achiral) → (S)-1-phenylethanol **97.5 ee** + (R)-1-phenylethanol **2.5 ee**



2-(6-methoxynaphthalen-2-yl) acrylic acid → (*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid **97.0 *ee*** + (*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid **3.0 *ee***



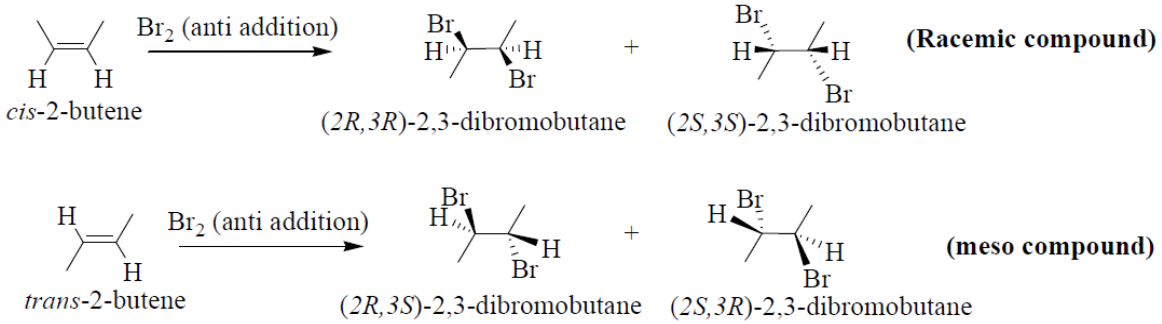
(*R*)-methyl 3-hydroxybutanoate **98.5 *ee*** + (*S*)-methyl 3-hydroxybutanoate **1.5 *ee***

Examples of asymmetric synthesis

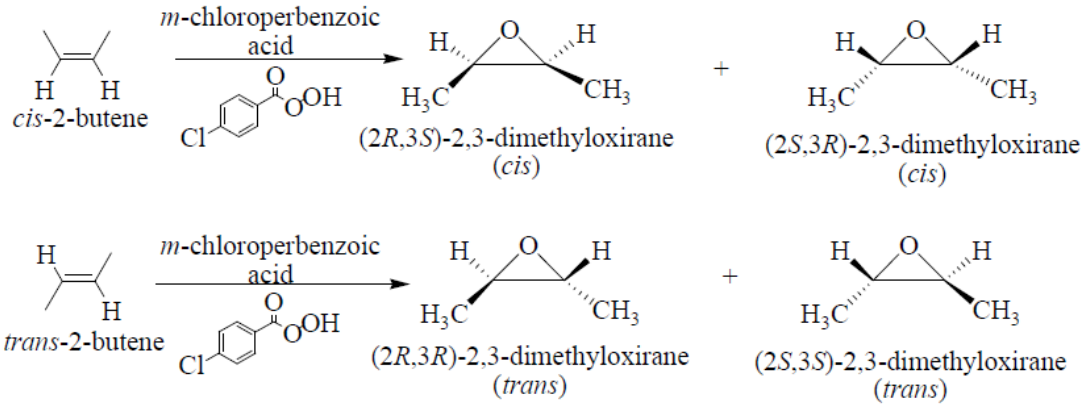
STEREOSPECIFIC AND STEREOSELECTIVE REACTIONS:

Stereospecific reactions: Stereospecific reactions or synthesis are those reactions in which a particular stereoisomer reacts with given reagent to give one specific stereoisomer of the product. This property is called stereospecificity. Thus each individual stereoisomeric substrate under stereospecific synthesis gives a different isomer of the product.

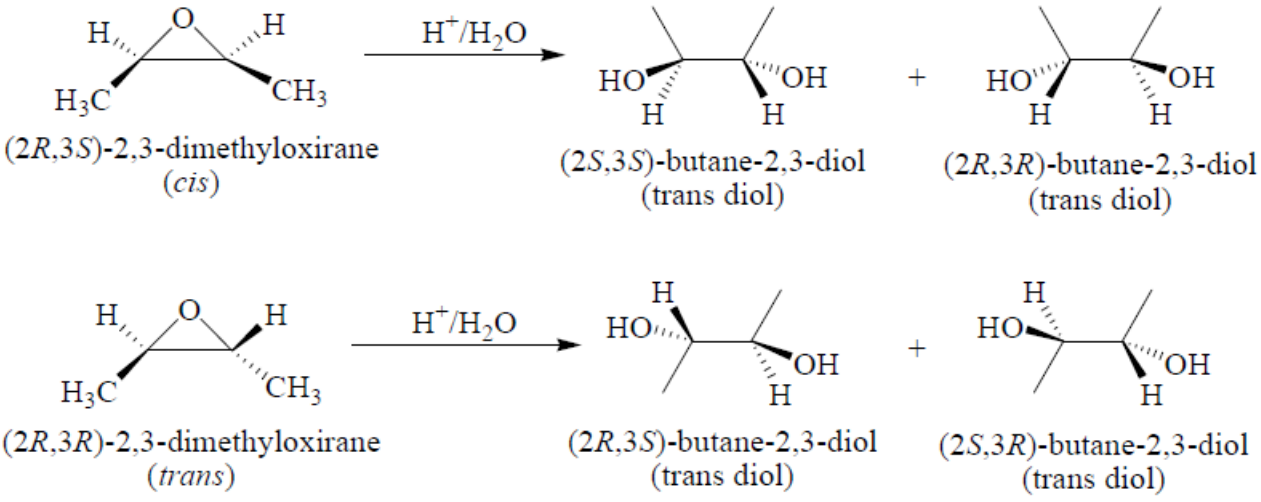
Example: For example, anti addition of bromine to cis-2-butene gives racemic mixture of 2,3-dibromobutane, while the anti addition of bromine to trans-2-butene gives meso-2,3-dibromobutane. These kinds of reactions are called stereospecific because different stereoisomeric substrate leads different stereoisomeric products.



Similarly, syn addition of peroxyacid to cis- and trans- alkenes gives stereospecific reaction. **Example**: For example, syn addition of meta-chloroperbenzoic acid (m-CPBA) to cis-2- butene gives cis-2-dimethyloxirane [(2R,3S)-2,3-dimethyloxirane], while syn addition of meta-chloroperbenzoic acid (m-CPBA) to trans-2-butene gives trans-2,3-dimethyloxirane [(2R,3R)- 2,3-dimethyloxirane]. Thus the reaction is stereospecific.


m-chloroperbenzoic acid
cis-2-butene
(2R,3S)-2,3-dimethyloxirane (cis)
(2S,3R)-2,3-dimethyloxirane (cis)
trans-2-butene
(2R,3R)-2,3-dimethyloxirane (trans)
(2S,3S)-2,3-dimethyloxirane (trans)

Example: Another example of stereospecific reaction is also considered as the ring opening freactions of oxirans (epoxides). Hydrolysis of epoxides (oxiranes) obtained by the syn addition of peroxyacid to cis- and trans- alkenes leads to the formation trans- diols (diols = dihydroxy compounds) in which both the vicinal hydroxy groups are trans to each other.

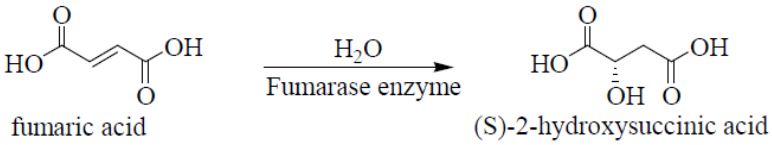


Stereoselective reactions: Stereoselective reactions or synthesis are those reactions in which one stereoisomer (or one pair of enantiomers) is formed predominantly or exclusively out of several possible stereoisomers. This property is called stereoselectivity. In such reactions one stereoisomer is formed more rapidly than other, thus one stereoisomer forms in excess in the resulting mixture of the products. For every stereoselective reaction there is more than one mechanistic path by which reaction may proceed; however, it is observed that the reaction proceeds either via the most favorable path (for which rate of reaction is fast i.e. kinetic control) or via the path that gives the most stable stereoisomer as the major product (i.e. thermodynamic control). The stereoselective reactions/synthesis or the stereoselectivity can be further subdivided in to two categories, a) enantioselective reactions/synthesis or enantioselectivity, b) diastereoselective reactions/synthesis or diastereoselectivity.

a)Enantioselective reactions or enantioselectivity: Enantioselective reactions are defined as the reactions or processes in which one of the enantiomer forms predominantly over the other. This property is known as enantioselectivity. Enantioselectivity is achieved when a stereoselective reaction is performed in the presence of using a chiral environment (i.e. either a chiral substrate, or a chiral

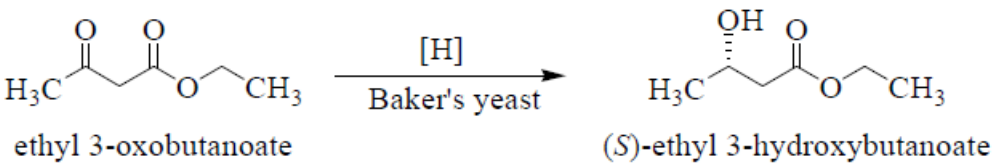
reagent, or a chiral catalyst, or a chiral solvent).

Example: For example, Fumaric acid when hydrolyzed in presence of Fumarase (a chiral enzyme) gives (S)-2-hydroxysuccinic acid exclusively.

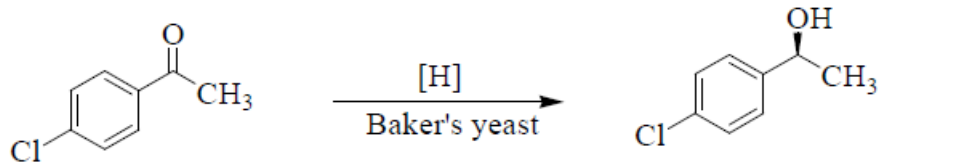


fumaric acid (S)-2-hydroxysuccinic acid

Example: Similalry, reduction of carbonyl group by Baker's yeast exclusively leads to the formation of S- enantiomer. Examples of reduction of carbonyl groups by baker's yeast are shown below.

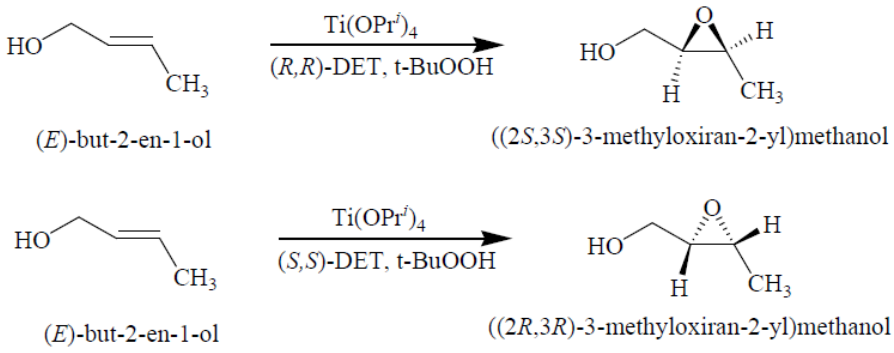


ethyl 3-oxobutanoate (*S*)-ethyl 3-hydroxybutanoate



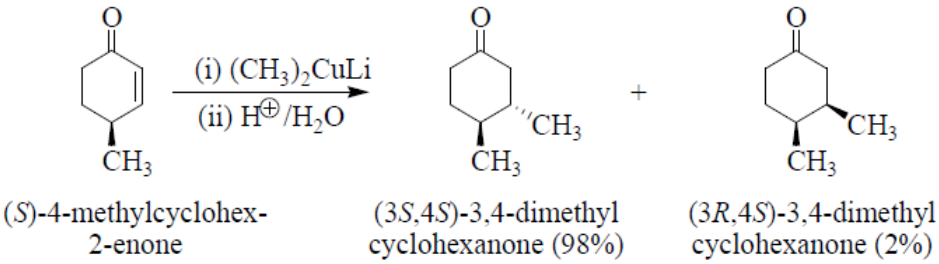
1-(4-chlorophenyl) ethanone (*S*)-1-(4-chlorophenyl)ethanol

The Sharpless epoxidation of allylic alcohol in presence of titanium tetraisopropoxide, t-butylhydroperoxide and enantiomerically pure diethyltartrate (DET) gives enantiomerically pure epoxide. The stereochemistry of product depends on the stereochemistry of diethyltartrate. The diethyltartrate is readily available in its enantiomerically pure forms (i.e. R,R and S,S). (R,R)-diethyltartrate (DET) gives (S,S)- epoxide, whereas, (S,S)-diethyltartrate (DET) gives (R,R)-epoxide.

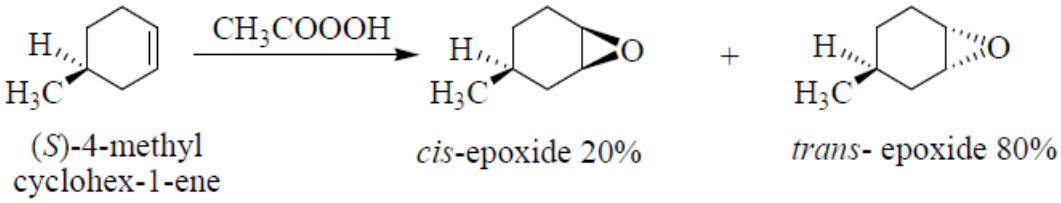


a) **Diastereoselective reactions or diastereoselectivity:** Diastereoselective reactions are defined as the reactions or processes in which one of the diastereomer forms predominantly or exclusively over the other. This property is known as diastereoselectivity. Diastereoselectivity is usually achieved through in the presence of steric hindrance.

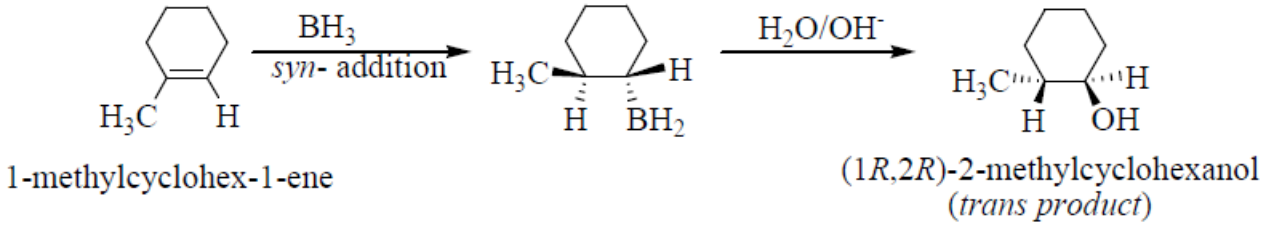
Example: Let us consider the conjugate addition of lithium dimethylcuprate [$(CH_3)_2CuLi$] to 4-methylcyclohexenone. In this reaction cuprate reagent has equal possibilities to react from the either faces of the 4-methylcyclohexenone; however, the bulky cuprate reagent prefers to approach from the less hindered face (i.e. opposite to the methyl group) of the 4-methylcyclohexenone. As a result one diastereoisomer (i.e. trans- product: methyl groups are trans- to each other) out of two possible diastereoisomers forms in excess. Thus, this reaction is called diastereoselective reaction.



Example: Another example of diastereoselective reaction/synthesis is the epoxidation of cyclic alkenes with peroxyacids. In such reactions the epoxidation also takes place from the less hindered face. Epoxidation of 4-methylcyclohexene by peroxyacetic acid gives 80% addition product from the less hindered face (i.e. opposite to the methyl group) and 20% addition product from the more hindered face (i.e. from the face of methyl group).



Example: Similarly, synthesis of alcohols from alkenes by the hydroboration-oxidation is another class of example of diastereoselective reactions. Hydroboration-oxidation of 1-methylcyclohexene gives the trans- product as the major product.



STEREOCHEMISTRY OF NITROGEN COMPOUNDS:

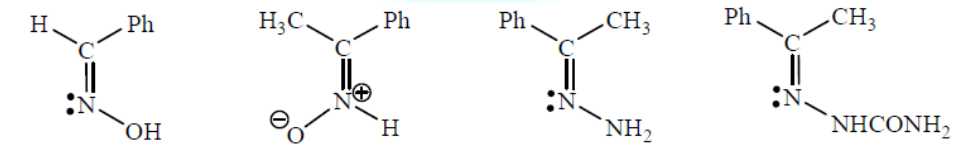
Geometrical isomerism of nitrogen compounds: Nitrogen containing compounds like >C=N- as well as –N=N- bond also exhibit geometrical isomerism. The important classes of compounds that exhibit geometrical isomerism due to >C=N- bond are (Figure 22):

(a) Oximes

(b) Nitrones

(c) Semicarbazones

(d) Hydrazones

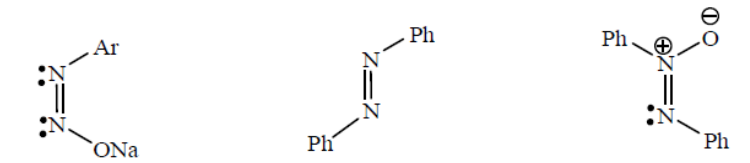


(*Z*)-benzaldehyde oxime | (*E*)-nitrone | (*E*)-1-(1-phenylethylidene) hydrazine | (*E*)-1-(1-phenylethylidene) semicarbazide

Geometrical isomers of compounds having >C=N

Oximes are the most common compounds among all above classes. Both carbon and nitrogen atom in oxime are sp^2 hybridized the C=N bond of oxime consists a sigma (σ) and a pi (π) bond. Therefore, there is no free rotation possible around C=N bond; hence, oximes of aldehyde and ketones (unsymmetrical) exhibit geometrical isomerism.

Some examples of compounds exhibiting geometrical isomerism containing –N=N- are shown

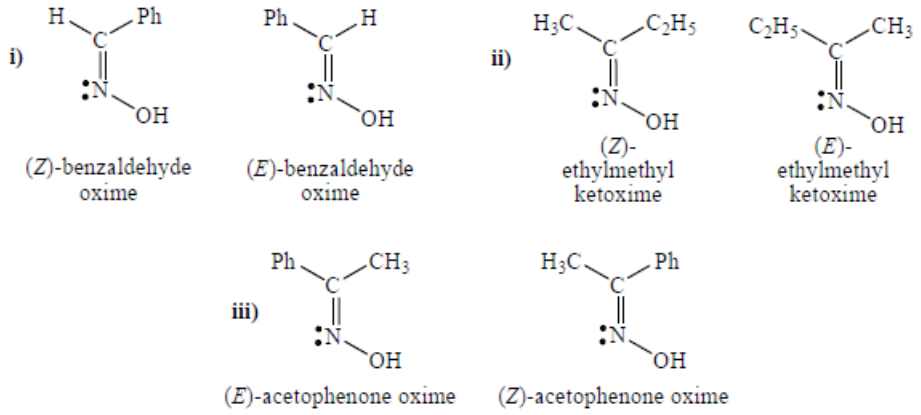


(*Z*)-Diazoate | (*E*)-Azobenzene | (*E*)-Azoxybenzene

Geometrical isomers of compounds having -N=N

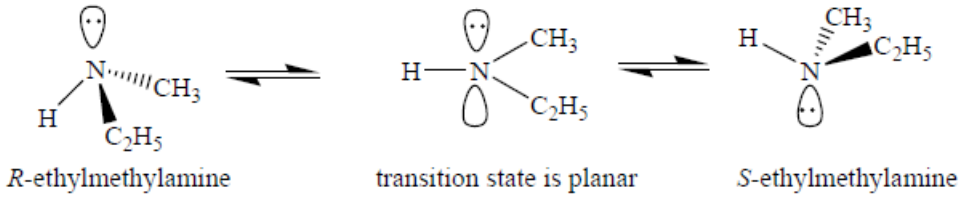
The configuration of such compounds is also based on priority of the groups/atoms attached to

the double bonded carbon and nitrogen. Lone pair of the nitrogen always considered to be the lowest priority group. The priority of the groups/atoms is assigned as per the sequence rule which we have already discussed in Unit 4. If the higher priority groups/atom on double bonded carbon and nitrogen are on same side of the double bond the isomer is considered as *Z*- isomer, whereas if the higher priority groups/atoms are on opposite side the isomer is considered as *E*-isomer.



E/Z isomerism is shown by i) benzaldoxime, ii) ethylmethylketoxime and iii) methylphenylketoxime

Enantiomerism of nitrogen compounds: The tetrahedral concept of carbon has also been successfully extended to nitrogen containing compounds. The only difference in nitrogen compounds is that one of the sp^3 hybridized orbital of nitrogen usually contains a lone pair of electrons which is not involved in bonding. Thus nitrogen containing compound have three ligands and one lone pair in sp^3 orbital. Thus in terms of a chiral center, nitrogen is analogous to carbon. The tertiary amines of with all three different atoms or groups attached with center nitrogen atom have chiral nitrogen, but do not have optical activity. Thus is due to the rapid interconversion of lone pair from one face of the other resulting in rapid racemization Figure 24. The amine interconversion is described as an inversion, such enantiomers are called invertomers.



Inversion of lone pair in nitrogen containing compounds